EMJ EUROPEAN MEDICAL JOURNAL

DERMATOLOGY

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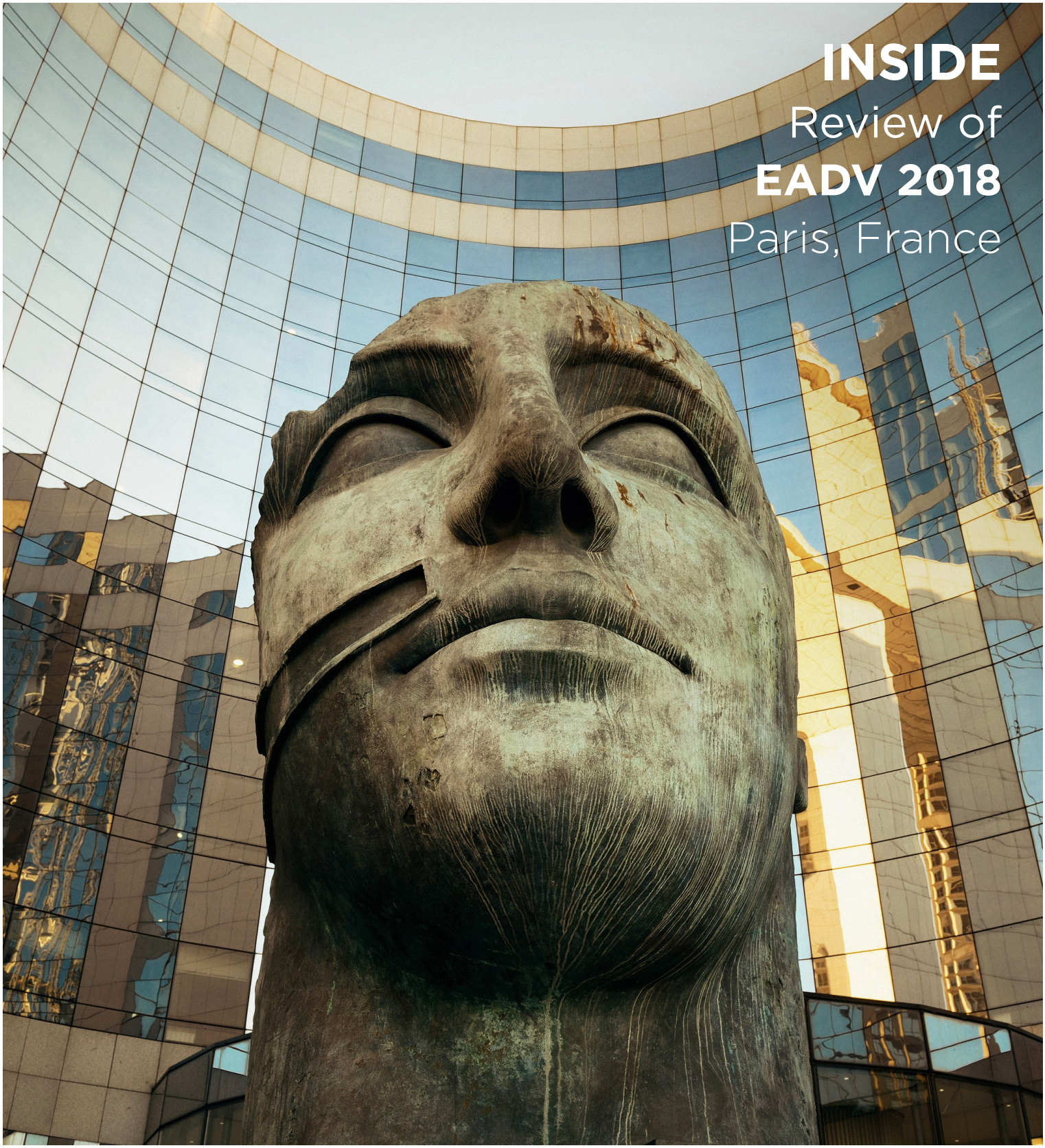

INSIDE

Review of
EADV 2018
Paris, France

Bring balance to your psoriasis patients

Skilarence®

dimethyl fumarate

Skilarence® is an oral treatment option for moderate-to-severe plaque psoriasis in adults in need of systemic therapy.[1]

- **A cost-effective** choice over apremilast that **improves quality of life** vs. placebo[2,3]*
- **Flexible dosing** that allows for a balance between **efficacy** and **tolerability**[1]
- **A higher drug survival** rate with FAEs compared to methotrexate[4†]

Skilarence 30 mg & 120 mg gastro-resistant tablets Active Ingredient: Skilarence 30 mg Each gastro-resistant tablet contains 30 mg dimethyl fumarate. Also contains 34.2 mg lactose (as monohydrate). **Skilarence 120 mg** Each gastro-resistant tablet contains 120 mg dimethyl fumarate. Also contains 136.8 mg lactose (as monohydrate). **Indication:** For the treatment of moderate to severe plaque psoriasis in adults in need of systemic medicinal therapy. **Dosage and Administration:** For oral use. To improve tolerability, it is recommended to begin treatment with a low initial dose with subsequent gradual increases. In the first week, Skilarence 30 mg is taken once daily (1 tablet in the evening). In the second week, Skilarence 30 mg is taken twice daily (1 tablet in the morning and 1 in the evening). In the third week, Skilarence 30 mg is taken three times daily (1 tablet in the morning, 1 at midday, and 1 in the evening). From the fourth week, treatment is switched to only 1 tablet of Skilarence 120 mg in the evening. This dose is then increased by 1 Skilarence 120 mg tablet per week at different times of day for the subsequent 5 weeks. If a particular dose increase is not tolerated, it may be temporarily reduced to the last tolerated dose. The maximum daily dose allowed is 720 mg (3 x 2 tablets of Skilarence 120 mg). *Consult SmPC and package leaflet for the titration table and full method of administration.* **Contraindications, Warnings, etc:** *Contraindications:* Hypersensitivity to the active substance or to any of the excipients listed in SmPC section 6.1. Severe gastrointestinal disorders, Severe hepatic or renal impairment, Pregnancy and breast-feeding. *Precautions:* Skilarence may decrease leukocyte and lymphocyte counts. It has not been studied in patients with pre-existing low leukocyte or lymphocyte counts. Prior to initiating treatment with Skilarence, a current complete blood count (including differential blood count and platelet count) should be available. Treatment should not be initiated if leukopenia below $3.0x10^9$/L, lymphopenia below $1.0x10^9$/L or other pathological results are identified. During treatment a complete blood count with differential should be performed every 3 months. *Leukopenia:* Discontinue treatment if a marked decrease in the total number of white blood cells is at levels below $3.0x10^9$/L. Lymphopenia: If the lymphocyte count falls below $1.0x10^9$/L but is ≥$0.7 x10^9$/L, blood monitoring should be performed monthly until levels return to $1.0x10^9$/L or higher for two consecutive blood tests at which point monitoring can again be performed every 3 months. If the lymphocyte count falls below $0.7x10^9$/L, the blood test must be repeated and if the levels are confirmed to be below $0.7x10^9$/L, then treatment must be stopped immediately. Patients developing lymphopenia should be monitored after stopping treatment until their lymphocyte count has returned to the normal range. *Infections:* Initiation of therapy should only be considered once a pre-existing infection has resolved. If a patient develops an infection during treatment with Skilarence, suspension of treatment should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Skilarence should be instructed to report symptoms of infection to a physician. *Progressive multifocal leukoencephalopathy (PML)* Cases of opportunistic infections, particularly of PML have been reported with other dimethyl fumarate-containing products. PML is an opportunistic infection caused by the John-Cunningham virus (JCV) that can be fatal or cause severe disabilities. A modified or weakened immune system as well as genetic or environmental factors can also constitute risk factors. Persistent moderate or severe lymphopenia during treatment with dimethyl fumarate is also considered a risk factor for PML. Patients who develop lymphopenia should be monitored for signs and symptoms of opportunistic infections, particularly for symptoms indicative of PML. Renal and hepatic function should be checked prior to initiation of treatment and every three months thereafter. *Fanconi syndrome:* Early diagnosis of Fanconi syndrome and discontinuation of Skilarence treatment are important to prevent the onset of renal impairment and osteomalacia, as the syndrome is usually reversible. *Flushing:* Patients should be made aware that they are likely to experience flushing in the first few weeks of taking Skilarence. *Lactose:*

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FAE, fumaric acid ester.
*No head-to-head studies were performed.
†Mean survival time was 35.6 months for FAE (n=158) vs. 22.3 months for methotrexate (n=174).

References:
1. Skilarence® Summary of Product Characteristics. Almirall. Available at: https://www.medicines.org.uk/emc/product/752. Accessed: October 2018.
2. NICE. Dimethyl fumarate for treating moderate to severe plaque psoriasis. TA475. 2017. Available at: https://www.nice.org.uk. Accessed: October 2018.
3. Van de Kerkhof P, *et al.* Treatment with LAS41008 (dimethyl fumarate) improved health-related quality of life and has a positive impact on the patient benefit index in adults with moderate-to-severe chronic plaque psoriasis: results of the BRIDGE study. European Academy of Dermatology and Venereology. Vienna, Austria. 28 September – 2 October 2016. E-poster: P1998.
4. Arnold T, *et al. J Dtsch Dermatol Ges* 2016;14:1089–1099.

This material has been developed and funded by Almirall.
October 2018 UKDMF3943

Skilarence contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. *Interactions:* Skilarence should be used cautiously in combination with other systemic antipsoriatic therapy (e.g. methotrexate, retinoids, psoralens, ciclosporin, immunosuppressants or cytostatics). During treatment with Skilarence, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided. Concurrent therapy with nephrotoxic substances (e.g. methotrexate, ciclosporin, aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential for renal adverse reactions (e.g. proteinuria). In cases of severe or prolonged diarrhoea during treatment with Skilarence, absorption of other medicinal products may be affected. Caution should be exercised when prescribing medicinal products with a narrow therapeutic index that require absorption in the intestinal tract. The efficacy of oral contraceptives may be reduced and the use of an alternative barrier contraceptive method is recommended to prevent possible failure of contraception. Consumption of large quantities of strong alcoholic drinks (more than 30% alcohol by volume) should be avoided because it may lead to increased dissolution rates of Skilarence and, therefore, may increase the frequency of gastrointestinal adverse reactions. Vaccination during treatment with Skilarence has not been studied. Immunosuppression is a risk factor for the use of live vaccines. There is no evidence for Skilarence interaction with cytochrome P450. *Fertility Pregnancy and lactation:* Skilarence is not recommended in women of child-bearing potential not using appropriate contraception. In patients experiencing diarrhoea during Skilarence treatment, the effect of oral contraceptives may be reduced and additional barrier methods of contraception may be necessary. There are limited data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity. Skilarence is contraindicated during pregnancy and breast-feeding There are no human or animal data on the effects of Skilarence on fertility. *Ability to drive and use machines:* Skilarence may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur. *Consult SmPC and package leaflet for more information.* **Adverse Reactions:** *Very common (≥1/10);*Lymphopenia, leukopenia, flushing, diarrhoea, abdominal pain and distention, nausea. *Common (≥1/100 to <1/10):* Eosinophilia, leucocytosis, headache, paraesthesia, vomiting, dyspepsia, constipation, abdominal discomfort, flatulence, erythema, skin burning sensation, pruritis, fatigue, feeling hot, asthenia, hepatic enzyme increased. *Very rare (<1/10,000):* Acute lymphatic leukaemia, irreversible pancytopenia. *Not known (cannot be estimated from available data)* PML, renal failure, Fanconi syndrome. *Consult SmPC and package leaflet for other adverse reactions.* **Legal Category:** POM **Marketing Authorisation Number(s):** EU/1/17/1201/001, EU/1/17/1201/004, EU/1/17/1201/007. **NHS Cost:** 30 mg - 42 tablets = £89.04 ; 120 mg - 90 tablets = £190.80, 180 tablets = £381.60 (excluding VAT). **Marketing Authorisation Holder:** Almirall, S.A., Ronda General Mitre, 151, 08022 Barcelona, Spain. **Further information is available from:** Almirall Limited, Harman House, 1 George Street, Uxbridge, Middlesex, UB8 1QQ, UK. Tel: 0800 0087 399. Email: almirall@professionalinformation.co.uk
Date of Revision: 06/2017
Item code: UKDMF3708

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Spencer Gore, CEO

Editorial Board

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Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

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EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines.
- Invited contributors are recognised authorities from their respective fields.
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

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Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area.

All peer review is double blind.

Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected.

Editorial staff have final discretion over any proposed amendments.

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We seek papers with the most current, interesting, and relevant information in each therapeutic area and accept original research, review articles, case reports, and features.

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Open Access

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This Publication

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Front cover and contents photograph: Paris, France, home of the EADV 2018. © Songquan Deng / 123rf.com

EMJ Dermatol.

European Medical Journal 3.1

This edition is packed with an assortment of peer-reviewed articles from a body of therapeutic areas, including reproductive health, dermatology, and cardiology, to name a few.

VIEW ALL JOURNALS ←

Welcome

A very warm welcome to *EMJ Dermatology 6.1*, a much-anticipated annual journal detailing the cutting-edge advances from the field of skin diseases. Contained within this eJournal is an independent review of the European Academy of Dermatology and Venereology (EADV) Congress 2018, as well as fascinating interviews and peer-reviewed articles by experts at the forefront of dermatology research.

A mammoth 180 scientific sessions formed part of the 5-day EADV Congress programme, spanning from the 12th–16th September 2018, and were attended by 700 speakers from 60 countries. Bringing attendees up to speed with all aspects of dermatology, key topics from this year's event include improving psoriasis patient quality of life and the harmful effects of sun exposure, summarised alongside abstract and symposium reviews within this new issue. I would also like to bring your attention to an exclusive interview with Dr Francesca Sampogna, who kindly discussed her presentation at the event, focussing on the psychosocial impact of skin diseases. As an opportunity to re-live this fantastic event and learn from the experts, the captivating Congress Review section should not be missed. Complementing the Congress Review, you will also find a selection of interviews with esteemed members of the *EMJ Dermatology* Editorial Board, in which they share their experiences in dermatology and hopes for the future of the discipline.

With high-quality peer-reviewed articles forming a key part of the EMJ publications, the articles in *EMJ Dermatology* will not disappoint. The Editor's Pick for this edition, selected by Editor-in-Chief Prof Lawrence F. Eichenfield, comments on the common theme of psoriasis and evaluates the psychiatric symptoms associated with this chronic skin condition, highlighting the importance of managing both dermal and extradermal disease manifestations in inflammatory disorders. Chronic urticaria and herpes simplex labialis are other key areas of research explored by the authors, providing an informative overview of some of the most common dermatological conditions seen in clinical practice today.

Available for established professionals as well as new members of the medical community, *EMJ Dermatology* provides the perfect opportunity to gain insights into a fast-paced medical discipline. With skin diseases responsible for a significant burden on healthcare providers, patients, and society in general, the EMJ team is proud to provide a compilation of the latest advances to enhance research and clinical practice. We hope you enjoy reading this latest edition!

Kind regards,

Spencer Gore

Chief Executive Officer, European Medical Group

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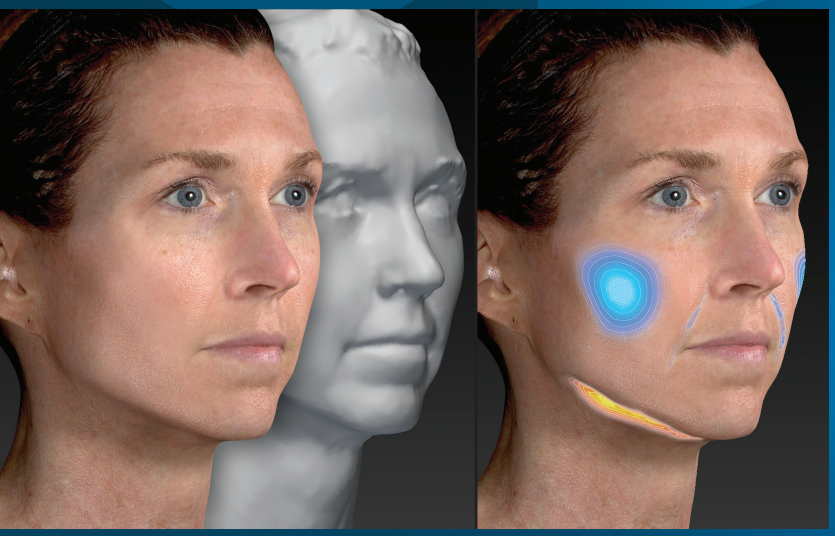

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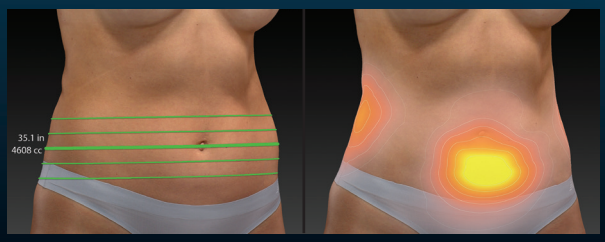

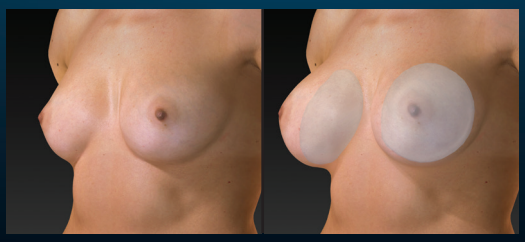

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Foreword

Dear colleagues,

Welcome to the latest edition of *EMJ Dermatology*, which covers the recent European Academy of Dermatology and Venereology (EADV) Congress in beautiful Paris, France. This year's event was a roaring success! Over 10,000 attendees from around the world participated in a programme rich in scientific content, with a tremendous collection of new research in dermatologic diseases and evolving therapeutics. The programme included new scientific insights, including those drawn from bench research, epidemiological studies, clinical trials, and clinical experience, capturing state-of-the-art dermatologic care and laying groundwork for future advances.

The amount of new information presented was astounding, and I was particularly impressed with the material presented on inflammatory skin and allergic diseases. For example, I counted >60 presentations and posters covering atopic dermatitis! This included Phase III study results on the use of dupilumab in 12–17 year olds with moderate-to-severe atopic dermatitis, extended treatment data for a systemic JAK inhibitor (upadacitinib), a Phase II study of a topical JAK inhibitor (ruxolitinib), and new targets for biologic agents, such as the OX40 pathway and IL-17C. The continued research on biologics and novel small molecular agents for psoriasis, along with insights into comorbidities, is truly revolutionising the field and impacting patient outcomes. *EMJ Dermatology 6.1* highlights some interesting articles, including a discussion of oral psoriasis and the successful treatment of lingual pustular psoriasis and acrodermatitis continua of Hallopeau with adalimumab. In addition, my Editor's Pick for this issue probes the relationship between psychological distress and the immune system in psoriasis.

Other papers of interest highlighted in *EMJ Dermatology 6.1* look at predicting the response of chronic urticaria to omalizumab based on biomarkers. In addition, an excellent systematic review evaluates topical therapies for herpes simplex labialis; the study shows the agents are safe to use but only have marginal efficacy.

I am sure you will enjoy this latest edition of *EMJ Dermatology*!

My best wishes,

Prof Lawrence F. Eichenfield

University of California, San Diego, San Diego, California, USA

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Confidence starts with clearance

Kyntheum® (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy[1]

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- **Complete clearance** with **Kyntheum®** induction was sustained through to **1 year**[1,3,4]
- 1 in 4 patients achieved PASI 75 at **week 2** with **Kyntheum®**[5]
- By achieving **PASI 100** at week 12, a greater proportion of patients experienced no impairment to their **health-related quality of life** from psoriasis (DLQI 0 or 1) versus those with a lower response[6]

August 2018. MAT-18351

Abbreviated Prescribing Information for Kyntheum® 210 mg solution for injection in pre-filled syringe Please refer to the full Summary of Product Characteristics (SmPC) approved in your country before prescribing. This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. **Active ingredient:** Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution. 1 ml solution contains 140 mg brodalumab. **Dosage and administration:** *Posology: Adults:* The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. Each pre-filled syringe is for single use only. *Elderly:* No dose adjustment recommended. *Hepatic and renal impairment:* No dose recommendations can be made. *Children and adolescents below the age of 18 years:* Safety and efficacy of Kyntheum have not been established. *Method of administration*: Subcutaneous (SC) injection. Kyntheum should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken. After proper training in SC injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active Crohn's disease. Clinically important active infections (e.g. active tuberculosis). **Precautions and warnings:** *Crohn's disease*: Exercise caution when prescribing Kyntheum to patients with a history of Crohn's disease. They should be followed for signs and symptoms of active Crohn's disease. If patients develop active Crohn's disease, treatment should be discontinued permanently. *Suicidal ideation and behaviour*: Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established. Carefully weigh the risk and benefit of treatment with Kyntheum for patients with a history of depression and/or suicidal ideation or behaviour, or patients who develop such symptoms. Patients, caregivers and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum. *Infections:* Kyntheum may increase the risk of infections. Caution should be exercised when considering the use of Kyntheum in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and Kyntheum should not be administered until the infection resolves. Kyntheum should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Kyntheum in patients with latent tuberculosis. *Reduced absolute neutrophil count*: A decrease in absolute neutrophil count, generally transient and reversible, has been observed in 5.6% of patients receiving Kyntheum. *Vaccinations:* It is recommended that patients be brought up-to-date with all immunisations in accordance with local immunisation guidelines prior to initiation of treatment with Kyntheum. Live vaccines should not be given concurrently with Kyntheum. The safety and efficacy of Kyntheum in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. **Drug interactions:** Live vaccines should not be given concurrently with Kyntheum. **Fertility, pregnancy and lactation:** *Women of childbearing potential*: Use an effective method of contraception during treatment and for at least 12 weeks after treatment. *Pregnancy*: There are no or limited amount of data from the use of brodalumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Kyntheum in pregnancy. Benefit risk for exposure of the infant to live vaccines following third trimester exposure to Kyntheum should be discussed with a physician. *Breast-feeding:* It is unknown whether brodalumab is excreted in human milk. A risk to the newborns/infants cannot be excluded. Whether to discontinue breast-feeding or discontinue Kyntheum therapy should be decided, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *Fertility*: No data are available on the effect of brodalumab on human fertility. **Adverse reactions:** *Common (≥1/100 to <1/10)*: Influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, oropharyngeal pain, diarrhoea, nausea, arthralgia, myalgia, fatigue, injection site reactions (including injection site erythema, pain, pruritus, bruising, haemorrhage). *Uncommon (≥1/1,000 to <1/100)*: Candida infections (including oral, genital and oesophageal infections), conjunctivitis. **See SmPC for a full list of adverse reactions. Precautions for storage:** Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Kyntheum may be stored at room temperature (up to 25°C) once, in the outer carton, for a maximum single period of 14 days. Once Kyntheum has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 14 days or discarded. **Marketing authorisation number and holder:** EU/1/16/1155/001, LEO Pharma A/S, Ballerup, Denmark. **Last revised:** September 2017

Reporting of Suspected Adverse Reactions
Adverse reactions should be reported according to local guidelines.

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References:
1.Kyntheum® (brodalumab) Summary of Product Characteristics. English version, September 2017. **2.** Campa M, et al. *Dermatol Ther* 2016;6:1–12. **3.** Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28. **4.** Supplement to: Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28. **5.** Blauvelt A, et al. *J Am Acad Dermatol* 2017;77:372–74. **6.** Strober B, et al. *J Am Acad Dermatol* 2016;75:77–81.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

LEO


METRO

Congress Review

Review of the European Academy of Dermatology and Venereology (EADV) Congress 2018

Location: Paris, France – Palais des Congrès de Paris

Date: 12.09.18–16.09.18

Citation: EMJ Dermatol. 2018;6[1]:14-26. Congress Review.

Held in the city of Paris, France, on the 12th–16th September 2018, the 27th European Academy of Dermatology and Venereology (EADV) Congress lived up to the enormous expectations preceding it. With a programme peppered with 180 scientific sessions to bring the audience up to speed with the latest movements in the dermatology world, the stage was set for a truly spectacular 5-day event.

Home to the iconic Eiffel Tower and draped in years' worth of iconic history, Paris was the perfect backdrop for this year's EADV Congress focussing on clinical oncology. Topics throughout the event ranged from genetic predisposition and targeting the tumour environment to rare skin tumours and the effects of chemotherapy and targeted therapy. Prof Luca Borradori took to the stage for the opening address to a rousing applause from the audience. In his final presidential opening of a EADV Congress, Prof Borradori spoke of his fondness for Paris and how privileged he felt to be able to host his final EADV Congress as EADV President in the city that he trained in. Alongside urging the EADV attendees to explore the wonderful city, Prof Borradori also incited excitement for the forthcoming event by highlighting the astonishing array of scientific sessions, with 700 speakers from 60 countries, and the much-anticipated 2,500 abstracts on display.

The scientific programme also included three plenary lectures, including presentations from six of the most prominent and prolific dermatology specialists from across Europe and the USA. Beginning on the first day of the congress, Dr Warren Piette, Chicago, Illinois, USA, presented on the consequences of differential diagnosis on the treatment of vasculitis and vasculopathies, shortly followed by a presentation on atopic dermatitis and skin infection by Dr Tilo Biedermann, Munich, Germany. The following day's plenary lecture presentation saw Dr Christian Blank, Amsterdam, Netherlands, ask the poignant question of whether we can cure metastatic melanoma. Concluding the plenary lectures

on Saturday, Dr Elisabeth Grice, Philadelphia, Pennsylvania, USA, presented on the skin microbiome and its link to health and disease, while Dr Veronica Kinsler, London, UK, took the audience through the diagnosis, spectrum, and therapy of congenital nevi, and, finally, Dr Leena Bruckner-Tuderman, Freiburg, Germany, presented on a variety of skin fragility syndromes.

Prof Borradori encouraged all attendees to visit the patient society village, which was open for the duration of the congress where clinicians and medical professionals can speak to patients, patient associations, and societies to understand patient expectations, wishes, and needs; after all, patients are at the centre and the reason of all that the medical community do.

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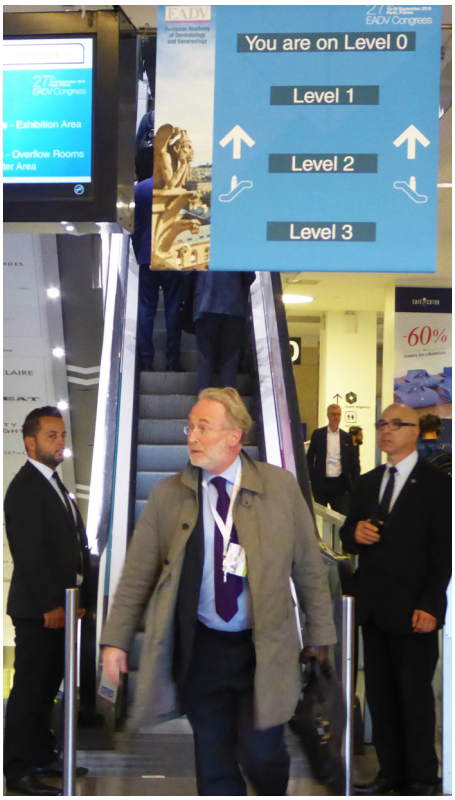
Concluding the 5-day event, 'Aesthetic Sunday' was a day much-anticipated by all. Set up in response to requests for further training in aesthetics and cosmetic dermatology, the event included sessions at both basic and advanced levels of cosmetic dermatology understanding. Topics covered by 10 of the most renowned specialists in cosmetic and aesthetic dermatology included fillers; botulinum toxin; peels; scars; energy-based devices, such as lasers; as well as the associated complications with the aforementioned topics.

For a further comprehensive review of the thought-provoking EADV Congress 2018, please read on to find out more about the call for greater sharing of information regarding HPV vaccinations, strategies and programmes to improve psoriasis patient quality of life by reducing stigmatisation, the risks associated with sun exposure for outdoor workers, and the debate surrounding tattoo regulations coming into line with those for cosmetic procedures.

The EMJ team thoroughly enjoyed attending this year's EADV Congress and is already looking forward to and preparing for the already much-anticipated EADV Congress 2019, which is to be held in the magnificent city of Madrid, Spain.



Improving Social Acceptance for Psoriasis Patients

APPROXIMATELY 125 million people across the globe are affected by psoriasis, with 2 million in Germany alone. Although not curable, the skin disease is managed through the implementation of multidisciplinary therapeutic strategies that can improve patient quality of life. However, >60% of patients experience episodes of depression and negative effects on their quality of life, especially if the psoriasis plaques affect their face, hairline, or hands. New strategies and programmes with the aim of improving patient quality of life by reducing stigmatisation were outlined in a EADV press release dated 12th September 2018.

"One of the main demands of the WHO was therefore to disseminate knowledge about psoriasis among the population and to show clearly that these people do not deserve to be stigmatised."

Alongside the physical symptoms associated with the disease, psoriasis patients often face rejection, disgust, fear of contagion, and exclusion. According to a recent FORSA survey of >2,000 people, 10% believed that psoriasis might be infectious and 20% stated that they would not enter a swimming pool with an individual with psoriasis. In 2014, the World Health Organization (WHO) adopted a resolution that elevated psoriasis to a serious non-communicable disease. The long-term aim of this WHO resolution, and the 2016 Report on Psoriasis penned by field experts, is to sensitise the public to the disease and remove the stigma associated with the condition. "One of the main demands of the WHO was therefore to disseminate knowledge about psoriasis among the population and to show clearly that these people do not deserve to be stigmatised," explained Prof Dr Swen Malte John, University of Osnabrueck, Neuer Graben, Germany.

In 2018, the ongoing ECHT EVAL study was initiated. The study aims to gather information and generate strategies to educate the general public about skin disease. Additionally, the Action Network Against Stigmatisation group has developed a 2018–2020 programme. Similarly to the ECHT EVAL study, the programme aims to improve social acceptance of the disease and drive the implantation of the WHO recommendations. Although a cure for the disease is not available, the work of the WHO, Action Network Against Stigmatisation, and the ECHT EVAL study will hopefully improve the quality of life for the millions of people living with the disease.

Sun Exposure Risks for Outdoor Workers

THE STANDARD erythemal dose (SED) was developed as an erythemally weighted measure

of sun exposure, independent of skin type. The World Health Organization (WHO) set a daily limit of 130 SED; however, new data collated by the GENESIS-UV project, and reported in a EADV press release dated 12th September 2018, has highlighted that this daily limit is regularly exceeded 5-fold by outdoor workers in Germany.

"A further increase in the future can be expected because of the sunniest summer in a century."

Statistics from 2017 revealed that regular SED exposure 5-fold higher than the WHO recommended limit was associated with an increased incidence of occupational skin cancer. It was further noted that the summer of 2017 was not as sunny as this year's record-breaking summer in Europe. "A further increase in the future can be expected because of the sunniest summer in a century," explained Prof Dr Swen Malte John, University of Osnabrueck, Neuer Graben, Germany.

The majority of skin cancer cases involve non-melanoma skin cancer, such as basal cell carcinoma, squamous cell carcinoma, and actinic keratoses, and outdoor workers are at particular risk. It is widely reported that this proportion of the population has a 43% increased risk of developing basal cell carcinoma, while their risk of squamous cell carcinoma is doubled. Furthermore, people that have worked outdoors for ≥5 years have a 3-fold higher risk of developing basal cell carcinoma, squamous cell carcinoma, and actinic keratoses compared with their indoor working counterparts. Furthermore, one study has shown that outdoor workers are also at an even greater risk of developing particularly aggressive forms of non-melanoma skin cancer.

An additional problem across Europe is the lack of consistency in the recording and reporting of non-melanoma skin cancer cases; for example, in Italy only 96 cases of occupational-related cancer between 2010 and 2014 were recorded, despite the actual estimates being much higher. In response to this, the EADV is promoting the standardised registration of all cases of white skin cancer.

The risk of developing non-melanoma occupational skin cancer is clear and the EADV has encouraged the implantation of simple sun protection strategies for those working outdoors, including mounting sun shields, avoiding work during the hottest part of the day, and providing sun protection factor 50+ sunblocks.

Call for Increased Regulations Around Tattoo Inks

"Tattoo inks should at least meet the same safety standards as cosmetic products," declared Dr Christa De Cuyper, a EADV Board Member. As reported in a EADV press release dated 12th September 2018, Dr De Cuyper reiterated the EADV's call for proper safety testing of tattoo inks and for tattoos to be held to higher safety standards than they currently are. Such a call is of great importance, especially considering that tattoos are becoming increasingly popular in the Western world, with approximately 10% of the German, Finnish, and French populations having a tattoo.

The EADV argues that current regulations do not go far enough to ensure satisfactory safety standards. Currently, the quality and sterility of tattoo inks is not controlled, which raises the potential for infection. Indeed, a Danish study that investigated 58 new tattoo inks showed that 10% were contaminated by bacteria, highlighting the risk of potential infection following tattooing. Additionally, the current regulations are not believed to be stringent enough to ensure that tattoo ink is not toxic and does not cause allergic reactions. Further to this, some of the pigments found in tattoo inks are not approved for use in cosmetic products because they have not been listed by the Scientific Committee for Consumer Products (SCCP).

"Tattoo inks should at least meet the same safety standards as cosmetic products."

Although the European Chemical Agency (ECHA) has prepared pathways for ensuring improved tattoo ink quality that are expected to be published by the end of 2018, the EADV does not believe these new proposals go far enough. Dr De Cuyper declared: "To eliminate carcinogenic substances and to limit long-term toxic effects, strict measures and well-defined safety limits are needed with appropriate analytical methods for controlling such use; the ECHA proposals do not provide adequate solutions to meet these requirements." Dr De Cuyper went on to suggest that perhaps tattoo inks should be held to even higher standards than cosmetic products as they are injected under the skin and there is evidence that ingredients from tattoo inks are ingested into the body.

This call for better safety standards for tattoos will no doubt ensure that all those who choose to have a tattoo can be assured that they will be conducted in the safest way possible.

EADV Calls for Greater Information Sharing about HPV Vaccine

A vaccine currently exists that would prevent genital warts associated with HPV and HPV-associated cancers, so why are these conditions present today? In fact, in 2008, there were approximately 529,000 new cases of cervical cancer globally, which is the most common type of cancer associated with HPV. The World Health Organization (WHO) recommends that girls should be vaccinated as a matter of priority in order to help prevent and control cervical cancer. However, vaccination programme participation rates are still too low to impact the prevalence of cervical cancer in many countries. It was in this context at the EADV Congress that the EADV outlined recommendations for tackling this problem, as reported in a EADV press release dated 12th September 2018.

As already noted, nationwide participation in HPV vaccination programmes is low in many countries. For instance, in Germany only 40% of girls are vaccinated and only a very small percentage of boys. There is no need for this disparity in vaccination rates between the sexes, as men are infected just as frequently with HPV as women and HPV infection in men can lead to the development of penile and anal cancer. An additional reason to ensure men are also vaccinated against HPV is that this will make achieving herd immunity easier. It is estimated that 85% of boys need to receive the HPV vaccine in order to contribute to herd immunity.

Basilica of the Sacré-Coeur

Landmark of Paris, France,
home of EADV 2018

"The health authorities do not seem to have realised the cost savings that vaccination can produce for the health systems..."

The EADV attributed the low vaccination rate to a lack of dissemination of information within the population, both in regard to the general public and policymakers. Prof Mihael Skerlev, Chairman, EADV taskforce for HPV infection, commented: "The health authorities do not seem to have realised the cost savings that vaccination can produce for the health systems, even direct and immediate cost savings, over and beyond the prevention of cancer, simply as a result of a declining incidence of external genital warts." Therefore, the EADV recommended a strategy for targeted information campaigns across platforms used by the desired audience, such as across social media to reach younger generations. It is believed that this policy will result in the successful breaking of the HPV infection chain.

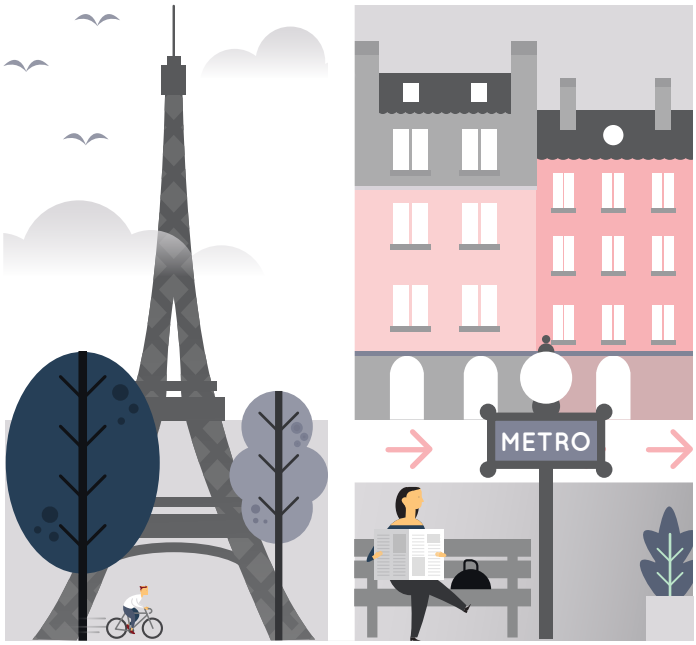
Dupixent (dupilumab) Significantly Improves Disease Severity in Adolescents with Moderate-to-Severe Atopic Dermatitis

Dupixent® (dupilumab) (Sanofi, Bridgewater, New Jersey, USA and Regeneron Pharmaceuticals, Inc, Eastview, New York, USA), an IL-4 and IL-13 inhibitor, has been shown for the first time to significantly improve symptoms of atopic dermatitis (AD) along with quality of life measurements in adolescents with moderate-to-severe (MTS) AD, according to a late-breaking oral presentation at EADV on the 15th September 2018.

Dupixent is already approved for the treatment of MTS AD in adults, but this trial assessed Dupixent's safety and efficacy in an adolescent population. This Phase III trial is also the first trial of a biologic in patients 12–17 years old with MTS AD that could not be controlled by topical therapies. A total of 251 patients were included in the 16-week long trial and were randomised to three treatment arms:

- Treatment with Dupixent at a dose of 200 mg or 300 mg (based on weight) every 2 weeks, with an initial dose of 400 mg or 600 mg, respectively.
- Treated with 300 mg Dupixent every 4 weeks with an initial dose of 600 mg.
- Treated with placebo every 2 weeks.

The coprimary endpoint outside of the USA was 75% improvement in Eczema Area and Severity Index (EASI-75) at 16 weeks; in the USA, the primary endpoint was the proportion of patients achieving Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear).



"The results we are presenting today show the potential for Dupixent in adolescents to not only help clear the skin and reduce itching, but also improve certain aspects of quality of life in adolescents who may be dealing with these unbearable symptoms."

Results at 16 weeks showed that 41.5% and 38.0% of patients who received Dupixent every 2 weeks and every 4 weeks, respectively, achieved ≥75% EASI-75 compared to 8% in the placebo group ($p<0.001$). Clear or almost clear IGA scores were achieved by 24% of patients who received weight-based dosing and by 18% of those receiving fixed-dose Dupixent every 4 weeks, compared to 2% of the placebo group ($p<0.001$).

Results of the secondary endpoints were just as encouraging; 49% and 39% of patients who received Dupixent every 2 weeks and every 4 weeks, respectively, achieved a minimum of a 3-point improvement in the Peak Pruritus Numerical Scale compared to 9% of the placebo group ($p<0.001$). Significant improvements in quality of life as measured by the Children's Dermatology Life Quality Index (CDLQI) and patient reported symptoms as measured by the Patient-Orientated Eczema Measure (POEM) compared with placebo ($p<0.001$) were also observed.

Adverse effects were reported in 72% of patients in the Dupixent every 2 weeks group, 64% of patients in the Dupixent every 4 weeks group, and 69% in the placebo group.

Dr Amy S. Paller, Director, Northwestern University Skin Disease Research Center, Northwestern University, Evanston, Illinois, USA, and principal investigator for the trial, commented on the importance of these results: "The results we are presenting today show the potential for Dupixent in adolescents to not only help clear the skin and reduce itching, but also improve certain aspects of quality of life in adolescents who may be dealing with these unbearable symptoms."

A Historical Look at the Hôpital Saint-Louis

The arrival of the EADV Congress to Paris offers the perfect opportunity to dig beneath the surface and discover more of the city's rich dermatological past.

Although today the Hôpital Saint-Louis is well-known for its specialism in dermatology, the road it took to achieve this accolade is an interesting one that started in 1606 when a new plague was spreading across France. Although King Henry IV had fled the city in an effort to ensure his own safety, he was petitioned by his advisors to establish a hospital for the effective treatment of the plague. In response, he ordered the construction of the Hôpital Saint-Louis, which was completed in 1610.

The next milestone in the history of the Hôpital Saint-Louis was at the time of the French Revolution. The French Revolution, which lasted from 1789–99, was transformative for hospitals: in 1801, the city's hospitals were reorganised into general and specialised institutions. This saw the Hôpital Saint-Louis designated for the treatment of contagious diseases, such as scabies, and chronic conditions, such as cutaneous ulcers. During this time, Jean-Louis-Marc Alibert was appointed to the hospital, and it was under his influence that the hospital grew to become a focal point for dermatological teachings and learnings. This was further emphasised in 1889 when the hospital was the location for the first world congress of dermatology.

One of the most impressive collections in the hospital museum is the moulage collection, which comprises >4,800 moulages in various states of repair. It is believed that the beginning of this collection was commissioned by Charles Lailler, a French dermatologist, who wanted an artist to produce realistic depictions of skin diseases. Fortuitously, he walked past a small shop that sold papier-mâché fruit, and later found the artist, Jules Pierre Francois Baretta. Baretta was later tasked with creating dermatological moulages for Lailler. After initially working privately for Lailler, Baretta became the hospital's modeller in 1870. He also sold models to other hospitals and to dermatologists from abroad. By the time Baretta retired in 1914, it is estimated he had cast 3,000 models for the Hôpital Saint-Louis. Barret's successors went on to add to the collection, with the final model created in 1958.

The Creation of Baretta's Moulages

- The making of moulages is a process shrouded in secrecy. Barretta remained tight-lipped about the techniques he used.
- This secrecy is probably one of the main reasons why Baretta's moulages differ somewhat from those created by the moulages who succeeded him.
- Analysis conducted in the laboratory has shown that Baretta's moulages were composed of a mixture of beeswax and a resin believed to be gutta-percha.
- Some of the colours may have been incorporated into the initial mixture.
- The mixture was heated to a temperature of roughly 200°C and then poured into a plaster cast.
- Following casting, Baretta would have most likely painted the finer details by hand.

Although in the present day moulages have long since been superseded by photographs in the teaching of dermatology, they represent a fascinating historical perspective, shedding light on historic teaching methods and the representation of illness that can still be studied today.

Quality of Life and Psychosocial Issue in Skin Disease

An Interview with Dr Francesca Sampogna

Awareness of the impact that skin diseases can have on a patient's quality of life has improved markedly within the dermatology community in recent years. Yet the extent to which these symptomatic and psychosocial issues affect the daily lives of patients is still being uncovered in daily practice. During the recent EADV Congress in Paris, France, the EMJ took the opportunity to speak to Dr Francesca Sampogna, a leading researcher in this area from the Clinical Epidemiology Unit, Istituto Dermopatico dell'Immacolata IDI-IRCCS, Rome, Italy. In our interview, we discussed the study she presented during this event, entitled: 'Sexual problems and quality of life in patients with skin diseases,' before talking about trends in the field and new initiatives taking place to help clinicians assess the impact of the skin disease on a patient's quality of life.

Growth in Understanding

Dr Sampogna described how coverage of quality of life has grown in recent times at major dermatological meetings, such as the annual EADV Congress, although she would still like to see sessions on this topic gain greater prominence than they currently do. This is something that she and colleagues who work in this area are continually emphasising. "Around 15 years ago there were almost no specific sessions on quality of life," she explained. "Now, we always have specific sessions on quality of life and psychosocial impact of dermatological conditions."

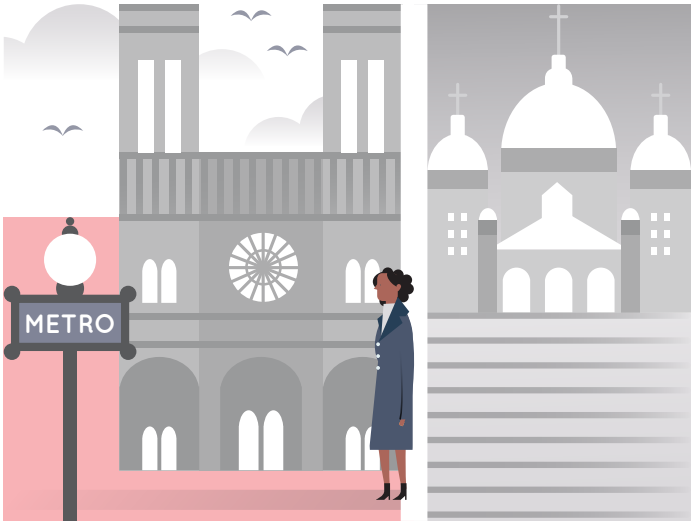
"Around 15 years ago there were almost no specific sessions on quality of life. Now, we always have specific sessions on quality of life and psychosocial impact of dermatological conditions."

In general, there has been a vast improvement in the appreciation of the symptomatic and psychological aspects of skin diseases during the course of Dr Sampogna's career, which has changed the way these conditions are looked at and treated. "If you read books 30 years ago, they say that psoriasis is an asymptomatic disease, but if you look at data it is not true at all because it causes a lot of itching, burning, and pain. And psoriasis patients also have a lot of psychosocial problems, especially in relationships and social life, which is its main impact," she elucidated. "Atopic dermatitis also has a similar effect in terms of itch and social life. In our group, we studied vitiligo which is a chronic condition but has no symptoms, meaning it was previously considered as just a cosmetic problem with white spots being the only issue. But we observed that it has a huge impact from a psychosocial point of view. This shows that diseases that are not severe from a clinical point of view can have a major psychological impact."

This increase in awareness has led to the stage where clinical trials will generally always include quality of life measurements, which is undoubtedly a big step forward in ensuring that doctors are more aware of the non-clinical impact of new treatments.

Bridging the Gap

Nevertheless, Dr Sampogna does believe there remains a separation between researchers and clinicians in dermatology, and this can prevent new discoveries being translated into clinical practice as much as they could be. Continuously finding scenarios in which professionals from the two areas can interact with each other is therefore crucial in bridging this gap. "The problem is the connection with clinical practice. Dermatologists who are also involved in research will of course change their clinical practice. But it is difficult for all the dermatologists in the world to have this information, so there is a gap, a disconnect. That is why it is so important to give information at congresses such as EADV," she said.



Study at EADV

A study presented by Dr Sampogna at this year's event primarily analysed the sexual problems faced by dermatology patients. Dr Sampogna's particular analyses came from a large multicentre study of almost 3,500 dermatology patients covering 13 European countries regarding psychological problems they face. Here, data were collected from a single question from the Dermatology Life Quality Index (DLQI) questionnaire, which read: 'Over the last week, how much has your skin caused any sexual difficulties?' Overall, more than 11% of respondents reported problems in their sexual life, and the results also showed that this was especially prominent in certain conditions. Hidradenitis suppurativa was the highest of these, at 43%, and other skin diseases in which it was also a notable issue included pruritis and atopic dermatitis. In the view of Dr Sampogna, these findings demonstrate the benefits a simple questionnaire can have in informing a doctor about the quality of life issues their patient is facing. "One of our main conclusions is that a simple question such as this can help to deal with a sensitive issue because it is very difficult for a physician to ask; therefore, if you give a questionnaire an answer can be written," she added.

Measuring Quality of Life

Developing tools such as questionnaires to measure quality of life in patients with skin diseases is something that Dr Sampogna and her colleagues are continuously seeking to develop further. "From a practical point of view, we are trying to create new, very easy questionnaires because we know in clinical practice it is always difficult to deal with these issues," she explained. "The first questionnaire that was created was DLQI, which only has 10 items, and so we are creating new instruments that have no more than 10 items because it has to be something very quick."

Dr Sampogna described an example of a visual measurement that was developed to measure quality of life in psoriasis: the Psodisk. The aim of this is to enable the patient to visualise the extent to which their quality of life has been impacted and then observe the difference when the results are recorded at a later date.

It is hoped these kinds of initiatives can help physicians better understand the needs of their patients without taking much of their time. She additionally commented that there should be a greater emphasis on communication and the psychological aspect of diseases in the training of medical doctors.

Hidradenitis Suppurativa

As the study Dr Sampogna presented during the EADV Congress eluded to, the skin disease that can arguably have the greatest impact on a patient's life is hidradenitis suppurativa. This is a condition that her group are now focussing on to a great extent in their studies as the awareness of it remains limited. "Hidradenitis suppurativa is not very frequent but is more common than people believe. And it has a big symptomatic and psychological impact." She further outlined that this psychological impact is akin to severe depression, demonstrating the vitality of spreading greater awareness of it. One way the team is now doing this is to make comparative analyses of quality of life in hidradenitis suppurativa with more widespread dermatological conditions, such as psoriasis.

"The problem is the connection with clinical practice. Dermatologists who are also involved in research will of course change their clinical practice. But it is difficult for all the dermatologists in the world to have this information, so there is a gap, a disconnect. That is why it is so important to give information at congresses such as EADV."

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[a]Demonstrated up to 52 weeks[1,2]

The FIRST BIOLOGIC for adults with moderate-to-severe ATOPIC DERMATITIS

Dupixent® (dupilumab) – Abbreviated Prescribing Information
Name and Presentation: Dupixent 300 mg solution for injection in pre-filled syringe. Each single-use pre-filled syringecontains 300 mg of dupilumab in 2 ml solution (150 mg/ml) Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signaling, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. **Therapeutic indications:** moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy. **Posology and method of administration:** Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis. **Posology:** The recommended dose of Dupixent for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection. Dupixent can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks. **Special populations:** The safety and efficacy of Dupixent in children below the age of 18 years have not been established. **Method of administration:** Dupixent is administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used. For the initial 600 mg dose, administer two 300 mg Dupixent injections consecutively in different injection sites. It is recommended to rotate the injection site with each injection. Dupixent should not be injected into skin that is tender, damaged or has bruises or scars. **Contraindications:** hypersensitivity to the active substance or to any of the excip ients. See full SmPC for full list of exipients. **Warnings and precautions:** Safety and efficacy in children < 18 years have not been established. If systemic hypersensitivity reaction occurs, discontinue administration and initiate appropriate therapy. Very rare cases of serum sickness/serum sickness-like reactions have been reported. Treat any pre-existing helminth infections prior to initiating treatment. If patients become infected while receiving treatment and do not respond to anti- helminth treatment, discontinue treatment. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. Safety and efficacy have not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatments without consultation with their physicians. Carefully monitor patients after discontinuation. Do not mix with other medicinal products. Use solution only at room temperature. Contains < 1 mmol Na (23 mg) per 300 mg, i.e. essentially " sodium-free." **Drug interactions:** The safety and efficacy of concurrent use of Dupixent with live vaccines has not been studied. Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study. Therefore, patients receiving Dupixent may receive concurrent inactivated or non-live vaccinations. **Fertility, pregnancy and lactation:** Dupixent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It is unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. A decision must be made whether to discontinue breast-feeding or to discontinue Dupixent therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. **Effects on ability to drive:** Dupixent has no or negligible influence on the ability to drive or operate machinery. **Undesirable effects:** observed in clinical trials: *Infections/infestations:* common: conjunctivitis, oral herpes. *Blood/lymphatic system disorders:* common: eosinophilia. *Immune system disorders:* very rare: serum sickness/serum sickness-like reactions. *Nervous system disorders:* common: headache. *Eye disorders:* common: allergic conjunctivitis, eye pruritus, blepharitis. *General disorders/administration site conditions:* very common: injection site reactions. **Overdose:** There is no specific treatment for Dupixent overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately. **Special precautions for storage:** Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original carton in order to protect from light. **Pharmacological properties:** Pharmacotherapeutic group: Immunosuppressants: ATC code: D11AH05. **Marketing authorization holder:** sanofi-aventis groupe, 54, rue La Boétie, 75008 Paris, France. **Date of last revised:** June 2018. SAGLB.DUP.18.06.0680. Abbreviated Prescribing Information based on the EU SmPC as of September 2017.Before prescribing always refer to your full local prescribing information as this information may vary from country to country.

▼This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

References: 1. DUPIXENT Summary of Product Characteristics, Sanofi-Aventis, France, September 2017. **2.** Blauvelt A et al. *Lancet.* 2017;389(10086):2287-2303. doi:10.1016/S0140-6736(17)31191-1

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Interviews

Delve into the minds of our dermatology experts on the *EMJ Dermatology* Editorial Board and find out more about their illustrious careers with this selection of interviews

Featuring: Assoc Prof Pichardo, Dr Ribero, and Dr Ionescu

Assoc Prof Rita Pichardo

Wake Forest University, USA

What first inspired you to become a dermatologist?

After graduating from medical school, I had the opportunity to work in a rural setting for 1 year. I was offered a job at an institution called Malaria and Rural Endemic Diseases, and I was assigned to a small community in Barquisimeto, Venezuela. People in this community presented with malaria, leishmaniasis, leprosy, and deep fungal infections, such as paracoccidiodomycosis. The stark lack of resources possessed by these people motivated me to contribute my time to improve their quality of life with educational campaigns and by visiting their houses even at very remote locations to provide them with medical care and supervised treatments. I feel that this experience allowed me to discover a new passion and a way to make a difference to patients' lives.

"I love all aspects of dermatology and dermatopathology."

You have 24 years' experience in the field of dermatology. What would you pinpoint as your greatest challenge during this time?

I came to the USA in 2002 for a 1-year international fellowship in dermatopathology, and after completion of this programme, I was offered a research fellowship in dermatology and dermatopathology for a further 2 years. One of my most challenging projects was to select, classify, and create an online library with the amazing contributions of the late Dr James Graham; he donated >50,000 Kodachrome slides from his fascinating work during his entire productive academic life. Through much work, this online library is now a reality and has been free to all for teaching purposes since 2009.

In the clinical setting, the greatest challenge has been working with the less fortunate people in our community, especially the Hispanic population, who often lack medical insurance and other essential resources. Our amazing

scientific advances cannot be applied to individuals who cannot afford medical insurance or those who lack economic resources to buy medicine. If I could change anything in the medical system, it would be to offer more equal and affordable healthcare to all individuals.

Which dermatological condition do you find most interesting to study?

I love all aspects of dermatology and dermatopathology. My professional career has shifted in different ways, trying to focus on conditions that affect people's quality of life and those patients who have been neglected for many years. In recent years, I have found women's health, especially vulvar dermatosis and hidradenitis suppurativa, the most interesting conditions to study.

You specialise in hair and scalp diseases; what are the most common hair and scalp conditions you see in the clinical setting?

I have worked in the field of hair disorders since my early years as a dermatologist in Venezuela; however, the population is different in the USA. I see a variety of patients, but those who attend my hair clinic are a combination of lichen planopilaris, alopecia areata, telogen effluvium, female pattern hair loss, and central centrifugal scarring alopecia patients.

Many dermatological conditions are visible and can carry varying levels of social stigma as a result. To what extent does stigmatisation reduce a patient's quality of life and what steps can be taken at a societal level to reduce this problem?

I believe there are many dermatological conditions that reduce a patient's quality of life, both physically and emotionally. For example, depigmentation of the skin in a patient with vitiligo; the total hair loss of a patient with alopecia areata; the obvious red scaly plaques in a patient with psoriasis; and the malodour associated with active hidradenitis. These are examples of patients who avoid contact with the community to the extent that it promotes personal isolation and depression due to the social stigma.

The first management step at a social level involves education of the patient, their families, and the community. We have to increase public awareness of dermatological conditions and try to integrate these individuals into society. Although the lives of some will not be improved, the combination of medical disease control and improved education of the population that these are true diseases should make life more enjoyable for many patients.

"Our amazing scientific advances cannot be applied to individuals who cannot afford medical insurance or those who lack economic resources to buy medicine."

Many skin conditions are directly related to ageing. Please could you briefly explain how the ageing process makes a patient more susceptible to certain conditions? How can patients best maintain their skin health throughout their life?

Ageing is an inevitable part of life; with the passing years, our experiences and memories increase but also our skin undergoes many changes. It is fundamental to learn how to find a balance between skincare and enjoying life, especially regarding outdoor activities. With ageing, our skin gets thinner and displays cumulative damage from sun exposure without protection during our younger years. Smoking has also been associated with many skin conditions, such as psoriasis, hidradenitis, and general skin ageing. Thus, protection from the damaging effects of sunlight and smoking is an important preventative measure against skin conditions. I always recommend to my patients that they should avoid the use of cigarettes, maintain a healthy weight, and protect against the sun, and I believe a good, balanced lifestyle is important for emotional and physical health. I promote relaxing practices such as yoga and meditation, taking part in activities that we feel passionate about, and enjoying time with family and friends to cultivate a healthy lifestyle and to age graciously and appropriately.

You recently published a paper on pemphigoid gestationis, a rare autoimmune condition associated with pregnancy. Are there any other dermatological conditions that are particularly prevalent in pregnant women?

Pruritic urticarial papules and plaques of pregnancy, prurigo of pregnancy, cholestasis of pregnancy, and atopic eruption of pregnancy are the most common conditions that affect pregnant women. Some of these conditions present with severe pruritus and may recur in subsequent pregnancies. As dermatologists, we should be able to recognise the clinical and pathological findings of these conditions, as well as identify early interventions to avoid risk to the fetus.

What has been the most interesting clinical case you have dealt with?

That is a very difficult question to answer; I have seen many interesting cases during my professional career. I feel very passionate about complex medical dermatology and the consultants at the hospital. For example, we see many cases of drug reactions, including Steven–Johnson syndrome, drug reaction with eosinophilia and systemic hypersensitivity (DRESS), toxic epidermal necrolysis (TEN), and bullous diseases such as pemphigus vulgaris, linear IgA, and bullous pemphigoid. These conditions may be life-threatening and require a multidisciplinary team to work together to care for the patient.

Skin cancer rates continue to rise in many countries around the world. To what do you attribute this raise and what should be done about it?

In recent decades, skin cancer screening campaigns have expanded all over the world, making a big difference in early diagnosis, sun protection, and the avoidance of tanning beds. Certain populations are most at risk of developing skin cancer; fair skin, geographic location, and skin protection practices are the most important factors that contribute to the disease. These factors are fundamental for the increased rates of skin cancer around the world.

"It is fundamental to learn how to find a balance between skincare and enjoying life, especially regarding outdoor activities."

I promote skin cancer awareness and screening in my daily practice, in my department, and in my institution. The American Academy of Dermatology (AAD) runs a wonderful campaign in May as part of the SPOT Skin Cancer™, AAD, Schaumburg, Illinois, USA, programme, during which dermatology departments all over the USA offer free skin cancer screening to the community. I believe in education as the most powerful way to make a difference in the world. This is especially true of the younger population; pale is the new tan.

If you had the opportunity to donate $10 million to a dermatological charity or research group, which would you choose and why?

There are many dermatological foundations that do a great job in terms of research, public awareness, and impact on the population. I would choose the Hidradenitis Suppurativa Foundation (HSF) because I feel there is a lot of work that needs to be done for this condition and we can achieve this together. I believe in organisation, education, opportunities for research, and developing support for less fortunate patients who lack medical insurance or financial resources. My model of a foundation is the National Psoriasis Foundation (NPF), a solid, well-organised, and well-known society that offers lots of opportunities to dermatologists and patients.

"We have to increase public awareness of dermatological conditions and try to integrate these individuals into society."

Dr Simone Ribero

University of Turin, Italy

As a professor in dermatology, what do you find most fascinating about the skin and its associated conditions? Are there any other medical disciplines that interest you?

Dermatology is a wide speciality, as wide as the skin conditions can be. From allergology to oncology, mycology, inflammatory diseases, and many others, skin diseases represent a systemic condition, which requires holistic care.

During your career you have worked in various countries across Europe, including the UK, Switzerland, Spain, and currently Italy. How has travelling and meeting medical professionals from across the world enhanced your career?

It was the best experience of my life and career thus far. Getting to know new healthcare systems and coming face-to-face with patients from different cultures was simply great and taught me a lot. Moreover, the opportunity to work with many research groups opened my mind to many research fields.

Are there any dermatological conditions that you would like to investigate that are not commonly seen in European clinics?

Diseases that are not common in Europe but are more common in Africa are currently classified in the field of tropical medicine; however, as dermatologists we have to be aware of them due to the global population movement.

What rare dermatological conditions do you believe require more awareness and attention from the medical community?

There are skin infections, which are not rare in underdeveloped countries, that we no longer consider in Italy. We have to reconsider them in clinical practice. Moreover, skin semeiology is different according to phototype; this should be taught during trainees' residency.

You are part of the Sentinel Lymph Node Study Group in Melanoma (SENTIMEL). What are the objectives of this group and what role do you play in its organisation?

The objective of this research group is to evaluate the prognostic role of sentinel lymph node biopsy in melanoma. This procedure has been performed for 20 years in Europe, but it still deserves better definition in regard to predictive factors and inclusion criteria.

One of your research interests is the diagnosis and management of melanoma patients. Why do you feel so passionately about melanoma research and improving the care of melanoma patients?

I developed my interest in melanoma during my last years at medical school. The advancements made to combat melanoma have pioneered modern oncologic treatment (including immunotherapy and targeted therapy). The last 8–10 years of melanoma history were probably the most fascinating time of the entire history of this disease. Many steps forward have been taken and many fascinating revolutions have appeared.

"...coming face-to-face with patients from different cultures was simply great and taught me a lot."

What advances would you like to see in the field of melanoma research over the next 5 years?

Licensed clinical practice for adjuvant therapy will definitely change the scenario for Stage 3 melanoma. Moreover, understanding the gene expression profile of the primary melanoma will most likely impact on prognosis and give us a clear indication regarding which are the true low risk melanomas in regard to progression compared to the high-risk ones.

"Sunbed use has been reported to increase the risk of skin cancer and skin ageing. Two countries in the world have carried out major awareness campaigns (Brazil and Australia). However, so far, no other big campaigns have been performed in other countries..."

The use of sunbeds is still extremely common across Europe, particularly in the younger population, despite the harmful effects being well-documented. What more do you believe governments should do to reduce the number of people using sunbeds?

Sunbed use has been reported to increase the risk of skin cancer and skin ageing. Two countries in the world have carried out major awareness campaigns (Brazil and Australia). However, so far, no other big campaigns have been performed in other countries, despite the well-known bad effects of this practice. I think that this fact is enough to explain why the use of sunbeds is still extremely common.

On a personal level, what are your career goals for the next 10 years? What would you like to achieve during this time?

I cannot complain about my personal results thus far. My goal in the future is to consolidate my position and contribute in the development of a group of young researchers on melanoma at my University.

If you could meet one inspiring figure from the medical profession, past or present, who would you choose and why?

I had the luck of meeting the top melanoma dermatologists, surgeons, and oncologists in the world. One person I missed, and probably would have loved to meet, was Ackerman Bernard, an expert dermopathologist who interpreted the disease in a very fascinating way, even if sometimes not in complete agreement with the modern molecular vision of the disease. I would have enjoyed discussing his ideas on melanoma development with him, but, unfortunately, he passed away years ago. His books are still well cited everywhere today.

Dr Marius-Anton Ionescu @LinkedIn

University Hospital "Saint-Louis", France

Firstly, what first inspired you to begin a career in medicine and, more specifically, in dermatology?

My father was a cardiologist, and I was very impressed by him. He was a strong influence on all my decisions, including my medical career. Initially I wanted to be a cardiologist; however, the choice of dermatology came when I was a student when I discovered that dermatology is strongly linked to internal medicine, and it was (and is) as complex and interesting as other medical specialities.

According to the American Cancer Society (ASC), cutaneous lymphomas contribute to 4% of non-Hodgkin lymphoma cases. In your opinion, what should be done to increase the awareness of lymphomas?

I have had the opportunity to work with Prof Martine Bagot, who dedicated all her research to lymphomas. Thanks to her, and also to my hospital's long tradition in this field, we can see the many different cases of lymphomas (not only cutaneous). The 4% incidence that you quote is true, but it seems too low to me, but this is a subjective reaction,

of course. I will quote here Patrice Morel, my first professor of dermatology at Saint-Louis hospital (who, I think, was quoting his professor, Prof René Touraine): "The difference between a good dermatologist and a very good dermatologist is that the first one recognises quickly 98% of skin diseases, the latter one 99%. This 1% of difference can be reached only through good medical training and long-term hard work."

The ASC also states that cutaneous lymphomas are difficult for even experienced physicians to diagnose. What steps would you suggest the medical community takes to improve cutaneous lymphoma diagnoses? Are there any tell-tale signs that you look for when examining a patient?

Many clinical and/or histopathologic variants of cutaneous lymphomas have been described; this family of diseases is too big to summarise here. Correct and early diagnosis is very important, but this can be very difficult as skin lymphomas can mimic a wide variety of inflammatory skin diseases; therefore, differential diagnosis must be conducted by all clinicians. Besides systematic clinical examination, histology, and immunochemistry, simple blood tests can provide important information as primary cutaneous T cell lymphomas can be distinguished even in their early stages by many important elements. Among these elements, persistent blood hypereosinophilia (>1,500/mm^3) represents a poor prognosis marker in primary cutaneous T cell lymphomas (a prognosis factor that we described >10 years ago).

Earlier this year, you published the article 'Topical non-occlusive polymers in hand-foot syndrome.' Could you outline the key findings of your study? What do you think the major impact of your findings will be?

This paper is less about key findings and more about the easy to use, insulating, steroid-free, topical medication that we assessed in a series of patients with hand-foot skin syndrome and hand-foot skin reaction as a result of chemotherapy's adverse events (AE), in a multicentric pilot study (from France and Italy). In these AE, there was no standard of care, and I think that this modest article will be a trigger for initiating larger studies with this topical medication or with other new topical medications. This is in the context where the incidence of cancer in general is continuously growing (linked to an older population), and the use of classical chemotherapies and new anti-cancer therapies is increasing rapidly, as are the frequency and complexity of skin AE.

"The difference between a good dermatologist and a very good dermatologist is that the first one recognises quickly 98% of skin diseases, the latter one 99%."

There is still much debate about the use of biosimilars in medical therapeutics. What is your take on the use of biosimilars in the treatment of inflammatory diseases, such as psoriasis?

Monoclonal antibodies known as biotherapies (or biologics) released in the last two decades changed the face of inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis. Some successful biotherapy patents have expired or will expire soon; the biosimilar versions of these molecules made in the same research complex conditions are now available or are currently undergoing development. These are not generic drugs; a biosimilar is more like 'another batch' of an original biotherapy. A biosimilar is a product highly similar to an approved molecule and for which it has been shown there are no significant differences in clinical results and safety profile compared with the reference molecule. Biosimilar development and approval follows the same rules as for original molecules in all countries. Biosimilars are, by definition, less expensive than the original molecule; this can open the access to biotherapy for patients with less good health insurance. Several anti-TNF biosimilars are available in Europe, the USA, and other countries, and published articles and our personal experience with patients with moderate-to-severe plaque psoriasis show a similar efficacy and safety profile between biosimilars and the original biotherapies.

What do you make of the Australian 'Slip, Slop, Slap!' campaign regarding its success in increasing skin cancer awareness? What further work must be done to combat skin cancer that could be prevented with the use of sun cream?

Australian dermatologists are an example of efficacy in their actions against sun-induced skin damage, shown particularly in their fight for early detection and prevention of melanoma, which is a huge health problem in a population with fair skin living in a very sunny country. In the USA and in many European countries, including France, dermatologists are participating in Annual Melanoma Day by providing free consultations and dermoscopy examinations for the general population. This is for the same purpose as the Australian project: the early detection and treatment of melanoma.

What has been the most interesting case you have dealt with in the dermatology clinic?

This is a very difficult question, I am thinking of a rather recent case of a patient presenting with severe plaque psoriasis resistant to classical systemic immunosuppressors (cyclosporine and then methotrexate). Treating the patient with biotherapy using a TNF-blocker completely cleared the psoriasis plaques quickly.

"Australian dermatologists are an example of efficacy in their actions against sun-induced skin damage, shown particularly in their fight for early detection and prevention of melanoma..."

One and a half years after, the patient developed a B cell lymph node lymphoma (a well differentiated type; chemotherapy cleared the lymphoma; no relapse at 3 years). With biotherapies being contraindicated at that moment, I initiated a systemic retinoid treatment (acitretin) associated with small doses of psoralen and ultraviolet light. The patient responded well to treatment. Six months after the patients developed an *in situ* melanoma (detected early by dermoscopy); the excision and re-excision of the margins were made; today, after 2 years, there has been no recurrence. The oral treatment by anti-phosphodiesterase-4 that followed was not well tolerated. The problem is that beside systemic retinoids and intermittent treatment with topical corticosteroids (and cold cream moisturisers) we have no other therapy options for the patient. I am open to any advice from my colleagues from the hospital and from those reading this interview.

The European Academy of Dermatology and Venerology (EADV) Congress 2018 will, yet again, have a vast scientific programme on offer, but what is the one dermatological disease or condition that you feel requires more attention from the medical community?

EADV is a more and more appreciated annual congress for its diversity and large range of topics on offer for dermatologists, who are involved in a fast-moving speciality covering many more fields than 25 years ago. The problem is that young and older dermatologists alike are more and more attracted by dermo-aesthetic procedures and less by classical dermatology. Prof Klaus Wolff from Vienna gave a plenary lecture at the American Academy of Dermatology (AAD) Annual Meeting in San Francisco in 2000, entitled *'Quo vadis* dermatology?'. The message of Prof Wolff detailed that dermo-aesthetic procedures in dermatology are attracting more and more young specialists and this is good as long as it is not becoming a massive phenomenon. The risk is that the majority of dermatologists will one day perform more laser and filler treatments than classical dermatological procedures, and if this occurs then inflammatory diseases, autoimmune diseases (such as psoriasis, lupus, and dermatomyositis) may leave dermatology and be fully considered within the field of rheumatology, while lymphomas, melanoma, and other skin cancers will be treated byoncologists and plastic surgeons. Little by little, the speciality could disappear. EADV, AAD, the French Dermatology Society (SFD), the International League of Dermatological Societies (ILDS), and other societies are trying to attract young dermatologists towards the complex and beautiful aspect of internal medicine that is dermatology.

How important do you feel congress attendance is, not only for the progression of the field, but also for personal growth and development?

To echo my previous answer, every dermatologist needs a continuous medical education, and this is obtained by subscription to medical journals and by participating in meetings such as EADV, AAD, Journées Dermatologiques de Paris (JDP), the World Congress of Dermatology, and other events.

Finally, if you could go back in time and give your younger self one piece of advice, what would it be?

I feel like I am being psychoanalysed... I now just work part-time at the hospital, and I realised that I never should have left research and university activity years ago.

"EADV is a more and more appreciated annual congress for its diversity and large range of topics on offer for dermatologists, who are involved in a fast-moving speciality covering many more fields than 25 years ago."

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PASI 90/100, DLQI 0/1, and IL-17 Receptor/Cytokine: Does it Make a Difference and Are We Ambitious Enough?

This symposium took place on 14th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairperson: Christopher Griffiths[1]

Speakers: Andrea Chiricozzi,[2] Matthias Augustin[3]

1. The Dermatology Centre, Salford Royal NHS Foundation Trust, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
2. Dermatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
3. Institute for Health Services Research in Dermatology and Nursing (IVDP), University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany

Disclosure: Prof Griffiths has received honoraria and/or research funds from AbbVie, Almirall, Amgen, Bristol-Meyers Squibb, Celgene, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sandoz, and UCB Pharma. Dr Chiricozzi has acted as a consultant and/or speaker and/or scientific advisor for AbbVie, Biogen, Janssen, LEO Pharma, Lilly, Novartis, Sanofi, and UCB Pharma in the last 3 years. Prof Augustin has acted as a consultant and/or paid speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene Corporation, Centocor, Lilly, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB, and XenoPort.

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Meeting Summary

The main objectives of the symposium were to review recent evidence on what difference targeting Psoriasis Area Severity Index (PASI) 90 or 100 and Dermatology Life Quality Index (DLQI) 0 or 1 treatment outcomes, or targeting the IL-17 cytokine or receptor, make to patients with psoriasis and whether our current approaches are ambitious enough. Prof Griffiths introduced the symposium and discussed the importance of recognising that psoriasis is stigmatising for patients and that clear skin plays a major role in reducing the burden of disease. Prof Griffiths then provided an overview of approaches to assessing psoriasis disease severity, such as PASI, and described recent clinical efficacy data indicating that a treatment outcome of PASI 90 and even PASI 100 response is a realistic aim. Dr Chiricozzi explained the evidence for the role of the IL-17 cytokine family in psoriasis pathogenesis and inflammation and how the only therapeutic strategy to simultaneously block all the inflammatory signals stimulated by IL-17 cytokines is blockade of the IL-17 receptor subunit A (IL-17RA). Finally, Prof Augustin discussed the importance of patient-reported outcomes (PRO) in obtaining the

patients' perspective on the value of treatment. He described the use of DLQI in practice and summarised findings from real-world studies that demonstrated that DLQI 0 or 1 highly reflects patient benefit from treatment.

Does it Make a Difference and Why Should You Care?

Professor Christopher Griffiths

Patients with psoriasis still face stigmatisation and consequently use 'avoidance coping' to try and reduce the stigma they experience. The psychosocial impact of psoriasis is considerable, with patient-reported physical outcomes comparable or slightly worse for psoriasis than those for diabetes, arthritis, heart disease, depression, and cancer.[1] Therefore, discussing raising the bar for treatment outcomes, such as PASI 90 or 100 and DLQI 0 or 1 responses, is important so that we may aim to achieve the greatest benefit for patients.

Although PASI 75 is the current gold standard treatment outcome with new treatments, such as IL-17 inhibitors, complete skin clearance (PASI 100) should become a realistic goal for many patients. In an analysis of a real-world observational study (PSO-BIO-REAL) of patients with moderate-to-severe plaque psoriasis who were initiating or switching biologics, 23% and 26% of patients achieved PASI 100 at 6 months and 12 months, respectively.[2] A slightly higher proportion of patients who were biologic-naïve compared to biologic-experienced (25% versus 20%, respectively, at 6 months) achieved PASI 100.[2] While biologics, including IL-17 inhibitors, have demonstrated high levels of skin clearance in clinical trials,[3] it remains to be established whether similar levels can be achieved in clinical practice and more effective treatments are needed.

In summary, it is important to recognise that psoriasis is stigmatising for patients and that clear skin plays a major role in reducing the burden of the disease. Therefore, there is a need to discuss optimal, ambitious, and holistic treatment of our patients.

What is the Difference between PASI 100 and PASI 90, and is PASI 100 a Realistic Treatment Goal in Daily Clinical Practice?

Professor Christopher Griffiths

There are several methods for assessing psoriasis severity. PASI assessment is now a standard measure and changes in this score are commonly used as treatment outcome measures. However, PASI is not a very accurate assessment of severity because it only considers erythema, desquamation, and induration, and the surface area involved according to anatomical sites, giving a total score ranging from 0–72. Given that a PASI score of >12 represents severe psoriasis, there is huge redundancy in the scale, with scores of >50 very rare. Additionally, dermatologists may not know what a PASI of 10, 20, or 30 looks like. Consequently, using a more holistic approach to assess psoriasis severity is needed. One such assessment is the Simplified Psoriasis Index,[4] a summary measure consisting of three component aspects of psoriasis: current severity, current psychosocial impact, and a historical course and intervention score. The sum of these component scores shows whether a patient will be relatively straightforward or difficult to treat, as it not only includes the body surface area affected but is weighted towards more sensitive areas, such as the face or hands, and includes psychosocial disability and previous response to treatment.[4]

In terms of assessing response to treatment, two randomised clinical studies (AMAGINE-2 and 3) in patients with moderate-to-severe psoriasis evaluated PASI 100 as an endpoint for the comparison of brodalumab, an anti-IL-17 receptor antibody, and ustekinumab, an anti-IL-12/IL-23 antibody.[5] In a post-hoc analysis of AMAGINE-2 and 3, the cumulative incidence of patients receiving brodalumab 210 mg every 2 weeks (Q2W) achieving PASI 100 in four body regions by Week 52 were 91% (head and neck), 90% (trunk), 86% (upper limbs), and

83% (lower limbs).[6] This reflects what is seen in clinical practice, with the fastest response observed for the head and neck and the slowest for the lower limbs. In a further post-hoc analysis evaluating PASI <75, 75, 90, and 100 responses over time, the PASI 100 response rate for patients treated with brodalumab 210 mg Q2W increased over time to ~55%.[7] Thus, the efficacy of new biologics indicates that we should realistically be aiming for an outcome of at least PASI 90 and even PASI 100. The change in absolute PASI scores may also be used to evaluate outcomes. In AMAGINE-2 and 3, the proportion of patients treated with brodalumab 210 mg Q2W who achieved a PASI score of 0 or >0 and ≤1 over time reached ~65%,[7] providing evidence to further evaluate absolute PASI (Figure 1).

It is also important to consider what complete skin clearance means and to understand the mechanism and drivers at the molecular and immunological level of the characteristic relapses of psoriasis in the same sites. One concept is that of the 'molecular scar', whereby microscopic residual abnormalities with a predominance of psoriasis or disease-related genes remain, even in clinically resolved psoriasis lesions.[8] At an immunological level, there are residual populations of tissue-resident memory T cells in clinically resolved lesions.[9]

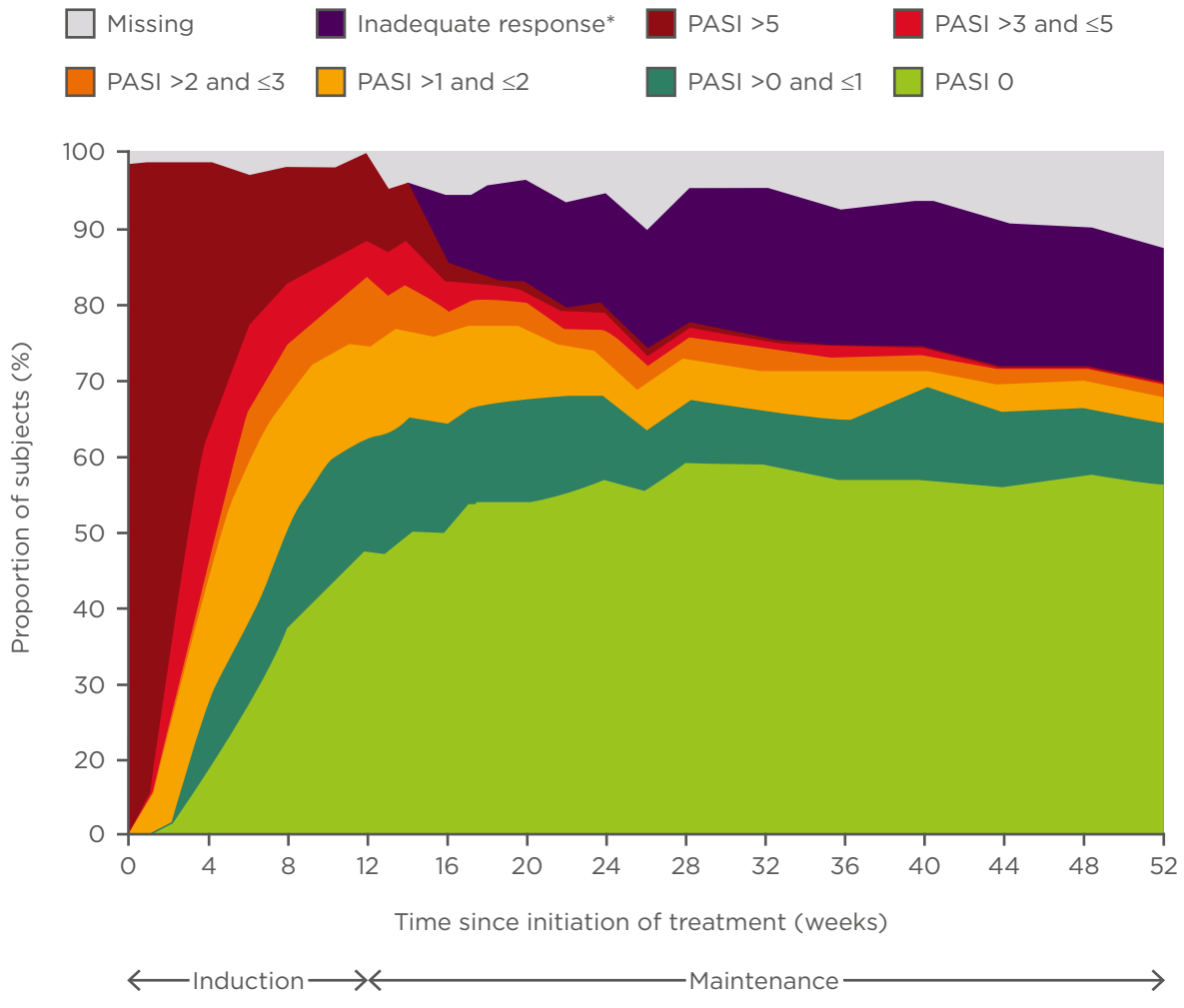

Figure 1: Proportion of patients over time with absolute Psoriasis Area Severity Index scores for brodalumab 210 mg every 2 weeks.

*Defined as static Physician's Global Assessment (range 0–5) ≥3 or persistent values of 2 over at least a 4-week period at or after Week 16.

PASI: Psoriasis Area Severity Index.

Adapted from Zachariae et al.[7]

These T cells respond to autoantigens that stimulate a psoriasis flare, then predominantly produce IL-17, which results in the recurrence of the lesion in the same site. This raises the possibility that, in addition to resolving the lesion, we should also aim to clear these residual T cells to reduce the risk of relapse.

Lastly, there is ongoing debate about whether dermatologists should see patients much earlier in the psoriasis disease cycle. Rapid referrals from primary care to specialists help ensure patients are on the correct treatment pathway and aim to prevent the sequelae of psoriasis by educating patients on the risk factors for comorbidities, such as cardiovascular disease, and screening for psoriatic arthritis.[10] Additionally, the concept of treating some patients very early with new biologics, such as anti-IL-17 or anti-IL-23 antibodies, to see if they could prevent the continuance of residual T cells and thereby switch-off the disease and prevent relapses, should be investigated.

Where is the Difference in the IL Pathways? Does it Make a Difference Whether the Treatment Targets the Cytokine or the Receptor?

Doctor Andrea Chiricozzi

The IL-17 cytokine family plays an important role in psoriasis pathogenesis and inflammation and consists of six members from IL-17A to IL-17F.[11,12] IL-17A and IL-17F can form both homodimers and IL-17A/F heterodimers. IL-17 cytokines signal through heterodimeric receptor complexes in the IL-17R family (Figure 2).[11–13] IL-17A, IL-17C, IL-17E, and IL-17F all signal through the IL-17RA subunit;[14] therefore, IL-17 RA represents a therapeutic target in psoriasis. The general biological activity and pathogenic role of IL-17B and IL-17D in psoriasis are not well understood and, as such, were not further discussed in this symposium.

IL-17A

IL-17A is a central cytokine in psoriasis and, with IL-23, constitutes the main axis driving the development of the psoriasis phenotype.[15] In this axis, IL-23 stimulates a wide array of immune cells to produce and express IL-17A, including Th17, Tc17, Tγ/δ+, natural killer, innate lymphoid, neutrophils, and mast cells.[12,14] These cells infiltrate lesional psoriatic skin and produce IL-17A. Neutrophils are not likely to express IL-17A mRNA, but instead internalise IL-17A produced by other cells and, once activated, are able to release it.[16] The infiltration results in increased expression of IL-17A that can be detected in lesional and non-lesional psoriatic skin compared to normal skin, as well as increases in IL-17A serum levels versus healthy controls and increases in IL-17 concentration in the tear liquid of patients with psoriasis.[17–19]

IL-17A is a proinflammatory cytokine that directly affects tissue cells, particularly keratinocytes.[16] Keratinocytes are considered the key responding cells to the skin cytokine microenvironment and are important for inflammation induced in the skin. In keratinocytes, IL-17A stimulates the expression of proinflammatory mediators, such as antimicrobial peptides (e.g., lipocalin, S100A proteins, and beta defensins), and, in synergy with TNF-α, it stimulates the expression of proinflammatory cytokines (e.g., IL-1β, IL-6, IL-17C) and chemokines (e.g., IL-8 and CCL20). The stimulation by IL-17A results in feed-forward loops that sustain skin inflammation.[20,21]

In vitro experiments in a three-dimensional skin model showed that IL-17A can regulate the expression of >630 genes.[22] Furthermore, IL-17A induced a gene expression profile that strongly correlated with the altered gene expression profile in lesional psoriatic skin,[22] meaning that IL-17A is a good therapeutic target. For example, secukinumab[23] and ixekizumab[24] neutralise IL-17A in both the homodimer and heterodimer, resulting in selective inhibition that suppresses the inflammatory gene expression regulated solely by IL-17A.[11,25,26] However, other IL-17 cytokines can contribute to inflammation in psoriasis.

IL-17F

IL-17F shares 55% sequence homology with IL-17A and is upregulated in lesional psoriatic skin compared to non-lesional and normal skin.[27,28] Moreover, IL-17F is produced by Th17 cells that also produce IL-17A and its expression is regulated by IL-23.[29–31] IL-17F homodimers and

IL-17A/F heterodimers (and IL-17A homodimers) signal through the receptor consisting of IL-17RA and IL-17RC subunits (Figure 2).[12,13] Biologically, IL-17F almost overlaps with IL-17A, stimulating genes similar to those stimulated by IL-17A. In a recent study, similar gene expression signatures were induced in human skin explants treated with IL-17A, IL-17F, and IL-17A/F heterodimers.[32] Thus, IL-17F can induce gene expression of the same antimicrobial peptides, cytokines, and chemokines that have been previously described for IL-17A.[32] While there is an overlap in IL-17A and IL-17F signalling, IL-17A is 10–30-fold more potent than IL-17F at inducing downstream gene expression.[32]

IL-17F may also contribute to the psoriasis transcriptome. In an *in vitro* study in healthy skin explants treated with IL-17A, IL-17F, and IL-17A/F, the gene expression profile induced by IL-17F (and other IL-17 cytokines) significantly correlated with upregulation of the psoriasis transcriptome (MAD3-PSO; $p<10^{-16}$).[32] Therefore, IL-17F may also be considered a good therapeutic target, and bimekizumab, an antibody that neutralises both IL-17A and IL-17F and their heterodimers, is in clinical development for the treatment of psoriasis.[33] Bimekizumab blocks IL-17 inflammatory pathways regulated by both IL-17A and IL-17F (Figure 2). Theoretically, however, there are still inflammatory signals regulated by IL-17C and IL-17E that could also contribute to psoriasis pathogenesis.

IL-17C

IL-17C is a proinflammatory cytokine that shares 23% sequence homology with IL-17A. It is produced by keratinocytes and is synergistically induced by IL-17A and TNF-α.[34] IL-17C may synergise with other cytokines, such as TNF-α and IL-1β, and it binds to the IL-17C receptor, which consists of the IL-17RA and IL-17RE subunits (Figure 2).[13,14] Expression of IL-17C mRNA in lesional skin is significantly higher than in unaffected and non-lesional skin.[27]

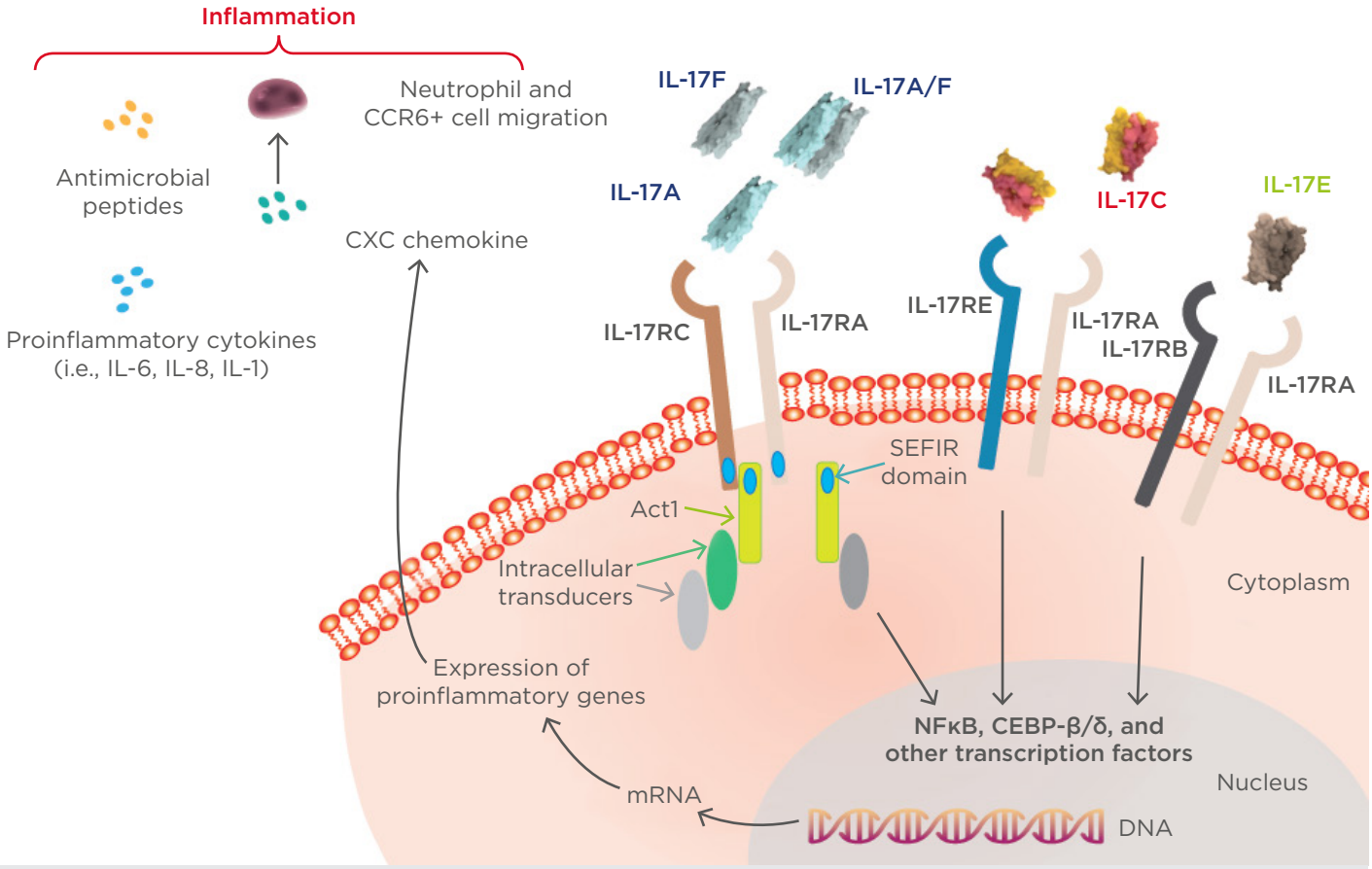

Figure 2: IL-17 cytokine family-mediated inflammatory pathways in psoriasis.

Adapted from Beringer et al.[13]

Interestingly, IL-17C protein levels are ~100-fold higher than IL-17A levels,[27] suggesting that IL-17C is markedly active in stimulating inflammation in psoriatic skin.

The effects of IL-17C overlap with those of gene expression induction by IL-17A and IL-17F. IL-17C stimulates the genes in keratinocytes that have been previously described for IL-17A and IL-17F, namely cytokines, chemokines, and antimicrobial peptides.[34] IL-17C may then generate an autoinflammatory loop because it is not only produced by, but can also act on, keratinocytes to produce downstream genes that are also regulated by IL-17A and IL-17F. Thus, IL-17C potentiates and amplifies IL-17A and IL-17F signals.[20,34] IL-17C signalling contributes to psoriasis pathogenesis, albeit to a lesser extent than IL-17A and IL-17F. The gene expression profile induced by IL-17C *in vitro* weakly but significantly correlated with the upregulated psoriasis transcriptome (MAD3-PSO) in healthy skin explant ($p<10^{-16}$).[32]

IL-17E

Lastly, IL-17E (also known as IL-25) is recognised as a therapeutic target in atopic dermatitis because it supported a Th2-mediated inflammatory response in a mouse model, stimulating expression of IL-4, IL-5, and IL-13.[35] The pathogenic role of IL-17E in psoriasis is controversial, with contrasting data on its expression level in lesional psoriatic skin,[27,36] as well as its effects on Th17 activation, as it is supposed to suppress IL-17A signalling.[11] It binds to the IL-17E receptor, which consists of the IL-17RA and IL-17RB subunits (Figure 2).[11,13]

Previously, data did not support a role for an IL-17E-mediated pathway in psoriasis pathogenesis, as no upregulation of IL-17E was identified in lesional skin compared to non-lesional or normal skin,[27] and no correlation was detected between the gene expression profile induced by IL-25E and the psoriasis transcriptome.[32] Conversely, in another study, significantly higher IL-17E mRNA levels were found in lesional skin compared to non-lesional and unaffected skin, and keratinocytes were identified as a major source of IL-17E.[36] Additionally, *in vitro*, IL-17E induced macrophages to express *CCL20*, *IL-8*, and *TNF-α*,[36] which are genes central to psoriasis pathogenesis and inflammation. Hence, we may hypothesise an alternative inflammatory pathway in psoriasis that is driven by IL-17E and is not related to the main IL-17A pathway.

Blocking Inflammatory Pathways in Psoriasis

In psoriasis, multiple inflammatory pathways are driven by different IL-17 cytokines. The main pathway is driven by IL-17A and potentiated by IL-17F and IL-17C, plus a likely contribution from IL-17E. The only therapeutic strategy to simultaneously block all these inflammatory signals is blockade of the IL-17RA subunit, through which all of these cytokines signal (Figure 2).[11,13,25,26] By blocking the IL-17RA subunit with an agent such as brodalumab, we can control all the inflammation regulated by IL-17 cytokines. The advantage of this approach compared with neutralising a single cytokine that only partially controls the IL-17 family activity needs to be confirmed, and mechanistic studies should be conducted to provide data to address this issue. Furthermore, head-to-head studies should be performed to determine whether there is any clinically meaningful difference in rapidity of effect, response duration, and safety in targeting IL-17RA over the cytokine.

What Difference Does a DLQI 0 or 1 Make to Patients? Are We Ambitious Enough?

Professor Matthias Augustin

Many patients with psoriasis do not receive optimal treatment, often waiting years to achieve relief of their symptoms. This was exemplified by a patient testimony video in which the patient described experiencing 10 years of uneven treatment before finally receiving biologic treatment and feeling well. This provided an example of the cumulative life course impairment patients experience. Thus, it is important to obtain the patient's perspective and determine what difference achieving complete restitution of quality of life (i.e., a DLQI score of 0 or 1) would mean to them. As physicians, we should ask whether we

are ambitious enough to help patients achieve this goal.

As advocated in the World Health Organization's (WHO) Global Report on Psoriasis,[37] dermatologists should have a patient-centred and holistic approach, beginning from their initial contact with patients. However, dermatologists may only have 10–20 minutes in their initial consultation with patients to identify their needs and to reach a treatment decision. Consequently, the availability of new psoriasis treatments is good for patients but challenging for dermatologists to make treatment choices in partnership with patients.

Why We Measure Patient-Reported Outcomes in Psoriasis

In evaluating treatment outcomes, we must not only consider objective outcomes but also the value to the patient.[38] PRO provide a way of translating the outcomes of treatment decisions into value from the patient perspective and, therefore, provide support for the complex treatment decision-making process in psoriasis.

There are many tools to measure outcomes in psoriasis, such as objective, hybrid, and PRO,[39] but we currently mainly use DLQI for quality of life assessment. Objective outcomes and PRO measures are both necessary because there is a degree of discrepancy between them. For example, in an early study evaluating the correlation of absolute PASI and DLQI scores in real-world care, no significant correlation was found between PASI and DLQI until the skin improved, and, at that point, DLQI also improved.[40] DLQI was included in the 2011 European consensus of treatment goals for moderate-to-severe psoriasis.[41] Although the treatment goal thresholds for PASI response are now higher, the principle remains of combining an objective measurement of treatment response with the patient perspective via DLQI to come to a treatment decision.[41]

The Use of DLQI

The DLQI consists of 10 questions and results in a score ranging from 0–30. The use of DLQI has been recommended in most guidelines,[42] quality of care guidelines,[43] and European registries.[44] While complete clearance is the current goal, treatment goals should be agreed with the patient and should include quality of life measures. Indeed, data from 2,345 patients in the PsoBest German registry on the association between percentage improvement in PASI from baseline to 3 months and DLQI showed that greater proportions of patients with higher PASI response achieved DLQI 0 or 1, with almost 70% of patients who achieved PASI 100 reaching DLQI 0 or 1 (unpublished data).[45]

In routine practice, there are challenges associated with using DLQI, including determining the meaning of the DLQI score for the treatment decision. In fact, physicians should discuss the DLQI answers with the patient to focus on their most important needs, (e.g., reducing itch). A limitation of the DLQI is that 8 out of 10 questions allow a response of 'not relevant', which may lead to a bias in the sum score.

What Goals Should We Share with Our Patients?

When sharing treatment goals with patients, whether DLQI is enough to measure the patient perspective should be considered. To obtain a wider view of patient perspectives, 3,425 patients in large national healthcare studies in Germany were asked about their needs from treatment.[46,47] The three most frequent answers were 'to get better skin quickly' (93%), 'to be healed of all skin defects' (91%), and 'to have confidence in the therapy' (89%), but patients listed many other items that they considered important.[46,47] The Patient Benefit Index (PBI) was developed and has been used to evaluate the overall benefit as a sum of single benefits, such as 'to be free of itch'.[46,48]

A further way to measure treatment benefit is to evaluate the association of PASI response, DLQI, and PBI with anchoring variables. Patients in the PsoBest registry were asked if they were 'very satisfied with treatment' after 3 months (unpublished data).[45] Their response was used as the anchoring variable and a linear correlation was found between increasing PASI response, DLQI, and PBI benefit, and the proportion of patients who reported treatment satisfaction (unpublished data).[45] Of note, the proportion of patients satisfied with treatment was much higher for those achieving DLQI 0 or 1 than DLQI 2–5. If 'all skin lesions healed' was used

as the anchoring variable, it was achieved for ˜80% of patients with DLQI 0 or 1 but <40% with DLQI 2–5 (unpublished data).

Some patients in PsoBest exhibited poor PASI response (PASI <50) but had a DLQI 0 or 1 (unpublished data).[45] In this situation, potential bias in the DLQI sum score should be checked. The association of other PASI response measures (change in PASI score or absolute PASI score after 3 months) with DLQI was also evaluated, and absolute PASI score may best reflect the DLQI response.[45] The achievement of DLQI0 or 1 was also associated with the greatest patient benefit, as assessed by PBI (unpublished data).[45] In conclusion, DLQI 0 or 1 highly reflects patient benefit from treatment and the goal of reaching DLQI 0 or 1 should be integrated into clinical practice.

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Navigating the Road to Psoriasis Control in Women: Strategies to Optimise the Reproductive Journey

This symposium took place on 15th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairperson: Caitriona Ryan[1]

Speakers: Caitriona Ryan,[1] Matthias Augustin,[2] C. Elise Kleyn[3]

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Meeting Summary

The importance of discussions around the management of women of childbearing age with psoriasis, an issue that has been largely neglected for many years, was introduced and emphasised by Prof Ryan as the topic for this symposium. The changing needs and hurdles faced by this patient population due to the different hormonal phases throughout a woman's reproductive life can reduce quality of life (QoL), aggravate disease burden, and complicate treatment decisions. This was exemplified by Dr Kleyn using three case studies for which delegates provided useful insights on management options. It was noted that fears and misconceptions often result in women of childbearing age delaying the decision to start a family and that improved doctor–patient interactions are key to helping women overcome concerns surrounding conception and pregnancy.

Prof Augustin discussed the significant impact of psoriasis on physical and psychological comorbidities and stigmatisation using the concept of cumulative life-course impairment (CLCI) as a measure. He then presented clinical trial data on anti-TNF biologic therapy during pregnancy, with a particular focus on results relating to placental transfer and transfer into breast milk. The delegates' opinions on family planning and postpartum flares were then sought for three relevant clinical scenarios illustrated by Prof Ryan. The use of anti-TNF agents in women who are actively trying to conceive, are pregnant, or are breastfeeding was discussed, with the majority of delegates indicating that they would recommend anti-TNF treatment to patients where appropriate. The lack of practical guidance in dermatology the management of women of childbearing age with psoriasis was highlighted, and the symposium concluded with an overview of current recommendations by the European League Against Rheumatism (EULAR) for patients with rheumatological conditions. These emphasise the importance of discussing family planning with female patients and directly involving them in treatment decisions to optimise their reproductive journey.

The Imprint of Psoriasis on the Patient's Life

Professor Caitriona Ryan

A characteristic feature of psoriasis is that it affects all aspects of a patient's life.[1,2] It typically develops during the teenage years, when major decisions regarding relationships and careers are made and, therefore, the cumulative impact on social, emotional, and work life can be substantial, with negative effects on the individual's ability to achieve their full potential.[1,2] Furthermore, each patient is affected in a unique way by the condition, with constantly changing needs that may complicate treatment decisions.[1,2]

The major impact of psoriasis on both QoL and physical and mental health has been amply demonstrated in a USA-based study of data collected from 2003–2011 from >5,600 patients with psoriasis or psoriatic arthritis.[3] Each measure of emotional burden, including self-consciousness, embarrassment, and frustration, was reported by nearly 90% of respondents.[3] Physical symptoms, namely itching and pain, were reported by 93% and 83% of patients, respectively.[3]

Interestingly, there is evidence of a differential impact of psoriasis across sexes. An observational study of 2,450 patients found that, compared with men, women generally scored higher on subjective but not objective disease activity measures, indicating a greater experienced disease burden and worse QoL, potentially as a result of undertreatment.[4] More women than men (37.7% versus 27.7%) had Dermatology Life Quality Index (DLQI) scores >10, but more men than women (35.3% versus 27.0%) had a high (>10) Psoriasis Area Severity Index (PASI).[4] Of the patients receiving biologic therapy, the majority were men (67.1%).[4]

Hawro et al.[5] demonstrated that women with psoriasis are also more likely than men to experience feelings of stigmatisation (e.g., anticipation of rejection, feelings of being flawed, sensitivity to others' opinions; $p=0.05$, $p=0.002$, and $p<0.001$, respectively). This is important because stigmatisation is the strongest predictor of reduced QoL and depressive symptoms in psoriasis.[5,6]

The impact of psoriasis in women versus men is exacerbated by genital symptoms. In a study of 354 men and women with the disease, 63% had current or previous history of genital manifestations, such as burning, itching, pain, and stinging.[7] These were reported more frequently by women, with a statistically significant difference for pain, burning, and discomfort during intercourse.[7]

Additionally, the course and risk of psoriasis can be affected by hormonal factors during puberty, pregnancy, and menopause.[8,9] For example, there is evidence that in some patients, symptoms improve during pregnancy when oestrogen levels increase, and there is also evidence that the majority of women experience a worsening of symptoms soon after childbirth.[8,9] In terms of psoriasis risk, a prospective analysis of 163,763 women concluded that those with irregular menstrual cycles or surgical menopause were more likely to develop the disease than women with regular

cycles and natural menopause (multivariate hazard ratio [HR]: 1.32; 95% confidence interval [CI]: 1.01–1.73 and HR: 1.19; 95% CI: 1.01–1.40, respectively).[10] By contrast, the risk was lower in women who had multiple births (≥2) or a breastfeeding duration ≥24 months than in women who had one birth or who had not breastfed (HR: 0.85; 95% CI: 0.71–1.01 and HR: 0.69; 95% CI: 0.51–0.93, respectively).[10]

Stories in Psoriasis: Exploring the Hurdles Encountered on the Road

Doctor Elise Kleyn

Three case studies were used to exemplify the impact of psoriasis on female patients (Box 1).

A common theme emerging from the discussion of these case studies was that women of childbearing age with psoriasis often delay the decision to become a mother or abandon the idea altogether. Studies in patients with other chronic inflammatory conditions have shed light on the concerns and misconceptions behind such decisions. In one of these studies, 54% of women (n=622) aged 18–45 years living with rheumatic disease reported delaying their decision to start a family.[11] The most frequently given reasons included fear of passing on the disease to the baby (46%), concerns about not being healthy enough to conceive and carry a child to term (23%), and not being emotionally ready to become a mother (19%).[11] Additionally, and importantly, 10% of the women who admitted delaying the decision to start a family also reported a lack of support from their family physician.[11]

With regard to the actual genetic risk of passing on psoriasis to the offspring, it is worth noting that there is a 50% chance if both parents have psoriasis but a 16% and 8% chance if only one parent or neither parent, respectively, has the condition; there is also no evidence that psoriasis causes disease-specific defects in newborns.[12] In terms of the ability to conceive and carry a child to term, research suggests that young women (<35 years) with psoriasis have a 22% lower pregnancy rate and 39% lower live birth rate compared to women without the condition.[13]

Of note, an estimated 50% of pregnancies in the USA are unplanned.[13] While a good patient–physician relationship would be desirable, especially in the context of family planning, evidence suggests this is less than optimal at present. In a survey of 300 patients with psoriasis in Italy, >50% of participants emphasised that physicians should listen to their needs.[14] Frequently reported desirable physician qualities included the ability to communicate in a simple language and convey feelings of control and hope about the curability of psoriasis.[14]

Beckman and Frankel[15] published detailed data on the state of the patient–physician relationship. They found that patients are generally able to express their concerns in only 23% of office visits; the most common reason for this was interruptions by the physician, which were reported in 69% of office visits.

Box 1: Case studies demonstrating the impact of psoriasis on women.

Case Study 1: A 32-year-old woman with psoriasis who had been on anti-TNF therapy for 2 years. She was 8 weeks pregnant and decided to stay on treatment until the end of the second trimester. However, she missed several follow-up appointments and returned to the clinic when she was 29 weeks pregnant. At that point, it was found that treatment had been stopped due to concerns about the fetus' health. The patient subsequently delivered a healthy baby.

Case Study 2: A 46-year-old woman with chronic plaque psoriasis since her teens. The disease had had a substantial impact on her life course, affecting her education and relationships with peers. The patient then developed psoriatic arthritis and decided not to start a family due to concerns regarding treatment and the risk of passing on the disease to her children.

Case Study 3: A 68-year-old woman who developed psoriasis after the birth of her second child and had received systemic treatment for many years. Her son developed psoriasis in his teens but, despite his mother's history, it took several years before he was seen by a dermatologist. The patient was adamant she would not have started a family if her psoriasis had manifested at an earlier age. Despite the patient having a supportive family, the disease had clearly taken a toll on her and the people around her.

The amount of time physicians spend listening to patients before taking the lead is a mean of 23.1 seconds, according to other research.[16] However, data have suggested that just 2 minutes of physician listening would be enough for approximately 80% of patients.[17] There is clearly a requirement among doctors for greater awareness of their patients' needs and of ways to improve their relationships with them.

Avoiding the Obstacles Along the Way: From Puberty, Through Pregnancy, to Menopause

Professor Matthias Augustin

In his introductory overview on treatment-related needs in patients with psoriasis, Prof Augustin quoted the results of German registry data analyses,[18,19] which showed that the most frequently reported needs are rapid improvements in skin appearance (93%) and healing of all skin defects (91%) (unpublished data). These results are somewhat expected given the nature of the disease and that such improvements would be straightforward to measure with PASI. However, the same analyses identified a broad range of other needs in all different aspects of life, including the need to be able to lead a normal life, feel less depressed, and be free of pain.

Additionally, it is evident that treatment-related needs differ across age groups and sexes. For example, compared with patients aged ≥65 years, those <65 years are more likely to report the need to be able to work and have a normal sex life.[20] Needs such as feeling less depressed, sleeping better, and being more productive are more prevalent among women than men.

It is crucial to be able to identify and measure needs in different patient populations to be able to optimise treatment,[20] and young women of reproductive age were perceived by the audience to be among those with the highest needs. The CLCI concept is useful in this regard because it measures the cumulative burden of psoriasis over a patient's lifetime rather than at certain points in time.[21] Specifically, it is possible to calculate for each patient a CLCI score that captures the effects of the condition over time in terms of its impact on physical comorbidities (e.g., psoriatic arthritis), psychological comorbidities (e.g., depression and anxiety), and stigmatisation (e.g., public rejection and self-image).[21] The CLCI is influenced by coping strategies and factors, such as treatments and support from family and healthcare professionals. Tailoring these to the needs of the individual patient can help mitigate or reverse the burden of psoriasis.

Members of the audience noted the importance of early intervention to prevent the disease from having a cumulative effect on patients. It was highlighted that establishing good patient–doctor relationships has the potential to modify the trajectory of the life course of patients, empowering them to achieve their full potential.

Since psoriasis develops by 16 years of age in approximately 30% of patients,[8] it is often already present during puberty. An analysis of data from 33,981 patients in Germany in 2005 found that those aged 0–20 years had double the comorbidity rate of subjects without the condition.[22] More specifically, children and adolescents with psoriasis had increased rates of high cholesterol (2.12% versus 0.99%), obesity (8.40% versus 4.90%), hypertension (1.65% versus 0.83%), diabetes (0.86% versus 0.43%), rheumatoid arthritis (8.40% versus 4.90%), and Crohn's disease (0.51% versus 0.14%).[22] These results clearly indicate that comorbidities are also important to consider in patients with psoriasis.

Pregnancy can be a particularly vulnerable time for psoriasis patients. It has has been reported to be a trigger for the onset of psoriatic arthritis after childbirth in 30–40% of women.[23] Furthermore, although an estimated 55.3% of women with psoriasis report symptomatic improvement during pregnancy, 65.2% experience substantial worsening soon after giving birth.[9] An important implication of these findings is that adequate treatment in women of childbearing age with psoriasis is crucial. However, despite therapies being available, their use during pregnancy remains suboptimal.

Current therapies include topical treatments (e.g., mild corticosteroids), systemic drugs (e.g., cyclosporine), and biologics (e.g., anti-TNF agents). With regard to anti-TNF agents specifically, Marchioni and Lichtenstein[24] conducted a systematic review of studies reporting on birth outcomes following maternal exposure to infliximab (IFX), adalimumab (ADA), or certolizumab pegol (CZP). They concluded that, although these therapies are promising, the benefits demonstrated in clinical trials must be weighed against the potential risks for the baby. When comparing the three agents in terms of their presence in newborns and the umbilical cord on the day of birth, IFX and ADA, but not CZP, were found to have higher concentrations than in the mothers.[25] This was observed in a USA-based study of pregnant women (N=31) with inflammatory bowel disease (IBD).[25] At birth, the median levels of IFX, ADA, and CZP in the umbilical cord were 160.0%, 153.0%, and 3.9% those of the mother, respectively.[25] Although no serious congenital effects were reported, IFX and ADA were still present in the babies up to 6 months after their birth.[25]

The aforementioned results for CZP are corroborated by those reported by Mariette et al.[26] in the CRIB study. This was a prospective, post-marketing, pharmacokinetic study of pregnant women (N=16) with autoimmune diseases, including rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and Crohn's disease. It used blood sampling of mothers at delivery and of newborns and cords at delivery and 4 and 8 weeks after birth. Data for 14 mother–newborn pairs showed that blood CZP levels were within the expected therapeutic range in mothers at delivery (median [range]: 24.4 [5.0–49.4] µg/mL) and were below the level of quantification (0.032 µg/mL) in 13 out of the 14 babies at birth and in call baby samples at Week 4 and 8, indicating a lack of or minimal placental transfer during pregnancy.

Exposure to anti-TNF agents during pregnancy has an impact on immune system development in newborns. Recent research revealed that newborns of mothers with IBD who received IFX or ADA throughout pregnancy had a less mature immune system at the age of 6 months compared with healthy controls.[27] The effect was no longer observed by 12 months of age;[27] nonetheless, this result must be considered in terms of vaccine recommendations. EULAR advises delaying the use of live vaccines by 6 months in newborns exposed to biologic therapy during the late-second and third trimester of pregnancy.[28] It also recommends that paediatricians should be informed of whether and when the mother received biologic therapy during treatment of their psoriasis.

Transfer of anti-TNF agents into breast milk has also been investigated. In two studies by Ben-Horin et al.,[29,30] mothers exposed to IFX or ADA had detectable levels of the biologics in their breast milk. In nursing women (n=3) with IBD, IFX increased 12 hours after the first infusion, peaked at 90–105 ng/mL within 2–3 days, and plateaued thereafter.[29] In one nursing woman with Crohn's ileitis, ADA levels in milk reached 31 ng/mL within 6 days of the first infusion and declined thereafter.[30] No relevant breast milk CZP concentrations were detected in a study of patients with chronic inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, and Crohn's disease. All milk samples (N=137) collected from 17 nursing mothers were below the lower level of quantification (max: 0.076 µg/mL) and 56% had no measurable CZP.[31]

The audience were asked whether, based on the data presented, they would recommend patients with moderate-to-severe psoriasis who are trying to conceive or are pregnant to discontinue anti-TNF therapy. The majority said they would advise their patients to continue treatment. However, it was emphasised that this should be an informed decision made by the patient after discussions around the potential for placental transfer of anti-TNF agents.

Nurturing the Woman Through the Psoriasis Journey: From Burden to Empowerment

Professor Caitriona Ryan

The symposium continued with a panel discussion on ways to enable women of childbearing age with psoriasis to feel empowered to make decisions about family planning and pregnancy. The members of the panel were

first invited to share their experience regarding the best time to introduce family planning to their patients. The majority indicated that this is generally at treatment initiation. This was considered important given the high rates of unplanned pregnancies. For example, in the USA alone an estimated 50% of all pregnancies are unplanned.[13]

Three additional clinical scenarios were then presented. The first was that of a 30-year-old woman whose psoriasis has had a significant impact on her life, resulting in a loss of confidence. The patient was stable on anti-TNF therapy and leading a normal life. She presented to the clinic to discuss her plan to start a family since she was concerned about discontinuing treatment and having her psoriasis uncontrolled.

The audience highlighted the importance of reaching a shared decision with the patient to remain on anti-TNF therapy. Discussions about lifestyle were said to be crucial because patients with psoriasis are often overweight, with comorbidities, including depression, that can potentially affect adherence to treatment. Education on the impact of psoriasis on fertility was also recommended. For example, there is little awareness that untreated psoriasis can impair fertility in males aged 18–55 years;[32] however, the time to pregnancy >5 months is not increased in women with psoriasis versus those without.[33]

The second clinical scenario was a 24-year-old woman with psoriasis and psoriatic arthritis (PASI: 7.8; body surface area [BSA]: 8.0%; DLQI: 24). Currently on ADA plus methotrexate symptomatic treatment, she returned to the clinic for a regular follow-up appointment. Discussions with the patient about the potential for teratogenic effects of methotrexate and the need for contraception were said to be paramount. Identifying and addressing factors other than skin issues (e.g., depression) that may be responsible for the high DLQI, despite relatively low PASI and BSA, were also indicated as important.

For the third clinical scenario, the audience was asked to consider a 35-year-old woman with psoriasis 6 weeks after giving birth (BSA: 40%; DLQI: 27). The patient discontinued anti-TNF treatment after becoming pregnant and had postpartum flares but wanted to continue to breastfeed. There was consensus that treatment should be resumed and that, based on the data presented, in particular for CZP, biologic therapy can coexist with breastfeeding.

The audience was then asked whether they would initiate or delay anti-TNF therapy or recommend another systemic agent for a woman with severe psoriasis who is breastfeeding. Seventy percent said they would initiate treatment with an anti-TNF agent, 15% said they would delay therapy, and the remaining 15% said they would use a different systemic agent. On the last point, it was noted that the only feasible systemic alternative would be cyclosporine. However, this transfers into breast milk in elevated amounts and, therefore, regular monitoring of the baby would be required if cyclosporine was administered.

Smoothing the Patient's Journey Towards Better Outcomes in Psoriasis

Professor Caitriona Ryan

When asked what strategies may help lessen the CLCI of psoriasis in women of reproductive age, the audience agreed on the need to inform patients about therapy options and encourage them to use available treatments. Recommended strategies also included providing reassurance that the potential risks of life-long treatment are minimal in most cases, establishing a relationship of trust and collaboration with the patient, asking them what they hope to gain from the therapy, being positive about disease outcomes, and discussing the risks and benefits of each treatment option. Early intervention was said to be crucial to improving outcomes in psoriasis.

The opinion of the audience was sought on whether they felt comfortable prescribing anti-TNF therapy for women with psoriasis who are trying to conceive or pregnant. Overall, 80% reported being comfortable with prescribing anti-TNF therapy for women who are trying to conceive, compared with 64% for women who are pregnant, based on the presentation.

Research has been conducted recently on the level of comfort among dermatologists in Europe and the USA with prescribing anti-TNF therapy for women of childbearing age with chronic inflammatory disease.[34] The findings showed that more European than North American dermatologists believed that anti-TNF therapy should be avoided during breastfeeding and discontinued before conception and during pregnancy.[34] Overall, 54% and 83% of dermatologists in Europe and the USA, respectively, said they were comfortable with prescribing anti-TNF agents to female patients of childbearing age; 10% and 21%, respectively, said they were comfortable with prescribing during pregnancy.[34] Of note, only 15% of surveyed dermatologists in Europe and the USA strongly agreed that keeping the disease controlled was their primary goal; in addition, 23% and 48%, respectively, admitted being very concerned about adverse events when prescribing anti-TNF therapy to pregnant women with chronic inflammatory disease.[34]

Conclusion

For women of reproductive age with psoriasis, navigating the road to disease control can be challenging since symptom severity may fluctuate or be influenced by the different hormonal phases experienced throughout life. In addition, concerns surrounding pregnancy and breastfeeding often result in patients delaying the decision to start a family. Biologic therapies have demonstrated the ability to reduce the burden of psoriasis. Through careful evaluation of the risks and benefits of treatment, and the implementation of multidisciplinary management strategies and shared decision-making, dermatologists can empower women to change the trajectory of their life's course and progress through their reproductive journey with confidence.

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Is Complete Skin Clearance in Psoriasis the Answer?

This symposium took place on 14th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairperson: Kristian Reich[1]

Speakers: Lars Iversen,[2] Hervé Bachelez[3]

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Meeting Summary

Prof Reich outlined the new understanding of psoriasis pathogenesis, with IL-23 rather than IL-12 considered the pivotal cytokine pathway. This understanding, along with new therapeutic agents, suggests that complete clearance is becoming a realistic treatment goal for patients.

Prof Iversen gave a detailed description of the pathogenesis of psoriasis. Psoriasis was previously thought to be driven by Th1 cells, but the key driver is now believed to be the IL-23/Th17 pathway. In a newly understood intermediate step, immature T cells develop into either inducible or regulatory T cells; the inducible Th17 cells mature into either pathogenic or non-pathogenic T cells, differentiation is dependent on IL-23 levels. Prof Iversen described findings that suggest IL-12 may have anti-inflammatory properties. This cytokine model may explain the different effects of drugs that target IL-12 and IL-23 versus those that target IL-23 alone.

Prof Reich and Prof Bachelez presented key clinical data on new IL-23-targeted therapeutic agents. The VOYAGE 1 study with guselkumab found Psoriasis Area Severity Index (PASI) 90 rates of 81.1% at Week 100 and PASI 100 rates >49.0%.[1] The reSURFACE trials with tildrakizumab demonstrated lower PASI 90 and PASI 100 response rates than VOYAGE 1, but, again, responses were durable and the agent was well-tolerated.[2] UltIMMa 1 and 2 were replicate studies that compared the IL-23 inhibitor risankizumab with the IL-12 and IL-23 inhibitor ustekinumab. At Week 52, PASI 90 response rates were 82% for risankizumab, 78% in the group switched to risankizumab after placebo, and 44% for those on ustekinumab.[3] This suggested that blocking IL-23 alone is superior to blocking both IL-12 and IL-23. The response to risankizumab was stable and durable; the safety profile was comparable to the comparator ustekinumab. IMMvent[4] and IMMhance[5] demonstrated robustness of response to risankizumab among patients who had failed prior therapies. The speakers and the audience concluded that these early trials suggest that the IL-23 inhibitors are an attractive new class of agents for the treatment of psoriasis.

Are We in a Psoriasis Evolution or Revolution?

Professor Kristian Reich

The world of psoriasis therapy is expanding rapidly with new therapeutic groups, biosimilars, and small molecules, explained Prof Reich. For decades, cold tar, phototherapy, and methotrexate were the mainstays of treatment. Methotrexate is still used, but has only a 35% PASI 75 response rate.[6] The first treatment revolution was the introduction of TNF-α blockers, such as infliximab, which had a 58% PASI 90 response rate at 24 weeks in the EXPRESS study.[7] More recently, IL-17 inhibitors showed strong efficacy in psoriatic arthritis, and PASI 90 and PASI 100 response rates 20% higher than with methotrexate (their introduction was another evolution). IL-23 inhibitors make up the third major group of targeted therapy, and the question raised was whether their arrival is an evolution or revolution.

According to the historical model of psoriasis,[8] activated myeloid dendritic cells release IL-12, which activates Th1 cells, and also IL-23, which activates Th17 cells. The Th cells release cytokines that activate keratinocytes and bring about the phenotype of psoriasis. Prof Reich said it is becoming clear that the IL-23 pathway drives the development of psoriasis, rather than the IL-12 pathway.

The p40 subunit is common to both IL-12 and IL-23 (Figure 1); drugs that inhibit p40 block both IL and are effective psoriasis treatments,[9] said Prof Reich, but the inhibition of IL-23 is the more probable mechanism rather than that of IL-12. A study in 2010[10] demonstrated that p40 (IL-12Rβ1) is elevated in psoriasis, as is p19 (IL-23R) but not p35 (IL-12Rβ2). Experimental work on human skin biopsies, comparing psoriatic and normal skin, found increased expression of IL-23 p19 and p40 in psoriatic skin and suggested that IL-23 plays a more dominant role in psoriasis than IL-12.[11]

The pathophysiology of psoriasis is now thought to involve a feed forward response by which the immune system activates the epidermis and a feedback response is delivered from the epidermis to the immune system.[12] This concept, along with the introduction of new therapies, is changing treatment goals. Eight years ago, Prof Reich believed that long-term skin clearance could never be a realistic treatment goal; it is now becoming technically possible and treatment goals need to be adapted. The traditional approach, scaling up treatment over months or years, may be the worst approach from an immunological point of view. Furthermore, treatments may eventually be introduced that modify the disease in the same way as antirheumatics modify rheumatoid arthritis. It could mean that patients remain free of psoriasis for prolonged periods of time after treatment has stopped. There might be markers to indicate that an individual patient will develop psoriasis; treatment could prevent the disease from ever breaking out. There is progress towards this vision; Prof Reich said the management of psoriasis is undergoing an evolution that might turn into a revolution.

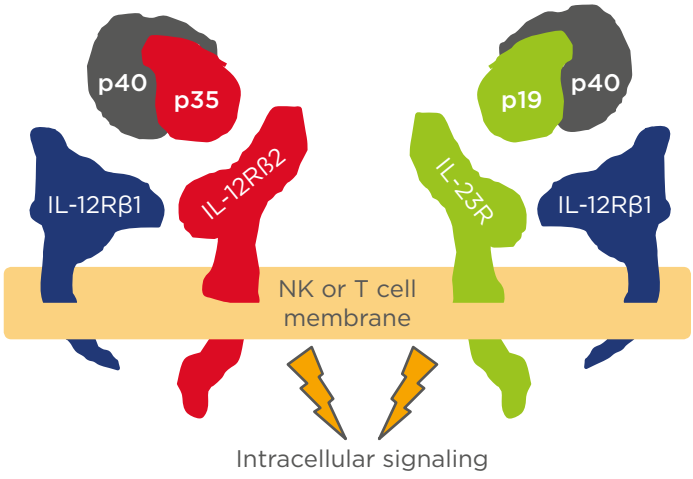

Figure 1: The rationale for targeting IL-12 and IL-23 in psoriasis.

NK: natural killer cell.

Adapted from Benson et al.[9]

Take Home Message

It is becoming clear that the IL-23 pathway plays a more dominant role in the development of psoriasis than the IL-12 pathway. Treatments that inhibit both pathways may owe their efficacy to inhibition of the IL-23 pathway. The new IL-23 inhibitors are contributing to new goals in psoriasis therapy: long-term skin clearance may now be a realistic aim of treatment.

IL-23: A Master Regulatory Cytokine in Psoriasis?

Professor Lars Iversen

An understanding of the pathogenesis of psoriasis is essential to distinguish between treatments with distinct modes of action, Prof Iversen stated. Psoriasis patients have a genetic predisposition, which does not cause disease unless triggered. A streptococcal infection, for example, could activate keratinocytes that release cytokines that activate dendritic cells, which drive the disease process.[8]

Activated dendritic cells migrate to lymph nodes and induce the maturation of immature Th cells. The cytokine milieu will determine the direction in which the Th cells differentiate. IL-23 drives the maturation of Th cells into Th17 cells, a key driver in psoriasis. Th17 cells release cytokines, such as IL-17, which causes the phenotypical changes in the skin seen in psoriasis.[13] Many recent drug developments in psoriasis have therefore targeted IL-17 and results have been promising. Secukinumab and ixekizumab are approved inhibitors of IL-17A. Brodalumab, also approved, targets the receptor that signals IL-17 A, F, C, and E. Bimekizumab, currently undergoing clinical trials, is an antibody directed against IL-17A and IL-17F.

Approved IL-23 inhibitors include guselkumab and tildrakizumab. Phase III trial data are available for risankizumab, but the drug is not yet approved. Mirikizumab is in earlier clinical trial development. As previously mentioned, psoriasis was previously thought to be driven by Th1, but the key driver is now believed to be the IL-23 Th17 pathway.[14,15] Naïve T cells exposed to IL-23 differentiate into Th17 cells and release signature cytokines, such as IL-17A, IL-17F, and IL-22.

It is now known that there is an intermediate step in T cell maturation. The interaction between dendritic cells and immature T cells is regulated by surrounding concentrations of TGF-β and IL-6. High concentrations of TGF-β favour the development of regulatory T cells; low concentrations of TGF-β and IL-6 favour development into inducible Th17 cells.[14,15]

The subsequent differentiation of inducible Th17 cells is driven by IL-23.[14,15] As illustrated in Figure 2, high concentrations of IL-23 drive the maturation of inducible Th17 cells into pathogenic Th17 cells. These pathogenic cells release the cytokines that result in psoriasis. However, in conditions of no IL-23, or very low concentrations, inducible Th17 cells mature into non-pathogenic Th17 cells that release cytokines such as IL-17 and IL-10. These cytokines may be anti-inflammatory and have a protective effect at mucous and possibly cutaneous membranes. In this way, IL-23 concentrations determine whether the mature Th17 cells are pathogenic or non-pathogenic.

This scheme may explain why agents that target both IL-12 and IL-23 may have lower efficacy than those that target IL-23 alone, Prof Iversen explained. Ustekinumab targets

the p40 subunit and inhibits both IL-12 and IL-23, while risankizumab blocks IL-23 alone. A Phase II, 48-week trial of risankizumab versus ustekinumab[16] randomly assigned a total of 166 patients to receive one of three doses of risankizumab (a single 18 mg dose at Week 0 or 90 or 180 mg [according to body weight] doses at Weeks 0, 4, and 16) or ustekinumab (45 or 90 mg [according to body weight] at Weeks 0, 4, and 16). At Week 12, the percentage of patients with a ≥90% reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90 mg and 180 mg groups, pooled), compared with 40% (16 of 40 patients) for ustekinumab ($p<0.001$). Risankizumab was associated with clinical responses superior to those associated with ustekinumab.

Potential explanations for this difference include drug affinity or dosing, but Prof Iversen stated that it is also possible that IL-12 (blocked by ustekinumab but not risankizumab) has a beneficial role. A recently published study[17] listed the IL-12 family according to proinflammatory profile. The study suggested that IL-23, which is part of this family, is more proinflammatory than IL-12. IL-12 has some anti-inflammatory properties, and it may be beneficial to maintain IL-12 during treatment for psoriasis. Other research supports the inhibitory role of IL-12 on inducible Th17 cells.[14,15,18]

Prof Iversen also discussed the difference between targeting IL-23 and IL-17. IL-17 is the downstream driver of phenotypical changes in the skin, and IL-17A inhibitors are effective in the treatment of psoriasis. However, inhibition of IL-17A may have the potential for a higher risk of adverse events or infections compared with IL-23 inhibitors.[19,20] Mucocutaneous candidiasis is seen more often with IL-17A inhibitors than with IL-23 inhibitors.[14,15] The effect is not large or proven, but Prof Iversen commented that it may be because IL-17 inhibitors block the IL-17 produced by non-pathogenic as well as by pathogenic Th17 cells. The contribution of IL-17 from non-pathogenic Th17 cells, left intact by IL-23 blockers, may have a beneficial effect.

Discussion on the pathogenesis of psoriasis should focus on immune modulation rather than immune suppression. Prof Iversen said IL-23 is a master regulatory cytokine in the pathogenesis of psoriasis. It regulates the differentiation of inducible Th cells into pathogenic and non-pathogenic Th17 cells. Inhibition of IL-23 reduces the pathogenic Th17 cell population and potentially results in prolonged downregulation of immune activation.

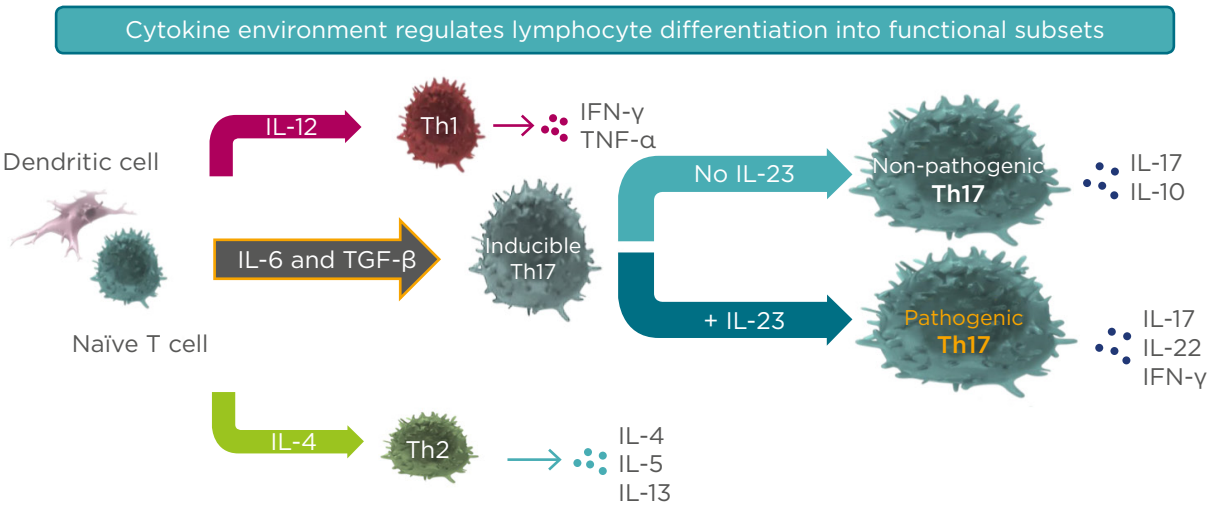

Figure 2: Inducible Th17 differentiation in the presence or absence of IL-23.

Selective targeting of IL-23 helps preserve protective, non-pathogenic Th17 cells that produce IL-17 involved in mucosal defense and barrier tissue integrity.

TGF-β: transforming growth factor β.

Adapted from Leung et al.[14] and Zhu et al.[15]

Take Home Message

Discussion of the pathogenesis of psoriasis should focus on immunomodulation rather than immunosuppression. The differentiation of immature T cells into either regulatory T cells or inducible Th17 cells is regulated by surrounding concentrations of TGF-β and IL-6. Concentrations of IL-23 then drive the maturation of inducible Th17 cells into either pathogenic or non-pathogenic Th17 cells. High concentrations of IL-23 favour the development of pathogenic Th17 cells that release the cytokines that result in psoriasis.

The cytokine IL-12 is involved in the differentiation of immature cells into Th1 cells. Th1 cells produce IFN-γ, which is a negative regulator of inflammatory cytokine production by Th17 cells, γδ T cells, and innate lymphoid cells. Thus, preserving the IL-12 pathway and inhibiting IL-23 alone could lead to better treatment outcomes compared with combined blockade of IL-12 and IL-23.

Inhibition of Il-17, the downstream driver of phenotypical changes in the skin, may have the potential for a higher risk of adverse events compared with IL-23 inhibitors. This could be because IL-17 inhibitors block the IL-17 produced by non-pathogenic as well as by pathogenic Th17 cells. Selective targeting of IL-23 helps preserve protective, non-pathogenic Th17 cells that produce IL-17 involved in mucosal defense and barrier tissue integrity.

IL-23 Inhibition: The Potential For Durable Disease Control?

Professor Kristian Reich

Guselkumab

The first IL-23 inhibitor to be approved was the monoclonal antibody guselkumab. The VOYAGE 1 study[1] compared its efficacy and safety with the TNF-blocker adalimumab. Patients were randomised to receive 100 mg guselkumab (Weeks 0 and 4, then every 8 weeks, n=329); or placebo (Weeks 0, 4, and 12, switching to guselkumab at Week 16 and 20, then every 8 weeks, n=174); or adalimumab (80 mg Week 0, 40 mg Week 1, then 40 mg every 2 weeks until Week 47, n=334). At Week 16, guselkumab was superior to both adalimumab and placebo (73.3% versus 49.7% versus 2.9% of patients achieved PASI 90; p<0.001), respectively. The placebo group was then switched to guselkumab for the remainder of the study. At Week 52, 78.9% of this group had achieved PASI 90, similar to the 80.1% of patients receiving guselkumab from the beginning of the study and substantially higher than the 50.5% of those receiving adalimumab.[21]

The response seen in VOYAGE 1[1] was maintained. From Week 52, all patients were switched to guselkumab and at Week 100, PASI 90 rates were similar across all groups, ranging from 81.1–82.3%; PASI 100 rates were >49.0%.[21] Prof Reich stated that the curves are flat and represent long-term, stable, safe control of psoriasis, adding that the data in VOYAGE 1 are conservative. The non-responder imputation of 72.3 for PASI 90, and 43.2 for PASI 100, represents longevity of response. As long as patients remain on the drug, the response is stable over a 2-year period.

A common theme among IL-23 inhibitors is that the disease takes longer to return than the pharmacology would predict when the drug regimen is stopped in responding patients. In the withdrawal arm of VOYAGE 2, the last dose of guselkumab was given at Week 20. At Week 48, 36.8% (67 out of 182) of patients still had a PASI 90 response.[22]

Findings from VOYAGE 2 demonstrate that treatment with guselkumab reduced cytokines in peripheral blood to levels similar to those found in healthy controls.[22] Those who maintain a PASI 90 response after drug withdrawal had continued suppression. Loss of response (<PASI 75) was associated with increased levels of serum IL-17A, IL-17F, and IL-22.

Early results suggest the safety of IL-23 inhibitors is encouraging. Serious infections are the most common adverse events, with 1.03 reported per 100 patient-years in from Week 0–48 of giving guselkumab,[21] which is probably similar to the background rate suggested Prof Reich.

Tildrakizumab

Tildrakizumab targets the p19 subunit of IL-23. The reSURFACE 1 trial randomised patients to tildrakizumab 200 mg, 100 mg, or placebo. In reSURFACE 2, patients were randomised to the same three groups plus an extra arm receiving 50 mg etanercept.[2] In reSURFACE 1 at Week 12, >60% of patients in both tildrakizumab arms achieved PASI 75 compared with 6% of those on placebo. Patients on placebo were then switched to tildrakizumab arms, and at 28 weeks >70% of patients in all arms achieved PASI 75. Results from reSURFACE 2 were similar.[2]

Prof Reich highlighted data from a pooled analysis of reSURFACE 1 and 2, plus P05495, which showed that 37% and 39% of patients on 200 mg or 100 mg of tildrakizumab achieved PASI 90 at Week 12, and 54% and 58% at Week 28, respectively.[2] Both PASI 90 and PASI 100 response rates were slightly lower than with guselkumab. Drug affinity is one potential explanation; a simple dose effect is unlikely because response rates were similar with both doses of tildrakizumab.

Responders to tildrakizumab who achieved PASI 75 at Week 28 maintained the effect off-drug. Tildrakizumab responders were switched to placebo at Week 28; at Week 64, 57% of patients on 200 mg tildrakizumab and 49% of patients on 100 mg remained PASI 75 responders.[2,23] The reSURFACE studies found tildrakizumab shared the same safety profile as other IL-23 inhibitors and was comparable to etanercept.[2]

Risankizumab: UltIMMa-1 and UltIMMa-2

Professor Hervé Bachelez

The Phase III trial UltIMMa-1 compared risankizumab and ustekinumab; UltIMMa-2 is a replicate study.[3] In UltIMMa-1 and 2, patients were representative of clinical practice in terms of demographics and disease severity. Prior biologic use, a surrogate marker of the severity of disease, was unusually high at between 30% and 56% across the various arms.

In both UltIMMa-1 and 2, patients were randomised using a 3:1:1 ratio to receive either 150 mg risankizumab, 45 or 90 mg ustekinumab (as indicated according to bodyweight), or placebo. In the induction phase, treatment was administered at 0 and 4 weeks and the primary response assessment took place at Week 16. At this point, patients who had been on placebo switched to risankizumab. All patients were treated at Week 16 and every 12 weeks thereafter.[3]

Results at Week 16 showed that, of the patients treated with risankizumab, 75.3% of those in UltIMMa-1 and 74.8% of those in UltIMMa-2 achieved PASI 90, one of the co-primary endpoints. This compares with 4.9% and 2.0%, respectively, of patients on placebo. The other co-primary endpoint, the proportion of patients achieving clear or almost clear status (static Physicians Global Assessment [sPGA] 0–1) in the two trials, was 87.8% and 83.7% with risankizumab, compared with 7.8% and 5.1% with placebo ($p<0.001$).[3]

At Week 52, the PASI 90 response was 82% for patients on risankizumab, 78% for those switched to risankizumab after placebo, and 44% for those on ustekinumab. Figure 3 demonstrates the stability of response with risankizumab, and contrasts with the fluctuations in response with ustekinumab. A similar pattern is seen in sPGA 0–1 scores up to Week 52: 56% of patients achieved clear skin at Week 52 (PASI 100 and sPGA 0). Prof Bachelez said the two analyses were remarkably convergent and promising.

Speed of effect was also notable in these studies. At Week 16, there was a 90% and 92% mean improvement in PASI from baseline among patients on risankizumab in UltIMMa-1 and UltIMMa-2, respectively;[3] this effect is compelling since patients had only received two doses of risankizumab at this timepoint.

Patient-reported outcomes mirrored the clinical responses. The proportion of patients receiving continuous risankizumab reported limited-to-no impact on quality of life; the Dermatology Life Quality Index (DLQI) of 0 or 1 was 66% and 67% of patients in UltIMMa 1 and UltIMMa-2 at Week 16 and 75% and 71% at Week 52, respectively, significantly higher than with ustekinumab ($p<0.001$).[3] The same trend is seen on the patient symptom scale, which measures pain, burning, itching, and redness.[3]

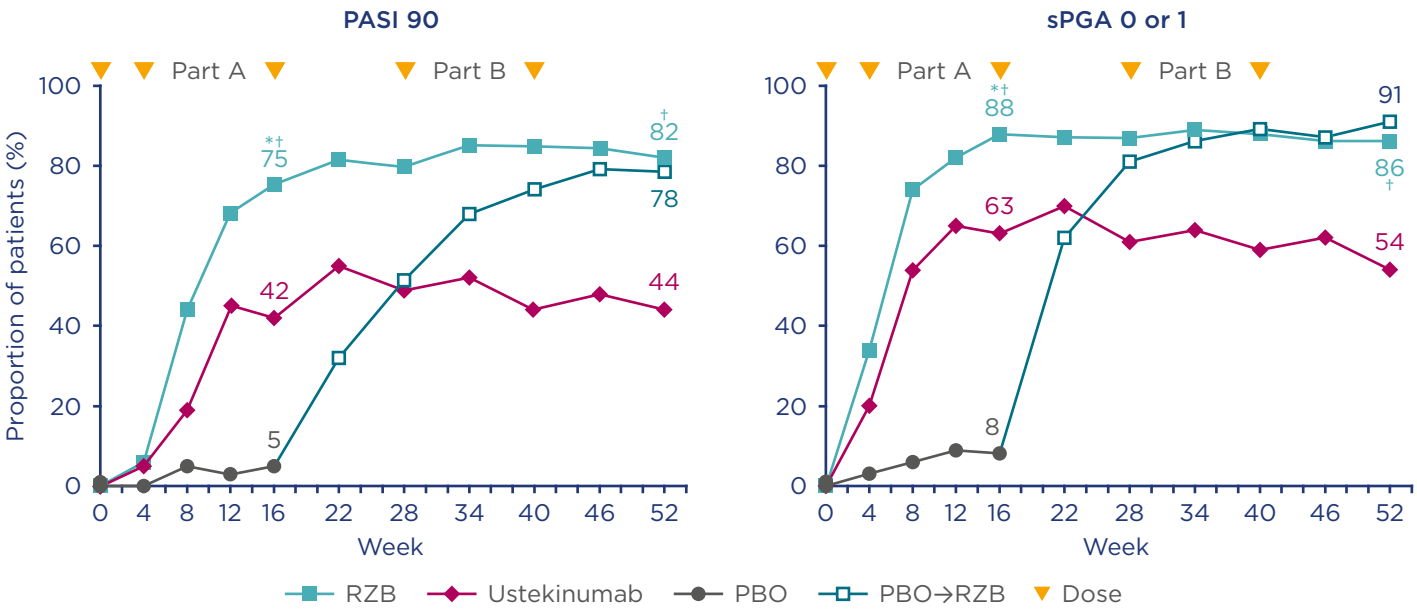

Figure 3: UltIMMa-1: Psoriasis Area Severity Index 90 and static Physicians Global Assessment 0 or 1 through to Week 52 (nonresponder imputation).

*p value for comparison versus placebo; p<0.0001. †p value for comparison versus ustekinumab; p<0.0001.

PASI: Psoriasis Area and Severity Index; PBO: placebo; RZB: risankizumab; sPGA: static Physicians Global Assessment; →: corssover

Adapted from Gordon et al.[3]

Prof Bachelez said there is no doubt of risankizumab's superiority over ustekinumab in these data.

Risankizumab had a safety profile comparable to ustekinumab. Drug-related adverse events were balanced across the three arms, and two major adverse cardiovascular events that occurred were considered not related to the treatment by investigators.[3] Prof Bachelez acknowledged that the numbers in the trial are not huge, but concluded that the results show the "clear superiority" of IL-23 specific blockage with risankizumab over dual inhibition of IL-12 and IL-23 with ustekinumab.

Risankizumab: IMMvent and IMMhance

Professor Kristian Reich

IMMvent, a head-to-head study comparing risankizumab with adalimumab, found that risankizumab achieved statistically higher PASI 90 and PASI 100 response rates than adalimumab at all time points starting at Week 8.[4] Of patients on risankizumab, 72.4% reached PASI 90 at Week 16, compared to 47.4% on adalimumab (p<0.001).

At Week 16, patients with PASI responses between 50 and <90 were rerandomised either to continue on adalimumab or switch to risankizumab. At Week 44, of patients switched to risankizumab, 66% achieved PASI 90, and 40% achieved PASI 100. This compares to 21% and 7%, respectively, of patients who remained on adalimumab (p<0.001).[4] Risankizumab is effective and IMMvent found no new safety signal, Prof Reich surmised that these are early results, with small participant numbers, but they look promising.

Previous failure with a biologic is the biggest predictor of suboptimal response to a second biologic. In an integrated analysis of 1,005 patients from Phase III trials: IMMhance,[5] UltIMMa-1, and UltIMMa-2,[3] PASI response at Week 16 was assessed in subgroups based on past treatment history. In this integrated analysis, 487 patients had nonbiologic systemic therapy experience and 452 had biologic

therapy experience. In patients receiving risankizumab, PASI 90 was achieved by 73% (n=168) who previously failed one biologic; and 69% (n=108) who had failed ≥2 biologics, non-responder imputation.[24] Prof Reich stated that he had not seen such robustness of response in any other study.

In summary, the IL-23 inhibitors are an attractive class of drugs with risankizumab proving a very promising treatment option. Trial data have yet to be matched in the clinic but Prof Reich said the class looks promising.

Take Home Message

The first IL-23 inhibitor to be approved was guselkumab, which was superior to both adalimumab and placebo in the VOYAGE 1 study. Guselkumab demonstrated long-term, stable, safe control of psoriasis.[1] In the reSURFACE 1 and 2 trials, tildrakizumab demonstrated slightly lower PASI 90 and PASI 100 response rates than with guselkumab, but patients who responded to tildrakizumab had relatively long disease control off-drug.[2] The UltIMMa-1 and 2 trials found that, at Week 16, 75% patients on risankizumab, reached PASI 90.[3] Risankizumab had a safety profile comparable to ustekinumab in these trials and the results demonstrate the superiority of IL-23 specific blockage with risankizumab over dual inhibition of IL-12 and IL-23 with ustekinumab.

Conclusion

Discussion on the pathogenesis of psoriasis should focus on immune modulation rather than immune suppression. New understanding suggests that the IL-23 pathway plays a more dominant role than the IL-12 pathway; IL-23 may be considered a master regulatory cytokine. High concentrations of IL-23 favour the maturation of inducible Th17 cells into pathogenic (rather than nonpathogenic) Th17 cells; these pathogenic cells release the cytokines that result in psoriasis.

Clinical trials have found promising PASI 90 and PASI 100 response rates with the new IL-23 inhibitors. Some work suggests that targeting IL-23 alone is more effective than targeting both IL-12 and IL-23.[3] This may be because IL-12 has some anti-inflammatory properties and may have an inhibitory role on inducible Th17 cells.

The new IL-23 inhibitors are contributing to new goals in psoriasis therapy: long-term skin clearance is now a realistic aim. Psoriasis is considered a non-scarring disease, but it tends to reappear in the same site, which supports the idea that it leaves a 'molecular scar'. Early studies suggest that the skin is populated by memory cells that produce the cytokine profile seen with pathogenic Th17 cells.[25] Complete skin clearance, which could eliminate the memory cells, may be important for long-term control of psoriasis. In conclusion, the IL-23 inhibitors are a new class of safe and effective drugs that may help achieve complete skin clearance for many patients with psoriasis.

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IL-23 Inhibition in Psoriasis: Changing the Present, Shaping the Future

This symposium took place on 13th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairpeople: Kristian Reich,[1] Richard Warren[2]

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Meeting Summary

This symposium took place at the 27th European Academy of Dermatology and Venereology (EADV) Congress. The session examined the latest data for contemporary therapeutic agents in psoriasis, focussing on IL-23 inhibitors as the most recently approved class of therapies, and provided perspectives on the implications of these data for clinical practice. With a wide array of potential treatment options now available for psoriasis, the symposium initially explored remaining areas of unmet treatment need, highlighting correct and timely diagnosis, effective management of comorbidities, undertreatment, and real-world data as key aspects requiring further improvement. The speakers subsequently reviewed the current evidence for the latest therapeutic strategies in psoriasis, concentrating on the therapeutic attributes that are considered most desirable for an 'ideal' agent, including efficacy for psoriasis and related comorbidities, durability of effect, improvement in quality of life, safety, and convenience. In this context, the rationale for selective IL-23 inhibition was examined, with the faculty highlighting how this approach differs from IL-17 inhibitors, at both the mechanistic and clinical levels. In addition, the session called attention to areas of ongoing investigation where there may be opportunities for the latest therapies to

provide further patient benefit, with focus on the potential for novel, less frequent dosing intervals with IL-23 inhibitors.

Introduction

Professor Kristian Reich

Despite recent advances, there remains substantial unmet need in the treatment of psoriasis and further progress is required. IL-23 inhibitors represent the latest class of therapies to emerge, adding to already available agents, which include TNF inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors. Given the spectrum of potential treatment options available, it is important to understand the role and importance of each class of agent in the therapeutic armamentarium.

Are There Still Unmet Needs in the Evolving Psoriasis Treatment Landscape?

Professor Richard Warren

Psoriasis is a serious global problem, as acknowledged by the World Health Organization (WHO) in their recent Global Report on Psoriasis, issued in 2016.[1] Worldwide, 125 million patients are affected by psoriasis,[2] approximately 14 million of whom reside in Europe.[3] Key areas of unmet medical needs in psoriasis relate to correct and timely diagnosis, effective management of comorbidities, addressing undertreatment, overcoming the challenges posed by psoriasis occurring in difficult-to-treat areas, and the lack of real-world patient data with newer therapeutic agents.[1,4-6]

Improving the management of psoriasis requires early diagnosis, timely referral, and correct assessment of disease severity.[1] Patient and physician perceptions of psoriasis severity may differ,[1] as illustrated by evidence from the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey.[4] In the MAPP survey, 22% of patients who had ≤3 palm lesions considered their psoriasis to be severe,[4] which is likely to differ from the physician-perceived severity of such cases of psoriasis. The lack of concordance between patient and physician-perceived severity indicates a need for improved methods for assessing severity in the clinic. Beyond the severity of psoriasis, it is also important to consider the presence of comorbidities when selecting an appropriate therapeutic strategy. Psoriatic arthritis, hypertension, depression, Type 2 diabetes mellitus, obesity, and hyperlipidaemia are all common comorbidities in patients with psoriasis.[7,8] In addition, Crohn's disease is genetically linked with psoriasis and represents a further potential comorbidity.[9] Taken together, the physical and psychological impact of psoriasis and associated comorbidities may have a cumulative impact on patients' lives over time, particularly for those patients who are less adept at coping with their condition, ultimately altering patients' life choices and impacting the course of their lives.[10,11] This concept is known as 'cumulative life-course impairment' and highlights a need for early and effective treatment of psoriasis and related comorbidities.[10,11]

With regard to treatment standards and the unmet need in psoriasis, the recently conducted 'Clear About Psoriasis' survey of >8,000 patients with moderate-to-severe psoriasis from 31 countries indicated that a large number of patients remain dissatisfied with their psoriasis treatment.[12] Within this study, 57% of patients reported having not achieved clear or almost clear skin with their current treatment regimen.[12] While 56% of patients reported that they were 'satisfied' with their treatment, 24% were 'uncertain' and 20% were 'dissatisfied', with the majority of dissatisfied patients (89%) not achieving clear or almost clear skin.[12] Such dissatisfaction may be linked with undertreatment; in the MAPP survey, nearly 40% of patients with >10 palm lesions were receiving no treatment, and only 11% of those patients were receiving oral or biologic therapy.[4] Among the audience members at this symposium, the majority considered undertreatment to be a bigger unmet need for patients with psoriasis than delayed (or incorrect) diagnosis. The challenge of undertreatment may be related to the high proportion of

patients who are affected by psoriasis in difficult-to-treat areas, such as the scalp, face, nails, genitals, intertriginous areas, palms, and soles.[6] These psoriasis subtypes may disproportionately impact patients' quality of life, while simultaneously not meeting the criteria for access to the most effective therapies if assessed using thresholds such as body surface area affected of >10%, leading to undertreatment.[6] Furthermore, treatment of such subtypes may require a tailored therapeutic strategy, as agents commonly used for psoriasis are not always suitable or effective in treating psoriasis affecting these specific areas.[6]

Over 70% of attendees at the symposium indicated that long-term real-world data have greater influence on their prescribing decisions than robust Phase III data from clinical trials. The representativeness of clinical trials to real-world clinical practice is therefore key and has been explored in several analyses.[5,13] In the UK, when data from the British Association of Dermatologists Biologic Interventions Register (BADBIR) registry were analysed, it was found that just over half (53%) of patients were considered to meet the enrolment criteria for the Phase III licensing studies for etanercept, adalimumab, or ustekinumab.[5] Around one-third of patients (32%) had insufficient baseline data to allow analysis or missing data, and the remainder were considered ineligible (15%).[5] Among the ineligible group, there were more elderly patients (aged ≥70 years) than in the eligible group and patients tended to have higher BMI, more comorbidities, and experienced smaller reductions in Psoriasis Area Severity Index (PASI) with treatment.[5] Crucially, a higher rate of serious adverse events was observed in the ineligible patient group when treated with etanercept, adalimumab, or ustekinumab than in those patients considered eligible for the clinical trials.[5] When interpreting clinical trial results, it is therefore critical to consider how representative the trial is of the real-world patient population; there is a need to improve under-representation of real-world patient subsets within clinical studies.

In summary, there are still numerous unmet medical needs affecting patients with psoriasis. Future efforts need to focus on encouraging earlier diagnosis of psoriasis and associated comorbidities, curtailing undertreatment, and addressing the under-representation of real-world patient subsets in clinical studies.

What is the Best Target for Psoriasis: IL-23 Versus IL-17A?

Doctor Andrew Blauvelt

While methotrexate and phototherapy formed the backbone of early management of psoriasis, recent decades have seen revolutionary changes in treatment, first with the emergence of TNF inhibitors, and more recently with IL-12/23, IL-17, and IL-23 inhibitors.[14] The emergence of each class of new treatment option has reflected an evolving understanding of the pathogenesis of psoriasis, which is now understood to be primarily an immunologic disease mediated by dysfunction in regulation of the IL-23/Th17 axis.[15-17] A key benefit of specifically targeting the IL-23/Th17 pathway is that although the pathway is involved in mucocutaneous immune defences,[18] it is not involved in systemic immunity.[19]

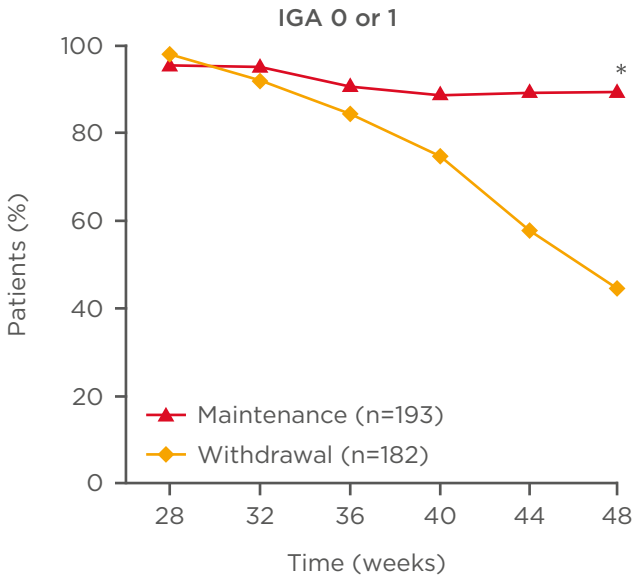

Figure 1: Investigator's Global Assessment 0 or 1 response rate among patients withdrawn from or maintaining guselkumab therapy following an initial response† in the VOYAGE 2 trial.

*p<0.001; †≥90% improvement in Psoriasis Area Severity Index after 28 weeks' guselkumab treatment.

Adapted from Reich et al.[25]

Modern treatment options provide the opportunity to inhibit this pathway at various stages, including at upstream (e.g., IL-23 inhibitors), intermediate (e.g., IL-17 inhibitors), or downstream points (e.g., IL-17 receptor antagonists).[16,17] Physicians are now faced with the challenge of determining whether to select an inhibitor targeting IL-23 or IL-17 as the therapeutic strategy for their patients.

Focussing first on treatment efficacy, primary endpoint data from pivotal clinical trials in moderate-to-severe psoriasis with biologic agents targeting IL-17 indicated PASI 75 response rates of 77–82% at Week 12 with the IL-17A inhibitor secukinumab (300 mg),[20] 87–90% at Week 12 with the IL-17A inhibitor ixekizumab (80 mg; every 2 weeks),[21] and 85–86% at Week 12 for the IL-17 receptor agonist brodalumab (210 mg; every 2 weeks).[22] In similar studies with IL-23 inhibitors, PASI 75 response rates of 61–64% were observed at Week 12 with tildrakizumab (100 mg),[23] with rates of 86–91% seen at Week 16 with guselkumab (100 mg).[24,25] Although the current lack of head-to-head clinical trials between IL-17 and IL-23 inhibitors limits the possibility of drawing robust conclusions about the comparative efficacy of these agents, ongoing studies are being conducted to address this question, including the ECLIPSE study,[26] which will directly compare the efficacy of guselkumab with secukinumab.

Given the chronic nature of psoriasis, it is important that therapeutic agents have durable efficacy. Sustained PASI response rates over time have been demonstrated with up to 5 years' treatment with secukinumab,[27] with up to 3 years' treatment with ixekizumab,[28] and with up to 2 years' treatment with guselkumab.[29] In addition, it is interesting to note that the efficacy of guselkumab appears to be sustained for a substantial duration of time after withdrawal of therapy.[25] In the VOYAGE 2 study,[25] patients who had received 28 weeks' guselkumab treatment and achieved PASI 90 were randomised to continued guselkumab therapy or withdrawal (placebo). Although PASI 90 and Investigator's Global Assessment 0 or 1 (cleared or minimal) response rates at Week 48 were significantly greater in those receiving continued guselkumab therapy versus those who were withdrawn from therapy ($p<0.001$), 37% of patients in the withdrawal arm still had a PASI 90 response at Week 48 (28 weeks after the last guselkumab dose), and >40% had Investigator's Global Assessment 0 or 1 responses (Figure 1).[25]

A previous study has explored the potential for prolonged efficacy to enable dosing-interval extension using the IL-12/23 inhibitor ustekinumab.[30] In this study, patients with moderate-to-severe psoriasis responding (Physician's Global Assessment [PGA] of 0 or 1) to 28 weeks' ustekinumab treatment were randomised to either dosing every 12 weeks (in line with the recommended dosing regimen) or to a response-based dosing regimen, with a variable dosing interval ranging from every 12 weeks for those who lost response at Week 32 to every 24 weeks for those who maintained response at Week 40.[30] This study found that in some patients, dosing can successfully be extended to every 6 months, with higher PGA 0 or 1, PASI 75, and PASI 90 response rates observed from Week 40–112 in patients in the subgroup who received 24-week dosing from Week 40 compared with those receiving more frequent dosing.[30] Taken together, the results of the these studies of IL-12/23 inhibition with ustekinumab and selective IL-23 inhibition with guselkumab suggest that upstream inhibition of the IL-23/Th17 axis may be linked with sustained pharmacodynamic effects after the drug has been eliminated from the body. Given that Th17 cells are known to be dependent on IL-23 for cell survival, this result may indicate that IL-23 inhibition leads to death of pathogenic skin-resident memory Th17 cells, potentially leading to more prolonged disease control.[31]

Psoriatic arthritis is prevalent among patients with psoriasis,[7] and it is therefore important to consider the efficacy of potential psoriasis treatment options on this comorbidity. Both secukinumab and ixekizumab have been approved in the European Union (EU) and the USA for the treatment of psoriatic arthritis.[32-35] In Phase III trials in patients with psoriatic arthritis, these IL-17 inhibitors have been shown to significantly improve American College of Rheumatology (ACR) 20 response rates compared with placebo over 24 weeks.[36-39] With regard to the efficacy of IL-23 inhibitors in patients with psoriatic arthritis, Phase II data have recently been published for guselkumab

that showed significantly greater ACR 20 response rates at Week 24 versus placebo,[40] with similar response rates to those seen in the previous studies with IL-17 inhibitors. These encouraging early data for guselkumab require verification in larger Phase III studies, which are currently ongoing.[41,42]

Safety is a critical factor when evaluating potential treatment options for psoriasis, given a likely need for long-term treatment. Agents directly targeting IL-17 or its receptor (e.g., secukinumab, ixekizumab, and brodalumab) are considered to be generally well-tolerated;[43] however, consistent with the known role of the IL-17 pathway in resistance to mucocutaneous infections, such agents are associated with mucocutaneous candidiasis infections.[32,33,44] In addition, exacerbations of Crohn's disease have been seen in clinical studies with secukinumab,[32] and cases of new onset or exacerbated Crohn's disease and ulcerative colitis have been reported with ixekizumab.[33] It has been hypothesised that IL-17 may play a protective role in the gastrointestinal tract, and therefore IL-17 inhibition may block this protective action, predisposing some patients to the development or exacerbation of inflammatory bowel diseases.[45] Agents inhibiting IL-23 (e.g., ustekinumab, guselkumab, and tildrakizumab) are also considered to be generally well-tolerated[43] but have not been reported to be associated with candidiasis or inflammatory bowel disease.[46-48] Furthermore, ustekinumab is in fact indicated for the treatment of Crohn's disease.[47] In this context, it is important to note that not all IL-17A-producing cells are regulated by IL-23, including in the gut.[49] These IL-23-independent pathways may allow for continued protective IL-17A production during IL-23 inhibition.[49]

An additional consideration when selecting the therapeutic regimen for psoriasis is the required frequency of dosing, which is an aspect in which IL-17 and IL-23 inhibitors differ. While IL-17 inhibitors require dosing every 2–4 weeks,[32,33,44] IL-12/23 and IL-23 inhibitors are dosed less frequently, typically every 8–12 weeks.[46-48]

In summary, while IL-17 and IL-23 inhibitors both represent highly efficacious and broadly well-tolerated classes of therapy for psoriasis,[43] differences exist between agents in durability, safety, and posology. It is also important to acknowledge that the therapeutic profiles of individual agents within each class may differ, likely driven by differences in antibody binding affinity, dose, dosing frequency, or other attributes.

Are We Thinking Long Enough? Applying Clinical Evidence to Practice

Professor Kristian Reich

Plaque-type psoriasis is driven by the interaction between the immune system and the epidermis. In the initial 'feed-forward' response, dendritic cells activate T cells via IL-23 release, which in turn release mediators, such as IL-17, that activate keratinocytes and stimulate keratinocyte proliferation, ultimately leading to psoriatic plaque formation.[16] Once keratinocytes are activated, they release further mediators that signal back to the immune system, such as IL-8 which attracts neutrophils to the skin,[16] creating a vicious circle with both feed-forward and feed-back responses between the immune system and skin.

In clinical studies in patients with psoriasis, high response rates have been observed with IL-17A inhibitors. With secukinumab, an average PASI 90 response rate of 75% was observed after 24 weeks' treatment across the FIXTURE, CLEAR, and PRIME clinical studies, and a similar proportion of patients (75%) achieved absolute PASI scores ≤2.[50] Response rates at Week 24 with secukinumab in these studies were higher than those seen with etanercept (PASI 90: 40%; PASI ≤2: 38%) or ustekinumab (PASI 90: 61%; PASI ≤2: 61%).[50] Similarly, ixekizumab has demonstrated greater clinical efficacy in terms of PASI 90 and PASI ≤2 response rates at Week 24 (83% and 84%, respectively) compared with ustekinumab (59% and 62%, respectively; $p<0.01$).[51] Taken together, these data suggest that IL-17A inhibitors provide greater response rates than ustekinumab. Ustekinumab is a monoclonal antibody that binds to the p40 subunit common to both IL-12 and IL-23, thereby inhibiting receptor binding and suppressing both the IL-12-mediated Th1 pathway and the

IL-23-mediated Th17 pathway.[47] In contrast, the IL-23-specific inhibitors, such as guselkumab, bind to the p19 subunit of IL-23, providing the opportunity for selective blockade of IL-23-mediated pathways.[16,46]

Pivotal clinical studies of guselkumab in patients with psoriasis include the VOYAGE 1 and 2 trials.[24,25] In VOYAGE 1, patients receiving guselkumab achieved a PASI 90 response rate of 80% after 24 weeks' treatment, with superior response rates to adalimumab (53%; p<0.001) (Figure 2).[24]

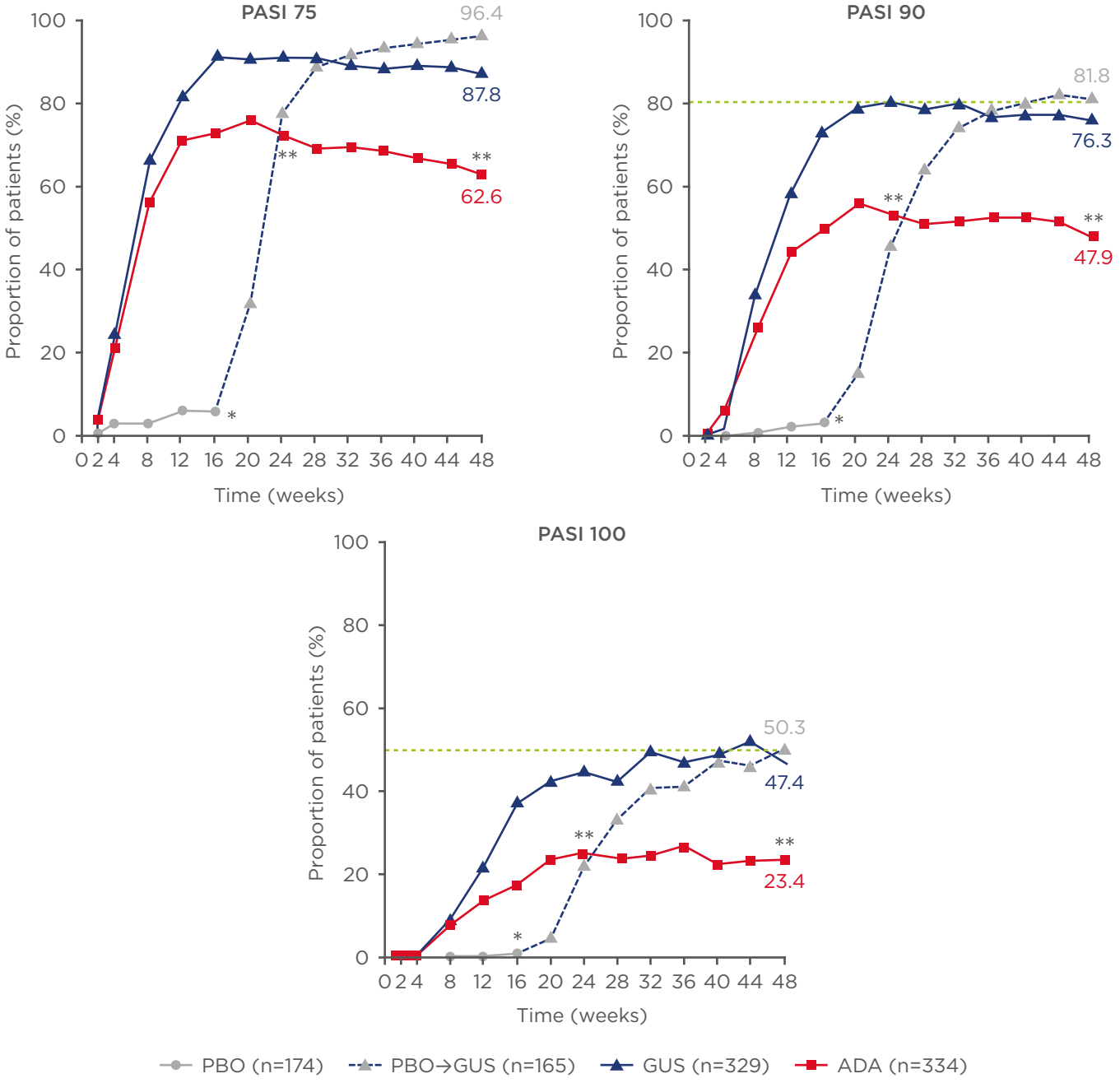

Figure 2: Psoriasis Area Severity Index response rates over time with placebo, guselkumab, and adalimumab in the VOYAGE 1 trial.

Data are from a non-responder imputation analysis. Patients in the placebo group switched to guselkumab treatment from Week 16 onwards.

*p<0.001 for GUS versus PBO; **p<0.001 for GUS versus ADA.

ADA: adalimumab; GUS: guselkumab; PASI: Psoriasis Area Severity Index; PBO: placebo.

Adapted from Blauvelt et al.[24]

Notably, at the end of the 1-year study, almost half (47%) of patients in the guselkumab group achieved PASI 100, indicating clearance of psoriasis, compared with 23% of adalimumab-treated patients (p<0.001).[24]

The high rate of complete resolution of psoriasis with guselkumab may be important in the context of durability of efficacy and potential extension of the dosing interval, particularly given that a previous study with ustekinumab identified achievement of PGA 0 (cleared disease) as a predictor of ability to successfully extend the dosing interval while maintaining response.[30] As mentioned in the previous presentation, VOYAGE 2 explored the efficacy of guselkumab after withdrawal, with patients responding to 28 weeks' guselkumab therapy randomised to either withdrawal of therapy or continued guselkumab.[25] In those patients withdrawn from guselkumab, the estimated median time to loss of PASI 90 response was >3 months (15 weeks).[25] However, this evidence alone does not imply that patients with well-controlled psoriasis achieving PASI 90 with guselkumab can be withdrawn from therapy or switched to less frequent dosing in clinical practice; further data are required.

As highlighted earlier, many patients present with psoriasis involving the nails, hands, or feet.[6] In the VOYAGE 2 study, among the subgroup of patients with hand/foot (hf) psoriasis, 77% of guselkumab-treated patients achieved a hf-PGA of 0 or 1 with a ≥2-grade improvement at Week 16, a significantly greater proportion than those receiving placebo (14%; p<0.001) and numerically more than those receiving adalimumab (71.4%).[25,52] At Week 24, a significantly greater proportion of patients in the guselkumab group achieved the hf-PGA endpoint (82%) compared with adalimumab (66%; p=0.046),[25,52] consistent with the previously discussed superiority of guselkumab over adalimumab for plaque psoriasis. In contrast, in those patients with fingernail involvement, no significant difference was seen between guselkumab and adalimumab in fingernail-PGA 0 or 1 response rates, which were significantly greater with guselkumab versus placebo at Week 16 (52% versus 15%, respectively) but not significantly different versus adalimumab at Week 24 (63% versus 67%, respectively; p=0.376).[52] These results may indicate that the pathogenic contribution of TNF-α and IL-23 varies between different subtypes of psoriasis.

Given the impact of psoriasis on patients' daily lives, including their psychological wellbeing, it is important to evaluate the effectiveness of treatment on patient-reported outcomes. In VOYAGE 2, among those patients with Hospital Anxiety and Depression Scale (HADS) scores indicating anxiety (HADS-A ≥8) or depression (HADS-D ≥8) at baseline, guselkumab was associated with greater improvements in anxiety and depression compared with adalimumab, as indicated by higher rates of patients achieving HADS-A <8 (58% versus 43%, respectively; p=0.028) or HADS-D <8 (60% and 46%, respectively; p=0.079).[53] Improvements in anxiety and depression were correlated with improvements in psoriasis (assessed via PASI scores).[53] More broadly, the clinical benefits of guselkumab appear to translate into improvements in quality of life, with significantly more patients achieving Dermatology Life Quality Index of 0 or 1 with guselkumab versus adalimumab at both Week 24 (61% and 40%, respectively; p<0.001) and Week 48 (63% and 39%, respectively; p<0.001) in the VOYAGE 1 study.[24] At Week 52 in the VOYAGE 1 study, patients receiving adalimumab were switched to guselkumab; by Week 100, the proportion of patients achieving Dermatology Life Quality Index of 0 or 1 was similar in those switched from adalimumab to guselkumab (74%) compared with those who had received 2-years' guselkumab (71%).[29]

With regard to the safety profile of guselkumab, a pooled analysis of the VOYAGE 1 and 2 studies, including 1,221 patients, indicated a low incidence of serious infections (1.06 infections per 100 patient years [including Week 0–100 data from patients randomised to guselkumab and those who crossed-over to receive guselkumab]).[29] Similarly, the rates of malignancy and major adverse cardiovascular events were very low (both 0.38 events per 100 patient years).[29]

In summary, IL-23 inhibitors are an important component of the treatment repertoire for psoriasis. Such therapies demonstrate high levels of therapeutic efficacy, are well tolerated, and have durable responses that allow long injection intervals,[24,25] which may have the potential to be extended further in the future.

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From Evolution to Revolution: IL-23 in the Treatment of Psoriasis Patients

This symposium took place on 14th September 2018, as part of the 27th European Academy of Dermatology and Venereology (EADV) Congress in Paris, France

Chairpeople: James Krueger,[1] Lluís Puig[2]

Speakers: Ernesto Muñoz-Elías,[3] Lluís Puig,[2] James Krueger,[1] Curdin Conrad[4]

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Disclosure: Dr Muñoz-Elías is an employee of Janssen Research and Development, LLC. Dr Puig has received consultancy fees, speaking fees, and honoraria from AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, Leo Pharma, Lilly, Merck-Serono, Merck Sharp and Dohme, Novartis, Pfizer, Regeneron, Roche, and Sandoz. His institution has received research funding related to the treatment of psoriasis from AbbVie, Amgen, Janssen, Lilly, Novartis, and Pfizer. Prof Krueger has acted as a scientific advisor or clinical study investigator for Janssen, Boehringer, Abbvie, Novartis, Lilly, Ortho Dermatologics, Leo Pharma, Merck, Admiral, and Union Chimique Belge. Dr Conrad is a consultant and/or paid speaker and/or principal investigator in clinical trials for AbbVie, Actelion, Amgen, Almirall, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo Pharma, MSD, Novartis, and Pfizer.

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Meeting Summary

This symposium, which took place during the 2018 meeting of the European Academy of Dermatology and Venereology (EADV) in Paris, France, provided an overview of the IL-23 revolution in psoriasis, with a specific focus on psoriasis pathogenesis and its relation to potential treatment targets and the development of novel targeted immune therapies. The session focussed on the discovery and development of IL-12 and IL-23-targeted therapies for psoriasis, the role of IL-23 in disease control, and the implications of recent data for clinical practice.

An increasing number of potential treatment options are becoming available for psoriasis, and the differential effect of these agents on various signalling pathways has facilitated a greater understanding of the molecular mechanisms driving disease progression. The symposium initially explored the central role of IL-23 in psoriasis, the mode of action of the monoclonal antibody (mAb) guselkumab in targeting this heterodimeric cytokine, and the parameters associated

with a maintenance of response in patients with psoriasis undergoing treatment. The speakers subsequently reviewed current data relevant to the blockade of IL-23 versus dual blockade of IL-12/23, or blockade of the downstream effector IL-17, and the relative effects of these different strategies in psoriasis at the molecular and cellular levels. The concept of 'disease memory' in psoriasis was also explored, with an examination of recent data of patients with long-lasting remission, and disease models and future investigations discussed.

Introduction

Dermatologists need to understand the unmet needs in the management of psoriasis and how current data from recently approved or pipeline compounds can help address these needs in clinical practice. This symposium aimed to promote an understanding of psoriasis pathogenesis and its relation to the development of novel targeted immune therapies. The presenters discussed how treatment strategies could be used to optimise long-term patient outcomes and addressed the concept of potential disease modification effects of targeted therapies in psoriasis.

The Road of Discovery: IL-12 and IL-23-Targeted Therapies in the Treatment of Immune-Mediated Inflammatory Diseases

Doctor Ernesto Muñoz-Elías

The proposed model for the immunopathology of psoriasis was, until recently, based on an equal contribution of IL-12 and IL-23 when produced by activated macrophages and dendritic cells. In this model, IL-12 activates Th1 cells and IL-23 activates both Th17 and Th22 cells, which leads to the proliferation of keratinocytes, production of multiple proinflammatory cytokines, increased inflammation, and the formation of psoriatic plaques. However, accumulating data from various sources suggest that the most important driver of pathogenesis in psoriasis is IL-23 rather than IL-12.[1] For example, gene expression data show psoriasis lesions have raised expression levels of genes encoding IL-23 (p19, a unique subunit of IL-23, and p40, a subunit of both IL-23 and IL-12) compared with a gene encoding a subunit associated with IL-12 only (the p35 subunit).[2] In addition, clinical data showed that the blockade of IFN-γ (primarily a downstream cytokine of IL-12) with anti-IFN-γ was not efficacious in treating psoriasis.[3,4] Furthermore, in a knockout mouse model in which IL-12 was silenced, IL-12 was shown to have a protective role in psoriasis-like disease.[5] Molecular data show that the first-in-class mAb guselkumab, which binds specifically to the p19 subunit of IL-23, blocks IL-23 signalling while having no effect on IL-12 signalling.[6] The downstream production of IL-17 by IL-17-expressing CD8+ T (Tc17) cells, when blocked by a mAb with specificity for IL-17A, such as secukinumab or ixekizumab, precludes the keratinocyte activation that is characteristic of psoriasis.[7] Ongoing studies are evaluating the possible effects of IL-23 in multiple immune cell types.

Data from clinical studies are being evaluated to gain insights into the effect of guselkumab on cytokines downstream of IL-23. Response to guselkumab has been examined in patients with moderate-to-severe psoriasis in the Phase III VOYAGE 1 and 2 trials. In the VOYAGE 1 study[8] (N=837), patients receiving guselkumab achieved a Psoriasis Area Severity Index (PASI) 90 response rate of 76.3% after 48 weeks of treatment, with superior response rates to adalimumab (47.9%; $p<0.001$). Guselkumab significantly reduced the levels of key serum effector cytokines, including IL-17A, IL-17F, and IL-22, in the IL-23 pathway at 48 weeks compared with adalimumab.[9] The psoriasis transcriptome of patients from VOYAGE 1 was also analysed. Following treatment with guselkumab, an improvement was observed at 4 weeks, 24 weeks, and 48 weeks, and at the 24 and 48-week timepoints, the profile resembled that of non-lesional skin.[9] Improvement of the psoriasis transcriptome was more prominent in patients treated with guselkumab than adalimumab. When evaluating multiple gene sets relevant to inflammation, similar results were observed.[10] One limitation of whole skin biopsy gene expression analysis is that it does not

allow for the characterisation of a drug's effect on immune cell numbers or phenotypes. Therefore, methods have been developed that allow the dissociation of skin biopsies into single cell suspensions that can then be analysed by flow cytometry for surface and intracellular protein expression. Skin-resident T cells isolated from biopsy samples have been examined, showing that epidermal T memory cells are pathogenic producers of IL-17A, IL-17F, TNF-α, and IL-22.[11] Fluorescence-activated cell sorting analysis of skin immune cells represents a new approach for understanding drug effects on skin tissue immune cells and is being incorporated into ongoing studies.

Maintenance of clinical response (PASI 90) after withdrawal of guselkumab has been evaluated in the VOYAGE 2 study,[12] in which patients who had received 20 weeks of guselkumab treatment and achieved PASI 90 at 28 weeks were randomised to receive continued guselkumab or switch to placebo. PASI 90 response rates at Week 48 were significantly greater in those receiving continued guselkumab therapy versus those who were withdrawn from therapy ($p<0.001$); however, 36.8% of patients in the withdrawal arm maintained a PASI 90 response at Week 48 (28 weeks after the last guselkumab dose). Compared with maintained response, loss of response (PASI <75) among patients in the withdrawal arm was associated with significantly increased levels of serum IL-17A, IL-17F, and IL-22 at Week 48.[13] Conversely, parameters associated with maintenance of PASI 90 following guselkumab withdrawal included a shorter duration of disease, lower BMI, and lower IL-17F at baseline, as well as complete skin clearance and higher guselkumab concentration at Week 28.[14] Further models of single and combined parameters and biomarkers are being investigated to better understand response to guselkumab and the mechanisms behind its action.

In conclusion, the data discussed support the hypothesis that IL-23 is a central driver of psoriasis. Studies show that blockade of IL-23 with guselkumab is associated with a clinical response, a normalisation of the psoriasis transcriptome, and a reduction in inflammatory cytokines of the IL-23/IL-17 pathway, such as IL-17A, IL-17F, and IL-22.

The Role of IL-23: From Disease Control to Disease Remission

Doctor Lluís Puig

Since the 1980s, it has been recognised that T cells are implicated in psoriatic disease, but the role of IL-23 only began to gain prominence in 2004.[15] In the current model of psoriasis pathophysiology, environmental stress causes keratinocytes to produce primary cytokines that activate antigen-presenting cells (usually dendritic cells), which then produce IL-23. In turn, via the IL-23 receptor (IL-23R) expressed on their surfaces, Th17 cells are stimulated to produce IL-17, which leads to the release of various cytokines that promote local keratinocyte activation, epidermal remodelling, and psoriatic plaque formation.[15] Therefore, the main rationale for blocking IL-23 in psoriasis treatment is to prevent the IL-23/Th17-mediated 'feed-forward' mechanism, which self-amplifies the inflammatory response in keratocytes of psoriatic skin.[7] Hence, blockade of the upstream regulator (IL-23) rather than the effector (IL-17) cytokine may be a more effective approach to psoriasis control. This question is currently being addressed in clinical trials involving a range of mAb that block either IL-23 or IL-17, with the latter group requiring a relatively high frequency of dosing in maintenance treatment to be effective.

Another possible advantage of IL-23 blockade is that the effects are not limited to targeting Th17. For example, the effects of IL-23 on regulatory T cells may promote differentiation into Th17 cells,[16] as well as affecting cell types known to be present in the skin, such as mast cells, which may be stimulated to promote extracellular trap formation and degranulation, and neutrophils.[17] As discussed, a localised disease memory, in the form of epidermal Th22 and Tc17 cells, can form in cases of clinically healed psoriasis. In this setting, epidermal CD8+ T cells are activated and a proportion become enriched in tissue that has healed, including those that express IL-23R as well as cutaneous lymphocyte-associated antigen, CCR6, and CD103.[11] These CD8+ T cells respond to *ex vivo* stimulation by producing IL-17A, while epidermal CD4+ T cells respond

by producing IL-22 for as long as 6 years following TNF-α inhibition.[11] These pathways have the potential to be modified by agents that target IL-23.

Other clinical advantages of blocking IL-23 include differential impacts on the bowel mucosa important for inflammatory bowel disease (IBD), a reduced risk of candidiasis or other opportunistic infection versus the risk with blockade of IL-17, and potential impacts on neoplasm formation. In the gut, unlike other tissues such as the skin, IL-17 promotes homeostasis and tissue repair rather than driving pathogenic inflammation; nevertheless, it is clear that antibodies targeting IL-23 ameliorate IBD. Data from a mouse model of IL-17A-producing gut cells suggest that the activity of these cells is independent of IL-23, implying that antibodies against IL-23 would not impair IL-17 production by innate lymphocytes. These data help to explain the observation that targeting IL-17 is ineffective in IBD.[18] In opportunistic infections of the mucosa caused by *Candida albicans*, IL-17 signalling is key to immunity and absence of the IL-17 receptor (IL-17R) in mice or humans leads to chronic infection;[19] therefore, blockade of IL-23 may represent an alternative therapeutic strategy. More generally, the marked redundancy seen in pathways involved in the IL-effector response to a wide range of pathogens suggests that IL-12/23 blockade should not have a significant impact on signalling, implying a favourable safety profile for IL-23 targeted agents (Figure 1).[20]

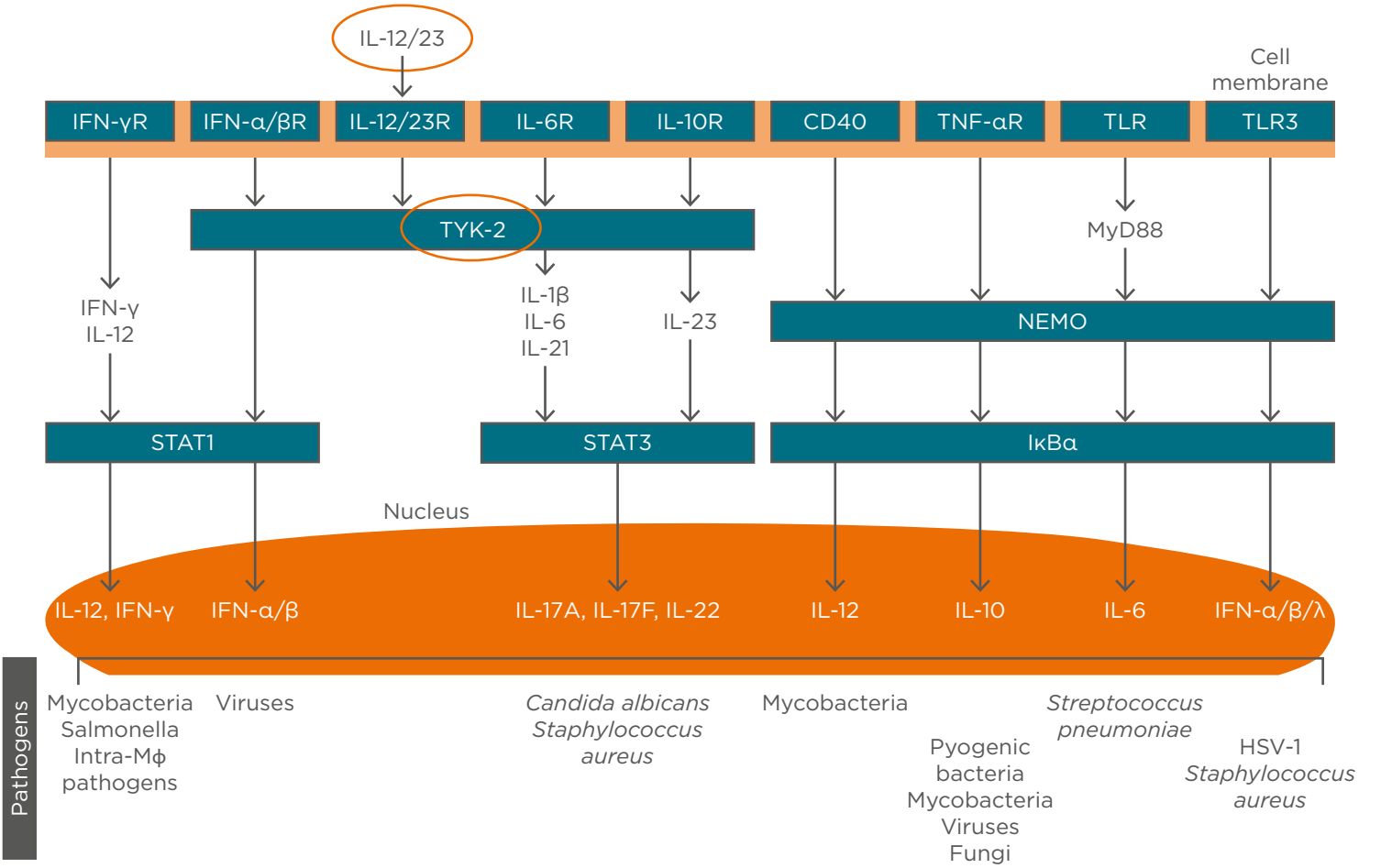

Figure 1: The role of cytokines in the pathogenesis of psoriasis and immune defence against infectious agents, showing redundancy in pathways downstream of IL-12/23 in Th cells that may favour the targeting of regulatory, rather than effector, cytokine blockade in the avoidance of infection.

HSV: herpes simplex virus; NEMO: NFκB essential modulator; R: receptor; TLR: toll-like receptor; TYK: tyrosine kinase.

Adapted from Blauvelt et al.[20]

Finally, in immune surveillance, IL-12 acts on lymphoid cells, such as natural killer cells and CD8+ cytotoxic T lymphocytes, which then produce IFN-γ and prevent tumour initiation, growth, and metastasis. In mouse tumour models, there is evidence for various activities of IL-23 in disease: as a tumour suppressor in ultraviolet-induced skin cancer, as an inducer (when overexpressed) of *de novo* intestinal tumours, and as a target for eliminating residual tumour cells from occult tumours.[6] Ultimately, head-to-head clinical trials will determine the extent of the advantages in blocking IL-23 versus IL-17A. Several such clinical trials are currently ongoing in patients with psoriasis.

Cellular and Molecular Changes in Response to Selective IL-23 Versus Dual IL-12/23 Blockade in Psoriatic Skin

Professor James Krueger

The two founding members of the IL-12 cytokine family, IL-12 and IL-23, share a common p40 subunit but are distinguished by their unique p35 and p19 subunits and their predominant downstream activity of IFN-γ or IL-17 activation, respectively.[6] The accepted disease model in psoriasis was, until less than a decade ago, one of inflammatory dendritic cells stimulating keratinocytes to produce a range of multiple cytokines, chemokines, and other inflammatory molecular and cellular effects that resulted in lesion formation, plus feedback and perpetuation of this reaction.[21] However, with the more recent availability of specific antibodies to p40 (e.g., ustekinumab) and p19 (e.g., guselkumab), the pathogenic axis was more specifically recognised as IL-23/IL-17, and the respective clinical effects of these differentially targeted mAb have generated much discussion and research interest.

As noted earlier in the symposium, data from head-to-head studies of guselkumab and ustekinumab are lacking. However, biopsy data comparisons have been made using samples from individuals treated in separate clinical trials of the two agents: the Phase III ACCEPT (T12)[22] study, combining patients treated with high-dose guselkumab 100 mg and 300 mg, and the Phase I study,[23] in which patients were treated with ustekinumab 90 mg. The two patient cohorts shared similar characteristics, with comparable baseline demographics, disease characteristics, and skin histopathology, and all the samples were fed into identical analyses.[24] Expression analyses indicated that >2,900 gene transcripts were upregulated in psoriasis lesion tissue, but in 'recovered' tissue 12 weeks post-treatment, a higher rate of renormalised (i.e., modulated ≤2-fold) transcripts was seen in those treated with guselkumab (77%) versus ustekinumab (45%) (unpublished data). Also, 75% of transcripts returned to a baseline level ≥75% of normal with guselkumab treatment, versus only 27% with ustekinumab. A 'molecular scar' can be identified at Week 12 of treatment versus baseline, in which the transcriptome recovers to 17% of its previous value with guselkumab, versus 58% with ustekinumab. After both 1 and 12 weeks of treatment, the neutralisation of activity of relevant transcriptomic genes following high-dose guselkumab was significantly more extensive than that with ustekinumab (unpublished data). These data were further supported in a real-time PCR analysis of the *DEFB4* and *LCN2* gene products, showing that these IL-17-responsive antimicrobial proteins recovered to a greater extent with guselkumab versus ustekinumab.[24] Histological staining of tissue using markers for keratin 16, T cells, dendritic cells, and other markers also demonstrated 12-week recovery with ustekinumab. These observations prompt the question of the relative potency of guselkumab and ustekinumab, and data show that, across a range of assays, there is a 2–14-fold difference in potency in favour of guselkumab.[24]

There are several factors that could contribute to the superiority of guselkumab over ustekinumab in neutralising psoriasis-related gene expression. In a mouse model of IL-17-mediated inflammatory activity in skin, knockout of the IL-12 subunit p40 resulted in inflammation, thin skin, and a doubling in transepidermal water loss.[5] Therefore, IL-12 may counter-regulate the IL-23/Th17 axis, which is critical for sustaining psoriasis. In addition, there is complexity within the IL-12 family of cytokines, and gene expression data reveal a possible role for other, less well-characterised members. As well as

changes in the levels of various members of the IL-12 family, such as K16, IL-17A, p19, and p40, psoriasis is also associated with raised IL-27 (unpublished data). IL-27 is composed of the subunits p28 and Ebi3 (named for homology to an Epstein–Barr virus gene),[25] neither of which are targeted by guselkumab or ustekinumab. As the IL-12 cytokine family is promiscuous and protein subunits of the family can combine with different partners to activate other pathways, Ebi3 could pair with p19 to form IL-39.[25] In a mouse model of lupus, IL-39 drives inflammation, including neutrophil activation,[26] and although a native human IL-39 has not been identified, the subunits are both elevated in psoriasis cells (unpublished data). Moreover, p40 can pair with p28 to form IL-Y,[7] which has anti-inflammatory activities; therefore, it is possible that some of the benefits of blocking IL-12 and IL-23 activity could be reduced by downregulating beneficial IL-Y activity. Furthermore, there may be functional plasticity in the Th17 lineage, such that removal of IL-23 from pathogenic T cells can convert them to non-pathogenic, regulatory T cells.[27] Any or all of these effects may play a role and require further investigation. In summary, although molecular data have shown very clear differential effects of guselkumab and ustekinumab on the transcriptome of psoriasis-associated cells, other potential cytokine activities in psoriasis still require full characterisation.

Disease Modification in Psoriasis: Fantasy or Reality?

Doctor Curdin Conrad

In patients with psoriasis receiving anti-IL-23 treatment, a positive response to continuous treatment can be very long-lasting. A high rate of freedom from disease has been seen with continuous guselkumab treatment in the Phase III VOYAGE studies[8,12] and with risankizumab in a Phase II study.[28] This clinical benefit is beyond that anticipated based on the half-life of the drugs and raises the possibility that, by some mechanism, a form of disease modification has resulted from treatment. Such a mechanism may involve activated T cell migration to the lymph nodes, where they perform a central memory function and/or reside in the skin for a long period. As noted, evidence for the latter originates from disease memory in clinically healed skin, which shows relatively high levels of IL-17-producing T cells.[29] It has been proposed that, following successful treatment, the *in situ* activation of epidermal T cells resident in psoriatic skin can lead to IL-17A production, resulting in recruitment of further inflammatory T cells from the blood and subsequent clinical relapse.[12] This suggests that, to have any long-term disease-modifying effect, skin-resident memory T cells should be targeted.

In psoriasis, Th17 and Tc17 cells coproduce IL-17A and other cytokines, with their expansion dependent on IL-23.[30,31] The physiological function of these cells is thought to be protection from extracellular pathogen attack (Figure 1); however, overexpression in autoimmune disease is also common.[30] It is clear that to achieve a response to psoriasis treatment, a reduction of IL-17 levels is necessary,[32] and with the array of targeted agents available (e.g., TNF inhibitors, IL-12/23 or IL-23 inhibitors, IL-17A or IL-17R inhibitors) there are many methods to achieve this. Relapse following discontinuation of IL-17R blockade generally occurs within a few weeks,[33] suggesting that blockade of IL-17 rather than its receptor may be a more efficacious long-term approach. In Crohn's disease, in which IL-17 is highly expressed, expectations for anti-IL-17 treatment were not fulfilled; indeed, cases of aggravated IBD following anti-IL-17 treatment were observed.[30,34] One explanation for this is the existence of two types of IL-17-producing cells: pathogenic Th17 cells and non-pathogenic Th17 cells that also produce IL-10 (which also provide a beneficial barrier and pathogen defence function) independent of IL-23 signalling.[35] Only the former are blocked by IL-23 targeting.

How can we effectively assess the effects on IL-17 and IL-22-producing skin-resident memory T cells present in non-lesional tissue? Following treatment discontinuation, psoriasis tends to revert to its baseline severity.[11] In a recent study of secukinumab treatment discontinuation, gene expression analysis of non-lesional skin in patients who did not relapse showed a robust, durable effect 1 year after stopping therapy.[36] This may be due to the removal of memory T cells from non-lesional skin. From hypotheses

about any long-term effects on these cells, it has been suggested that targeting IL-23 may be beneficial in preventing Th17/Tc17 cells from becoming pathogenic. In addition, single nucleotide polymorphisms in *IL-23R* are associated with autoimmune disease, including psoriasis, and IL-23R is preferentially expressed in these skin cells in psoriasis patients. Possibilities for purging memory T cells include antibody-dependent cell-mediated cytotoxicity or lack of stimulus through IL-23R, though evidence for any of the available drugs exerting either mechanism in non-lesional skin is lacking. In conclusion, multiple observations suggest disease modification in patients with psoriasis receiving anti-IL-23 treatment: a clinical effect beyond drug half-life and biological half-life of the treatment, possible effects on skin-resident memory T cells that mediate disease memory, and the effect of blocking only pathogenic (not non-pathogenic) Th17 cells.

WATCH THE FULL SYMPOSIUM ONLINE ←

https://www.youtube.com/watch?v=jW9kpRu4ccI

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Emerging Insights in the Treatment of Psoriasis and Psoriatic Arthritis

These posters were presented at the 5th World Psoriasis & Psoriatic Arthritis Conference 2018, held from 27th–30th June in Stockholm, Sweden

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Overview

Guselkumab is a monoclonal antibody targeting IL-23 that is approved for the treatment of patients with moderate-to-severe plaque psoriasis. Two of the posters reviewed in this article provide new insights into the clinical efficacy of guselkumab in patients with plaque psoriasis from the VOYAGE trials, firstly among those previously failing to respond to adalimumab and secondly in the setting of drug withdrawal and subsequent retreatment. In addition, data from a study reporting 56-week results from a Phase IIa study exploring the efficacy and safety of guselkumab in patients with psoriatic arthritis (PsA) are reviewed. The article concludes with a summary of the results of a survey highlighting the potential importance of evaluating gastrointestinal (GI) signs and symptoms during the management of patients with psoriasis.

Clinical Response After Guselkumab Treatment Among Adalimumab PASI 90 Non-Responders: Results from the VOYAGE 1 and 2 Trials (Poster P042)

Professor Christopher E.M. Griffiths

Guselkumab is a fully human monoclonal antibody that selectively binds to the p19 subunit of IL-23, thereby inhibiting interaction with the IL-23 receptor and preventing downstream release of proinflammatory mediators.[1,2] Guselkumab is approved in the USA and Europe for the treatment of adults with moderate-to-severe plaque psoriasis.[1,2] The pivotal clinical trial programme for guselkumab in patients with plaque psoriasis included two Phase III, double-blind, placebo and adalimumab-controlled studies, VOYAGE 1 and 2.[3,4] The analysis presented in this article was conducted to evaluate clinical response and patient-reported outcomes among those patients who initially received adalimumab and failed to achieve Psoriasis Area Severity Index (PASI) 90 responses in VOYAGE 1 and 2 and were subsequently switched to guselkumab. In addition, the safety of the crossover to guselkumab was explored.

As this analysis focussed on the patients in VOYAGE 1 and 2 who were initially randomised to adalimumab, those initially randomised to placebo or guselkumab are not discussed herein.

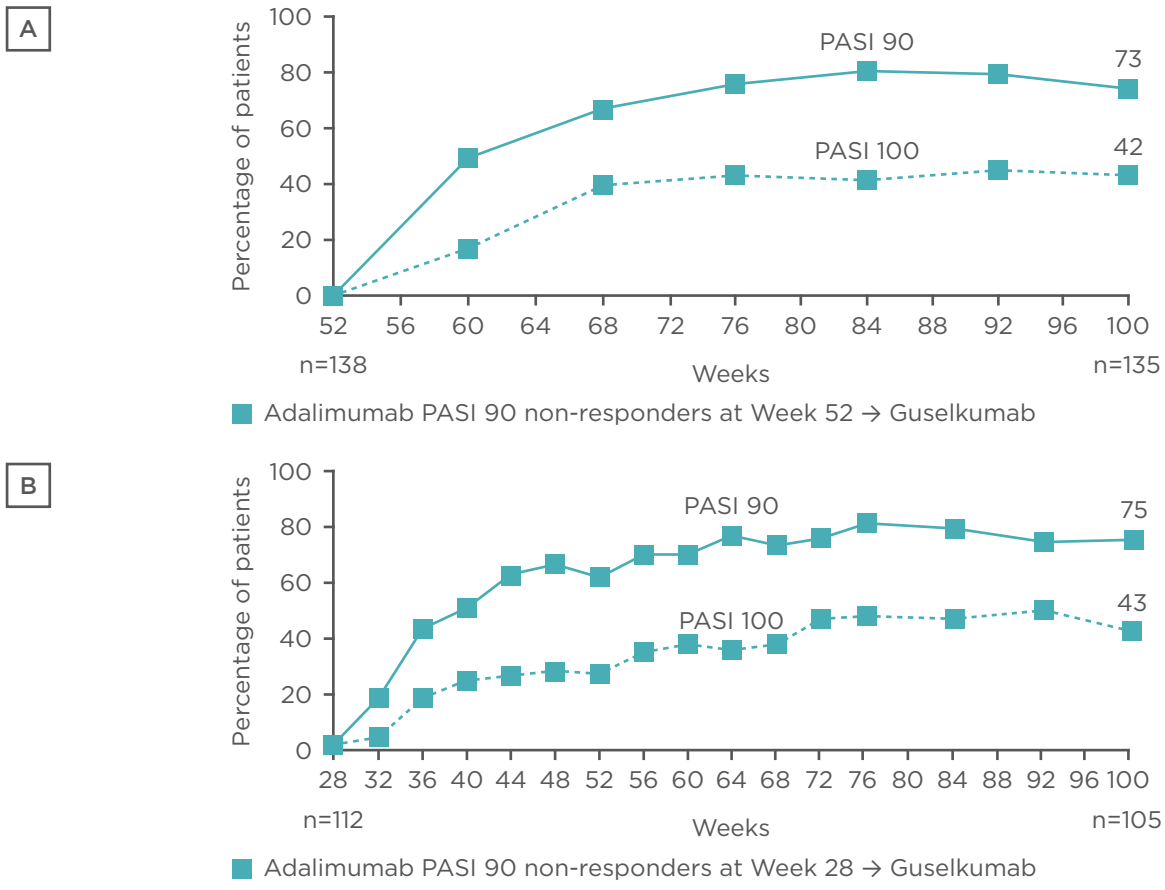

Figure 1: Proportion of PASI 90 and 100 responders among adalimumab PASI 90 non-responders who crossed over to guselkumab at Week 52 in VOYAGE 1 (A) and at Week 28 in VOYAGE 2 (B).

Analyses were performed using non-responder imputation through to Week 72 for Figure 1B and using observed data after applying treatment failure rules for Figure 1A and for Week 76–100 for Figure 1B.

PASI: Psoriasis Area Severity Index; →: crossover.

In VOYAGE 1, 334 patients were initially randomised to adalimumab 80 mg subcutaneously at Week 0, followed by 40 mg at Week 1 and 40 mg every 2 weeks thereafter through to Week 47.[3] All adalimumab-treated patients switched to guselkumab 100 mg at Week 52 and continued to receive guselkumab every 8 weeks until Week 100. The present analysis focussed on the 138 adalimumab-treated patients who were PASI 90 non-responders at Week 52. A similar initial adalimumab treatment regimen was used in VOYAGE 2 (n=248),[4] with the exception that patients were switched to guselkumab 100 mg at Week 28. Patients subsequently received a second guselkumab dose at Week 32 and then every 8 weeks until Week 100. In VOYAGE 2, 112 adalimumab-treated patients were PASI 90 non-responders at Week 28 and were included in this analysis.

The results of the analysis revealed a robust clinical response associated with switching to guselkumab among adalimumab-treated patients who had initially failed to achieve PASI 90 at Week 52 and 28 in VOYAGE 1 and 2, respectively. At Week 100, after ~1 year of guselkumab treatment following adalimumab non-response, 73% and 42% of patients achieved a PASI 90 and 100 response, respectively, in the VOYAGE 1 trial (Figure 1A). Similarly, in VOYAGE 2, 75% and 43% of adalimumab non-responders had PASI 90 and 100 responses at Week 100, respectively, ~1.5 years after switching to guselkumab (Figure 1B).[4] Improvements were also noted in the proportion of patients achieving an Investigator's Global Assessment (IGA) score of 0 or 1 (cleared or minimal) after crossing over to guselkumab. By Week 100, 79% and 81% of adalimumab PASI 90 non-responders who switched to guselkumab had achieved IGA scores of 0 or 1 in VOYAGE 1 and 2, respectively.

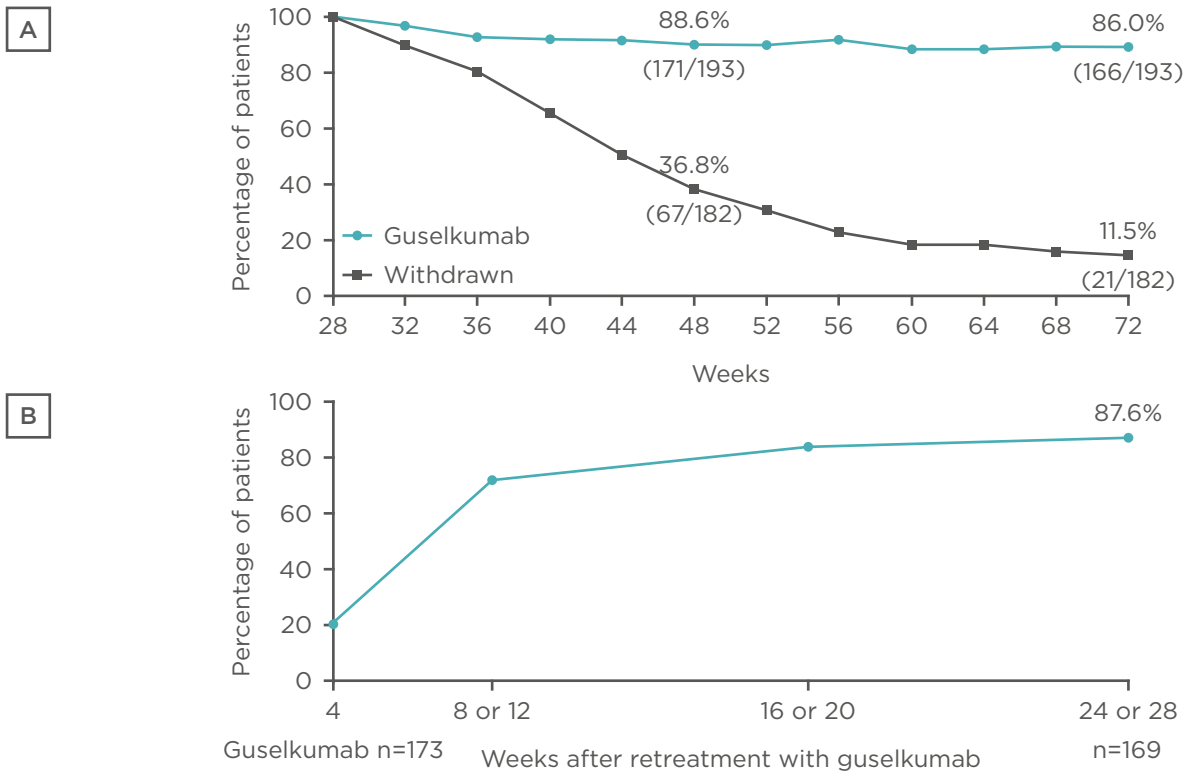

Figure 2: A) PASI 90 response among patients who were originally randomised to guselkumab, achieved a PASI 90 response at Week 28, and were subsequently randomised to withdrawal or continued guselkumab. B) Recapture of PASI 90 response following retreatment with guselkumab among patients randomised to withdrawal at Week 28.

Analysis performed with non-responder imputation for Figure 2A.

PASI: Psoriasis Area Severity Index.

To further explore the impact of switching from adalimumab to guselkumab on patients, effects on health-related quality of life were analysed using the Dermatology Life Quality Index (DLQI) Score and patient-reported psoriasis symptoms and signs were assessed using the Psoriasis Signs and Symptoms Diary (PSSD). Adalimumab PASI 90 non-responders who switched to guselkumab achieved improvements in DLQI in both VOYAGE 1 and 2; the proportion of patients achieving DLQI scores of 0 or 1 increased from 25% to 75% from Week 48 to 100 in VOYAGE 1 and from 14% to 65% from Week 28 to 100 in VOYAGE 2. Improvements were also observed in the proportions of adalimumab PASI 90 non-responders achieving PSSD symptoms or signs scores of 0 following crossover to guselkumab. By Week 100 in VOYAGE 1, 33% of patients had achieved a PSSD symptom score of 0 and 19% had achieved a PSSD sign score of 0. In VOYAGE 2, 33% and 18% of patients achieved PSSD symptom and sign scores of 0, respectively.

No new safety signals were observed following crossover to guselkumab in adalimumab-treated patients, with the safety profile consistent with the overall guselkumab safety data previously reported from VOYAGE 1 and 2.[5] Among the pooled population of patients in VOYAGE 1 and 2 (data through Week 100), rates of serious adverse events (AE) per 100 patient years in those treated with adalimumab (prior to guselkumab) and in those who crossed over to guselkumab were 7.77 and 4.44, respectively. Similarly, there was no notable elevation in the incidence of AE of interest with crossover to guselkumab: for adalimumab (prior to guselkumab) and adalimumab crossover to guselkumab groups, the incidence rates per 100 patient years were 1.8 and 0.0 for serious infections, respectively, 0.4 and 0.2 for major adverse cardiovascular events, respectively, 0.4 and 0.8 for non-melanoma skin cancer, respectively, and 0.4 in both groups for malignancy excluding non-melanoma skin cancer.

In summary, this analysis of data from the VOYAGE 1 and 2 studies established that, among adalimumab PASI 90 non-responders, switching to guselkumab provided robust levels of clinical response, enhanced health-related quality of life, and improved psoriasis signs and symptoms.

Long-Term Efficacy of Guselkumab Treatment After Drug Withdrawal and Retreatment in Patients with Moderate-to-Severe Plaque Psoriasis: Results from VOYAGE 2 (Poster P049)

Professor Kenneth Gordon

The VOYAGE 2 study[4] was a Phase III, double-blind trial that investigated the efficacy and safety of guselkumab compared with adalimumab in patients with moderate-to-severe psoriasis. Following the initial 28-week active comparator period, the study design of VOYAGE 2 included a withdrawal and retreatment period that explored the comparative clinical efficacy and safety of continued guselkumab therapy versus withdrawal and retreatment upon relapse. Given that discontinuation of biologics, and in some instances retreatment, is a relatively common occurrence in patients with psoriasis,[6] it is important to understand the impact of such events on clinical efficacy and safety. The study presented here reports the long-term results from the withdrawal and retreatment phase of VOYAGE 2.

In VOYAGE 2, 375 patients who were originally randomised to guselkumab 100 mg (at Week 0 and 4, and every 8 weeks thereafter) and achieved PASI 90 response at Week 28 were rerandomised to withdrawal (n=182) or continued guselkumab (n=193).[4] Patients in the withdrawal group initially received placebo but were retreated with guselkumab upon loss of ≥50% of the PASI improvement achieved at Week 28; all patients who did not require retreatment were switched back to guselkumab at the Week 72 timepoint.

Patients who were randomised to receive continuous guselkumab therapy following a PASI 90 response at Week 28 typically maintained PASI 90 responses, with a PASI 90 response rate of 86% observed at Week 72 (Figure 2A). In contrast, PASI 90 response rates gradually declined in the group randomised to withdrawal following initial guselkumab PASI 90 response at Week 28, by Week 48, 37% of

patients in the withdrawal group had PASI 90 response, and only 12% maintained PASI 90 response at Week 72. Among those patients in the withdrawal group who were retreated with guselkumab following loss of ≥50% of the PASI improvement achieved at Week 28, PASI 90 responses were recaptured in 88% of patients within 6 months of starting retreatment (Figure 2B).

The observed maintenance of PASI 90 response at Week 48 among approximately one-third of patients withdrawn from guselkumab in VOYAGE 2 has previously been reported to be associated with sustained suppression of serum cytokines, including IL-17A, IL-17F, and IL-22.[7] Conversely, loss of response (PASI <75) is associated with increases in serum levels of these cytokines.[7] For example, in those with loss of response, serum levels of IL-17A were significantly elevated from Week 28 levels (the time of withdrawal) at Week 40, 44, and 48 ($p<0.01$), and were significantly greater at Week 44 and 48 than the levels seen in those with maintained responses ($p<0.05$).

In addition to PASI response, the present study incorporated assessment of the effects of guselkumab withdrawal (and subsequent retreatment as needed) versus maintenance therapy on health-related quality of life using the DLQI score. Among those patients who had a PASI 90 response at Week 28, the proportion of patients achieving DLQI scores of 0 or 1 was maintained in the guselkumab maintenance group from Week 28 (70%) to Week 48 (69%) and increased to 80% by Week 100. In those who were randomised to withdrawal at Week 28, the proportion of patients with DLQI 0 or 1 scores decreased substantially after the switch to placebo, falling from 67% at Week 28 to 32% at Week 48. Retreatment with guselkumab in the withdrawal group led to recapture of the lost DLQI 0 or 1 response, with 68% of patients in the withdrawal group acheving DLQI 0 or 1 scores by the Week 100 timepoint. All withdrawal group patients reverted to guselkumab from Week 72 onwards.

In terms of safety and tolerability, no safety signals were observed with withdrawal and retreatment with guselkumab. The incidence of AE from Week 28–72 was similar in both the continued guselkumab and withdrawal groups, with 61% and 59% of patients per group experiencing ≥1 AE, respectively. Incidences of infections were similar in both maintenance and withdrawal groups (41% of patients in both) from Week 28–72, and there were no cases of tuberculosis, opportunistic infection, or serious hypersensitivity reactions. In those patients who were withdrawn from guselkumab, prior to retreatment with guselkumab there were two events of psoriasis rebound (≥125% increase in PASI score from baseline at any time during withdrawal) and no AE related to other forms of psoriasis.

In conclusion, the results of this long-term assessment of the efficacy of guselkumab treatment after withdrawal and retreatment following response at Week 28 provide several insights into guselkumab-based therapy. Firstly, the analysis demonstrated that continued treatment with guselkumab following PASI 90 response is associated with superior efficacy compared with treatment interruption, in terms of both maintenance of PASI 90 response over time and sustaining improvements in health-related quality of life. In contrast, guselkumab withdrawal leads to gradual declines in both of these variables. Maintenance of PASI 90 response after drug withdrawal was associated with continued suppression of IL-17A, IL-17F, and IL-22. Retreatment with 6 months' guselkumab after withdrawal led to the recapture of PASI 90 response in the majority of patients, and there were no safety concerns identified among those initially withdrawn and subsequently retreated.

Efficacy and Safety Results of Guselkumab in Patients with Active Psoriatic Arthritis over 56 Weeks (Poster P119)

Professor Wolf-Henning Boehncke

Guselkumab is approved for the treatment of moderate-to-severe plaque psoriasis[1,2] and is currently being evaluated in patients with PsA. PsA is a common comorbidity that has been estimated to affect approximately one in five patients with psoriasis,[8] and significantly impairs patients' physical function and ability to

work.[9] This poster describes the results from a randomised, double-blind, placebo-controlled, Phase IIa trial of guselkumab in PsA through Week 56.[10]

Eligible patients for this study included adults with active PsA, ≥3 tender and ≥3 swollen joint counts, and ≥3% body surface area affected by plaque psoriasis. In addition, patients were required to have previously experienced an inadequate response to current standard-of-care treatment, including non-biologic disease-modifying antirheumatic drugs, oral corticosteroids, or non-steroidal anti-inflammatory drugs. Prior exposure to an anti-TNF agent was permitted but limited to 20% of the enrolled population. Eligible patients were randomised 2:1 to receive guselkumab 100 mg subcutaneously or placebo at Week 0, 4, and every 8 weeks thereafter, until Week 44. Patients were subsequently followed-up until Week 56. At Week 16, those patients who achieved <5% improvement from baseline in swollen and tender joint counts were able to switch to open-label ustekinumab. The placebo-controlled period ended at Week 24, at which point placebo-treated patients were switched to guselkumab therapy until Week 44.

In total, 149 patients were randomised, with 49 receiving placebo and 100 receiving guselkumab. Baseline demographics and American College of Rheumatology (ACR) component measures were generally similar between the two groups. Twenty-seven patients switched to ustekinumab at Week 16 (placebo group: n=17; guselkumab group: n=10). Among those initially randomised to guselkumab, 84 patients completed the 56-week study. Twenty-nine patients randomised to placebo switched to guselkumab at Week 24, of whom 28 completed the remainder of the study.

The proportion of patients achieving a 20% improvement in ACR criteria (ACR 20) at Week 24 (the primary endpoint) was significantly greater with guselkumab (58% of patients) compared with placebo (18.4%; p<0.001). Significantly greater ACR 20 response rates were observed with guselkumab versus placebo at the first assessment timepoint (Week 4; p<0.001) and were sustained throughout the 24-week placebo-controlled period (p<0.05 to p<0.001). Among the group continuing guselkumab therapy after Week 24, ACR 20 responses rates were maintained, with 61% of patients achieving ACR 20 at Week 56. In addition, guselkumab therapy was associated with significantly greater response rates than placebo in terms of ACR 50 (34% versus 10%, respectively; p=0.002) and ACR 70 (14% versus 2%, respectively; p=0.023 [post-hoc analysis]) at Week 24, with response rates maintained to Week 56.

Improvements in ACR criteria with guselkumab were complemented by reductions in the severity of psoriasis, with significantly greater PASI 75, 90, and 100 response rates with guselkumab versus placebo at Week 24 (all p<0.001). In addition, the proportions of patients with unresolved enthesitis or dactylitis were significantly reduced in the guselkumab group versus placebo at Week 24 (p<0.05). Patient-reported health-related quality of life measures were significantly improved with guselkumab relative to placebo at Week 24, including when assessed via the Health Assessment Questionnaire (HAQ-DI) and the 36-item Short Form Health Survey (SF-36) physical and mental component scores (all p<0.01). At Week 24, a significantly greater proportion of patients achieved minimal disease activity with guselkumab than placebo (23% versus 2%, respectively; p=0.001). PASI response rates, enthesitis and dactylitis resolution rates, health-related quality of life scores, and minimal disease activity rate were generally well maintained to the end of the study with continued guselkumab therapy.

Guselkumab was well-tolerated over the 56-week study, with no injection site reactions reported among the 750 guselkumab injections administered. Through Week 24, incidences of AE and infections were comparable between the guselkumab and placebo groups (AE: 36% and 33%, respectively; infections: 16% and 20%, respectively). Longer guselkumab exposure through Week 56 did not lead to a disproportionate increase in the incidence of AE or infections. Serious AE were reported by six patients (6.0%) through Week 56 in the guselkumab group and two patients (2.0%) discontinued due to AE (leukopenia/neutropenia and pneumonia, respectively). A single malignancy (basal cell carcinoma) was reported by one patient (0.8%) who received

guselkumab. Neutropenia was reported in four guselkumab-treated patients through Week 24 (three cases of Common Terminology Criteria for Adverse Events [CTCAE] Grade 2, which resolved spontaneously, and one case of CTCAE Grade 3, in whom guselkumab was discontinued and neutropenia resolved without treatment). There were no infections reported in the patients developing neutropenia, and no additional cases with Grade ≥2 occurred after Week 24. Increases in alanine transaminase/aspartate transaminase were generally comparable between guselkumab and placebo groups. There were no deaths, opportunistic infections, cases of active tuberculosis, or anaphylactic reactions.

In summary, the study demonstrated significant improvements in joint symptoms, physical function, psoriasis, enthesitis, dactylitis, and quality of life with guselkumab in patients with active PsA, with efficacy well-maintained through Week 56. Furthermore, guselkumab was well tolerated over the course of approximately 1 year of exposure.

Gastrointestinal Symptoms are Common in U.S. Patients with Moderate-to-Severe Psoriasis (Poster P112)

Professor Steven Feldman

Patients with plaque psoriasis are at increased risk of developing inflammatory bowel disease (IBD), with the risk increasing with higher degrees of psoriasis severity.[11] Such concordance in disease incidence may arise from shared genetic susceptibilities and common inflammatory pathogenic pathways.[12] Understanding the frequency of GI symptoms in patients with psoriasis is important, as the presence of GI disease could impact which treatments are chosen. This survey study was conducted to evaluate the prevalence of GI signs and symptoms among patients with plaque psoriasis.

An electronic survey was undertaken in the USA using an online opt-in patient panel/database, with data collected from January 2017 to February 2017. Patients with self-reported moderate-to-severe plaque psoriasis and healthy controls were eligible for inclusion in the survey, with psoriasis patients categorised into two subgroups: those with recent (within 4 months) exposure to biologic therapy (the PsO^{RT} group) and those without such exposure (the PsO group). Patients were evaluated for GI signs and symptoms consistent with IBD, and the frequency and severity of such symptoms were compared across groups. Patients with a diagnosis of IBD, irritable bowel syndrome, or other GI disorders with symptoms overlapping with IBD were excluded from the analysis. To further explore the impact of psoriasis on IBD risk, CalproQuest scores were calculated; CalproQuest scores have recently been proposed as a potential tool for identifying patients who have elevated faecal calprotectin levels and increased risk of IBD.[13] The CalproQuest score is calculated from an IBD symptom questionnaire consisting of eight criteria (e.g., 'Does the patient report a bloody stool?'), with results considered positive if ≥2 major criteria, or one major and two minor criteria, are met.[13]

In total, 915 patients with self-reported moderate-to-severe plaque psoriasis (450 of whom had recent biologic exposure) were enrolled in the survey, along with 1,411 healthy controls. Demographics were broadly comparable between groups, although patients in the plaque psoriasis cohort were on average younger than those in the healthy control group. Among those with psoriasis, almost all patients had a disease duration >1 year, and 39% and 21% reported having had psoriasis for >10 years in the PsO and PsO^{RT} groups, respectively. Substantially more patients in the PsO^{RT} group (35%) had been hospitalised within the last year for psoriasis versus the PsO group (3% of patients).

GI signs and symptoms were more common among those in the PsO and PsO^{RT} groups compared with healthy controls for all variables assessed, including stomach pain, feeling full or bloated, diarrhoea, mucus in the stool, and blood in the stool (Table 1). A significantly lower incidence of stomach pain, a full or bloated sensation, and diarrhoea were reported in those without versus with recent exposure to biologic. Incidences of mucus or blood in the stool were numerically, but not significantly, lower among PsO versus PsO^{RT} patients.

Table 1: Gastrointestinal signs and symptoms among patients with psoriasis and healthy controls.

	PsO	PsO^{RT}	HC
Number of patients, n	465	450	1,411
GI signs and symptoms			
Stomach pain	20.6% p=0.002 vs. HC p=0.002 vs. PsO^{RT}	36.9% p=0.002 vs. HC	10.5%
Full or bloated	37.2% p=0.002 vs. HC p=0.002 vs. PsO^{RT}	48.4% p=0.002 vs. HC	25.3%
Diarrhoea	16.3% p=0.023 vs. HC p=0.002 vs. PsO^{RT}	29.3% p=0.002 vs. HC	12.2%
Mucus in stool	4.5% p=0.020 vs. HC p=0.317 vs. PsO^{RT}	6.0% p=0.002 vs. HC	2.4%
Blood in stool	4.3% p=0.004 vs. HC p=0.390 vs. PsO^{RT}	5.6% p=0.002 vs. HC	1.9%

*Within last 4 months.

GI: gastrointestinal; HC: healthy controls; PsO: psoriasis patients without recent biologic exposure; PsORT: psoriasis patients with recent biologic exposure.

Calculation of CalproQuest scores indicated a significantly greater proportion of patients with a positive CalproQuest result among the PsO group (10%) versus the healthy controls (6%; p=0.005). The greatest incidence of positive CalproQuest scores occurred among the PsO^{RT} group, with positive results for one in five patients (20%; p=0.002 versus both the PsO and healthy volunteer groups).

Although the cause of higher frequency of GI symptoms in those with recent biologic exposure was not assessed, one possible explanation is that patients with recent biologic exposure may have worse psoriasis, and that worse psoriasis has a greater association with IBD. Another possibility is that some agents used to treat moderate-to-severe psoriasis are associated with increased risk of IBD (in particular, IL-17 blockers) or simply GI intolerance (apremilast).

In summary, the present survey highlights that GI signs and symptoms are common in patients with moderate-to-severe plaque psoriasis, and occur at a higher incidence than seen in healthy controls. As such, it is important for healthcare professionals involved in the care of patients with psoriasis to consider assessing and monitoring GI signs and symptoms to identify patients who may be at risk of developing IBD.

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Efficacy, Sustainability, and Patient-Reported Outcomes of Guselkumab to Treat Plaque Psoriasis in the Post-Approval Setting

These posters were presented at the 27th European Academy of Dermatology and Venereology (EADV) Congress, held from 12th–16th September in Paris, France

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Overview

Plaque psoriasis is an autoimmune condition characterised by the development of red, dry, scaly skin lesions that cause irritation and pain for patients. It is a disabling and disfiguring condition and, alongside the physical effects, is associated with psychological comorbidities, including anxiety and depression.[1] Combined effects of the condition are known to affect productivity at work, with increased rates of absenteeism.

Novel targeted therapies have the potential to transform treatment in this field. Adalimumab is a monoclonal antibody that inhibits TNF and has been approved in Europe since 2007 for the treatment of patients with moderate-to-severe chronic plaque psoriasis who are eligible for systemic therapy or phototherapy. Guselkumab is a novel IL-23-blocking monoclonal antibody that has been approved for use in the same indication as adalimumab in Europe since 2017. Personalised treatment is becoming more common and the delivery of therapeutics is a changing landscape, with a shift towards patients administering their own medication through novel devices.

This article reviews four posters displayed at the European Academy of Dermatology and Venereology (EADV) Congress 2018 that present results demonstrating the efficacy of guselkumab compared to adalimumab for the treatment of psoriasis, as measured by a range of outcomes, a favourable drug delivery system, and a higher drug survival rate overall.

Drug Survival is Superior Among Patients Treated with Guselkumab Compared to Adalimumab in the VOYAGE 1 Trial (Poster P1937)

Doctor David Pariser

Drug survival, defined as the probability that a patient will remain on a given therapy, is an important measure of the success of a therapeutic, especially in chronic conditions. Drug survival demonstrates the long-term tolerability and efficacy of an agent indicated in a condition and can show favourability over other therapies in head-to-head trials to measure treatment sustainability.

A post-hoc analysis of data collected in the VOYAGE 1 study was carried out to determine drug survival of guselkumab compared with the active comparator adalimumab.[2] In VOYAGE 1, patients were randomised 1:1 to guselkumab (n=329) or adalimumab (n=334). Baseline demographic characteristics were comparable between the groups. Primary analyses of discontinuation for any reason up to 48 weeks of treatment were performed. Specific reasons for discontinuation were tabulated and a comparison of demographic and disease characteristics of patients discontinuing each treatment was carried out. Kaplan–Meier plots were produced to compare drug survival of guselkumab and adalimumab. The hazard ratio for risk of discontinuation of guselkumab versus adalimumab was calculated using Cox modelling. Secondary analyses were carried out, including evaluation of worsening disease or lack of treatment efficacy and adverse events.

Primary analyses compared baseline demographic characteristics of patients discontinuing the study drug. In the adalimumab group, patients discontinuing treatment had a higher median baseline body weight than those in the guselkumab arm (97.7 kg versus 84.9 kg, respectively). Other demographic and disease characteristics were comparable between discontinuing patients in both groups. Higher body weight has been associated with lower efficacy for a number of biologic agents, and this association has been reported to be more pronounced for adalimumab compared with guselkumab.[2] This may be reflective of differences in immunogenicity or other factors affecting the serum levels of each drug and, therefore, its biologic availability and efficacy.

Guselkumab showed a superior drug survival rate compared with adalimumab at 48 weeks of treatment. Fifty-two (15.6%) patients in the adalimumab group discontinued the agent for any reason, compared with 28 (8.5%) patients in the guselkumab group. This difference in failure rate was statistically significant (p=0.0053) and the hazard ratio of 1.88 for discontinuing adalimumab versus guselkumab (95% confidence interval [CI]: 1.19–2.98; p=0.0070) was also statistically significant. It was suggested that the greater efficacy seen with guselkumab largely accounted for its superior drug survival compared with adalimumab.

Secondary analyses revealed that lack of efficacy or worsening of psoriasis was the most frequent reason for cessation of adalimumab, with 17 (5.1%) patients discontinuing as a result, compared to 3 (0.9%) patients in the guselkumab group (hazard ratio: 5.714 [95% CI: 1.675–19.500; Cox model p=0.0054]). For patients discontinuing treatment for reasons other than lack of efficacy or worsening psoriasis, drug survival was similar in the two groups; guselkumab had a survival rate of 97.0% compared to 98.2% with adalimumab (p=0.2790).

Overall, drug survival was superior for the guselkumab group compared with the adalimumab group at Week 48 in the VOYAGE 1 study. Drug survival can be assessed using data from clinical trials with an active comparator arm, as is the case in this analysis, but it should be noted that analysis of real-world data from drug registries in the post-approval setting is required to confirm these conclusions.

Association Between Improvements in Patient-Reported Outcomes and Absolute Psoriasis Area Severity Index Score: Results from VOYAGE 2 (Poster P1944)

Professor Stephen Tyring

VOYAGE 2, a double-blind, placebo and active comparator-controlled study, investigated

the association between changes in patient-reported outcomes (PRO) and Psoriasis Area Severity Index (PASI) scores in patients with moderate-to-severe plaque psoriasis.[3] A number of PRO measures were used to assess health-related quality of life (HRQoL).

Patients (N=992) were randomised 2:1:1 to one of three treatment groups, receiving either 100 mg guselkumab via subcutaneous injection at Weeks 0, 4, 12, and 20 (n=496); placebo at Weeks 0, 4, and 12, followed by 100 mg guselkumab via subcutaneous injection at Weeks 16 and 20 (n=248); or adalimumab via subcutaneous injection, 80 mg at Week 0, 40 mg at Week 1, and then 40 mg every 2 weeks through to Week 23 (n=248). PRO measures were assessed using three questionnaires and results were stratified by five thresholds, defined according to absolute PASI score: 0, >0–<1, ≥1–≤3, >3–≤5, and >5.

The Dermatology Life Quality Index (DLQI) assesses HRQoL with 10 dermatologic disease-specific questions, producing a combined total score from 0–30. A score <1 indicates no impact of disease on a patient's daily QoL. In VOYAGE 2, there was a statistically significant association between lower PASI scores and proportions of patients with a DLQI score of 0 or 1 at Weeks 16 and 24 ($p<0.0001$ for both timepoints).

The Hospital Anxiety and Depression Scale (HADS) has two subscales, one for anxiety and one for depression, each producing a score ranging from 0–32. A score <8 on each respective subscale indicates no anxiety or depression. Both anxiety and depression scores correlated with PASI score in VOYAGE 2. For example, associations between HADS anxiety score at both Week 16 ($r=0.20$) and Week 24 ($r=0.16$) were statistically significant ($p<0.0001$ for both). Similarly, a statistically significant correlation between HADS depression score and PASI score was found at both Week 16 ($r=0.27$) and Week 24 ($r=0.22$) ($p=<0.0001$ for both).

Finally, the Medical Outcomes Study 36-Item Short Form (SF-36) derives mental and physical component summary scores, ranging from 0–100, from eight multi-item scales. A score ≥50 is indicative of normal HRQoL. Mental component scores ≥50 were significantly correlated with lower PASI scores at both Week 16 ($r=0.29$) and Week 24 ($r=0.25$) ($p<0.0001$ for both). Scores ≥50 in the physical component also showed a relationship with PASI assessment at Week 16 ($r=0.40$) and Week 24 ($r=0.30$) ($p<0.0001$ for both).

Improvement in absolute PASI score was strongly associated with improvement in HRQoL in all PRO measures that were investigated, showing statistically significant correlations in every measure used.

Association of Absenteeism and Presenteeism with Anxiety and Depression in Patients with Moderate-to-Severe Psoriasis and Improvement After Treatment: Results from the VOYAGE 2 Trial (Poster P1921)

Doctor Kristian Reich

Analysis of the effect of psoriasis on productivity, absenteeism, and presenteeism was also carried out using data from the VOYAGE 2 study.[4] Alongside physical manifestations of the condition, psoriasis is associated with psychological comorbidities and either or both can affect productivity, absenteeism, and presenteeism. The methodology of VOYAGE 2 up to Week 24 is described in the previous section. At Week 28, patients receiving guselkumab 100 mg subcutaneous injection at Weeks 0, 4, 12, and 20 who achieved ≥90% improvement in PASI were re-randomised to guselkumab 100 mg every 8 weeks or placebo. Responding patients who received placebo at Weeks 0, 4, and 12 and guselkumab 100 mg subcutaneous injection at Weeks 16 and 20 received placebo at Week 28; non-responders in this group continued guselkumab treatment. Patients who had been receiving treatment with adalimumab subcutaneous injections were given placebo at Week 28 if they had responded to treatment or crossed to guselkumab therapy. One hundred and ninety-three patients were randomised to guselkumab at Week 28. In all groups, patients received guselkumab upon loss of response on placebo.

Absenteeism and presenteeism data through to Week 48 of the study were presented. Absenteeism was reported using the DLQI question: 'Over the last week, has your skin prevented you from working or studying? [Yes=3]. If No, how much has your skin been a problem at work or at school? [A lot=2, A little=1, Not at all=0].' A score for presenteeism was derived from responses to the following domain from the Work Limitations Questionnaire: time management, physical demands, mental–interpersonal demands, and output demands. HADS responses were used to evaluate the impact of depression and anxiety on productivity.

At baseline in all treatment arms, 22.9% of study participants reported that their skin had prevented them from working or studying, according to their response to the DLQI question; patients who had anxiety or depression at baseline were more likely to report this outcome (43.2%) than those who did not (17.1%). Patients in active employment had HADS scores that correlated with productivity evaluation based on their responses to the Work Limitations Questionnaire domains (HADS anxiety: r=0.59; HADS depression: r=0.64; p<0.001 for both).

Guselkumab was shown to be an effective treatment in terms of work-related disease impact. At Week 24, 82% of patients treated with guselkumab who had scored 3 on the DLQI domain question at baseline now reported a score of 0, compared to 50% of patients treated with adalimumab (p<0.001). With further follow-up to Week 48, 83% of guselkumab patients had reduced their DLQI score from 3 at baseline to 0. Patients who were randomised to guselkumab treatment at Week 28 showed an improvement in absenteeism and presenteeism up to Week 48.

The improvement in presenteeism at Week 24 was significantly greater in the guselkumab group compared to the adalimumab group, in three out of the four domains. The mean percentage improvements for guselkumab and adalimumab, respectively, were 38% versus 21% in physical demands, 42% versus 22% in mental–interpersonal demands, and 40% versus 16% in output demands. A sustained improvement in presenteeism was seen at longer-term follow-up at Week 48. Mean improvements from baseline were 46% in physical demands, 37% in time management, 49% in mental–interpersonal demands, and 49% in output demands.

Guselkumab demonstrated an advantage over adalimumab in patients both with and without anxiety and depression when measured by the DLQI domain absenteeism question. In patients treated with guselkumab, 73.5% of study participants with anxiety or depression who scored 3 on the DLQI assessment at baseline reported a score of 0 at Week 24, compared to 38.7% of patients treated with adalimumab (p=0.002). For patients without depression or anxiety, 88.9% of patients scoring 3 in the DLQI assessment at baseline had improved to a score of 0 at Week 24 when treated with guselkumab, compared to 64.0% of patients treated with adalimumab (p=0.006). The odds ratio for patients treated with guselkumab achieving a score of 0 on the DLQI assessment at Week 24 was 2.85 (95% CI: 1.83–4.46) compared to patients receiving adalimumab (p<0.0001).

In conclusion, anxiety and depression have significant impacts on productivity at work, affecting absenteeism rates, productivity, and presenteeism in patients with moderate-to-severe psoriasis. Treatment with guselkumab demonstrated significantly better outcomes for patients in absenteeism and presenteeism domains compared to treatment with adalimumab.

Evaluation of the Usability and Acceptability of a Novel, Patient-Controlled Injection Device for the Treatment of Moderate-to-Severe Psoriasis: Results from the Phase III ORION Study (Poster P1898)

Doctor Laura Ferris

The Phase III ORION study is a multicentre, randomised, double-blind, placebo-controlled study of guselkumab in patients with moderate-to-severe psoriasis. At baseline, 78 patients were randomised to placebo (n=16) or guselkumab (n=62).[5] All study agents were administered

using a manually-operated, patient-controlled, disposable device that delivered the contents of a pre-filled syringe via subcutaneous injection. The device included an automatically locking safety guard to shield the needle and prevent accidental needle stick injury. This poster presented results of patient-reported satisfaction with the self-injection device, including its ease of use and their experience of psoriasis after initiating treatment delivered in this way, along with assessment of correct use of the device by an objective observer.

Objective usability of the device was assessed at Week 0 through a three-step Observer Injection Checklist that reported on the patients' removal of the device cap, positioning of the device, and completion of the injection. Patient-rated acceptability was assessed post-injection at Weeks 0, 4, and 12 using a Self-Injection Assessment Questionnaire (SIAQ) consisting of six domains (feeling about self-injections, self-image, self-confidence, pain and skin reactions during or after injections, ease of use of the injection device, and satisfaction with self-injection) (Table 1). The domains 'feeling about self-injection,' 'self-confidence,' and 'satisfaction with self-injection' were also scored pre-injection at Week 0. The SIAQ used a semantic Likert-type scoring method and responses were transformed into scores of 0–10 (worst to best). A three-question patient rating system was also used to assess speed of injection, handle design of the device, and ease of identifying completion of the injection.

Patients in both groups were primarily successful in the Observer Injection Checklist assessment for device-related problems associated with the injection at Week 0, with 98.7% (77 out of 78) of patients observed to have successful, problem-free injections. One patient in the guselkumab group used the device improperly. This indicates favourable usability, as assessed objectively.

Scores for the three SIAQ domains assessed prior to the first injection, 'feeling about self-injection,' 'self-confidence,' and 'satisfaction with self-injection,' ranged from 6.59–8.23 and showed a tendency to remain high or increase at assessment post-injection at Week 0 and at Week 12. In the self-confidence domain, mean SIAQ score in the placebo group was 6.35 at Week 0 pre-injection, increasing to 8.21 at Week 12. Patients treated with guselkumab had mean scores of 6.67 at Week 0 pre-injection and 8.48 at Week 12. This indicated an increase in self-confidence over time when using the patient-controlled injection device.

Similarly, SIAQ scores for 'satisfaction with self-injection' increased from pre-injection at Week 0 to Week 12. In the placebo group, the mean score at pre-injection was 6.33, increasing to 9.26 at Week 12, compared to 6.65 and 9.64, respectively, for patients treated with guselkumab.

Table 1: Summary of score changes in six patient-reported Self-Injection Assessment Questionnaire domains measured in the ORION Study.

SIAQ domain	Stable or increase in mean score	
Week 0 (Pre) to Week 12 (Post)	**Guselkumab**	**Placebo**
Feeling about self-injections	✓	×
Self-confidence	✓	✓
Satisfaction with self-injection	✓	✓
Week 0 (Post) to Week 12 (Post)		
Self-image	✓	✓
Pain and skin reactions during or after the injection	✓	✓
Ease of use of the self-injection device	✓	✓

SIAQ: Self-Injection Assessment Questionnaire.

Adapted from Ferris et al.[5]

Mean SIAQ scores for 'feeling about self-injection' decreased from 8.18 at pre-injection (Week 0) to 7.50 at Week 12 in the placebo group and increased slightly from 8.23 to 8.45 in the guselkumab group. Additionally, SIAQ scores only measured post-injection (at Weeks 0, 4, and 23) were favourable across all treatment domains and at all timepoints, suggesting that the patient-controlled delivery device was well-accepted by study participants. Median self-image scores remained at 10 from Week 0 to Week 12 in both placebo and guselkumab groups.

SIAQ reports of pain and skin reactions during or after the injection were relatively uncommon. A median score of 10, indicating no pain or skin reaction at all, was reported at all timepoints throughout the study. Mean scores also remained stable; in the placebo group, the mean score was 9.86 at Week 0, 9.77 at Week 4, and 9.89 at Week 12. In the guselkumab group, these were 9.82, 9.75, and 9.83, respectively, indicating that the injection device was well tolerated by users operating it correctly. SIAQ scores for the ease of use of the self-injection device remained consistent at the three timepoints measured in both groups. For the total study population (N=78), the mean ease of use was 8.81 at Week 0, 9.19 at Week 4, and 9.24 at Week 12.

Following the first injection at Week 0, study participants from across the treatment groups said that the injection device was easy or very easy to use; 94.9% of patients were either satisfied or very satisfied with the current method of medication administration. Results from the three-question patient questionnaire indicated that the injection device was well tolerated and well received by patients. Across both treatment groups (n=75), 97.3% of study participants either agreed or strongly agreed with the statements 'I liked being able to inject the medication at a speed that was comfortable for me' and 'The design of the handle made the device easy to use'; furthermore, 94.7% of patients agreed or strongly agreed that they were able to easily tell when the injection was finished.

Although this study did not compare the use of the self-injection device to other drug delivery systems, the results confirmed that the patient-controlled device was well tolerated and accepted by study participants, who had a favourable experience when using it, and showed an association between using the device and successful, problem-free injections.

Conclusion

Guselkumab has been assessed in the post-approval setting for the treatment of plaque psoriasis and a number of reporting measures, including safety and efficacy, usability, and PRO, have been used to determine its suitability. Guselkumab has been evaluated against adalimumab as a treatment for plaque psoriasis in active comparator studies, with generally favourable outcomes.

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Abstract Reviews

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Facial Lesions: A Dermoscopic Interactive Session

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Disclosure: The author has declared no conflicts of interest.

Keywords: Dermoscopy, face lesions, lentigo maligna (LM), macules, pigmented actinic keratosis (PAK).

Citation: EMJ Dermatol. 2018;6[1]:94-95. Abstract Review No. AR1.

The differential diagnosis of pigmented macules on sun-damaged facial skin is one of the most challenging procedures in daily dermatological practice. The differential diagnosis involves distinguishing between melanocytic skin neoplasms, such as lentigo maligna (LM) and LM melanoma (LMM), and nonmelanocytic skin neoplasms, including pigmented actinic keratosis (PAK), solar lentigo (SL), and lichen planus-like keratosis. A correct differential diagnosis between melanocytic and nonmelanocytic lesions is important to ensure the patient receives the appropriate therapy.

Dermoscopy is a noninvasive technique used in routine diagnostic procedures of pigmented lesions. LM, an *in situ* facial melanoma, has very different dermoscopic features to LMM and shares unspecific dermoscopic criteria with flat nonmelanocytic skin neoplasms. In differentiating between SL and LM, noting the overall colour of the lesion can help in the correct diagnosis: SL is brown-black on dermoscopy whereas LM is characterised by a blue-grey colour.[1]

LM also shares many features with PAK, including an asymmetric hyperpigmented rim around the follicles and peripheral grey dots and rhomboidal structures. The peripheral grey dots and rhomboidal structures have been found to vary according to colour: on dermoscopy, PAK is lighter in colour compared to LM.[1] These guidelines can be helpful in the differential diagnosis of pigmented macules of the face, but a differential diagnosis between PAK and LM remains difficult due to the presence of many common patterns.[1]

Recently, an important dermoscopic scoring scheme was described that can aid in the differential diagnosis between PAK and early LM.[2]

This novel procedure may improve the early detection of LM, while reducing unnecessary biopsies for PAK.[2] In this instance, white and evident follicles, scales, and a red colour represent significant diagnostic clues for PAK, while intense pigmentation and grey rhomboidal lines are highly suggestive of LM (Figure 1).[2]

Distinguishing LM and PAK, however, still remains challenging in some cases. Reflectance confocal microscopy may help diagnose difficult cases when the normal dermoscopic criteria are not suitable for making a correct diagnosis. For example, many confocal laser microscopy patterns have been found that correlate with the diagnosis of LM. One such pattern is the presence of dendritic cells around the follicles, with the disposition 'bulging' inside the follicular opening and a characteristic arrangement around the follicles' 'medusa-like structures' that is typical of the dermal–epidermal junction.[3,4]

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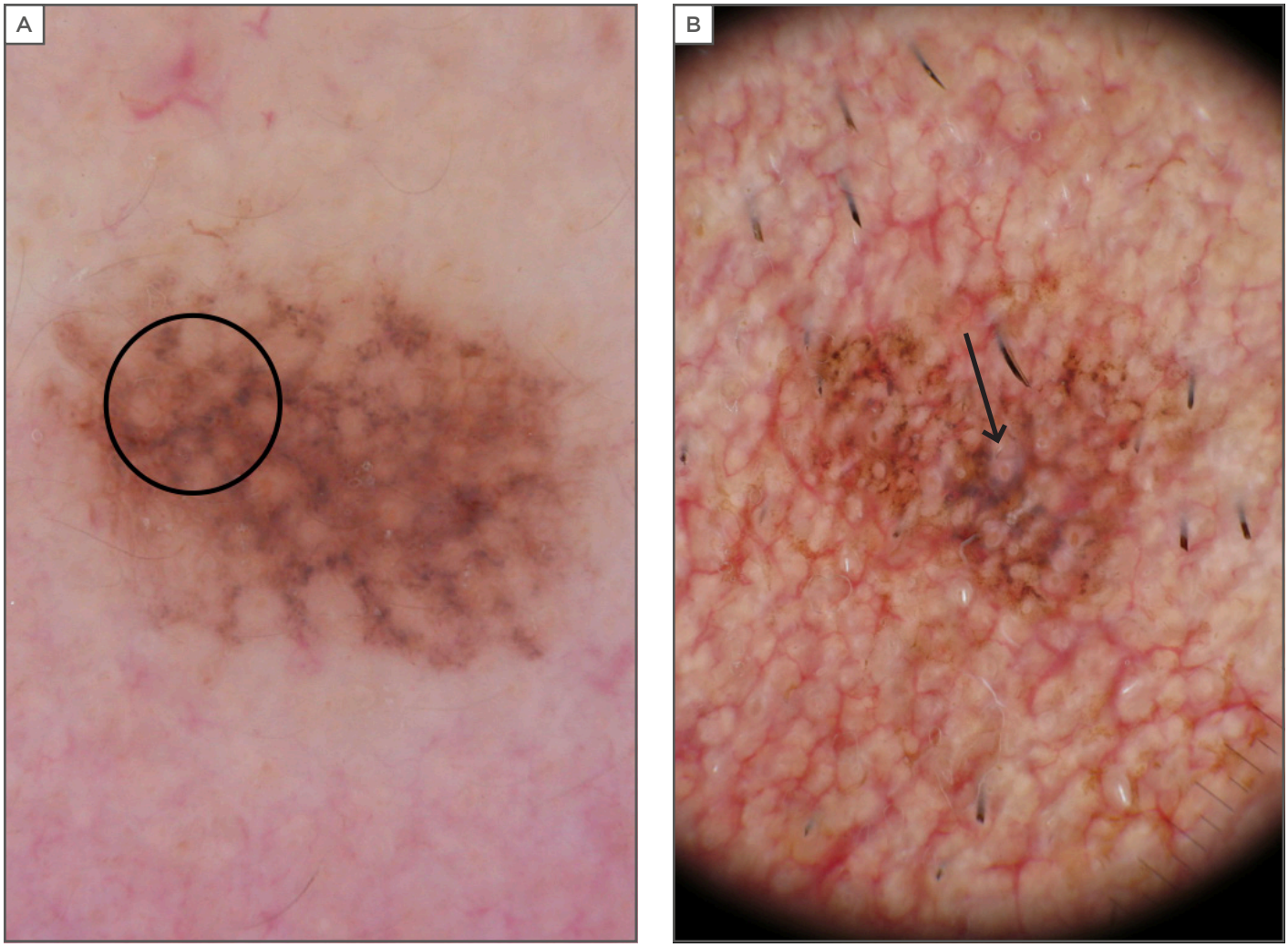

Figure 1: A) Dermoscopic image of lentigo maligna showing the presence of grey rhomboidal lines around follicles (black circle). B) Dermoscopic image of pigmented actinic keratosis showing the presence of white and evident follicles with a white border (black arrow).

The Influence of Itch and Pain on Sleep in Atopic Dermatitis Patients

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Atopic dermatitis (AD), itch, pain, quality of life (QoL), sleep quality.

Citation: EMJ Dermatol. 2018;6[1]:96-97. Abstract Review No. AR2.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease, with the average prevalence ranging from 2.1–4.9% in the general population.[1] The pathogenesis in AD involves genetic predisposition, environmental factors, and a hyperactive immune system.[2] AD is accompanied by itch and pain, and it negatively impacts different aspects of patient wellbeing.[3]

Sleep is a fundamental neurobiological state that is physiologically restorative and comprises around one-third of humans' lives. Sleep is carefully regulated by multiple processes, including homeostatic sleep drive and the circadian system.[4] Both itch and pain can significantly influence quality of life (QoL) and sleep.[5] Therefore, this study was undertaken to better characterise the influence of itch and pain on sleep in AD patients compared to controls.

MATERIAL AND METHODS

The study group consisted of 100 AD patients (42 females and 58 males) with a mean age of 39.2±15.4 years and 50 sex and age-matched controls. The mean disease duration was 20.3±16.1 years. Disease severity according to the Scoring Atopic Dermatitis (SCORAD) system was assessed as 33.6±10.7 points. The intensity of itch and pain was evaluated using the Visual Analogue Scale (VAS). Sleep abnormalities were estimated with the Athens Insomnia Scale (AIS) and Pittsburgh Sleep Quality Index (PSQI). AIS is a self-rated psychometric questionnaire that quantifies sleep difficulty based on the International Classification of Disease (ICD)-10 criteria over a 1-month time interval. Total AIS scores range from 0–24 points, with a total score of ≥6 points reflecting a diagnosis of insomnia.[6] PSQI is a self-reported questionnaire that is used to assess sleep quality and disturbances over a 4-week time interval. PSQI scores range from 0–21 points, with scores ≥5 reflecting a specific and sensitive measure of poor sleep quality.[7] Additionally, QoL was assessed by the Dermatology Life Quality Index (DLQI).

RESULTS

Itching was present permanently in every AD patient, while 43% and 34% of patients reported pain during the entire course of disease and within the last 3 days, respectively. The mean itch and pain intensity within the last 3 days were 7.1±2.7 points and 5.3±2.9 points, respectively. According to VAS cut-offs, 60% of patients with AD reported having severe to very severe itch. The mean AIS score among AD patients was assessed as 10.5±5.5, whereas controls scored significantly lower (5.5±3.4; $p<0.0001$). Moreover, the results suggest that there was a coexistence of insomnia in 82% of AD patients and in 50% of controls ($p<0.0001$). The average PSQI score among AD patients was estimated as 8.3±4.2 versus 3.1±1.9 for controls ($p<0.0001$). Eighty percent of AD patients and 22% of controls were classified as poor sleepers ($p<0.0001$). Mean QoL was estimated as 16.4±7.9 points. The severity of itch significantly correlated with AIS scores ($r=0.44$; $p<0.0001$). Moreover, both itch and pain intensity independently impacted QoL ($r=0.45$; $p<0.0001$ and $r=0.36$; $p=0.026$, respectively).

DISCUSSION

AD greatly impacts patient wellbeing and the disadvantageous influence of itch on sleep quality has been established in chronic

inflammatory dermatoses such as AD.[8] Results suggest that AD-related itch, but not pain, is significantly related to insomnia and sleep quality of patients, and its effect may be a partial mediator of psychological and somatic symptoms.[9] Itch management intervention studies are needed to improve QoL and sleep quality among AD patients.

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A Case of Bazex Syndrome (Acrokeratosis Paraneoplastica) with Atypical Features

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Keywords: Acral dermatosis, acrokeratosis paraneoplastica, Bazex syndrome, paraneoplastic syndrome.

Citation: EMJ Dermatol. 2018;6[1]:97-98. Abstract Review No. AR3.

Acrokeratosis paraneoplastica (Bazex syndrome) is a paraneoplastic skin condition that can be found in the context of various internal malignancies, including squamous cell carcinoma of the head and neck, carcinomas of the aerodigestive tract, cholangiocarcinoma, and lymphoma.[1,2] Men >40 years of age are the most commonly affected.[1]

The clinical aspects of this condition may mimic psoriasis, eczema, lupus erythematosus, hereditary palmoplantar hyperkeratosis, pityriasis rubra pilaris, mycosis fungoides, or syphilis.[2] For this reason, there can be a delay in recognising this entity, which, therefore, may extend the period of time until a neoplasm diagnosis is established. Sometimes, the cutaneous manifestations may coincide with the tumour diagnosis or can appear later in the evolution revealing metastases.[1,2] The clinical appearance of the eruption has three stages of development. Initially, acrokeratotic lesions are represented by scaly erythematous to violaceous papule and plaques can be observed on the fingers and/or toes, ears, and nose. Nail apparatus involvement can be noticed. In the second stage, the lateral part of the palms and soles becomes affected by keratoderma, without affecting the centre of the palms and soles. In the last stage, the eruption may extend to the limbs, trunk, and scalp.[1] Histopathological findings are nonspecific. Acrokeratosis paraneoplastica is usually refractory to topical (corticosteroids or keratolytic products) or systemic (acitretin) treatments.[3] The best

approach is based on treating the underlying malignancy, which will lead to the resolution of the skin lesions in a few months in >90% of cases.[3,4]

We presented the case of a 50-year-old female patient who was examined for hyperkeratotic lesions affecting the hands and feet, which she had noticed a few months before. She was previously diagnosed with chronic eczema, for which she received topical corticosteroids and emollients without improvement. The eruption worsened in the weeks leading up to the examination and were associated with an intense pain confined to the skin lesions. On dermatological examination, hyperkeratotic erythematous and violaceous plaques were present on the palmoplantar area and associated with scaly plaques on the dorsal part of the toes with a tendency to extend over the medial part of the feet. A few violaceous shiny papules with a lichenoid aspect were noticed on the dorsal part of the hands. The patient was cachectic and depressed. Her medical history revealed a diagnosis of pulmonary carcinoma of the right lung 3 years before, for which a complete right pneumonectomy was performed, as well as chemotherapy and radiotherapy. The presence of psoriatic hyperkeratotic acral lesions, resistant to topical steroids, in a patient previously diagnosed with an internal malignancy resulted in the diagnosis of Bazex syndrome or acrokeratosis paraneoplastica.

The appearance of Bazex syndrome was concomitant with the extension of the carcinoma to the left lung and with the occurrence of metastases. This case is of particular interest considering that the skin disorder was absent 3 years before, that the ears and the nose were not involved at the time of the primary tumour diagnosis, and that it was associated with an intense pain.

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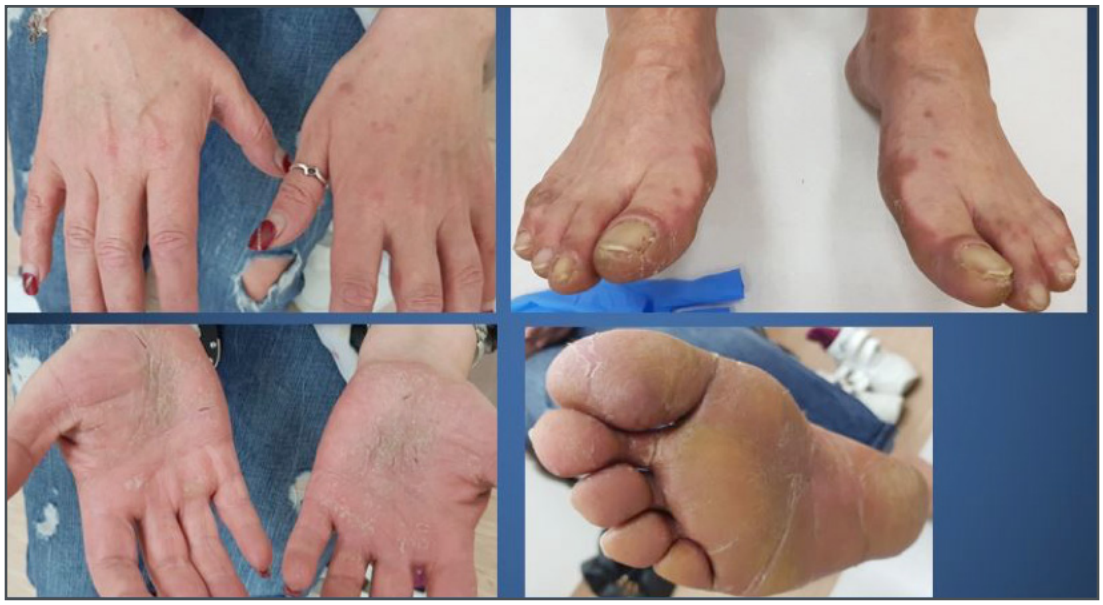

Figure 1: Bazex syndrome.

Hyperkeratotic erythematosus and violaceous plaques on palmoplantar area, associated with scaly plaques on the dorsal part of the toes and a tendency to extend over the medial part of the feet.

Polymorphic Eruption of Pregnancy with Postpartum Onset: A Case Report

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Acknowledgments: All authors contributed equally to this publication.

Keywords: Polymorphic eruption of pregnancy (PEP), pregnancy-related dermatoses, pruritic urticarial papules and plaques of pregnancy.

Citation: EMJ Dermatol. 2018;6[1]:99-100. Abstract Review No. AR4.

Polymorphic eruption of pregnancy (PEP), also known as pruritic urticarial papules and plaques of pregnancy, is a self-limiting inflammatory dermatosis that usually affects primiparous women in the last few weeks of pregnancy. PEP follows a benign course with spontaneous resolution, typically within 2 weeks postpartum, posing no increased risk of fetal or maternal morbidity other than maternal pruritus.[1–3] When confronted with a pruritic skin eruption associated with pregnancy or the immediate postpartum period, prompt evaluation and diagnosis is vital because more aggressive eruptions, such as gestational pemphigoid (GP), need to be excluded. At the 27th Congress of the European Academy of Dermatology and Venereology (EADV) in Paris, France, we presented an unusual case of PEP with postpartum onset.

A 33-year-old woman presented with a widespread, intensely pruritic eruption within abdominal striae, spreading to the inferior extremities and buttocks, with no periumbilical involvement (Figure 1). The eruption had appeared 3 weeks postpartum. Due to the uncommon postpartum onset and anxiety of the patient, a skin biopsy was performed. Histopathology showed mild epidermal hyperplasia, spongiosis and parakeratosis with dermal oedema, and perivascular and interstitial lymphocytic infiltrate containing eosinophils. Direct immunofluorescence demonstrated nonspecific granular deposits of C3 and IgM. No other laboratory abnormalities were present. The clinical and histologic pictures were diagnostic for PEP. The eruption subsided following a 2-week course of topical methylprednisolone aceponate, tapered to one application daily for another week.

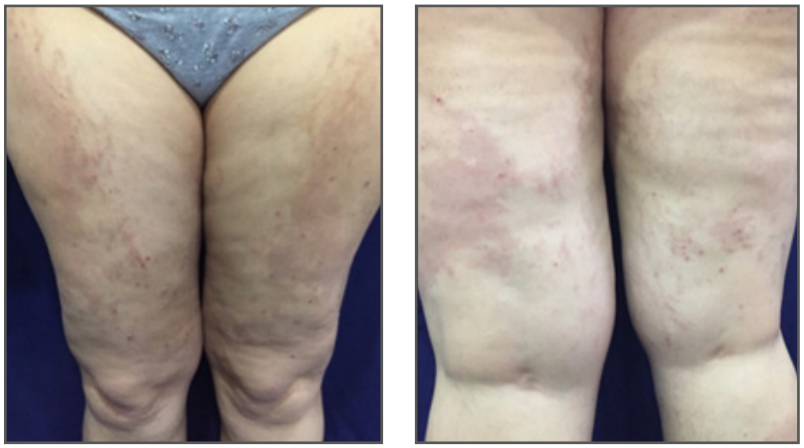

Figure 1: Antero-posterior view of inferior extremities involvement of a widespread, intensely pruritic eruption presented by a 33-year-old woman at 3 weeks postpartum. Note the distribution of lesions within striae distensae.

The diagnosis of PEP is mostly clinical, based on the patient's history and physical examination. Although a skin biopsy is not usually necessary for diagnosis, it may be performed in cases of diagnostic uncertainty, especially to rule out more aggressive eruptions associated with pregnancy, such as GP, which can mimic PEP in the early urticarial phases. Direct immunofluorescence helped distinguish these two entities. Nonspecific granular deposits of C3 and IgM or IgA at the dermal–epidermal junction or surrounding blood vessels can be seen in approximately 30% of PEP cases,[4] whereas in GP these deposits are linear. Indirect immunofluorescence is always negative in PEP. Other conditions that can mimic PEP include drug reactions, scabies, and viral syndromes.[2,4] Differentiation among these entities is made by clinical history, routine histology, and serology. There are no related laboratory abnormalities to PEP.[3]

PEP prognosis is excellent, with spontaneous resolution within a few weeks and no tendency to recur with subsequent pregnancies. There is no increased risk of fetal or maternal morbidity, other than the maternal pruritus.[2,3] The goal of treatment is relief of symptoms, which can usually be achieved following short-term use of topical corticosteroids and oral antihistamines.

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Clinical and Psychological Aspects in Patients with Alopecia Areata Treated with Diphenylcyclopropenone

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Alopecia areata (AA), diphenylcyclopropenone (DPCP), hair loss, topical immunotherapy.

Citation: EMJ Dermatol. 2018;6[1]:100-102. Abstract Review No. AR5.

INTRODUCTION

Alopecia areata (AA) is a condition that causes non-scarring hair loss; the estimated lifetime risk of developing the disorder is 1.7% but the aetiology of AA is still being investigated. AA has an autoimmune background, but is also related to various atopic and autoimmune disorders, such as vitiligo and thyroid disease.[1-3] The course of the disease is unpredictable, but it is known that early age of onset, extensive hair loss, nail changes, and comorbid autoimmune disorders are associated with a poor outcome. The disease also affects patient quality of life, as treatment of AA is often unsatisfactory. Topical or intralesional corticosteroids are used as the first-line therapy for AA. It has been demonstrated that topical immunotherapy with diphenylcyclopropenone (DPCP) is a good therapeutic option for patients with AA; DPCP is a contact allergen, and the effectiveness of the drug has been demonstrated in several reports.[4,5]

MATERIALS AND METHODS

A total of 106 (70 female and 36 male) patients with AA were enrolled in our study. The mean

age of the female patients was 38.4±13.3 years and male patients 30.9±12.0 years; the patients' average disease duration was 107.1±133.6 months. All patients underwent a standardised diagnostic protocol, which included the collection of clinical and demographic data and the evaluation of the severity of the disease with the Severity of Alopecia Tool (SALT). We divided SALT scores into five groups depending on percentage of hair loss: S1: ≤24%, S2: >24–49%, S3: >49–74%, S4: >74–99%, and S5: 100% of hair loss.

Hair regrowth after 6 months of treatment was calculated according to the formula: [(A-B)/A]x100%, where A is the percentage of hair loss before treatment and B is the percentage of hair loss after 6 months of treatment.[6] Treatment was performed with a $1x10^{-6}$–2% DPCP solution. After the first application of the DPCP solution, the DPCP concentration was slowly increased to the maximum concentration that was acceptable for the patients and was adjusted to clinical response. We also assessed quality of life using the Dermatology Life Quality Index (DLQI) before treatment and after 6 months of treatment.

RESULTS

The mean percentage of hair loss before treatment was 51.0±35.1% and after 6 months of treatment, the percentage was 43.6±40.7%. Women had more episodes of AA from the beginning of the disease and higher prevalence of thyroid disease than men (p=0.003). We found that the severity of hair loss did not correlate with thyroid disease or atopy (p>0.05). Moreover, the presence of thyroid disease did not affect hair regrowth (p>0.05). We found a correlation between severity of the disease (according to SALT scores) before and after treatment (p<0.001). The best results of treatment were observed in S3 and S4 group patients (Figure 1). Quality of life measured before treatment ranged from 0–24 points, with a mean score of 5.5±5.2 points, and after 6 months of treatment the mean value of DLQI was 3.2±5.1 points. We found that the DLQI scores of AA patients were significantly lower after 6 months of treatment (rho=0.376; p<0.05).

CONCLUSION

Treatment of AA with DPCP led to a decrease in disease severity. Topical immunotherapy is an effective treatment for AA and improves quality of life.

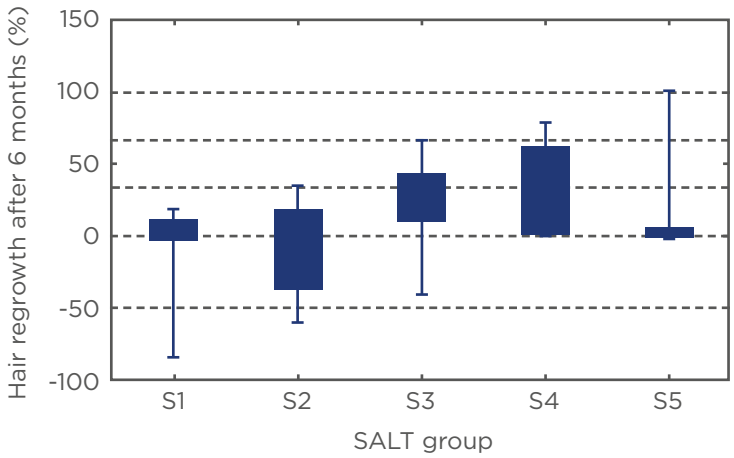

Figure 1: Hair regrowth in patients with various severities of alopecia areata (SALT S1-S5).

Data were analysed using the Kruskal–Wallis test. H(4;75)=9.41; p=0.051.

S1: ≤24% hair loss, S2: 25–49% hair loss, S3: 50–74% hair loss, S4: 75%– 99% hair loss, and S5: 100% hair loss; SALT: Severity of Alopecia Tool.

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Erosive Pustular Dermatosis of The Scalp: A Neutrophilic Folliculitis Within the Spectrum of Neutrophilic Dermatoses. A Clinicopathologic Study of 30 Cases

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Autoinflammatory dermatoses, erosive pustular dermatosis, neutrophilic folliculitis, pyoderma gangrenosum, scalp.

Citation: EMJ Dermatol. 2018;6[1]:102-104. Abstract Review No. AR6.

Erosive pustular dermatosis of the scalp (EPDS) is an uncommon, chronic, and progressive amicrobial pustular idiopathic disorder most commonly occurring on the scalp of elderly females and ultimately leading to scarring alopecia.[1] The combination of the clinical picture, negative microbiological exam, and the histopathological exclusion of other inflammatory conditions allows for a correct diagnosis. It is generally accepted that histopathology is nonspecific and of little value in diagnosing EPDS.[2,3] To delineate the clinicopathologic spectrum of the disease, the clinical and pathological records of patients with a diagnosis of EPDS from 2011–2016 were reviewed. Thirty patients were identified, including 22 males and 8 females (mean age at disease diagnosis: 77 years). The mean disease duration before diagnosis was 15 months, ranging from 3–36 months. EPDS was clinically suspected in only three patients, whereas nonmelanoma skin cancers comprised the majority of considerations (21/30). Severe androgenetic alopecia was present in 19 patients. Triggering factors included mechanical trauma in 10 patients, surgical procedures in four patients, and herpes zoster virus infection in one patient. Three patients were affected by autoimmune disorders. The vertex was the most common disease location and presentation varied markedly from tiny, erosive, scaly lesions to crusted and haemorrhagic plaques mimicking pustular pyoderma gangrenosum. The pathologic changes differed according to the lesion type, disease duration, and baldness severity.

Biopsies of patients with severe androgenetic or total baldness (Figure 1A) produced specimens showing nonspecific pathologic changes (22/30), including atrophic, eroded and/or thickened epidermis with spongiform pustules and overlying scale-crusts, granulation tissue, variable dermal fibrosis, and hair loss (Figure 1B). The infiltrate was a mix of lymphocytes, neutrophils, and plasma cells. Interestingly, in patients with a hair-bearing scalp (Figure 1C), histopathologic examination identified eight cases with a dense infiltrate of neutrophils and

lymphocytes around and within the infundibula of multiple, adjacent terminal hair follicles in concert with prominent spongiosis and focal or total disruption of the follicle wall (Figure 1D). Extravasated erythrocytes were also seen in the surrounding stroma. All patients were treated with high-potency steroids applied topically overnight; 27 patients showed marked improvement after 4 weeks. The remaining three patients were unresponsive to the topical steroids and were treated with low-dose systemic prednisone (0.5 mg/kg/day) for 2 weeks with gradual tapering, and then showed improvement. The maintenance regimen for all patients consisted of twice weekly clobetasol propionate 0.05% ointment applications and sun avoidance.

On the basis of our study, we believe that EPDS is a neutrophilic-mediated skin disorder in which the primary lesion (at least in patients with a hair-bearing scalp) is an infundibular spongiform pustule. The clinicopathologic similarities between EPDS and pustular pyoderma gangrenosum, when lesions do not usually develop into frank ulcerations and infundibular pustules may be observed, suggest EPDS should be included in the spectrum of autoinflammatory dermatoses for which pathergy may play a pathogenetic role.[4]

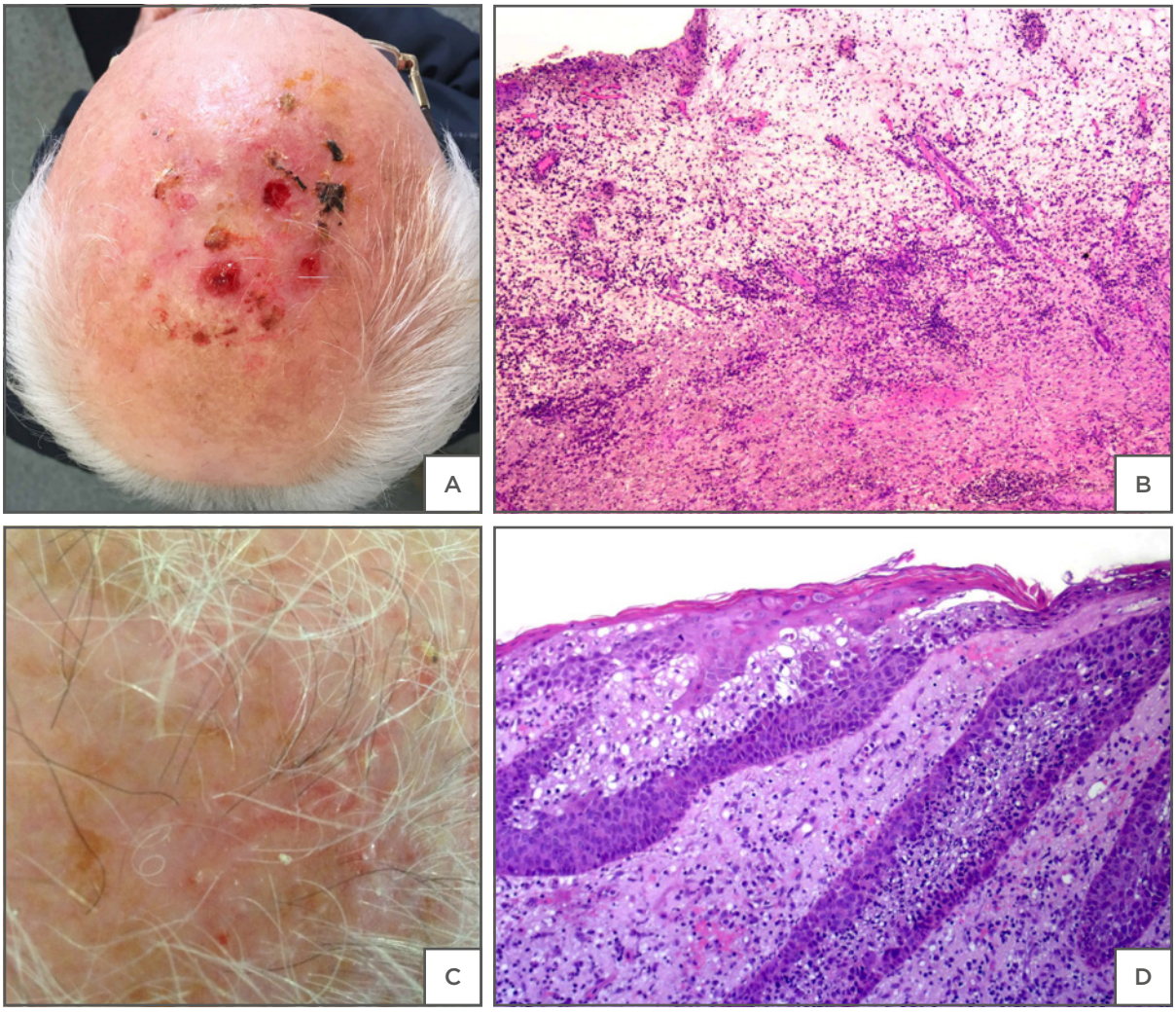

Figure 1: Erosive pustular dermatosis of the scalp.

A) Multiple eroded and crusting lesions localised on the scalp. Diagnostic considerations were actinic keratoses versus squamous cell carcinoma. B) Unspecific histopathological changes characterised by granulation and scar tissue with numerous neutrophils and haemorrhage, viewed using a haematoxylin and eosin stain. C) Follicular pustules and erosions on an atrophic scalp with androgenetic alopecia. D) Spongiotic pustules in the infundibula and erosion of the epidermis, viewed using a haematoxylin and eosin stain.

The recognition of EPDS is of utmost importance to avoid inappropriate surgical treatments that may lead to a worsening of disease.[5]

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Autoimmune Progesterone Dermatitis: A Thorough Clinical History May Lead to the Diagnosis of a Rare Disorder

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During their reproductive years, women may present with various menstrual-related disorders. A few women may develop a rare cyclic dermatologic condition known as autoimmune progesterone dermatitis (AIPD).[1] First described in 1921, AIPD is associated with increased progesterone levels during the luteal phase of the menstrual cycle, caused by an immune reaction to endogenous or exogenous progesterone.[2,3] Often confused with other dermatoses, cutaneous manifestations of AIPD vary and may present as eczema, folliculitis, stomatitis, mucosal lesions, papulovesicular lesions, papulopustular lesions, vesiculobullous reactions, erythema multiforme, urticaria, angioedema, and even anaphylaxis (progesterone-induced anaphylaxis).[1,4]

A 27-year-old secundigravid female, 13 weeks pregnant and undergoing exogenous progesterone therapy, was referred to our clinic for presentation with annular and round erythematous, scaly, pruritic plaques, some with vesiculation, excoriation, and impetiginisation localised on the dorsal side of her hands (Figure 1). The lesions slowly developed after the initiation of oral progestative treatment to prevent miscarriage. During her first pregnancy, which resulted in a spontaneous abortion, she also received progesterone therapy and noticed the appearance of less severe, similar eczematous cutaneous lesions. She described monthly transitory plaques ever since her menarche, 10 days prior to the onset of menstrual flow. The occurrence of skin lesions associated with the introduction of progesterone therapy on two occasions and observations from a clinical examination led us to the diagnosis of AIPD. Topical treatment was recommended (a short course of emollients and dermatocorticosteroids) and a multidisciplinary evaluation, both endocrinological and gynaecological, was carried out to assess specifically adapted pregnancy treatment options.

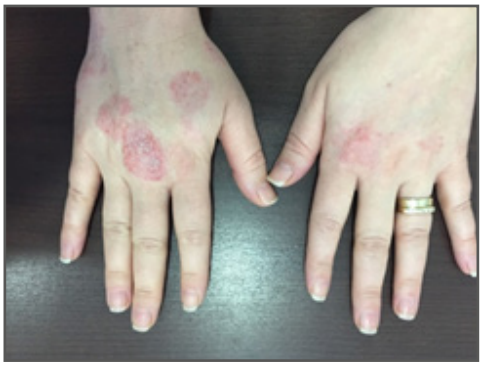

Figure 1: A 27-year-old secundigravid female, 13 weeks pregnant and undergoing exogenous progesterone therapy, presented with round erythematous, scaly, pruritic plaques, some with vesiculation, excoriation, and impetiginisation localised on the dorsal side of her hands.

This rare autoimmune complex syndrome that most commonly occurs during the luteal phase of the menstrual cycle presents as a wide spectrum of cutaneous manifestations that correlate with increased progesterone levels.[3,5] Symptoms of AIPD appear 3–10 days prior to menses due to the progesterone fluctuations in the luteal phase, and symptoms resolve 2 days after the outset of the menstrual flow.[4] The onset of AIPD is variable and has been described as occurring spontaneously at menarche, peripartum, and during pregnancy, which may impact the symptomatology of this disease.[4,6]

With a poorly understood pathogenesis and polymorphic characteristics, AIPD may easily be misdiagnosed.[6] A thorough clinical history and evidence of progesterone sensitivity may lead the physician to suspect progesterone autoimmunity and differentiate AIPD from other variable skin disorders.[1,7]

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Repeated Tick Bites Influence Basophil Kinetics and Production of Specific IgE Antibody to Galactose-α-1,3-Galactose

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Keywords: Galactose-α-1,3-galactose (alpha gal) syndrome, alpha gal carbohydrate, basophil, tick bite.

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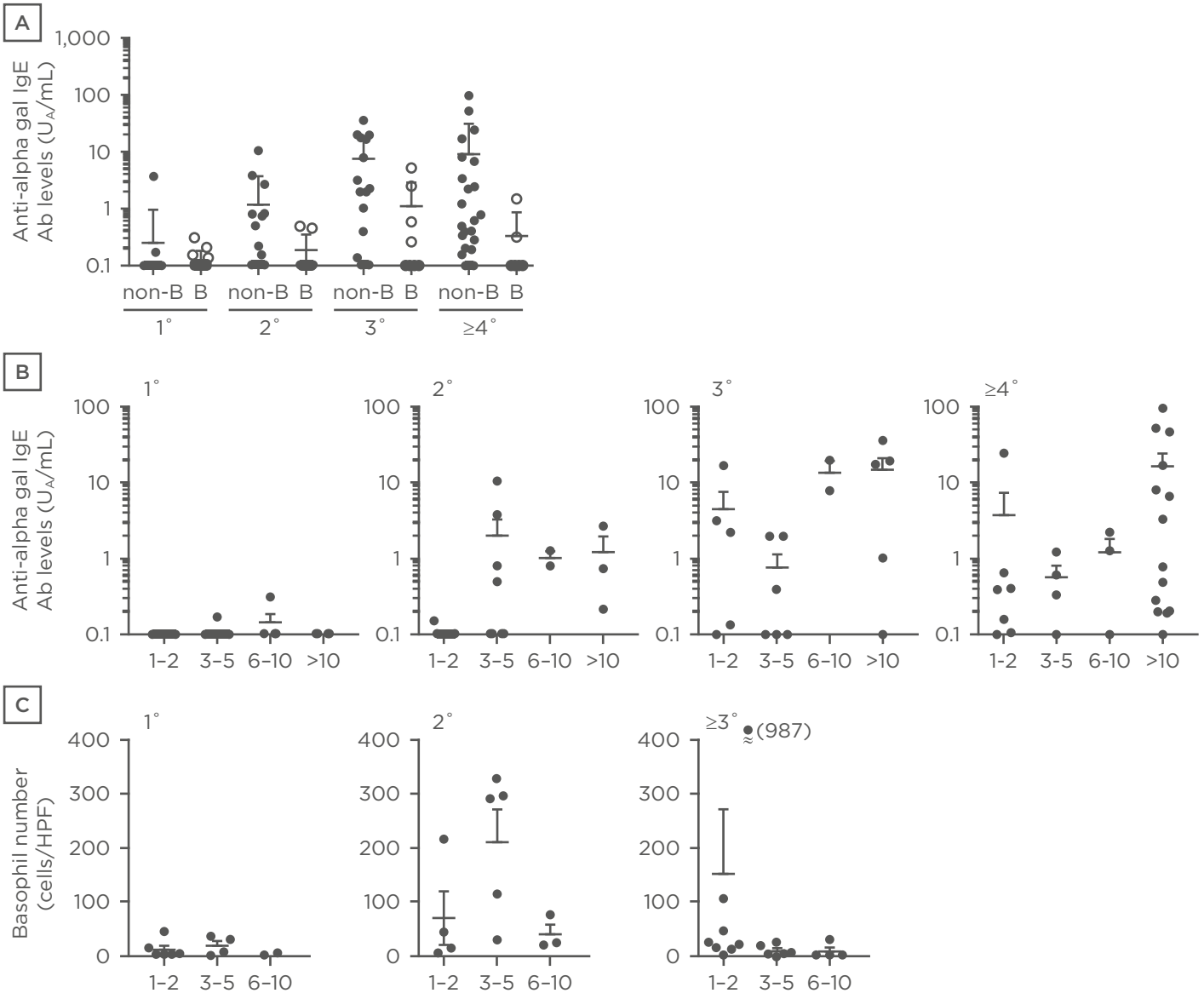

Figure 1: A) Anti-alpha gal IgE levels in patients with different tick bite frequencies who have the non-B (blood types A or O) or B blood types (blood types B or AB). B) Chronological variations of anti-alpha gal IgE levels. C) Chronological variations of basophil numbers in bitten skin.

1°: patients with 1 tick bite; 2°: patients with 2 tick bites; 3°: patients with 3 tick bites; ≥4°: patients with ≥4 tick bites; Ab: antibody; Alpha gal: galactose-α-1,3-galactose; HPF: high power field.

INTRODUCTION

The disaccharide galactose-α-1,3-galactose (alpha gal) is a typical component of glycoproteins in mammals.[1] Since primates, including humans, have lost the enzyme required for alpha gal production, it is immunogenic and large amounts of natural IgM and IgG antibodies to it are produced by sensitised B cells in humans. On the other hand, IgE antibodies specific to alpha gal are never produced in humans except for in patients with a delayed immediate-type reaction to red meat and drugs containing alpha gal.[2] It has been demonstrated that development of alpha gal syndrome is closely associated with tick bites,[3] suggesting that tick bites promote production of IgE antibody to alpha gal, although the mechanism remains poorly understood. To address this issue, we stratified patients by historical frequencies of tick bites and investigated the association between serum anti-alpha gal IgE levels and basophils.

METHODS

A total of 56 patients who presented at Shimada Municipal Hospital with tick bites were enrolled in this study after providing informed consent. Patients were categorised into four groups: patients with 1 tick bite (1°), patients with 2 tick bites (2°), patients with 3 tick bites (3°), and patients with ≥4 tick bites (≥4°). The study was performed according to the Declaration of Helsinki, and the study protocol was approved by the Shimada Municipal Hospital Ethical Committee.

RESULTS

Because the alpha-gal epitope is structurally related to the blood type B antigen, production of the specific IgE antibody was suppressed in patients who had the B antigen.[4] We found that the specific IgE antibody levels were significantly increased in association with tick bite frequency in patients with A or O blood types, but not with B or AB blood types (Figure 1A). Because the B antigen can disturb the processes of anti-alpha gal IgE antibody production, patients with B or AB blood types were excluded from further investigations.

Patient groups were stratified by historical tick bite frequencies and the chronological variations of the antibody levels among the groups (1–2 days, 3–5 days, 6–10 days, or ≥10 days after bites) were compared (Figure 1B). We found three distinctive patterns: marginal levels in the patients with 1°, a gradual increase in the patients with 2°, and a sharp increase in the patients with ≥3°.

We also compared chronological variations of the skin-infiltrating basophils among the groups. Although a marginal increase in the number of basophils was found in the patients with 1°, the number of basophils increased gradually in the patients with 2° and sharply in the patients with ≥3°, followed by a decrease there after (Figure 1C).

We propagated the skin-infiltrating T cells from the lesions of the patients by a previously described method[5] and investigated the cytokine production of these cells using intracytoplasmic staining with antibodies to cytokines, including IL-4, IL-5, IL-13, and IFN-γ, after stimulation with PMA. We found that Th2 cytokine production of skin-infiltrating T cells was augmented with increased bite frequency.

DISCUSSION

We found chronological variations of anti-alpha gal IgE levels and basophil kinetics in the patients with 1°, 2°, and ≥3° tick bite histories, respectively. Furthermore, we observed that tick bite histories were associated with Th2 cell infiltration in bitten skin. Because basophils have an antigen-presenting function to promote Th2 differentiation and IgE production, repeated tick bites causes accumulation of Th2 cells in bitten skin to provide a Th2 cytokine milieu, which is critical for class switching to IgE of sensitised B cells.

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Beneath the Skin: The Relationship Between Psychological Distress and the Immune System in Patients with Psoriasis

EDITOR'S PICK

My Editor's Pick for this journal is 'Beneath the Skin: The Relationship Between Psychological Distress and the Immune System in Patients with Psoriasis.' I selected this article because it explores the psychological effects of psoriasis, including depression and other mood disorders, and the fluctuation of physical and psychiatric symptoms in this chronic skin disease. It reminds us of the complex interplay between the many aspects of disease pathogenesis and expression, and how psychologic factors may influence and be influenced by inflammation.

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Abstract

Psoriasis is a chronic autoimmune skin disease with significant physical and psychiatric comorbidities. Research into psoriasis-associated depression has revealed several possible pathways linking the two very different diseases. Questions of causality arise when exploring the complex relationship of psoriasis and mood disorders, and studies have revealed that inflammation may serve as the common denominator linking psoriasis and depression. Conversely, many investigators have reported that psoriasis severity may fluctuate with perceived psychological distress, suggesting that psychological factors, rather than inflammation, may be the driving force behind disease exacerbation in these cases. The truth is likely a combination of both schools of thought: a bidirectional relationship between cutaneous and psychological disease manifestations with an overlapping biological mechanism associated with inflammation. Evidence has revealed multiple pathways by which this relationship can be explained, including hypothalamic–pituitary–adrenal axis hyperactivity, glucocorticoid receptor desensitisation, sympathetic nervous system activation,

and altered expression of various chemical signals in the central nervous system. This review summarises the existing evidence and seeks to elucidate how the physiologic disturbances in psoriasis may contribute to both the cutaneous disease manifestations and associated psychological comorbidities. Evidence suggests that treating the psychiatric comorbidities of psoriasis can significantly improve cutaneous disease severity and treating the underlying inflammation could have profound effects on psychological health and quality of life. Therefore, conceptualising psoriasis as more than a purely dermatologic disease is useful in formulating a comprehensive treatment plan; furthermore, addressing both the cutaneous and psychological facets of this disease could prove profoundly beneficial for decreasing the associated negative impacts on patient quality of life.

INTRODUCTION

Psoriasis is a chronic autoimmune skin disorder that affects 2–3% of people worldwide.[1,2] While the exact pathological mechanism is not fully understood, the disease seems to be associated with increased activation of cutaneous T cells, macrophages, and dendritic cells.[3] This is followed by an increase in proinflammatory cytokines such as IL-1, IL-6, IL-12, and TNF-α, which induce a more generalised inflammatory reaction.[4] Simultaneously, IL-6 and IL-23 activate Th17 cells, resulting in the subsequent release of IL-17, a potent stimulator of keratinocyte proliferation.[5] While we have seen dramatic advancements in psoriasis treatments in recent decades, there is still significant room for improvement in addressing the disabilities associated with this condition.[6]

Psoriasis confers levels of disability that rival many major diseases, such as chronic heart failure, chronic obstructive pulmonary disease, and cancer.[7] Psoriatic lesions can be physically disabling, especially if on the hands or feet,[8] and patients with psoriasis are also at increased risk of cardiovascular disease, diabetes, psoriatic arthritis, and inflammatory bowel disease.[9] Psychiatric comorbidities also have significant prevalence, estimated to affect at least 30% of patients with chronic dermatologic disease.[10] Psoriasis specifically has been associated with a 39% increase in depression, 31% increase in anxiety, and 44% higher rate of suicidality compared with the general population.[11] In addition, more severe clinical presentations have been associated with a 72% higher prevalence of depression when compared to milder disease.[11] This difference is seen consistently in epidemiologic studies, even when controlling for possible confounders such as age, sex, race, weight, medical comorbidities, and drug use.[12] Patients with severe psoriasis have also been found to be 69% more likely to attempt suicide[13] and 30% more likely to complete suicide than those with milder forms of the disease.[14] While one may reasonably assume that mood disorders experienced by patients with psoriasis are likely to be the consequence of social anxiety and stigma resulting from the disfigurement of their disease, this may not be the entire explanation. Psoriasis patients have significantly higher rates of depression and anxiety when compared to patients with skin disorders that are equally as disfiguring.[15] This finding has spurred investigations to determine the possible existence of physiologic factors underlying both psoriasis and psychiatric disease.

A parallel to the classic chicken or the egg argument arises when pondering the intricate relationship between psoriasis and psychological distress. Inflammation in psoriasis may cause or worsen symptoms of mood disorders;[16] however, the contrary may also be true, with some studies claiming that psychological distress may cause worsening disease severity in psoriasis patients, an effect that likely extends beyond the simple notion that depression can negatively impact compliance to psoriatic treatments.[17,18] The truth is likely more complex, involving a bidirectional positive feedback loop that can drive and propagate a cycle of worsening depression and inflammation.[19] In either case, patient quality of life is affected as a consequence of the psychological aspect of their disease, and there is a significant need for physicians to be able to treat psoriasis as more than solely a dermatologic condition.

PSYCHOLOGICAL DISTRESS CAUSING INFLAMMATION

There is ample evidence suggesting a strong link between depression and inflammation, particularly the Th1-like cell-mediated immune response.[19,20] Psychological stress and trauma are two of the most well-studied risk factors of depression and have also proven to be risk factors for inflammation.[21] In animal models, stress and trauma can increase inflammatory markers such as IL-1 and IL-6 in the brain, and these increases have correlated with greater depressive symptoms.[22-25]

Learned helplessness occurs when an animal endures recurrent stress or trauma that they have no control over, and repeated failures ultimately cause the animal to stop attempting to escape or alter their circumstances. In one common laboratory scenario, rats are repeatedly subjected to electrical shock through the floor of their cages. While initial trials evoke an escape response, as evidenced by a frantic rat clawing at its cage, this natural response is ultimately extinguished and subsequent shocks produce no apparent desire to flee, even if the cage door is opened. Learned helplessness has shown to be an effective simulation of depression and anxiety when testing the effectiveness of antidepressants in animals.[21,26] Blocking IL-1 receptors in rats interfered with their ability to express fear and learned helplessness;[23] this suggests that an inflammatory response in the brain might be necessary to enable full expression of depressive symptoms. Similar studies in humans have shown increased levels of IL-1β, IL-6, and TNF-α in response to mild emotional stress, which has led many to conclude that distress and depression are, at least in part, inflammatory reactions.[27,28] This may have implications in the setting of psoriasis, as several studies have linked these inflammatory markers with psoriatic plaque formation.[29] There have been great strides in this field but more research is needed before we can fully understand the complexities of the relationship between the mind and the immune system.

There is accumulating evidence that defines the skin as an extension of the neuroendocrine system, which is capable of responding to central hormone levels as well as controlling neuroendocrine environments locally.[30] A pathway linking psychiatric stress to an inflammatory immune response would have to activate cell-mediated autoimmunity and trigger the chronic inflammation seen in psoriasis patients. One possible mechanism that satisfies these criteria may involve hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, which is commonly seen in depression.[31] HPA axis hyperactivity results in the release of significantly more corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol compared to unaffected individuals.[32] The potential role of CRH in psoriasis is supported by the discovery that biopsies of psoriatic lesions express significantly more CRH compared to unaffected skin.[33] CRH in unaffected skin stimulates IL-6 and IL-11 proinflammatory cytokines, most likely through increased expression of NFκB in keratinocytes at a local level.[34] CRH also appears to increase keratinocyte intracellular adhesion molecule-1 (ICAM-1) expression, promoting immune cell migration and facilitating cell-mediated immune responses.[35] It is well documented that CRH stimulates production of pro-opiomelanocortin, which leads to ACTH production and glucocorticoidogenesis in the skin, but this signalling pathway was shown to be defective in psoriasis patients, possibly contributing to inflammation.[36] Some have hypothesised that ultraviolet B radiation increases pro-opiomelanocortin, ACTH, and glucocorticoid expression in the skin, resulting in an overall reduction of inflammation within the plaques.[37]

Another plausible mechanism by which psychological distress induces inflammation is through the dysfunction of cortisol receptors downstream from the HPA axis. There are two intracellular receptor subtypes to which cortisol can bind to exert an anti-inflammatory response: mineralocorticoid receptors (MR, Type I) and glucocorticoid receptors (GR, Type II).[38] MR have approximately 10-times more affinity to glucocorticoids and, as such, serve as the primary mediator of negative feedback in the HPA axis at lower glucocorticoid concentrations; however, cortisol levels can often increase 100-fold during times of stress, oversaturating MR and forcing the body to

rely on lower-affinity GR to regulate the HPA axis.[39] This can ultimately reduce the body's ability to regulate corticosteroid levels through negative feedback, resulting in decreased sensitivity to the anti-inflammatory effects of cortisol. HPA axis hyperactivity leads to an eventual decline in GR function, which stimulates the expression of NFκB and proinflammatory cytokines. These mediators subsequently contribute to an increasingly inflammatory milieu and fuel rapid keratinocyte proliferation, as seen in cases of worsening psoriasis.[40] The potential role of these receptors is supported by clinical data demonstrating that depressed patients are more resistant to the anti-inflammatory effects of dexamethasone, a potent GR agonist, and continue to express proinflammatory cytokines despite administration of this treatment.[32] HPA axis hyperactivity thus causes patients to have higher baseline cortisol levels but concomitant desensitisation to its anti-inflammatory effects. In psoriasis, patients with self-identified stress-responsive disease showed blunted cortisol production in response to stress, which is likely to be a consequence of desensitisation.[41] In addition, this desensitisation can result in a failed negative feedback loop leading to increased CRH, which can have significant local inflammatory effects on the skin, as previously discussed. These findings corroborate clinical studies that have demonstrated increased cortisol levels in patients with psoriasis and a dose effect positively correlating bedtime cortisol levels with Psoriasis Area Severity Index (PASI) score.[42,43] These studies, however, were limited due to small sample sizes and a lack of control groups.

Activation of the sympathetic nervous system in response to psychological stress may contribute to subacute flares of psoriasis.[44] Psychological distress, anxiety in particular, has been correlated with sympathetic activation.[45] A similar increase in sympathetic tone has been documented in depressed patients, correlating with severity of depression and diminishing when depressive symptoms were successfully treated with selective serotonin reuptake inhibitors (SSRI).[46,47] Similarly, psoriatic patients have been found to release more noradrenaline as a response to stress when compared to the general population.[48,49] Noradrenaline stimulates alpha adrenergic receptors on antigen-presenting cells and results in decreased expression of CC16 (uteroglobin), a potent anti-inflammatory protein involved in cell-mediated immunity and working in conjunction with the anti-inflammatory cytokine IL-10.[50-52] Through this pathway, a subsequent increase in inflammatory IL-6 and TNF-α can be observed, which drives a strong Th1 response.[53] Additionally, noradrenaline has stimulatory effects on dendritic cell migration and T cell activation, even when the effect is isolated from those of glucocorticoids alone.[54] Noradrenaline also opposes its own inflammatory effects by stimulating beta adrenergic receptors, resulting in a suppression of TNF-α release and increase in IL-10 production.[50] It is interesting to question whether interruption of this self-regulatory mechanism may help explain why psoriasis severity can be exacerbated by the use of beta-blockers.[55]

There are several retrospective case–control studies that correlate psoriasis flares to recent stressful life events;[17,18] for example, patients with a larger psychological burden experienced onset of psoriasis at a younger age.[56] However, due to the nature of retrospective case–control studies, recall bias is difficult to control and likely overestimates the link between stress and psoriasis. Until recently, a significant controlled, prospective study linking stress to psoriasis had not been performed.[57] A small, prospective study following nine women with what was believed to be stress-induced moderate psoriasis showed no relationship between perceived stress levels and timing of psoriasis exacerbations.[58] For psoriatic arthritis, however, a 25-year prospective study showed that psoriatic patients with depression were around 37% more likely to develop psoriatic arthritis.[59] Given the strong link between psoriatic skin disease and psoriatic arthritis, it is plausible to suspect that psychological distress plays a similar role in both entities.[60]

In cases when depression leads to worsening of inflammation and psoriasis symptoms, treatment of depression should logically improve outcomes for psoriatic patients. As expected, depressed patients who responded to treatment with the tricyclic antidepressant (TCA) amitriptyline showed a significant reduction in plasma TNF-α, IL-6, and IL-1β.[61] An improvement in

depressive symptoms correlates significantly with a drop in TNF-α, and a resistance to TCA treatment was associated with higher baseline IL-6.[62] This effect is not limited to TCA alone and has also been documented with SSRI, monoamine oxidase A inhibitors, and atypical antidepressants.[63,64] Antidepressants not only decrease overall inflammation but also cause a change in the characteristics of that inflammation, reducing IL-12 and consequently inhibiting Th1 cells that are needed for the cell-mediated immune response.[65,66] The notion that antidepressant treatment can help psoriatic disease was supported by the results of a double-blind controlled trial in which the addition of a monoamine oxidase A inhibitor resulted in significantly greater reductions in PASI scores after 6 weeks compared to monotherapy with topical corticosteroids alone (p=0.025).[67] An open-label study of bupropion, a noradrenaline-dopamine reuptake inhibitor, showed effectiveness as a monotherapy in the treatment of psoriasis, with 8 out of 10 patients reporting a mean PASI score reduction of 50%, which returned to baseline 3 weeks after treatment cessation.[68] Of note, case reports have since resulted in warnings about the possible induction of erythrodermic pustular psoriasis with the use of bupropion.[69] In a retrospective cohort study of 69,830 Swedish patients with psoriasis, patients exposed to SSRI were 66% less likely to require systemic treatments in the future and more likely to be tapered off systemic treatments during follow-up.[70] Considering the high cost of systemic treatments, such as biologics, antidepressants could play an important role in the cost-effective management of depressed psoriasis patients prior to starting more expensive systemic treatments, particularly for patients who see cost as a significant barrier.[71]

INFLAMMATION CAUSING PSYCHOLOGICAL DISTRESS

While depression may induce worsening of inflammation in psoriasis patients, the opposite is also likely and there is sufficient evidence to suggest that inflammation may be a strong aetiologic factor for psychological distress. Earlier studies showed that a low-grade, cell-mediated immune response causing diffuse oxidative damage could often result in depressive-like 'sickness behaviours,' such as psychomotor retardation, anorexia, weight loss, sleep disturbance, and loss of energy.[72] Since then, further investigation has revealed multiple other factors that play a role in the induction of these depressive symptoms, including decreased antioxidant levels, increases in oxidative and nitrosative stress, zinc deficiency, and decreased activation of indoleamine 2,3-dioxygenase.[73] Mice exposed to lipopolysaccharide and/or IL-1 (as a way to induce inflammatory cytokine release) showed more depressive symptoms, an effect that may have played an important evolutionary role since the display of sickness behaviour would theoretically conserve energy during times of illness or infection.[74,75] IL-17A, which has been implicated in the pathophysiology of psoriasis, has been shown to stimulate depressive symptoms in mice;[16,76] it is thought this occurs by activation of the NFκB/p38 MAPK inflammatory pathway in brain regions associated with psychological distress, including the hippocampus and prefrontal cortex.[16] Furthermore, when mice were treated with antibodies against IL-17A, they were significantly less likely to develop depressive symptoms.[76] In humans, however, there has been concern that the IL-17A blocker brodalumab may result in increased suicidal behaviour because four patients completed suicide during Phase III clinical trials.[77] Since then, the general consensus is that there does not seem to be a meaningful association between suicidal behaviour and IL-17A blockers.[78] In fact, the opposite has also been observed, with a prospective Phase III clinical trial finding that depressive symptoms significantly decreased after 12 weeks of treatment with brodalumab.[79] The U.S. Food and Drug Administration (FDA) has since approved the use of brodalumab for psoriasis, although with a black box safety warning for suicidal ideation.

As previously mentioned, mice that were treated with IL-1 antagonists showed a decreased fear response and decreased propensity toward learned helplessness, suggesting that inflammation is important for animals to fully express depressive symptoms.[23] These results are not limited to animals and seem to relate to humans also. Among cancer patients, those

who were exposed to IFN and/or IL-2 showed significantly more psychological distress and cognitive disturbances due to stimulation of their immune system.[80,81] In addition, IFN has long been used to stimulate cell-mediated immunity against the hepatitis C virus[82] and in patients with hepatitis C, depression has been detected in up to 80% of those receiving IFN therapy.[83] Similarly, depressive symptoms correlated with inflammatory markers like IL-6 and TNF-α in patients vaccinated for *Salmonella typhi*, even if they showed no physical signs of sickness.[84] Mice with an *IL-6* gene knockout were much more resistant to psychological distress and less likely to develop depressive symptoms, demonstrating that inflammatory cytokines play a direct role in the development of depression.[85] In line with this, postmortem mRNA analyses of the prefrontal cortex of teenage suicide victims revealed an overexpression of IL-1β, IL-6, and TNF-α.[86] The reason for these findings may be related to the understanding of how inflammatory cytokines affect important neurotransmitters in the brain.

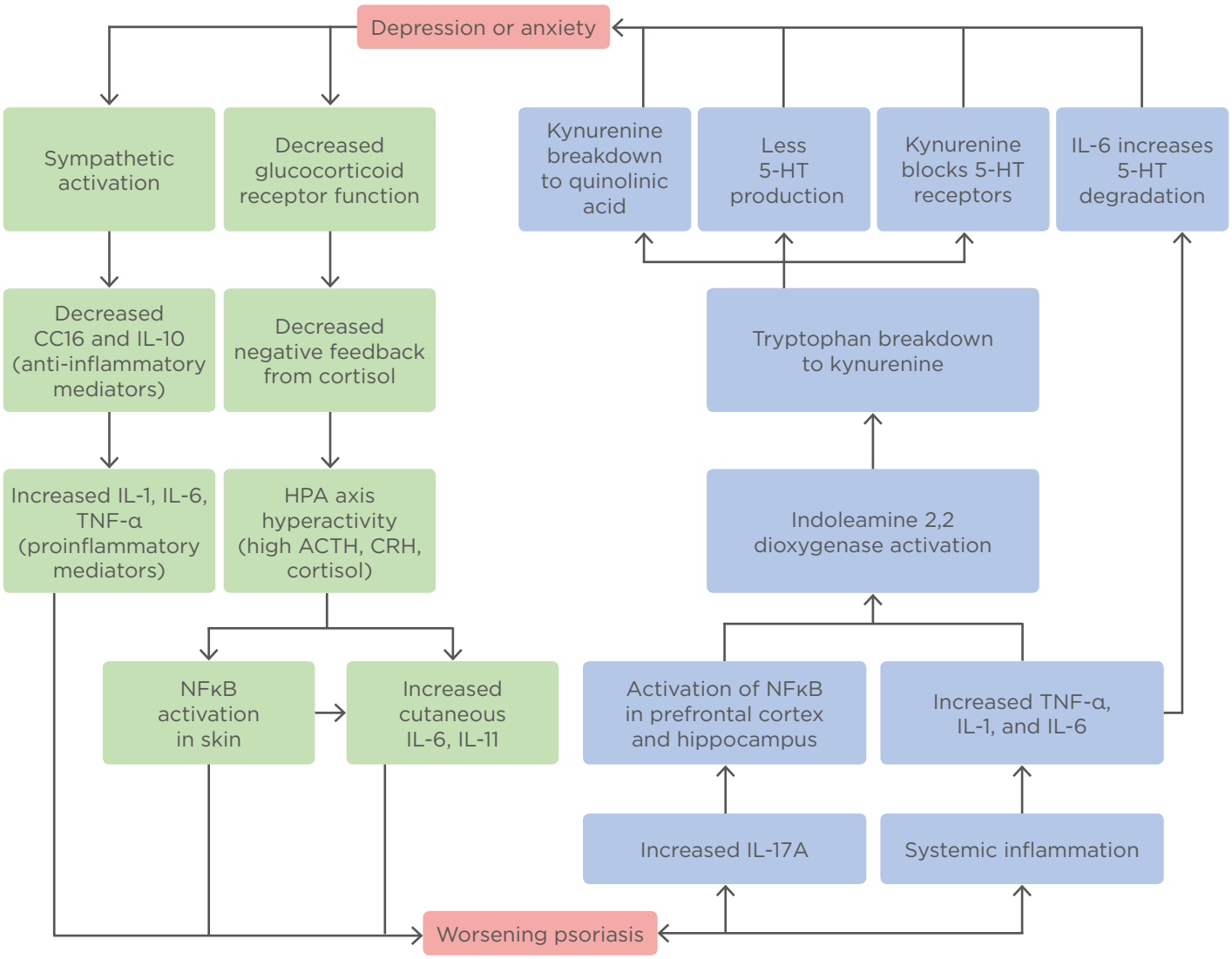

Figure 1: The bidirectional relationship between psoriasis and depression or anxiety.

This flowchart provides an illustrative summary of the biological mechanisms outlined and discussed in this review and demonstrates the complex interactions between these very different clinical entities.

5-HT: 5-hydroxytryptamine (serotonin); ACTH: adrenocorticotropic hormone; CC16: uteroglobin; CRH: corticotropin-releasing hormone; HPA: hypothalamic–pituitary–adrenal.

Systemic inflammation can cause an activation of indoleamine 2,3-dioxygenase, leading to increased breakdown of the serotonin precursor tryptophan into kynurenine, effectively reducing its availability for serotonin production.[87] The effect of this functional serotonin decrease is further compounded by the demonstrated ability of kynurenine to serve as a serotonin receptor antagonist and induce *de novo* depressive symptoms despite the presence of ample serotonin.[73] Additionally, kynurenine is subsequently broken down into quinolinic acid, a neurotoxin known to build up in the anterior cingulate gyrus of depressed patients.[88,89] Contributing further to this shift, IL-6 increases the breakdown of serotonin in the brain.[90] Therefore, inflammation simultaneously decreases serotonin production, increases serotonin breakdown, and inhibits serotonin receptors through a strong synergistic effect.[91] This mechanism may explain why inflammation has been associated with significant resistance to several antidepressants.[92,93]

If inflammation plays a significant role in the severity of depression, treating inflammation would intuitively cause a decrease in depressive symptoms. In a double-blind study, patients taking etanercept, an anti-TNF, showed at least a 50% improvement in the Beck Depression Inventory (BDI) when compared to placebo.[94] Improvements in depressive symptoms were not strongly correlated with improvements of objective measures of psoriasis severity, such as PASI. This suggests that improvements in depressive symptoms are a result of inhibition of inflammation and not solely a consequence of decreased disfigurement from disease. This notion is supported by the finding that phototherapy had no significant effect on patients' depression and anxiety symptoms despite significant improvements in the severity of their psoriasis.[95] The interventions that improve psoriasis-associated depression are those that treat the underlying systemic inflammation and not simply the clinical manifestations of the disease.

Further investigation on the matter has shown that the use of anti-inflammatory agents may be viable in depressed patients but treatment selection may be best guided by the identification of subgroups that could respond better to such therapies.[96] Clinical trials investigating this seem promising, as one randomised controlled trial testing infliximab for treatment-resistant depression found that the subgroup of patients with particularly high inflammatory markers experienced significant reductions in depressive symptoms after exposure to the TNF-α antagonist.[97] Moreover, while severity of psoriasis did not correlate with depression, treatment with ustekinumab, an anti-IL-12 and IL-23 biologic, resulted in a significant decrease in depressive symptoms.[98] More recently, guselkumab, an anti-IL-23 monoclonal antibody, was shown to reduce depression and anxiety after 16 weeks in a Phase III randomised double-blind placebo-controlled study.[99] These results imply that biologics could be a viable treatment option for psoriasis and the depression that is commonly associated with it.

CONCLUSION

There is undoubtedly a strong correlation between psoriasis and psychological distress. While more research is needed to determine the extent to which psychological distress causes the inflammation seen in psoriasis, or vice versa, one finding remains clear: both depression and psoriasis are inflammatory diseases at the basic, physiologic level (Figure 1). Psoriasis has historically been considered a purely dermatologic condition, often treated with topical steroids for temporary symptomatic relief. However, the paradigm has shifted to treating this disease more like a syndrome, with significant medical and psychiatric comorbidities spanning multiple body systems. The use of biologics and systemic anti-inflammatory drugs has been shown to reduce not only the severity of psoriatic lesions but the risk of developing serious comorbidities, such as myocardial infarction.[100] With these medications, dermatologists may now work towards fully treating the psoriasis patient, extending their attention and care further than the skin.

While treatment of psoriatic skin lesions would be expected to lessen psychological distress, the psychiatric and psychosocial morbidities experienced by patients have not reliably shown to be proportionate to the extent of their cutaneous lesions.[101] Failure to screen for and address psychiatric comorbidities in the

psoriatic population leads to the persistence of significantly reduced quality of life among these patients. Psychiatric referral is a reasonable step in caring for patients with suspected psychological distress, but dermatologists are truly at the frontline. While many dermatologists are uncomfortable prescribing antidepressants, this may be the only route by which patients can receive this valuable treatment, which will not only improve their quality of life but also improve their skin disease.[102] As investigation into the mind–skin connection continues, researchers will hopefully uncover the details required to specifically address the inflammation associated with psoriasis and its psychiatric comorbidities.

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A Systematic Review on the Efficacy of Topical Acyclovir, Penciclovir, and Docosanol for the Treatment of Herpes Simplex Labialis

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Abstract

Background: Herpes simplex labialis is a common skin condition caused by the herpes simplex virus. The prescription of antivirals for the treatment of herpes labialis is common. The objective of this study was to conduct a systematic review of the available evidence on the treatment of herpes simplex labialis with U.S. Food and Drug Administration (FDA)-approved topical antibiotics.

Methods: The literature search included searches of PubMed, Google Scholar, and Scopus. This review included studies that examined herpes labialis lesions and treatment with topical acyclovir, penciclovir, or docosanol in at least one of the study arms.

Results: Of the 1,485 papers initially identified, 20 papers representing 19 randomised controlled trials and one quasi-randomised trial met the inclusion criteria for the systematic review.

Conclusion: Our systematic review of the clinical studies performed on the three topical antiherpetics, acyclovir, penciclovir, and docosanol, showed that their efficacy compared to placebo is marginal at best (shortening the duration of pain by <24 hours), although the three topical antiherpetic drugs have no serious adverse reactions and are safe to use.

INTRODUCTION

Herpes labialis is primarily caused by herpes simplex virus Type I (HSV-1). Approximately 20–40% of adults are affected at some point in their lives.[1] There is currently no cure for herpes labialis outbreaks.[2] There is a wide variety of prescription and non-prescription medications used to treat herpes labialis. Topical antivirals, including U.S. Food and Drug Administration (FDA)-approved acyclovir, penciclovir, and docosonal, are often used to treat herpes labialis infections.

Acyclovir is a cyclic guanine nucleoside analogue that lacks the 2' and 3' positions normally supplied by ribose.[3] Acyclovir inhibits synthesis of viral DNA. This inhibition depends on interactions with thymidine kinase and DNA polymerase.[3] Elimination half-life of systematically administered acyclovir is approximately 2.5 hours in adults with normal kidney function.[3] Acyclovir is available in intravenous, oral, topical, or ophthalmic (not currently approved in the USA) treatments. Topical acyclovir is prepared as a 5% cream and ointment.[2]

Penciclovir is an acyclic guanine nucleoside analogue and is similar to acyclovir in potency and activity against HSV. Penciclovir inhibits viral DNA synthesis through competitive inhibition of viral DNA polymerase.[3] The half-life of penciclovir is approximately 7–20 hours,[3] and is available in a topical form, approved as a 1% cream.[2]

Docosonal is a long-chain saturated alcohol that inhibits the replication of HSV (lipid-enveloped virus).[3] Docosonal is approved as a topical 10% cream for treatment of the orolabial form of HSV only.[4] It is the only over-the-counter agent approved by the FDA for the treatment of HSV. As shown in Table 1, all three FDA-approved topical treatments are available in cream form and acyclovir is also available as an ointment. The bases and strengths differ, and the prices range from approximately $10 up to almost $200.[5-11]

Several systematic reviews focussing on the effectiveness of antivirals for the prevention of recurrent herpes labialis have been published. However, little has been published on treatment.[12] Worrall[1] published a systematic review looking at the effects of interventions aimed at preventing recurrent attacks of herpes labialis and found limited evidence that topical antiviral agents reduce healing in herpes labialis recurrent episodes. They also noted that the results from topical antiviral agents were inconsistent and of marginal clinical importance. Since there are a limited number of systematic reviews available that focus on treatment, this systematic review examines the current available evidence of the clinical effectiveness of topical FDA-approved antivirals for the treatment of herpes labialis in adults.

Table 1: Drug characteristics and information.

Drug	Type	Base	Strength	Approval date	Price*
Acyclovir	Ointment	Polyethylene glycol[5]	5%[5]	1982[6]	$12.00–$26.59
Acyclovir	Cream	Cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, white petrolatum[7]	5%[7]	2002[6]	$191.16
Penciclovir	Cream	Cetostearyl alcohol, mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, water, white petrolatum[8]	1%[8]	1996[9]	$194.88
Docosonal	Cream	Benzyl alcohol, mineral oil, propylene glycol, water, sucrose distearate, sucrose stearate[10]	10%[10]	2000[11]	$9.28

*Drug prices correct as of 07/06/2018; data obtained from LexiComp Online. Price of preparation is per gram. The above pricing represents current commercially available products. Please note that products used in the studies may vary from what is currently commercially available.

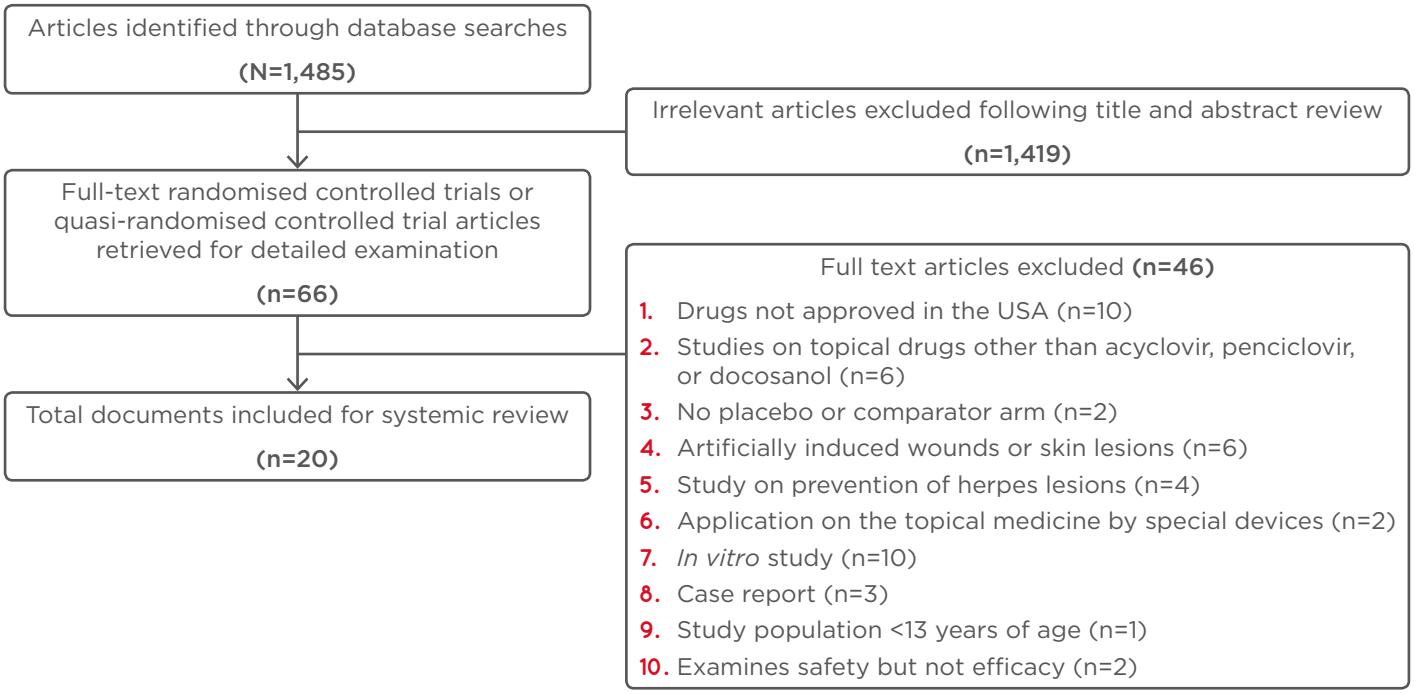

Figure 1: Flowchart representing the literature search carried out during the review.

METHODS

Literature Search

The authors conducted this systematic review in accordance with the PRISMA recommendations, which represents a standardised method and format for authors to report systematic reviews.[13] PubMed, Google Scholar, and Scopus (which includes content from the Embase database) were searched; the search was limited to the English language, with no time limitation of literature search. The last search was performed in May 2018.

The following search strategy comprising the MeSH and keywords was used: ((“penciclovir” [Supplementary Concept] OR “penciclovir”[Tiab] OR “Danavir”[Tiab]) OR (“Acyclovir”[Mesh] OR “acyclovir”[Tiab]) OR (“docosanol” [Supplementary Concept] OR “Tadenan” [Supplementary Concept] OR “abreva”[Tiab] OR “docosanol”[Tiab])) AND (“Herpes Labialis”[Majr] OR “herpes labialis”[Tiab] OR “cold sore*”[Tiab] OR “fever blister*”[Tiab]). References of all included articles were scanned for additional studies.

Selection

Reviewers included prospective randomised controlled trials (RCT) and quasi-randomised trials with no limitation for sex or country of origin, but excluded trials that examined individuals <13 years old. Studies that examined herpes simplex labialis lesions and included topical acyclovir, penciclovir, or docosanol in at least one of the study arms were included. Studies on comparison among these three topical antiviral agents were also included. Studies on artificially induced lesions, prevention of herpes lesions, and use of herbal therapies, self-concocted drugs, or non-FDA approved drugs were excluded. *In vitro* studies and studies that required application of the topical medication by a special device were also excluded.

A total of 1,485 unique articles found through the database search were independently reviewed. Studies were selected based on eligibility criteria, data sources, study methods, sample sizes, types of intervention, and authors’ conclusions.

Outcomes

The reviewers looked at the duration of episode and time taken for the lesion to heal, duration of pain, time to loss of crust, and other findings reported for each selected article.

Assessment for Risk of Bias

The reviewers evaluated the studies for risk of bias. Evaluation was based on Cochrane Collaboration's tool for assessing risk of bias.[14]

RESULTS

The results of the literature search are shown in Figure 1. Initially, 1,485 potentially relevant articles were identified through the database search. After reviewing the titles and abstracts, 1,419 articles were excluded and 66 full-text articles were eligible for detailed examination. Out of the 66 full-text articles reviewed, 46 articles were excluded based on the criteria cited in Figure 1. Overall, 19 RCT and one quasi-randomised trial met the criteria for systematic review. The characteristics of the 20 studies included in the systematic review are summarised in Table 2 (Click Here to view).[15-34]

Risk of Bias

The reviewers evaluated each included study for risk of bias (selection bias, performance bias, detection bias, attrition bias, and reporting bias) based on Cochrane Collaboration's tool for assessing risk of bias.[14] Out of the 20 articles included for systematic analysis, 15 were at low risk of bias, 4 at high risk, and 1 at unclear risk. The 4 studies at high risk of bias were all related to acyclovir (two committed attrition bias, one committed performance bias, and one committed both selection and performance bias).[15,20,28,30] The authors considered the study conducted by Habbema et al.[33] at unclear risk. Although the authors of this paper mentioned that "...patients were allocated at random on a double-blind basis...", there was no further description of how the randomised controlled trial was conducted.

Adverse Events

In the 20 studies that were reviewed, all three topical agents (acyclovir, penciclovir, and docosanol) were well tolerated. Most subjects had no reaction or minimal localised reactions that occurred at rates similar to placebo. Localised reactions included inflammation and dry skin. There were no systematic adverse events reported in any of the studies.

DISCUSSION

Acyclovir was evaluated in 14 studies, all of which were RCT. The results of these trials were mixed, with most studies showing no effect or modest improvement with acyclovir treatment. The studies varied in what type of base the acyclovir was prepared in, which may account for some of the variation in results. There were four studies reviewed regarding penciclovir. Two of the studies compared penciclovir to acyclovir and one study showed that penciclovir was superior to acyclovir; however, the other trial showed no difference in effectiveness.[30,31] The two other studies regarding penciclovir showed modestly improved healing and pain outcomes when compared to placebo.[29,32] Docosanol was compared to placebo in two studies included in this review and had conflicting results; one trial found significantly shorter healing time when compared to placebo, while the other study did not show a significant difference.[33,34]

All the studies included were prospective in nature. Two of the acyclovir studies included recurrent episodes in their analyses.[23,24] Prior to study enrollment, patients had 2–7 recurrences per year in the studies in which this information was specified.[18-22,25-34] Most of the studies included treatment with the topical antiviral products 4–8 times per day for an average duration of 4–10 days, and the majority of patients started treatment as soon as possible after symptoms developed, with a few exceptions (see Table 2 for details). None of the studies indicated the patients had associated conditions along with herpes labialis. One of the acyclovir studies was completed in immunocompromised patients;[17] however, the other studies were completed in immunocompetent patients.

Chen et al.[35] performed a systematic review and meta-analysis to evaluate the effectiveness of nucleoside antiviral drugs for the treatment of herpes labialis. They included 16 publications in their review that included both oral and topical treatments. Oral and topical antivirals shortened the disease course and blocked lesion progression. The only significant difference between oral and topical treatments was a reduction in the healing time of all lesions when using oral medication.

Jensen et al.[36] performed a review of oral antivirals for the treatment of recurrent herpes labialis episodes. They reviewed five placebo-controlled and two comparative studies and concluded that treatment with oral antivirals decreased the lesion duration by about 1 day with modest clinical implication.

Rosa et al.[37] published a systematic review on 5% acyclovir–1% hydrocortisone cream compared to placebo for herpes labialis treatment. Their meta-analysis showed that early treatment with 5% acyclovir–1% hydrocortisone was beneficial. However, their systematic review was limited to two studies.

This systematic review of 20 trials was limited to FDA-approved topical antivirals for treatment. The reviewers found that topical antiviral therapy has little benefit to treatment. Similarly, Rahimi et al.,[12] in their systematic review and meta-analysis reported a lack of benefit from topical antiviral therapy for prevention.

Some limitations of this review were that the systematic review is retrospective in nature, compares only studies that have been previously published by others, and does not prospectively compare the topical treatments. Furthermore, there were only a few studies that met the inclusion criteria for penciclovir and docosanol; most of the studies used acyclovir. Another limitation is that many studies assessing the efficacy of topical antibiotics have heterogeneic study designs, which makes comparison across studies difficult. This review did not investigate the effect of oral FDA-approved antivirals. Worrall's[1] 2009 review reported that oral antiviral treatments are more beneficial than topical agents for treatment. However, oral antiviral tablets are available only by prescription in most countries.[38]

CONCLUSION

It is well known that, unlike herpes zoster lesions (shingles), the majority of immunocompetent patients who develop recurrent herpes labialis lesions have mild local symptoms and the lesions eventually heal without sequelae, even without receiving systemic or topical treatment. This systematic review of the clinical studies evaluating the three topical treatments, acyclovir, penciclovir, and docosanol, also supports the notion that their efficacy compared to placebo is marginal at best (shortening the duration of pain by <24 hours), although the three topical antiherpetic drugs have no serious adverse reactions and are safe to use. It was noted that there is a lack of studies comparing the commercially available treatment options, as most of the studies compared active treatment with one of the three agents to placebo. Although none of the studies looked specifically at cost effectiveness based on the minimal clinical benefit, the self-limiting nature of lesions, and the high cost of medications, the authors would be hesitant to routinely recommend the use of topical antiviral medications for the treatment of herpes labialis.

TABLE 2 IS AVAILABLE TO DOWNLOAD VIA THIS LINK ←

https://goo.gl/zRRKqh

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Predicting Response to Omalizumab in Chronic Urticaria Based on Biomarkers

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Abstract

Chronic urticaria (CU) is characterised by intense recurrent itch, wheals, and/or angioedema, persisting for >6 weeks. CU can be subdivided into chronic spontaneous urticaria and chronic inducible urticaria; the latter usually appears with physical stimuli, such as heat, cold, pressure, and sunlight. The recommended treatment for CU is non-sedating oral antihistamines, administered up to four times a day. The monoclonal antibody omalizumab (anti-IgE) is recommended as an add-on therapy for patients with antihistamine-refractory CU. The fluctuating nature of urticaria symptoms and varying response to omalizumab often makes it difficult to predict the response to omalizumab; this often leads to individualised dosage regimens for CU patients. However, being able to predict the response to omalizumab treatment would lead to an improvement in dosage regimens and treatment plans in the clinical setting. Several studies have investigated potential CU biomarkers; however, no reliable biomarkers have been discovered that can be used to assess the treatment response to omalizumab in the clinic. Some potential biomarkers, such as plasma D-dimer, serum total IgE levels, the basophil histamine release assay, the autologous serum skin test, and the basophil activation test, have been suggested for predicting disease activity and response to omalizumab but are not implemented routinely in clinical practice. This paper presents an overview of the various biomarkers associated with response to omalizumab in CU.

INTRODUCTION

Urticaria is an itchy skin disease characterised by wheals and/or angioedema. Urticaria can be acute or chronic depending on the persistence of symptoms. In chronic urticaria (CU), symptoms are present for >6 weeks. CU can be subdivided into chronic spontaneous urticaria (CSU) or chronic inducible urticaria; the latter usually appears in response to physical stimuli, such as heat, cold, or sun exposure, or following the application of pressure.[1] The most common type of non-acute urticaria is CSU, which has an estimated prevalence of 0.5–1.0% in the general population.[2] Females are affected twice as often as males, with the highest incidence of CU seen

in patients between the ages of 20 and 40 years; the average duration of CU is 3–5 years.[2] The recommended treatment for CU is oral non-sedating antihistamines, taken up to four times a day, while omalizumab is used in cases of antihistamine-refractory CU.[1]

Omalizumab is a humanised monoclonal antibody that inhibits the binding of IgE to the high-affinity receptor FcεRI on the surface of basophils and mast cells;[3] thus, omalizumab reduces the levels of free IgE and downregulates IgE receptors on these cells. This modulation of FcεRI receptors plays an active role in the clinical management of CU with omalizumab. However, the fluctuating nature of urticaria symptoms and the varying effect of omalizumab often makes it difficult to predict the course of treatment. Some biomarkers have been associated with response to omalizumab in the clinical setting and this review presents an overview of these available biomarkers.

TREATMENT OF CHRONIC URTICARIA WITH OMALIZUMAB

Several clinical studies have established that omalizumab significantly reduces urticaria symptoms in CU patients.[4-7] Furthermore, omalizumab reduces the need for additional medication, improves patient quality of life, and reduces the number of days of urticaria symptoms.[8] Real-world studies of antihistamine-refractory patients with CU treated with omalizumab have reported similar observations as randomised clinical trials in terms of the efficacy and safety of omalizumab.[9]

The recommended dose of omalizumab is 300 mg every 4 weeks and around 65% of patients experience a complete or almost complete response.[4-7] Most patients experience flare-ups if administration of omalizumab is delayed by >30 days.[10] Although omalizumab has a significant effect on urticaria symptoms, patient response patterns vary; fast responders experience a response within 2–4 weeks after initiating treatment, while some patients experience a slower response, which is seen 12–16 weeks after initiation of treatment. Therefore, it is recommended that omalizumab treatment is continued for at least 6 months before considering other options.[11] However, no formal recommendation for the tapering or optimisation of omalizumab treatment exists when symptoms are well-controlled or reoccur. Nevertheless, in the case of symptom reduction, prolonging treatment intervals has been suggested in a treatment algorithm.[12] Relapse of urticaria symptoms is often seen 2–8 weeks after the last injection of omalizumab; in such cases, retreatment with omalizumab has obtained good results.[13] The most commonly reported adverse effects with omalizumab are headache, injection site itch and redness, and nausea.[4-7] No severe adverse effects or complications to omalizumab have been reported.

Assessment of response to omalizumab treatment is usually based on overall physician assessment or validated patient-reported outcomes (PRO),[14] such as Urticaria Activity Score in the past week (UAS7), which prospectively documents the intensity of itch and number of wheals daily on a scale from 0 (none) to 3 (severe) for 7 days. A UAS7 score ≥28 (score range: 0–42) indicates severe disease activity, while a UAS7 score ≤6 indicates well-controlled disease. The minimal clinical difference in UAS7 is equivalent to 10 points.[15,16] Urticaria Control Test (UCT) is a retrospective questionnaire (score range: 0–16) that assesses disease control in the last 4 weeks. A score ≤11 indicates poor disease control, while a score ≥12 indicates well-controlled disease.[17] The minimal clinical change in UCT is 3 points.[18] Other PRO, such as Dermatology Life Quality Index (DLQI) and Chronic Urticaria Quality of Life Questionnaire (CU-QoL), are used to evaluate the impact of CU on the quality of life of the patient.[19,20] These validated scores are of great value when monitoring urticaria patients, but a major disadvantage is that the scoring systems are subjective.

BIOMARKERS AND RESPONSE TO OMALIZUMAB IN CHRONIC URTICARIA

The fluctuating nature of CU symptoms and the varying response to omalizumab often leads to individualised dosage regimens for CU patients, making it difficult to predict response to treatment. Predicting omalizumab treatment response and changes in disease activity or severity would contribute to the development of a consensus treatment algorithm for clinical

use and work as an objective follow-up tool for patients with fluctuating disease activity.[14] Potential biomarkers for CU have been investigated in several studies (Table 1);[21-28] however, there are currently no reliable biomarkers that can be used to assess the treatment response to omalizumab in the clinic. Some studies have suggested potential biomarkers, such as D-dimer, IgE levels, and the basophil histamine release (HR) assay, for predicting disease activity and response to omalizumab; however, none of these are currently implemented routinely in clinical practice.[14,29]

OMALIZUMAB AND AUTOIMMUNITY

One of the most frequent causes of CU is thought to be autoimmunity. Autoantibodies against the high-affinity IgE receptor or to autoantigens have been described as possible causes for CU;[1] however, the pathological mechanism is not completely understood. Several laboratory tests can be used to measure autoimmunity in CU such as the basophil HR assay, autologous serum skin test (ASST), and basophil activation test (BAT). A positive basophil HR assay is often linked to autoimmune CU, treatment response, and disease activity in CU patients,[30] and is defined as when HR from stimulated and unstimulated cells is >16.5% in both children and adults.[31]

A retrospective Danish study[21] included 154 antihistamine-refractory CU patients from 2010–2014 and showed that a larger fraction of patients with a negative basophil HR assay had a complete or almost complete response to omalizumab compared to patients with a positive HR assay (77.3% versus 27.3%; p<0.01). However, in a 6-month prospective study of 117 CSU patients treated with omalizumab, the HR assay result was not predictive for omalizumab response measured with various PRO (UAS7, UCT, and DLQI).[32] In addition, other patient-specific factors such as age, sex, duration of symptoms, presence of angioedema, ethnicity, and previous use of antihistamines and immunosuppressant drugs were not significantly associated with response to omalizumab.[32]

In a German study of 64 CSU patients refractory to oral antihistamines, the authors investigated the relationship between the urticaria HR assay and response to omalizumab.[22] All patients were treated with 300 mg every 4 weeks and the follow-up time was 12 weeks. A total of 56 patients responded to omalizumab and 8 patients were unresponsive at Week 12. A response to omalizumab within 8 days was classified as fast (n=39), while a response after 8 days was classified as slow (n=17). Excluding one patient among the fast responders who had a positive urticaria HR assay, it was seen that patients with a positive urticaria HR assay only responded to omalizumab after the second injection and thus a slower response to treatment was seen; the median response time in patients with a positive urticaria HR assay was 29 days compared to 2 days in patients with a negative HR assay.[22] These observations indicated that having a positive urticaria HR assay may be predictive of a slow response to omalizumab.[22]

Table 1: Biomarkers associated with response to omalizumab in chronic urticaria.

Study	Biomarker	Prediction of response
Ghazanfar et al.,[21] 2016 Gericke et al.,[22] 2017	Basophil HR assay	Positive urticaria HR assay predicts a slower response to omalizumab.
Kolkhir et al.,[23] 2018	ASST	Positive ASST is related to a delayed response to omalizumab.
Palacios et al.,[24] 2016	BAT	Negative BAT is associated with a better response to omalizumab.
Cugno et al.,[25] 2018 Straesser et al.,[26] 2017 Ertas et al.,[27] 2017	IgE	High IgE levels before treatment predict a faster response to omalizumab but a faster relapse of symptoms after discontinuing treatment.
Cugno et al.,[25] 2018 Asero et al.,[28] 2017	D-dimer	High D-dimer levels before treatment are associated with a better response to omalizumab.

ASST: autologous serum skin test; BAT: basophil activation test; HR: histamine release.

The ASST is also associated with autoimmune CU and response to omalizumab. In the aforementioned German study,[22] an ASST was performed in 51 CSU patients. It was seen that CSU patients with a positive ASST responded slower to omalizumab treatment compared to patients with a negative ASST. A total of 33 patients were fast responders and 13 responded slowly to treatment. Of these 13 patients, 10 had a positive ASST. Additionally, a significant association was seen between a positive ASST and a positive basophil HR assay. ASST positivity has also been linked to higher levels of C-reactive protein (CRP) in urticaria patients. No studies specifically investigating CRP levels and response to omalizumab have been performed; however, CRP levels are often significantly higher among antihistamine-refractory patients and have therefore been linked to non-responsiveness to antihistamines.[23] Contrary to this, a prospective study from Korea that included 75 CSU patients reported that ASST positivity was a significant predictor for well-controlled CU.[33]

Basophil activation, quantified by flow cytometry, has also been suggested as a potential biomarker for severity of CU and the success of omalizumab treatment. Most studies have used CD63 or CD203c as markers for effective basophil activation. In a recent study from Spain, 139 patients with CSU were included to assess the diagnostic usefulness of BAT in combination with ASST in CSU disease activity.[34] It was observed that a positive BAT was significantly associated with a positive ASST; however, a positive ASST was not associated with positive BAT in the same way.[34] In another study of 41 CU patients, it was seen that a lack of upregulated CD203c correlated with clinical response to omalizumab. Thus, a negative BAT might be predictive of a positive response to omalizumab.[24]

In summary, positive autoimmunity tests such as the basophil HR assay, ASST, or BAT might be predictive of a poorer response to omalizumab in CU patients.

OMALIZUMAB AND IGE

It is becoming increasingly clear that IgE-mediated autoallergy and IgG-mediated autoimmunity contribute to the pathogenesis of CU; however, there are still many aspects of the disease that need to be explained.[35] Recent studies have shown that patients with IgG autoantibody-mediated CSU experienced a slow response to omalizumab compared to patients with IgE autoantibody-mediated CSU.[35] Omalizumab is an anti-IgE that reduces the free level of IgE and downregulates IgE receptors on basophils and mast cells. Therefore, it is acceptable to consider IgE as a potential predictor for response to omalizumab. Serum total IgE is, on average, elevated in patients with CU.[30]

In a recent German study of 113 (74 females) antihistamine-refractory CSU patients,[36] IgE levels were investigated before and after treatment with omalizumab. All patients were treated with 300 mg omalizumab every 4 weeks and clinical response was evaluated with UAS7. At Week 12, 43 patients showed complete response, 55 showed partial response, and 15 patients showed no response to omalizumab. High disease activity and presence of angioedema were more common in the non-responders. Furthermore, it was seen that non-responders had lower IgE levels at baseline and similar observations were made in other studies.[25,26] A two-fold increase in IgE levels from baseline to 4-week follow-up was also shown in complete and partial responders; hence, higher levels of IgE after treatment with omalizumab were associated with greater reduction of disease activity at follow-up. Additionally, it was seen that patients with higher levels of IgE at baseline also experienced faster relapse of urticaria symptoms after discontinuing omalizumab treatment.[27] Higher levels of IgE in patients prior to treatment with omalizumab can be used as a predictor of almost complete or complete responders.

OMALIZUMAB AND D-DIMER

In some CSU patients, activation of the coagulation cascade, specifically the tissue factor pathway, is observed, and studies have shown that D-dimer is related to disease activity in CU patients due to the activation of this cascade.[25] D-dimer is a fibrin degradation product and its presence reflects the expression of tissue factor by eosinophils, the activation of the coagulation cascade, and thrombin generation. Thrombin generation increases the permeability

and induces degranulation of mast cells, while eosinophil activation increases plasma levels of D-dimer.[37] Elevated D-dimer levels are often associated with refractory disease and poor response to antihistamine treatment in CU.[38]

It is also reported that D-dimer levels correlate with UAS7[39] and some studies have indicated that D-dimer is associated with response to omalizumab therapy. One study from Italy investigated D-dimer levels before and after treatment with omalizumab in 25 CSU patients with severe disease activity.[25] Cugno et al.[28] reported that baseline D-dimer levels were significantly lower in non-responders compared to partial and complete responders. In another recent study from Italy,[28] 32 antihistamine-refractory CU patients were treated with 300 mg omalizumab every 4 weeks for 3 months. A total of 75% of the patients reported a complete response to omalizumab. D-dimer levels were elevated in almost 60% of the patients and most of the patients with elevated D-dimer levels experienced complete response to omalizumab. Furthermore, an increase in D-dimer levels after administration of omalizumab was seen among non-responders.[28] These studies indicate that elevated levels of D-dimer before treatment are associated with better response to omalizumab compared to patients with lower levels of D-dimers.

DISCUSSION

Although there is little literature investigating potential biomarkers associated with response to omalizumab in CU, the available studies suggest that several biomarkers used in clinical practice, such as the basophil HR assay, ASST, BAT, serum levels of IgE, and plasma D-dimer levels, are all associated with response to omalizumab in CU patients. For example, some studies have suggested that a positive urticaria HR assay is a marker of autoimmunity in CU and might be useful for predicting a less favourable treatment response to omalizumab.[22,30] In contrast, a positive urticaria HR assay has also been associated with frequent spontaneous remission of CSU at 12 months and severe disease activity at onset.[40] It has also been observed that a positive ASST, another marker of autoimmunity in CU, is predictive of a slow response to omalizumab.[22] However, in one study ASST was described as a potential predictor for well-controlled CU.[33] Furthermore, a positive BAT has been associated with poor response to omalizumab.[24,34]

It has been suggested that high baseline levels of serum total IgE are linked to a favourable response to omalizumab but also to faster relapse of symptoms after discontinuing treatment with omalizumab compared to patients with low IgE levels before treatment.[25,26] Low levels of D-dimer before treatment were seen among non-responders to omalizumab, while elevated levels of D-dimer before treatment seem to be predictive of a positive response to omalizumab in CU patients.[28]

Recently, comprehensive proteomic profiling extending beyond single serological biomarkers has gained increasing popularity in possibly predicting disease activity and treatment response in CU. A recent study from Korea investigated differentially expressed proteins in the sera of CSU patients with positive (n=3) and negative (n=3) ASST and the correlation with disease control.[41] In the ASST-positive group, the investigators identified seven upregulated proteins (apolipoprotein E-precursor, apolipoprotein J/clustrin, haptoglobulin, α-1-acid, glycoprotein, dynein heavy chain 8, and 8 albumin-like protein) and five downregulated proteins (two cleaved antichymotrypsins, plectin, polycomb protein SCMH1 isoform f, and α-1-ß-glycoprotein). Furthermore, the immunoassay of serum clusterin involved in cytoprotection against oxidants in ASST-positive and ASST-negative patients disclosed that clusterin levels were significantly higher in patients with ASST positivity compared to patients with negative ASST. It was seen that patients with higher levels of clusterin responded better to antihistamine treatment.[41]

Furthermore, autoallergic mechanisms in CU have been suggested because of the efficacy of omalizumab and increased levels of IgE in CU patients. In a German study,[42] autoallergic targets of IgE were investigated in 1,062 CSU patients. Although >200 IgE autoantibodies were identified in CSU patients, it was noted that only IgE autoantibodies to IL-24 were found in all CSU patients. In these patients, IL-24 was associated with HR, disease activity, and reduced basophil count.[42] Thus, the presence of IL-24 and elevated

levels of clusterin might be useful in predicting response to omalizumab treatment in CU patients; however, more studies are needed to investigate this further before it can be translated into clinical practice.

CONCLUSION

In conclusion, the basophil HR assay, ASST, BAT, serum levels of IgE, and plasma D-dimer levels all show some usefulness in predicting treatment response to omalizumab in CU; however, they are not used regularly in daily clinical practice in all centres mainly because of the low-quality evidence in favour of their use. Future clinical studies are needed to identify new biomarkers in CU and provide evidence for their usefulness as tools in the management of CU in clinical practice.

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Lingual Pustular Psoriasis and Acrodermatitis Continua of Hallopeau Successfully Treated with Adalimumab: A Rare Case Report and Review of Oral Psoriasis

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Abstract

Psoriasis is a common skin disease with various cutaneous manifestations and is classified into two clinical groups: non-pustular and pustular. Pustular psoriasis is less common than non-pustular forms of psoriasis and is particularly resistant to treatment. Studies of the rarer variants of acrodermatitis continua of Hallopeau and pustular psoriasis of the tongue remain scant. The subtypes of psoriasis can present all over the body, including in uncommon locations, such as the oral cavity; however, there are limited presentations and data regarding oral involvement in psoriasis and its subsequent management. Although cases involving oral psoriasis are rare, with <100 publications in the literature, and generally asymptomatic, recent studies have suggested that it is more prevalent than once thought. In contrast, presentation and subsequent management of lingual pustular psoriasis have not been reported. Presented and discussed in this review is a rare case of symptomatic, painful lingual pustular psoriasis and acrodermatitis continua of Hallopeau with complete remission after the use of adalimumab, followed by a thorough review of the histopathology, diagnosis, and clinical management of oral psoriasis. The use of biologics for conditions involving the oral mucosa, particularly in the setting of cutaneous psoriasis, is a novel concept with potential application in the fields of dermatology, oral medicine, and rheumatology.

BACKGROUND

Psoriasis is a well-described dermatological disease with various cutaneous manifestations. The aetiology of this skin disorder is multifactorial, with a strong hereditary and genetic component, particularly regarding the *PSORS1* gene and the human leukocyte antigen (HLA)-Cw6 allele.[1] The subgroup of non-pustular psoriasis includes psoriasis vulgaris or chronic plaque, guttate psoriasis, erythrodermic psoriasis, palmoplantar psoriasis, inverse psoriasis, and psoriatic arthritis. The subgroups of pustular psoriasis are generalised pustular psoriasis, also known as von Zumbusch disease, and localised pustular psoriasis, which includes palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau (ACH), which targets the nailbeds and surrounding skin.[1] Pustular psoriasis is particularly resistant to treatment. Several 2–3 mm sterile pustules that can easily rupture develop from an erythematous base and can coalesce into large pustular lesions. In extremely rare cases, pustules can develop on the oral cavity mucosa, lips, and lingual mucosa.[2,3] Generalised pustular psoriasis is an uncommon, severe variant of pustular psoriasis. Some researchers believe generalised pustular psoriasis is a different inflammatory condition to generalised plaque psoriasis.[2] There is limited literature regarding the efficacy of management of pustular psoriasis and a very small number of publications on rarer variants and their management, including ACH and pustular psoriasis of the tongue.[4-6]

Clinical and scholarly debates continue as to whether oral lesions in psoriasis are distinct pathological entities or whether they are indeed oral presentations of psoriasis.[4,7] Oral psoriasis is described in the literature as temporary and generally asymptomatic, and is commonly referred to as geographic and fissured tongue (FT).[4,8] Cases involving lingual psoriasis are exceptionally scant, with <100 publications available,[6,9] and presentation and subsequent management of lingual pustular psoriasis have not yet been reported. Presented and discussed in this report is a rare case of symptomatic and painful lingual pustular psoriasis and ACH with complete remission following the use of adalimumab. A thorough review of oral psoriasis, including the histopathology and clinical management, is also included.

CASE REPORT

A 79-year-old Caucasian female presented with an 18-month history of recurrent painful oral lesions. She was diagnosed 3 years earlier with generalised pustular psoriasis (biopsy of the right thigh) and ACH (affecting left digits 1–3 and the right thumb, with ongoing nail involvement). Examination revealed dystrophic nails manifested by subungual hyperkeratosis and pustules, yellowish discolouration, and onycholysis, and the dorsal tongue was oedematous with widespread erythematous pustules (Figure 1). The rest of the body was unaffected. Her comorbidities included rheumatoid arthritis (RA), polycythaemia rubra vera (PRV, positive JAK2 mutation), iron deficiency anaemia, hypertension, and atrial fibrillation. Differential diagnoses of her clinical features included infectious causes (bacterial, fungal, viral), cellulitis, and herpetic whitlow.

An oral surgeon performed a diagnostic incisional tongue biopsy. The dermatohistopathology revealed typical features of pustular psoriasis, similar to the report of her prior thigh biopsy (Figure 2). The absence of yeast or hyphae after staining the specimen with haematoxylin and eosin or Periodic acid–Schiff–diastase ruled out the presence of oral candida or fungal infection as causes of pathology. Topical swabs and viral screens were negative for unusual bacterial or viral growths.

Initial management provided temporary relief and consisted of xylocaine oral viscous, clobetasol deproponate (Dermovate®, GlaxoSmithKline, Uxbridge, UK), anti-calcineurin ointment (Protopic®, LeoPharma, Ballerup, Denmark), acitretin (Soriatane®, Stiefel, a GSK company, Research Triangle Park, North Carolina, USA) 10–30 mg/day, and mycostatin mouthwash. Later she retried methotrexate 12.5 mg/week for her oral psoriasis; however, it only provided a slight improvement and was subsequently stopped due to elevated liver enzymes. Prednisone 10 mg/day was given intermittently. Her mouth pain was interfering with eating, mastication, and deglutition, resulting in significant weight loss over several months (her BMI decreased from 21 to 18). None of these medications (including acitretin, methotrexate, and low-dose prednisolone) controlled her disease.

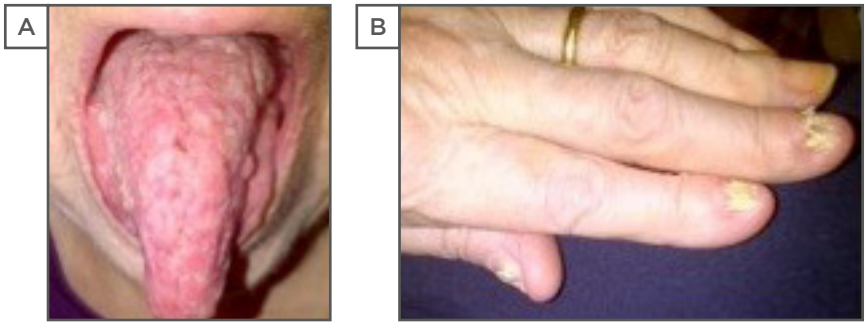

Figure 1: Psoriatic tongue (A) and nails (B) at presentation.

A) Extended tongue with pustular, erythematous lesions spread throughout the dorsal surface of the tongue and oral mucosa. B) Presentation of left hand with dystrophic nail changes on digits (thumb, index, and middle).

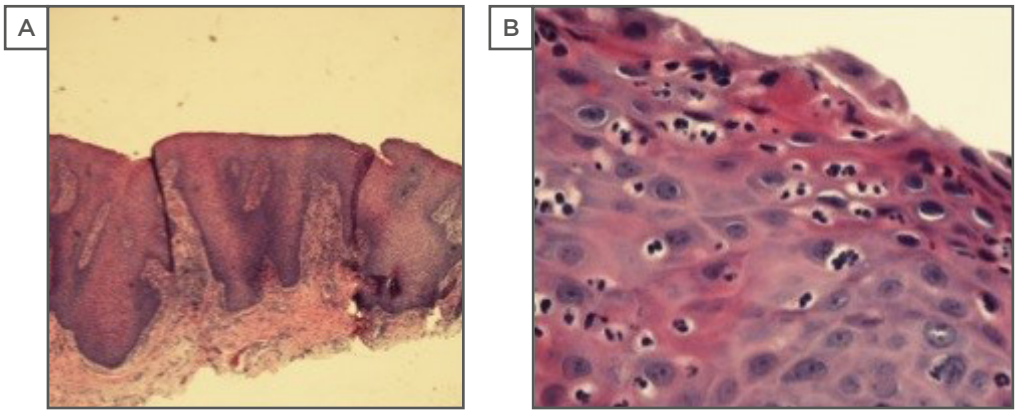

Figure 2: Histological specimens of the tongue biopsy with haematoxylin and eosin staining at 200x (A) and 400x (B) magnifications.

Histopathological features revealed subepithelial stroma with moderately dense perivascular and interstitial mixed inflammatory cell infiltrate consisting of lymphocytes and neutrophils, psoriasiform hyperplasia of the epithelium with suprapapillary plate thinning, and elongation of the rete ridges, acanthosis, and parakeratosis.[1] Spongiotic pustules and subcorneal pustule were noted. The lamina propria showed elongation and thinning of the overlying epithelium. Dilated tortuous capillary loops were present in the dermal papillae.

After consultations with her haematologists and discussions regarding the use of anti-TNF-α biologics, it was agreed with the patient to initiate adalimumab (Humira®, AbbVie, Ludwigshafen, Germany). An 80 mg loading dose of adalimumab infusion was given followed by a 40 mg subcutaneous injection every 2 weeks. Treatment with adalimumab was well-tolerated and effective. The psoriatic tongue lesions resulted in complete remission after 8 weeks and her nail involvement also cleared. Oral and additional arthritic symptoms were alleviated, which allowed the patient to start eating again, regain weight, and increase daily activities.

Although biologics are intended for long-term use in central psoriatic disease, they are not curative. The patient remained in remission for several years; however, in the spring of 2018, she developed congestive heart failure and adalimumab was stopped. Acitretin 10 mg was started during remission. After 3 months on acitretin, her oral psoriasis and ACH started to flare and she became symptomatic. Adalimumab will likely be restarted in the future because the patient is no longer experiencing congestive heart failure and had a good response when the drug was used previously.

Table 1a: Classification of oral psoriasis.[13]

Category*	Description
1	Well-defined, grey-yellowish-white lesions that are oval or round and appear independently to skin manifestations.
2	Lacelike, circinate, or horny white elevated lesions found on the mucosa and/or tongue that parallel skin manifestation.
3	Severe, intense, widespread erythema of the whole oral mucosa and tongue, seen mostly in the acute forms of psoriasis.
4	Benign migratory glossitis or fissured tongue, which occur more frequently in patients with psoriasis than without.

* Types 1, 2, 3, and 4 have progressive signs and symptoms in each category. Overlaps may occur.

Table 1b: Sub-categorisation of oral psoriasis.[4]

Category	Description of lesion
Major types	
	White
	Erythematous
Minor subtypes	
	Mixed white and red
	Ulcerative
	Vesicular
	Pustular
	Indurated

DISCUSSION

Review of Oral Lesions in Psoriasis

Oral psoriasis is a collective term for lesions presenting anywhere in the mouth, including the lips, tongue, buccal mucosa, palate, and gingivae.[10-12] Van der Waal and Pindborg[13] classified oral psoriasis (Table 1a), with further sub-categorisation described by Younai and Phelan,[9] consisting of two major types and five minor subtypes (Table 1b). Younai and Phelan[9] identified 57 cases of oral mucositis with similar histology to psoriasis, which appeared in various anatomical regions, including the oral cavity, buccal mucosa, tongue, gingiva, palate, floor of mouth, and the vermillion border of the lip. Although this report does not seemingly correspond with the criteria of oral psoriasis, the diagnosis of oral psoriasis should not be immediately excluded.

The involvement of the oral mucosa in psoriasis remains a controversial subject in the field and is thought to be uncommon and infrequent. However, Talaee et al.[14] demonstrated that the prevalence of oral involvement in psoriasis is common, occurring in 47% of patients (83% of these cases were generalised plaque psoriasis), and involvement of the oral mucosa is significantly associated with younger age (21–30 years), previous history of oral lesions, and an early disease onset. This may suggest oral involvement in psoriasis is under-reported in the literature. There were no cases of pustular psoriasis or pustules on the oral mucosa in the Talaee et al. study,[14] similar to the case presented in this report.

The occurrence of isolated oral psoriatic lesions without cutaneous manifestations is rare because oral involvement is more common in patients with severe forms of cutaneous psoriasis, particularly generalised plaque and pustular psoriasis.[1] There have been occasional reports of isolated oral psoriasis without cutaneous psoriasis; in a series of cases, ~50% occurred with skin psoriasis, in ~10% oral psoriasis preceded the onset of skin psoriasis, and in ~20% cases of oral psoriasis were isolated.[8,10,11]

The most common location for oral psoriatic lesions is the tongue[4,8-10,12] and these lesions can be categorised into two major groups. One group includes mucosal abnormalities with corresponding psoriasis-like histology and

often parallels the clinical course of cutaneous psoriasis, as seen in this case. The second category is more common and comprises a range of nonspecific lesions, such as benign migratory glossitis (BMG) and FT, that are thought to occur more often in patients with typical cutaneous psoriasis forms.[12,15,16] A previous literature review demonstrated that the prevalence of FT ranges from 9.8–48.5% and BMG ranges from 5.6–18.2% in psoriatic patients, with most cases commonly presenting in patients with plaque psoriasis.[17] There remains minimal description of oral mucosal presentation and involvement in pustular psoriasis cases in the clinical literature.[4,8-10,12,14,15,17]

BMG (also termed geographic tongue, migratory stomatitis/glossitis, annulus migrans, stomatitis areata migrans, erythema circinata, geographic stomatitis, and ectopic geographic tongue) is described as >1 sharply demarcated erythematous patch with raised white or yellow serpiginous borders, the colour and shape of which will change over time.[15] Migratory lesions change location and prominence daily and tend to occur during flares of psoriasis.[15] BMG is an inflammatory disorder of unknown aetiology (similar to psoriasis) and is generally described as asymptomatic with a psoriasiform mucositis of the dorsum of the tongue affecting the epithelium. This results in ulcerative lesions from loss of local filiform papillae surrounded by white lines.[15] Abe et al.[18] and Ishibashi et al.[19] reported three cases of long-standing symptomatic and painful BMG. BMG is thought to present similarly to psoriasis in regard to genetic and histopathological aspects and also has similar clinical features.[20] Accordingly, rather than being considered as an entity on its own, many clinicians and researchers consider BMG as an oral manifestation of psoriasis. Current publications on BMG are limited and the topic remains controversial as to whether BMG is a particular oral form of psoriasis or a clinical condition on its own.[17] Nevertheless, several studies have reported significant links between the prevalence of BMG in psoriatic patients, particularly in patients with more severe forms of psoriasis.[14,17,20]

FT (also termed lingua fissurata, lingua plicata, scrotal tongue, grooved tongue) is another common form of oral presentation in psoriasis. It is recognised clinically by an anteroposterior groove on the dorsal tongue, often with lateral extending branching fissures.[16] Darwazeh and Almelaih[21] showed that 23% of patients with FT experienced painful symptoms, particularly when eating.

BMG, FT, and generalised pustular psoriasis are three disorders that have polygenic inheritance patterns and it is feasible that affected patients may share genes for these conditions.[8,10] Several authors have claimed that BMG is more prevalent in patients with generalised pustular psoriasis and is associated with severity of disease.[15,16] Others dispute that FT is more prevalent than BMG in patients with generalised pustular psoriasis and assert that with increasing age of onset and severity of psoriasis (assessed by Psoriasis Area Severity Index [PASI] scores), FT occurs more often in generalised pustular psoriasis, while BMG incidence increases with disease severity in generalised plaque psoriasis.[12,15,16]

While the debate regarding oral involvement is ongoing, the presentations of oral lesions in psoriasis are generally described as asymptomatic or temporary.[9] The case presented in this report demonstrates a rare form of oral psoriasis, with an erythematous, oedematous, and pustular tongue that did not present clinically like BMG or FT and was refractory to various treatments. Also, there was debilitating long-standing pain involvement, which is an unusual and perhaps a new noteworthy feature for oral psoriasis.

ACH is a rare variant of pustular psoriasis that involves the nails and nailbeds of the fingers and toes, resulting in painful nail dystrophy and paronychial erythema.[22] ACH is linked with inflammatory arthritis and generalised pustular psoriasis.[23] Although rare, ACH is also associated with pustules occurring in the oral mucosa (particularly the tongue), conjunctiva, and urethra, and is distinct from Reiter's syndrome and Behçet's syndrome.[22,23]

Diagnosis of Oral Psoriasis

The diagnosis of oral psoriasis is most accurate when the clinical oral presentations parallel those of cutaneous lesions and are supported by histological findings from a biopsy. Criteria for clinical diagnosis solely have been suggested, including a positive family history for psoriasis,

oral lesions that parallel the clinical course of skin manifestations, HLA typing (commonly for B13, B17, B37, Cw4, and Cw6), and exclusion of other causes.[1,11,24] Studies have shown that HLA-Cw6 correlates with generalised plaque psoriasis, while BMG correlates with HLA-B15 and DR7 and FT is associated with HLA-DRB1.[1-12,14-25]

It is important to consider differential diagnoses in oral mucosal conditions, including malignancy, oral candidiasis, lichen planus, secondary syphilis, systemic lupus erythematosus, pemphigoid (bullous or cicatricial), pemphigus (vulgaris), leukoplakia, Behçet's syndrome, and Reiter's syndrome.[11,22,23] Since these entities have distinct histopathological criteria, clinical presentation along with biopsy is fundamental in confirming diagnoses of oral psoriasis by effectively ruling out other diagnostic entities. In the present case, while the patient did have arthritis, the other symptoms and histopathological features typical of the Reiter's syndrome triad were absent.[22] Generally, oral psoriasis pathology has similar histopathologic features to cutaneous psoriasis. Yet, clinical changes in the tongue are often nonspecific and histological correlation is helpful for confirming diagnosis.[4]

Histological findings of oral psoriasis comprise hyperkeratosis or parakeratosis, elongation and clubbing of rete ridges, and thinning of the epithelium superior to the dermal papilla. Infiltrates of inflammatory cells are prevalent and also reflect the stage of the lesion (leukocytes are a sign of early stage while lymphocytes signify later stages). Munro's microabscesses and spongiform pustules of Kogoj rarely occur in oral psoriasis compared to cutaneous psoriasis but may occur in early lesions.[11] Psoriasiform mucositis is nonspecific for other conditions (such as Reiter's syndrome).[22,24] Negative scrapings for excessive candida and repeated microbial swabs ruled out fungal or infective causes of pathology. Other differential clinical entities, such as oral lichen planus and lichenoid reactions, have distinct histological and clinical features and were not seen in this case. Accordingly, histopathology together with clinical presentation and investigation are essential to support a subsequent diagnosis.[22]

Treatment and Management of Oral Psoriasis and Acrodermatitis Continua of Hallopeau

Literature detailing clinical treatments for the rarer forms of psoriasis remain limited and need further investigation and guidance.[25,26] Management of oral psoriasis and other inflammatory conditions involving the oral mucosa are mostly based on case reports and off-label uses of biologics and systemic immunotherapy.[26] Currently, there are no reports of managing pustular psoriasis of the tongue. Discussed below are suggested measures used in the management of this case, which may be suitable for future applications in dermatology and other medical or dental specialities.

Topical and Conservative Measures

Suggested conservative measures that are quick and feasible include removal of irritants and infection and managing existing orodental pathology. Simultaneous candidiasis can complicate diagnosis and management and may be successfully treated with oral antifungals or mycostatin mouthwash.[20] Physical manipulations should be minimal and performed with caution because there may be a potential Koebnerization effect on the inflamed mucosal tissue.

Oral psoriatic lesions are usually temporary and asymptomatic, yet this patient experienced chronic painful lesions. Palliation with a topical anaesthetic, including viscous lidocaine or diphenhydramine, mucosal protectants (Orabase®, ConvaTec Inc., Reading, UK) or magnesium and aluminium hydroxides (Maalox®, Sanofi, Origgio, Italy), and alkaline rinses can be used to minimise painful discomfort. Topical corticosteroids, such as fluocinonide gel 0.05% (Lidex®, County Line Pharmaceuticals, Brookfield, Wisconsin, USA), may be applied for symptomatic relief.[20]

Systemic and Immunomodulating Therapies

Retinoids such as acitretin are often used as first-line systemic therapy in males and non-fertile females with psoriasis.[5] Case reports have shown successful management of ACH with acitretin in combination with topical calcipotriol.[5] However, the present case showed no nail or lingual improvement with acitretin.

Systemic use of the immunomodulator methotrexate is a recognised treatment for psoriasis, particularly severe and refractory cutaneous plaque psoriasis, and has been used for pustular psoriasis. It is also licensed for use in several other chronic and refractory inflammatory conditions, e.g., RA, ulcerative colitis, and malignancies.[27] Systemic use of methotrexate is often not tolerated by patients and carries inevitable risks with long-term use (e.g., pancytopenia, hepatotoxicity).[27,28] Methotrexate targets cells undergoing rapid turnover, such as those in the mucosa and bone marrow, often causing mucositis. Accordingly, methotrexate is not routinely used for oral inflammatory lesions because a common adverse reaction is oral ulceration.[28] While methotrexate provided some relief to our patient's nail symptoms, it did not resolve her oral symptoms. Calcineurin inhibitors (cyclosporine A and tacrolimus) are rapid and effective treatments for cutaneous psoriasis. They are useful for treating generalised pustular psoriasis and oral lesions, including gingival hypertrophy, mouth sores, swallowing difficulty, gingivitis, gum hyperplasia, xerostomia, abnormal taste, tongue disorder, and gingival bleeding.[24] Abe et al.[18] described the successful treatment of painful geographic tongue in a 54-year-old woman using systemic cyclosporine, while Ishibashi et al.[19] described two patients aged 77 years with symptomatic migratory glossitis that were successfully treated with 0.1% topical tacrolimus.

Often, immunomodulator drugs are used in combination with systemic retinoids, oral corticosteroids, and light therapy, which can generate satisfactory results.[29] Yet, with time, relapses and a lack of efficacy occur. Immunomodulators are known to become refractory, often not tolerated by patients, and carry inevitable risks with long-term use (e.g., pancytopenia, hepatotoxicity, nephrotoxicity).

Hydroxyurea is an older treatment once used for pustular psoriasis. Currently, it is not indicated or commonly used in practice for this condition;[30] however, hydroxyurea is clinically indicated for treating PRV, which this patient had as a comorbidity.[30] Interestingly, the patient started hydroxyurea for PRV, which likely had some mild additional benefit for her cutaneous and mucosal pustular psoriasis.

Biologic Therapies

TNF-α is a well-studied cytokine involved in the pathogenesis of psoriasis; specifically, it increases immune cell infiltration to the skin causing keratinocyte proliferation.[1,31] There are three main anti-TNF-α biologic drugs licensed for psoriasis and inflammatory arthropathies: two recombinant monoclonal antibodies that target TNF-α directly, adalimumab (Humira) and infliximab (Remicade®, Janssen, Leiden, Netherlands), and a fusion protein, etanercept (Enbrel®, Pfizer, Sandwich, UK), which antagonises the TNF-α receptor.[26,31] These biologics are licensed for severe refractory patients with inflammatory conditions, notably psoriasis, Crohn's disease, ulcerative colitis, RA, and systemic lupus erythematosus.[31] There are several off-label uses of these drugs for conditions with similar pathogenesis involving TNF-α, including ACH and various mucosal conditions.[26,32] The literature reports successful off-label use of biologics in patients with mucosal conditions, including Behçet's syndrome, recurrent aphthous stomatitis and ulcers, benign mucous membrane pemphigoid, and lichen planus.[26,33]

Few case reports exist of the use of biologic therapies for the targeted management of oral psoriasis; however, off-label use in inflammatory oral mucosal conditions is evident. Infliximab is a well-established biologic used in psoriasis vulgaris and psoriatic arthritis that has been shown to have the longest rates of efficacy and patient retention when compared with other anti-TNF biologics.[26] Connolly et al.[34] described the successful treatment of Behçet's syndrome in a young woman with a 30-year history of orogenital ulcerations using infliximab therapy.[34] A good initial response with infliximab for treating severe pustular psoriasis and ACH was shown by Newland et al.;[35] however, there was subsequent unresponsiveness after 18 months.

Adalimumab has been licensed for and used successfully in cutaneous psoriasis, including both generalised plaque psoriasis and pustular psoriasis.[32] Chao[36] described the success of adalimumab in treating cutaneous and oral lichen planus. For the present case, adalimumab was chosen after considering the patient's comorbidities and convenience. After 8 weeks of adalimumab, complete remission of lingual

pustular psoriasis was achieved, with added amelioration of ACH and inflammatory arthritis.

Other biologics for treating psoriasis exist. Secukinumab is a human Ig monoclonal antibody that targets and neutralises the inflammatory cytokine IL-17A, which has been found to induce transcription of other proinflammatory cytokines, chemokines, and effectors in inflammatory conditions like psoriasis.[37] A recent case report in 2017 of a 42-year-old female patient with a similar presentation of ACH and painful erosive oral mucositis of the tongue and palate causing pain and weight loss was described by Baron,[6] and successful use of secukinumab induced remission.[6] Adalimumab, cyclosporine, and methotrexate were considered possible options but secukinumab was found to better suit their patient. In Baron's case, secukinumab was effective at responding to the patient's atypical disease and symptoms.[6] At the time of the case described in the present report, secukinumab was not readily available, but now may be considered an option for future treatment.

CONCLUSION

Here the authors report the successful use of adalimumab for inducing remission of a rare presentation of symptomatic pustular oral psoriasis. This case represents interesting novel signs and symptoms of oral pustular psoriasis and describes the rationale for management deriving from challenging comorbidities. Oral psoriasis is typically described as asymptomatic but, as shown in this case, can be painful and debilitating. It should be considered in the differential diagnosis of painful lesions of the oral mucosa that are not responding to usual therapies, especially in the setting of psoriasis. Biopsies are helpful for diagnosis and can influence management plans; however, treatment remains challenging since few reports of successful therapies exist for such presentation.

Accordingly, the use of adalimumab in this case highlights a potential management strategy and the treatment of a complex dermatological case that overlaps with conditions from other medical specialities. The exact aetiology, pathogenesis, and optimal management of oral psoriasis, particularly pustular lingual psoriasis, remains obstinately obscure. More research, reporting, and biomedical investigations into this disease and its progression are needed. Furthermore, clinical suspicion should lead dermatology, rheumatology, immunology, and oral medicine and pathology specialists to consider the use of biologic anti-inflammatory therapies to relieve patients of disease progression and discomfort.

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