EMJ EUROPEAN MEDICAL JOURNAL

DERMATOLOGY

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FIGHT

Abbreviated Prescribing Information for Kyntheum® 210mg 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 210mg brodalumab in 1.5ml solution. 1ml solution contains 140mg brodalumab. **Dosage and administration:** *Posology: Adults:* The recommended dose is 210mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210mg 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:** November 2018

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

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November 2019
MAT-21978

References:
1. Kyntheum® (brodalumab) Summary of Product Characteristics. English version, November 2018.
2. Campa M, et al. *Dermatol Ther* 2016;6:1–12.
3. Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28.

FIGHT DIFFERENT

Kyntheum® (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.[1] Kyntheum® is a fully human monoclonal antibody and the only biologic that selectively targets the IL-17 receptor subunit A.[1,2]

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IN THE FIGHT AGAINST PSORIASIS THINK DEFENCE FIRST

*PASI 100 at 12 weeks with Kyntheum®: 44% in AMAGINE-2 and 37% in AMAGINE-3.[3]

LEO

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Spencer Gore, CEO

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VIEW IN FULL ←

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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.

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EMJ 4.3 2019

In this edition you will find a selection of peer-reviewed articles covering the latest developments across therapeutic areas including rheumatology, hepatology, plus more.

VIEW ALL JOURNALS ←

Welcome

To all our friends and collaborators: welcome to another exciting edition of *EMJ Dermatology*. We're very proud to present to you our journal which is filled to the brim with highly relevant and impactful peer-reviewed articles, as well as a comprehensive review of the European Academy of Dermatology and Venereology (EADV) 2019 Congress, held in the bustling Spanish capital of Madrid. This is an event we highly anticipate each year, and we were certainly not disappointed by the wealth of brilliant advancements shared, sure to benefit the dermatology landscape.

The 28th EADV Congress brought together >12,000 participants, from an estimated 100 countries, for spirited debate on a wide number of topics, including biologics in skin disease, topical corticosteroid use, and skin imaging: a key focus of the meeting. Our congress review collates some of the biggest stories to break at the event, including news of a new association between dietary habits and acne, and findings suggesting that atopic dermatitis patients' families are at risk of anxiety and depression. A collection of abstract summaries written by the authors themselves supplement these stories, including a description of the cutaneous adverse effects induced by the anticancer treatment nivolumab, and results from a clinical study of erythema multiforme. For those of you who missed out on all the action this year, our review provides a generous helping of highlights.

Additional to our congress content, we have included two informative interviews from Prof Alin Tatu and Dr Jaishree Sharad, who provide different perspectives on a range of topics. The diversity of dermatological inquiry is reflected in the articles presented in later pages. Tan and Tay contribute a novel description of an unusual presentation of hidradenitis suppurativa in the calf of a 69-year-old female, Pozzo-Magaña and Lazo-Langer review the literature surrounding serum sickness-like reactions in children, and Siedlikowski et al. consider the use of JAK inhibitors for atopic dermatitis treatment. Clinicians, researchers, and patients will all find value in these pages.

EMJ Dermatology 7.1 was an addition that our whole team worked incredibly hard on, to which I am equally thankful to in tandem with our valued contributors. Seeing first-hand the rapid progress being made in this field is inspiring to say the least, and I have no doubt that we will able to report on even more game-changing developments following next year's EADV congress in Vienna. Until then, I hope you enjoy this new edition.

Spencer Gore

Chief Executive Officer, European Medical Group

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Durable efficacy **FOR HER** skin and beyond[1,2]

cimzia®
(certolizumab pegol)

EU/EEA* ABBREVIATED PRESCRIBING INFORMATION

Name of the medicinal product: Cimzia® (certolizumab pegol) **Pharmaceutical form:** Solution for injection. Each pre-filled syringe, pre-filled pen or dose dispenser cartridge contains 200 mg certolizumab pegol in one ml. **Therapeutic indications:** ***Rheumatoid arthritis:*** Cimzia®, in combination with methotrexate (MTX), is indicated for: *the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate. Cimzia® can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate; *the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. Cimzia® has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with MTX. ***Axial spondyloarthritis:*** Cimzia® is indicated for the treatment of adult patients with severe active axial spondyloarthritis (axSpA), comprising: ***Ankylosing spondylitis (AS) (also known as radiographic axial spondyloarthritis):*** Adults with severe active ankylosing spondylitis (AS) who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs) and ***Axial spondyloarthritis without radiographic evidence of AS (also known as non-radiographic axial spondyloarthritis):*** Adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. ***Psoriatic arthritis:*** Cimzia®, in combination with MTX, is indicated for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous DMARD therapy has been inadequate. Cimzia® can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. ***Plaque psoriasis:*** Cimzia® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Posology and method of administration:** ***Loading dose:*** The recommended starting dose of Cimzia® for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For RA and PsA, MTX should be continued during treatment with Cimzia® where appropriate. ***Maintenance dose for rheumatoid arthritis and psoriatic arthritis:*** After the starting dose, the recommended maintenance dose of Cimzia® for adult patients with RA and PsA is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia® where appropriate. ***Maintenance dose for axial spondyloarthritis:*** After the starting dose, the recommended maintenance dose of Cimzia® for adult patients with axSpA is 200 mg every 2 weeks or 400 mg every 4 weeks. ***Maintenance dose for plaque psoriasis:*** After the starting dose, the maintenance dose of Cimzia® for adult patients with plaque psoriasis is 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered in patients with insufficient response. The total content (1 ml) of the pre-filled syringe or the pre-filled pen should be administered as subcutaneous injection only. The safety and efficacy of Cimzia® in children and adolescents below age 18 years have not yet been established. No data are available. No dose recommendations can be made for patients with renal and hepatic impairment as Cimzia® has not been studied in these patient populations. No dose adjustment is required in the elderly (≥ 65 years old) as population pharmacokinetic analyses showed no effect on age. **Contraindications:** Hypersensitivity to the active substance or any of the excipients, active tuberculosis or other severe infections such as sepsis or opportunistic infections, moderate to severe heart failure (NYHA classes III/IV). **Special warnings and precautions for use:** Serious infections, sepsis, tuberculosis (including miliary, disseminated and extrapulmonary disease) and opportunistic infections (e.g. histoplasmosis, nocardia, candidiasis) have been reported in patients receiving Cimzia®. Some of these events have been fatal. Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and up to 5 months after treatment with Cimzia®. Administration of Cimzia® should be discontinued if a patient develops a new serious infection until the infection is controlled. If latent tuberculosis is diagnosed, appropriate anti-tuberculosis therapy must be started before initiating treatment with Cimzia. Reactivation of hepatitis B virus (HBV) has occurred in patients receiving a TNF-antagonist including Cimzia®, who are chronic carriers of this virus (i.e., surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Cimzia®. In patients who develop HBV reactivation, Cimzia® should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. As the potential role of TNF antagonist therapy in the development of malignancies is not known, caution should be exercised when considering TNF antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. With the current knowledge, a possible risk for the development of lymphomas, leukemia or other malignancies in patients treated with a TNF antagonist cannot be excluded. A risk for the development of malignancies in children and adolescents treated with TNF antagonists cannot be excluded. Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), have been reported in patients treated with TNF-antagonists. A risk for development of hepatosplenic T-cell lymphoma in patients treated with Cimzia® cannot be excluded. Caution should be exercised when using any TNF antagonist in chronic obstructive pulmonary disease patients, as well as in patients with increased risk for malignancy due to heavy smoking. Cases of congestive heart failure have been reported in RA patients receiving Cimzia® and hence it should be used with caution in patients with mild heart failure (NYHA class I/II). Treatment with Cimzia® must be discontinued in patients who develop new or worsening symptoms of congestive heart failure. Adverse reactions of the haematologic system, including medically significant cytopaenia (e.g. leukopaenia, pancytopaenia, thrombocytopaenia) have been reported with Cimzia®. Discontinuation of Cimzia® therapy should be considered in patients with confirmed significant haematological abnormalities. Use of TNF antagonists has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Rare cases of neurological disorders, including seizure disorder, neuritis and peripheral neuropathy, have been reported in patients treated with Cimzia®. Severe hypersensitivity reactions (including anaphylactic shock) have been reported rarely following Cimzia® administration. Some of these reactions occurred after the first administration of Cimzia®. If severe reactions occur, administration of Cimzia® should be discontinued immediately and appropriate therapy instituted. The needle shield inside the removable cap of the Cimzia® pre-filled syringe, pre-filled pen and dose dispense cartridge contains a derivative of natural rubber latex. A potential risk of hypersensitivity reactions cannot be completely excluded in latex-sensitive individuals. Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF antagonists, including Cimzia®, to cause immunosupression, affecting host defences against infections and malignancies. Treatment with Cimzia® may result in the formation of antinuclear antibodies (ANA) and, uncommonly, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Cimzia®, treatment must be discontinued. As no data are available, live vaccines should not be administered concurrently with Cimzia®. The 14-day half-life of Cimzia® should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Cimzia® should be closely monitored for infections. Interference with certain coagulation assays has been detected in patients treated with Cimzia®. Cimzia® may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. **Fertility, pregnancy and lactation:** The use of adequate contraception to prevent pregnancy should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia® dose due to its elimination rate, but the need for treatment of the woman should also be taken into account. Data from more than 500 prospectively collected pregnancies exposed to Cimzia® with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia®. However, the available clinical experience is too limited to, with a reasonable certainty, conclude there is no increased risk associated with Cimzia® administration during pregnancy. Due to its inhibition of TNF alpha, Cimzia® administered during pregnancy could affect normal immune response in the newborn. Cimzia® should only be used during pregnancy if clinically needed. In a clinical study, 16 women were treated with certolizumab pegol during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 µg/ml with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. In a clinical study in 17 lactating women treated with Cimzia®, minimal transfer of certolizumab pegol from the plasma to breast milk was observed. The percentage of the maternal Cimzia® dose that reaches an infant during a 24-hour period was estimated to 0.04% to 0.3%. In addition, since certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant. Consequently, Cimzia® can be used during breastfeeding. **Undesirable effects:** Cimzia® was studied in 4,049 patients with RA in controlled and open label trials for up to 92 months. The commonly reported adverse reactions (1-10%) in clinical trials with Cimzia® were viral infections (includes herpes, papillomavirus, influenza), bacterial infections (including abscess), rash, headache (including migraine), asthaenia, leukopaenia (including lymphopaenia, neutropaenia), eosinophilic disorder, pain (any sites), pyrexia, sensory abnormalities, hypertension, pruritus (any sites), hepatitis (including hepatic enzyme increase), injection site reactions and nausea. Serious adverse reactions include sepsis, opportunistic infections, tuberculosis, herpes zoster, lymphoma, leukaemia, solid organ tumours, angioneurotic oedema, cardiomyopathies (includes heart failure), ischemic coronary artery disorders, pancytopenia, hypercoagulation (including thrombophlebitis, pulmonary embolism), cerebrovascular accident, vasculitis, hepatitis/hepatopathy (includes cirrhosis), and renal impairment/nephropathy (includes nephritis). In RA controlled clinical trials, 4.4% of patients discontinued taking Cimzia® due to adverse events vs. 2.7% for placebo. Cimzia® was studied in 325 patients with active axSpA in a clinical study for up to 4 years, in 317 patients with non-radiographic axial spondyloarthritis in a placebo-controlled study for 52 weeks (AS0006), and in 409 patients with PsA in a clinical study for up to 4 years. The safety profile for axSpA and PsA patients treated with Cimzia® was consistent with the safety profile in RA and previous experience with Cimzia®. Cimzia® was studied in 1112 patients with psoriasis in controlled and open-label studies for up to 18 months. The safety profile of Cimzia® 400 mg every 2 weeks and Cimzia® 200 mg every 2 weeks were generally similar. Please refer to the full Prescribing Information in your country before prescribing. Legal Classification: Medical product subject to medical prescription. **Date of revision:** June 2019. **Marketing authorisation holder:** UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Marketing authorisation number(s):** EU/1/09/544/001-002-003-004-005-006-007. **Date of authorisation:** October 2009.

References: 1. Gottlieb AB, et al. J Am Acad Dermatol 2018;79(2):302-314. **2.** van der Heijde D, et al. RMD Open 2018;4(1):e000582.

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Inspired by **patients.**
Driven by **science.**

Foreword

Dear colleagues,

Welcome to the latest edition of *EMJ Dermatology*, which also covers the recent European Academy of Dermatology and Venereology (EADV) Congress in sunny and vibrant Madrid, Spain. By all measures this year's event was a great success, bringing together almost 13,000 delegates from >100 countries. Attendees were offered a bewildering array of content via 166 sessions from 700 speakers complemented by 20 patient village exhibitors and 165 participating companies. Major themes for presentation and discussion included the recent dramatic developments in the application of biologics/immunotherapies (especially potent inhibitors of the so-called JAK inhibitors that impact on the JAK–STAT signalling pathway) to an increasing range of skin diseases.

Not only were the usual suspects of psoriasis, melanoma, and atopic dermatitis (see this issue of *EMJ Dermatology* for a systematic review of the treatment of atopic dermatitis using JAK inhibitors) a major focus, but there was also a much-anticipated focus on alopecia areata and vitiligo. Both conditions still have no U.S. Food and Drug Administration (FDA)-approved treatments and has been a frustrating area of clinical care. While there are pros and cons with the use of systemic JAK inhibitors for these latter conditions, there was some encouraging data on the first randomised controlled trials for topical use of ruxolitinib in vitiligo.

Other exciting elements of EADV 2019 were the roles big data and artificial intelligence may play in diagnosis and prognosis of skin diseases. Moreover, the EADV held its first 'Nurse Day', which finally reflects the increasingly sophisticated roles dermatologic nurses play working in multidisciplinary teams for optimal care of patients with skin disease.

This edition of *EMJ Dermatology* highlights an unusual presentation of an inflammatory skin disease that is currently distracting many in the dermatological research field, hidradenitis suppurativa, and joins a rather sparse literature on this skin disease of particularly high morbidity.

Included is an important review on the clinical features and current treatment options for children with the under-recognised or mistakenly diagnosed condition of serum sickness-like reaction. This edition includes valuable reviews of clinical efficacy, safety, and tolerability of IL-23 inhibitors in moderate-to-severe plaque psoriasis, and of topical and systemic treatment of acne in the USA.

I hope you enjoy this latest edition of *EMJ Dermatology*!

With kind regards,

Professor Desmond J Tobin

Charles Institute of Dermatology, University College Dublin, Dublin, Ireland

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Congress Review

Review of the 2019 European Academy of Dermatology and Venereology 28th Congress

Location:	IFEMA – Feria de Madrid – Madrid, Spain
Date:	9th–13th October
Citation:	EMJ Dermatol. 2019;7[1]:12-23. Congress Review.

Madrid, a city characterised by elegance and culture, welcomed an influx of dermatologists this Autumn for the annual European Academy of Dermatology and Venereology (EADV) congress, now in its 28th year. The city, with its perfectly manicured gardens and cobbled side streets, bustling with tourists and locals alike, hosted the event for the first time. Complete with a cornucopia of both historical and modern architecture, Madrid created the perfect backdrop for the congress which is 'the modern face of dermatology.

In the opening ceremony, EADV President Carle Paul highlighted the association's vision and mission, as the leading community to further the knowledge of healthcare professionals in the field of dermatology. They are dedicated to patient care and education; their mantra is to share, learn, and believe. After an inspiring talk from Ignacio Hernández Medrano on artificial intelligence and healthcare and the world of opportunities this presents, the opening ceremony ended with a quintessentially Spanish flamenco performance.

From the array of poster and abstract presentations that were on offer to delegates at EADV this year, we have hand-picked a selection to feature in our review of the event. The abstract summaries were provided by the authors themselves, offering a first-hand account of the research for our readers. Topics include the treatment of acneiform rash, dermatomyositis revealing the recurrence of bladder cancer, and methods of analysis of the demodex mites' diagnosis.

As always, a wealth of late breaking research was released at the congress, and our review contains an array of stories covering the press releases. Topics this year included the risk of hair loss posed by air pollution and the impact of dietary habits on acne. One piece of research of particular interest considered the location of malignant melanoma playing a

role in the risk of cancer spreading to other parts of the body: tumours found above the neck showed a higher rate of spreading.

Psoriasis featured in a lot of the late-breaking research at EADV, such as the study on anxiety in psoriasis patients who were undertreated and underdiagnosed. The researchers found that more than half of patients with >20% body coverage were not visiting a physician. Psoriasis was also considered in the context of nonalcoholic fatty liver disease, the severity of which could be related to severity of the skin condition.

Within the 166 sessions available for attendees to consume, a standout topic was building the patient–doctor relationship through effective communication. Sessions covered supporting the mental health of patients, best practice of communication to achieve the optimal doctor–patient relationship, and the consequences of poor doctor–patient communications. We cover this topic in more detail in our congress feature.

With so many experts in dermatology in one place, the possibilities of sharing of knowledge and collaboration are fruitful at EADV. We interviewed Prof Alin Tatu who shared his thoughts on the challenges of the field, areas of the field that deserve more attention, and the key take-home messages from the congress. Prof Tatu also discussed some research he published last year on the 'butterfly effect' in dermatology and the future of rosacea treatment.

The EADV 2019 congress was another incomparable event in the field of dermatology. Looking ahead to next year, Vienna will play host to dermatologists from all over the world as EADV celebrates their 29th annual event in the Austrian capital. For now, for those who missed the brilliant EADV in Spain this year, or for those who attended but want to relive the highlights, we present our review of the unmissable 28th EADV Congress 2019.

"Within the 166 sessions available for attendees to consume, a standout topic was building the patient–doctor relationship through effective communication."

"They are dedicated to patient care and education; their mantra is to share, learn, and believe."

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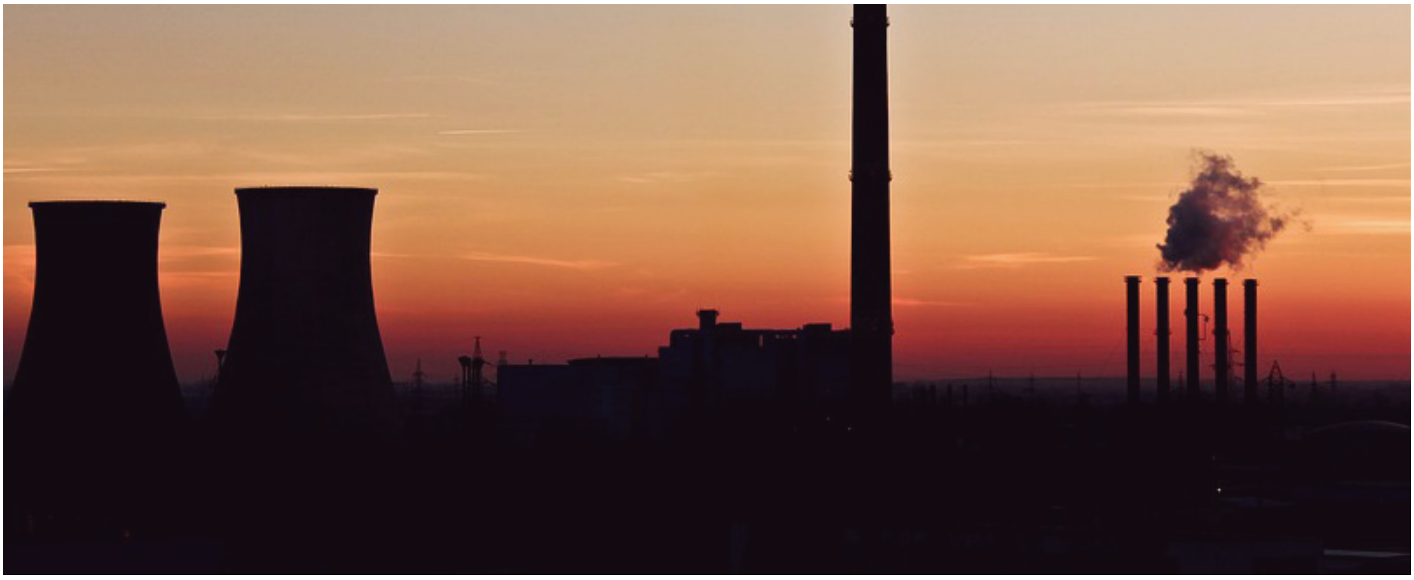

Air Pollution Poses Hair Loss Risk

POLLUTION could be a cause of hair loss in areas where the ambient air quality is particularly poor. This is according to findings presented at the 28th EADV Congress in Madrid, Spain, and reported in a press release dated 9th October 2019. This study is novel in that it is the first to question the connection between air pollutants and hair loss.

Air pollution is suggested to be responsible for 4.2 million deaths globally each year and hence is an area of increasing public interest. This research was led by Dr Hyuk Chul Kwon of the Future Science Research Centre, Seoul, Republic of Korea, who exposed human follicle dermal papilla cells for 24 hours to varying concentrations of particulate matter (PM), which is defined as the solid particles and droplets in the air, such as dust and diesel particulate. Dr Kwon and his team measured levels of the protein β-catenin, known to stimulate hair growth and morphogenesis, as well as cyclin D1, cyclin E, and cyclin-dependent kinase 2 (CDK2), all of which are involved in cycles of hair growth and retention.

"while the link between air pollution and serious diseases such as cancer, chronic obstructive pulmonary disorder, and cardiovascular disease are well established, there is little to no research on the effect of particular matter exposure on the human skin and hair in particular."

PM is divided into categories based on size; PM2.5 relates to particulate diameters of 2.5 µm and PM10 refers to particulate diameters of 10 µm. The researchers found that, after western blot analysis, PM10-like dust and diesel particulate presence resulted in decreased levels of β-catenin, cyclin D1, cyclin E, and CDK2. The burning of fossil fuels, including petrol, diesel, coal, oil, and biomass, is largely held accountable for the increasing levels of PM10.

Dr Kwon sought to discover more about the harmful dermatological effects of PM. He noted that "while the link between air pollution and serious diseases such as cancer, chronic obstructive pulmonary disorder, and cardiovascular disease are well established, there is little to no research on the effect of particular matter exposure on the human skin and hair in particular."

Dietary Habits Could Be Key Acne Trigger

ACNE could be associated with poor dietary habits, according to findings presented at the 28th EADV Congress in Madrid, Spain, and reported in a subsequent press release dated 9th October 2019. Analysis of 6,700 participants across North America, South America, and Europe revealed the influence of several worsening factors associated with acne; the most prominent being daily consumption of sweet and typically unhealthy foods.

The research, led by Professor Brigitte Dréno of the University Hospital of Nantes, Nantes, France, focussed on both internal and external factors, known as the exposome, which affect the severity and response to acne treatment. Results showed that, upon comparing individuals with acne, 37.0% consumed pastries and chocolate daily compared to 27.8% who did not. Other statistically significant results ($p<0.001$) include 48.2% of patients consumed dairy products daily, versus 38.8% who did not, and 35.6% consumed soda juices or syrups daily, compared to 31% who did not. The researchers also compared patients with and without acne and found that 11.0% of acne sufferers consumed whey products compared to only 7.0% without acne, and 11.9% consumed anabolic steroids compared to 3.2% without acne. In opposition to previous findings, no such association was observed with tobacco.

Acne is one of the most common diseases in dermatology and is estimated to be the eighth most prevalent disease worldwide. Studies have suggested acne increases anxiety levels, leads to feelings of social isolation, and sufferers are even at a disadvantage when it comes to being selected for employment. Additional results of this study found that pollution exposure and harsh skincare routines were other exposome factors. Therefore, knowledge of these exposome stressors is crucial to understanding the disease and its treatment. Dr Dréno is hopeful for the future of acne management and treatment efficacy, and believes that "for the first time, this study allows us to identify the most important exposome factors relating to acne from patient questioning prior to any treatment prescription."

"for the first time, this study allows us to identify the most important exposome factors relating to acne from patient questioning prior to any treatment prescription"

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Families of Atopic Dermatitis Patients at Risk of Depression and Anxiety

ATOPIC dermatitis (AD), a manifestation of cracked and itchy skin, affects around 10–20% of the paediatric population in Europe, constituting a significant therapeutic challenge. Whilst the dermatology community has invested extensive effort into treating these patients, little research has been done into the psychological impact of the condition on family members and caregivers. Now, results have emerged from a press release dated 10th October 2019 at the EADV Congress in Madrid, Spain, showing a significant link to depression in adults for whom children have AD.

In the analysis, the impact of AD was observed in the families of 35 children aged 1–6. The Hamilton Depression and Anxiety Rating Scales (HDRS and HAM-A, respectively) were used in the investigation alongside personal questions pertaining to concerns the participants had. Of the 35 family members and caregivers evaluated, all were found to report at least mild severe anxiety; a proportion of these presented symptoms of moderate severity anxiety. Alarmingly, 74% of the family members and caregivers appeared to show depressive symptoms, which alongside the anxiety scores were attributed to the persistence and longevity of AD in their children or care recipient as opposed to severity of the disease. Often the greatest worry the participants had was related to the information they received regarding disease nature, especially considering the long-term nature of the condition.

Complementary to physical symptoms, AD can be characterised by psychosocial stress, insomnia, and anxiety in patients. It is therefore understandable that the parents or caregivers of those affected will acquire some of this burden, leading to a situation in which entire families are in need of increased support. Lead researcher Dr Vesna Grivcheva-Panovska from the PHI Clinic of Dermatology, London, UK, provided her thoughts on the results: "In the future, we must take a wholesome view of the situation and a widened approach the management of AD not only of the patients but of their families as well."

"In the future, we must take a wholesome view of the situation and a widened approach the management of AD not only of the patients but of their families as well"

Mismanagement and High Levels of Anxiety Reported in German Psoriasis Patients

AFFECTING at least 100 million individuals worldwide, psoriasis is an extremely common and noncommunicable skin disease of which a precise cause is unknown. Released in a press release dated 11th October 2019 at the EADV 2019 Congress in Madrid, Spain, a group of German researchers have presented findings showing that, in a large patient cohort, feelings of mismanagement, undertreatment, and anxiety were abundant.

In the study, 650 psoriasis patients in Germany were asked questions pertaining to their satisfaction with their treatment and their general mental wellbeing and day-to-day life. Fifty-six percent of patients with >20% of their body surface psoriasis-affected reported not currently receiving advice or treatment from a doctor, indicative of poor patient–doctor communication and involvement. Forty-nine percent of patients expressed that their prescribed drugs did not appear to help with their condition, whereas 29% reported excessive numbers of side effects.

The investigators believe that despite the prevalence and profile of psoriasis, more attention needs to be given to developing appropriate treatment strategies to address patient needs; only doing this can the healthcare community avoid the neglection of patients currently dissatisfied with their disease management and doctor involvement. Lead researcher Maximilian Schielein from Ludwig-Maximilians-Universität München, Munich, Germany, concluded from the study that "reaching out to these patients is essential, and healthcare professionals have a duty of care to ensure that everyone with psoriasis receives optimal care."

An additional study discussed at EADV bolstered this message, revealing that 77% of acute stage psoriasis patients had anxiety disorders (this was compared to 19% in the general population). A need for interdisciplinary diagnosis and treatment approaches, as well as incorporation of psychosocial interventions, was highlighted as one course of action to take to improve the day-to-day life of these patients.

"reaching out to these patients is essential, and healthcare professionals have a duty of care to ensure that everyone with psoriasis receives optimal care"

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Severity of Psoriasis Related to the Severity of Non-Alcoholic Fatty Liver Disease

SEVERE psoriasis in patients who also have nonalcoholic fatty liver disease (NAFLD) were shown to have greater damage to the liver compared to individuals with milder forms of the skin condition. This is according to findings presented in a press release dated 10th October 2019 at the 28th EADV Congress in Madrid, Spain.

The study recruited 64 male patients who had a mean age of 53.4 years. The Psoriasis Area and Severity Index (PASI) Score was used to diagnose the severity of the psoriasis exhibited by each of the men. Each participant also had a diagnosis of NAFLD which was detected using ultrasound elastography. Measurements provided by ultrasound elastography also gave an indication of liver tissue stiffness, typically associated with NAFLD or liver fibrosis which can consequently lead to cirrhosis and end-stage liver disease.

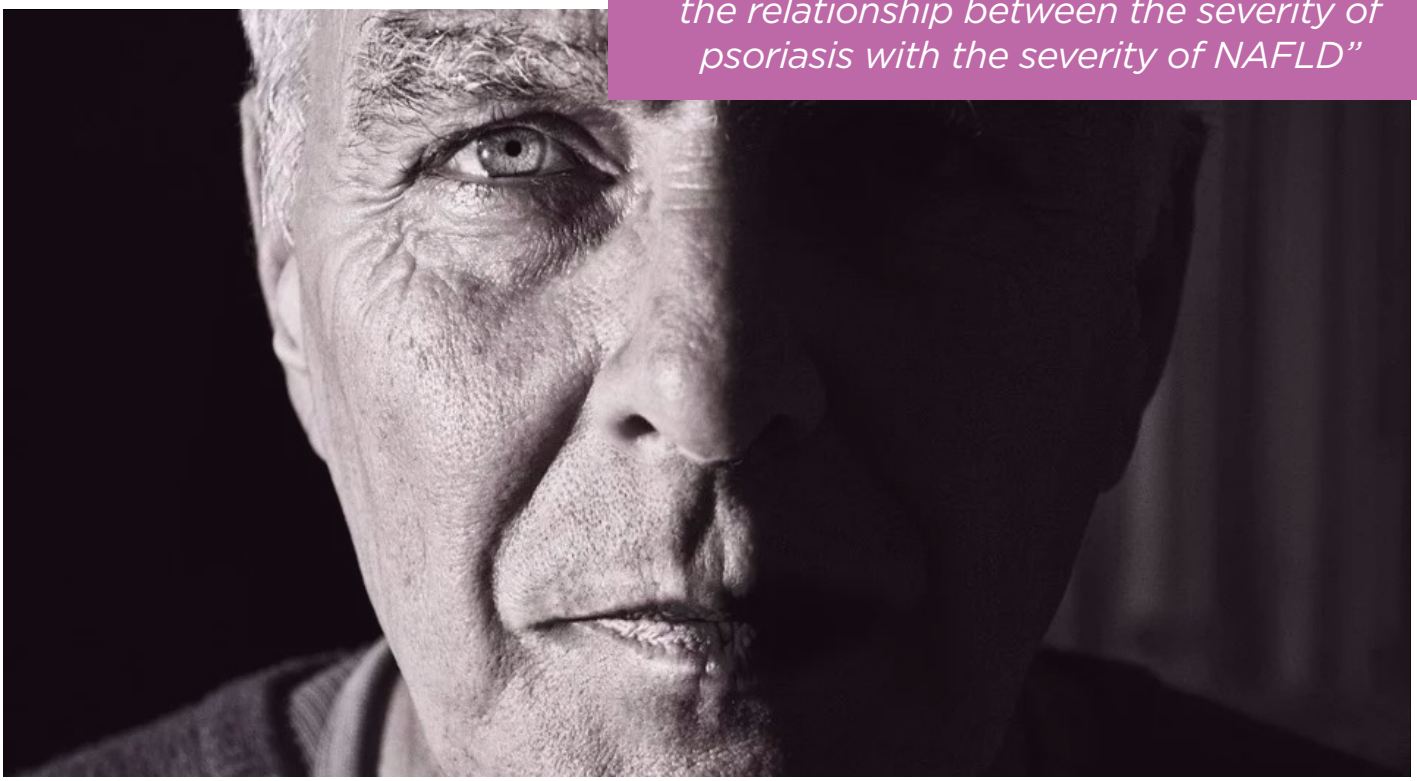
Dr Daniel Nieto, lead researcher of the study, from La Paz Hospital in Madrid, Spain, presented the results at EADV 2019.

He commented on the critical link between the two diseases: "Previous research has already established a link between psoriasis and NAFLD. This is one of the first studies to assess the relationship between the severity of psoriasis with the severity of NAFLD."

A separate study conducted in Iran also investigated this link, and the results corroborated with the results presented by Dr Nieto and his peers at the congress in Barcelona. The study in Iran comprised 54 male participants with psoriasis and NAFLD. The results of the study proposed that those with high-grade psoriasis had a greater degree of severity of NAFLD. The severity of the NAFLD also had a positive correlation with the degree of psoriasis assessed using the PASI Score. The positive correlation may be due to proinflammatory cytokines and adiopocytokines which trigger psoriasis, contributing to worsening of the disease. The data was analysed using SPSS16 statistical software, chi-square, and the Fisher exact test.

"In this context, increasing awareness and the continued assessment of the severity of NAFLD in patients with psoriasis by primary care physicians, specialists, health policy makers and patients, should be prioritised to help manage both conditions."

"This is one of the first studies to assess the relationship between the severity of psoriasis with the severity of NAFLD"



Malignant Melanoma Above the Neck Has Higher Chance of Spreading

"reaching out to these patients is essential, and healthcare professionals have a duty of care to ensure that everyone with psoriasis receives optimal care."

SKIN cancer that develops on the neck has an increased chance of spreading than that which is found below the neck, as shown in results from a 6-month study presented at EADV in Madrid, Spain, and reported in a press release dated 11th October 2019. Within the study, computed tomography was used to assess the presence and spread of cancer and determine whether location played a role.

Researchers studied 45 patients, who had new diagnoses of malignant melanoma (MM), over a 6-month period, with the aim of identifying whether location of MM was linked with likelihood of the tumour metastasising. A significantly higher portion of the patients had below neck MM (n=37) compared with 8 patients who presented with MM above the neck.

Results showed that none of the 37 below neck tumour patients had distant metastases. One patient in this group was found to have positive nodes (2.7%). Within the above neck group, two of the eight patients displayed positive nodes and distant metastases (25.0%). The authors drew the conclusion that MM above the neck had a higher chance of spreading when compared to MM found below the neck.

Of all the types of skin cancer, MM is the most dangerous and is increasingly common. As MM spreads deeper within the skin, treatment becomes considerably more challenging, and the cancer can be deadly. The melanoma *BRAF V600* gene can also undergo mutations, which impact the BRAF protein production and cause an increase in cell growth rates.

Lead researcher Dr Mohammed Al Abadie, Royal Wolverhampton NHS Trust, Wolverhampton, UK, discussed the study: "A mutation in the gene encoding BRAF has been well demonstrated to occur in association with MM, and this has revolutionised further management in patients with advanced disease. In this study, we have reviewed new MM diagnoses to see which ones are more likely to metastasize in terms of location. Understanding more about these locations also may help to determine and manage a patient's survival."

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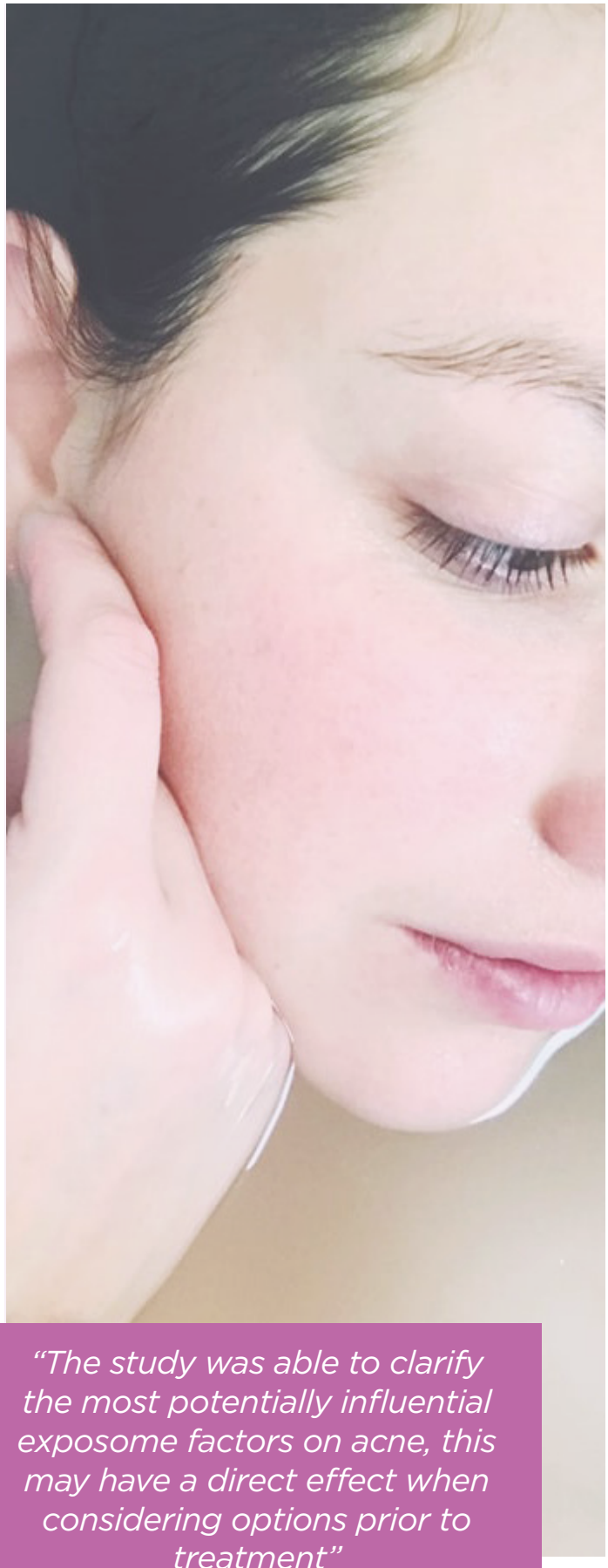
Identification of The Most Influential Exposome Factors on Acne



"The study was able to clarify the most potentially influential exposome factors on acne, this may have a direct effect when considering options prior to treatment"

RANKING of exposome factors affecting acne can now be established, according to the results of a study presented as part of a press release dated 12th October at this year's EADV congress in Madrid, Spain. The exposome is the totality of human environmental exposures, the sum of internal and external factors impacting the onset, duration, and severity of acne.

The study comprised an online international study in France, Germany, Italy, Brazil, Canada, and Russia. The French authors of the study recruited 10,040 individuals, who were required to complete questionnaires based on six exposome factors explained by Dréno B et al; resultantly, two study groups were created. Eligible participants in the acne group met specific criteria: exhibiting clinically diagnosed acne; or, receiving prescription for the treatment of acne by a clinician. A multivariate regression logistic analysis was performed and adjusted for age and gender.

Environmental factors monitored in 6,679 eligible participants included: daily consumption of dairy products, soda, chocolate, and sweets; frequent nibbling, use of harsh cleansers or peelings; regular whey protein consumption, and expressions of feeling stressed. In the acne group (n=2826), consumption of dairy products, sweets, nibbling, alcohol, cannabis, whey proteins, stress levels, and exposure to pollution were the exposome factors observed more often than in the control group (n=3853). The use of a dermo-roller or harsh cleanser were significantly more frequent in the acne group. Tobacco is widely considered to be a trigger of the disease; however, it did not generate significant results in this present study.

Under 'real-life' conditions, a total of ten of the exposome factors explored in this study had a significant impact on acne within the participants. The present study affirmed the role of nutrition, harsh skincare, stress, and whey protein consumption on acne. The study was able to clarify the most potentially influential exposome factors on acne, which may have a direct effect when considering options prior to treatment.

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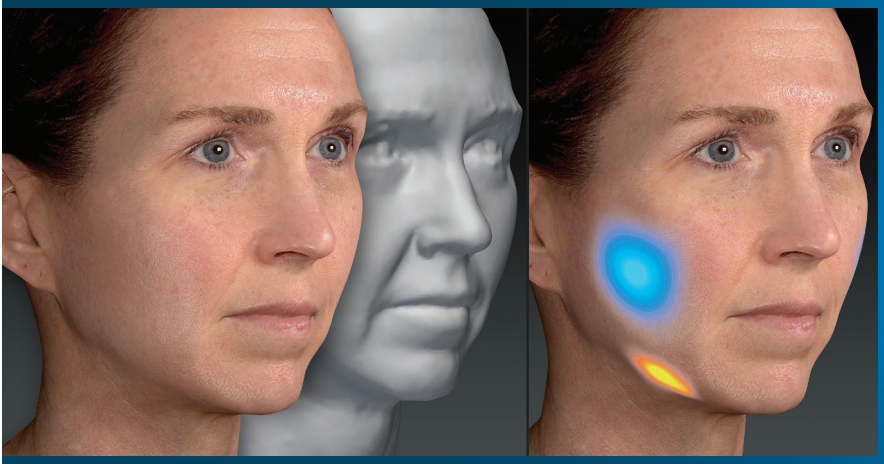

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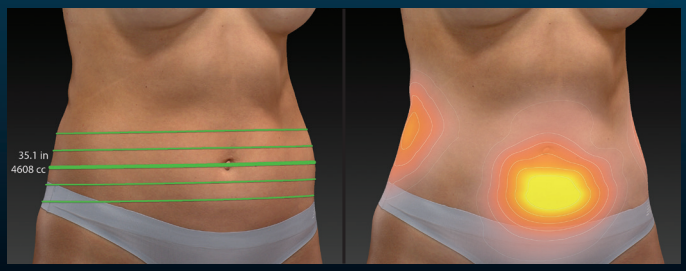

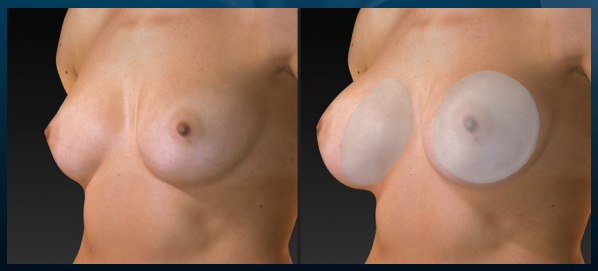

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Psoriasis and Atopic Dermatitis: Addressing Therapeutic Paradigms by Learning from Each Other

This symposium took place on the 11th October 2019 as part of the 28th European Academy of Dermatology and Venereology (EADV) Congress in Madrid, Spain

Chairperson: Mark Lebwohl[1]

Speakers: Richard Warren,[2] Stephan Weidinger[3]

1. Waldman Professor and Chairman of the Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York City, New York, USA
2. Professor of Dermatology and Therapeutics and Honorary Consultant Dermatologist at University of Manchester, Manchester, UK
3. Professor of Dermatology and Allergy at Christian-Albrechts-University and Vice-Head of Department of Dermatology at the University Hospital Schleswig-Holstein, Kiel, Germany

Disclosure: Prof Lebwohl's institution has received research funds from AbbVie, Amgen, Arcutis Inc., AstraZeneca, Boehringer Ingelheim, Celgene, Clinuvel Pharmaceuticals, Eli Lilly, Incyte, Janssen Research & Development, LLC, Kadmon Corp., LLC, LEO Pharma, MedImmune, Novartis, Ortho Dermatologics, Pfizer, SCIderm, UCB Inc., and Vidac. He has acted as a consultant for Allergan, Almirall, Arcutis Inc., Avotres Therapeutics, BirchBioMed Inc., Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Foundation for Research and Education in Dermatology, Inozyme Pharma, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, Neuroderm, Pfizer, Promius/Dr. Reddy's Laboratories, Theravance, and Verrica. Prof Warren has received research grants from/run clinical trials with AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, LEO Pharma, Novartis, Pfizer, and UCB. He has received consulting fees from AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Avillion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sanofi, and UCB. Prof Weidinger has acted as an advisor, speaker or investigator for AbbVie, Almirall, Galderma, Kymab, La Roche-Posay, LEO Pharma, Eli Lilly, Novartis, Pfizer, Regeneron, and Sanofi Genzyme.

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Citation: EMJ Dermatol. 2019;7[1]:24-33.

Meeting Summary

Psoriasis and atopic dermatitis (AD) are both T-cell driven, chronic inflammatory skin disorders. This symposium aimed to discuss the distinct and overlapping clinical characteristics of these diseases and described how improved understanding of the immunopathological pathways involved has impacted treatment paradigms. With insight from his clinical experience, Prof Lebwohl described the key clinical and histologic features of psoriasis and AD. He also gave an overview of the evolution of systemic treatments for these diseases, which reflects growing knowledge of the T-cell driven pathologies, notably the dominance of the Th17/IL-17 pathway in psoriasis and Th2/IL-13 pathway in AD. Prof Warren provided insight into the central role of the IL-23/IL-17 axis in the immunopathogenesis of psoriasis and overviewed the registrational clinical data for approved agents targeting IL-17 and its receptor. He also discussed the importance of complete skin clearance in improving patient quality of life (QoL) and provided an update on the scope of personalised medicine in psoriasis. Prof Weidinger provided insight into the immunological pathways involved in the pathogenesis of AD and its distinct molecular profile from psoriasis, explaining the scientific rationale for, and emerging clinical data supporting, the key role of IL-13 pathways in AD.

Psoriasis and Atopic Dermatitis: Common and Distinct Clinical Characteristics

Professor Mark Lebwohl

Psoriasis and AD are chronic, systemic inflammatory diseases of the skin characterised by upregulation of proinflammatory cytokines, infiltration of immune cells to the skin, and barrier breakdown and remodelling. Commonalities between these two conditions are such that one might question whether they are distinct or represent different poles of a single spectrum.[1] Psoriasis and AD are associated with distinct and overlapping symptoms which can sometimes cause confusion in terms of diagnosis. Common symptoms include itch, dry scaly skin, and redness; however, patients with psoriasis typically have clearly demarcated, chronic plaques, usually with coarse scale, whereas AD ranges from patches to thin plaques with excoriation and less defined demarcation.[1] Both diseases are associated with a significant negative impact on patient QoL.[2,3] There are some key differences, for example, AD usually has an early onset in childhood, whereas psoriasis generally occurs later in life. AD is often associated with comorbid allergic diseases such as asthma and/or allergic rhinitis, whereas psoriasis is commonly associated with psoriatic arthritis.[1] The location of the patches and plaques can also help to differentiate between the two diseases as psoriasis is often observed on the extensor aspects of elbows and knees, whereas AD is found on the flexural aspects of the elbows and knees.[1]

Itch is a key symptom for both diseases. Itch was reported as one of the most severe and bothersome symptoms in a recent study evaluating a novel patient-reported psoriasis symptom diary,[4] and in a recent psoriasis study, improvement in itch severity was the most important mediator of overall improvement in health-related QoL (HRQoL).[5] Severity of itch, however, can potentially be used to distinguish between the two diseases as itch is more severe in AD patients which is reflected in the Hanifin and Rajka major diagnostic criteria.[6] Patients with AD often have exfoliations, which is a sign of itching.

Despite the similarities between psoriasis and AD, presenting symptoms and disease history are generally sufficient to distinguish between them in the clinic. While histological features are often not needed to make a diagnosis, in some cases these can be helpful. For example, spongiotic tissue reaction patterns are commonly encountered in inflammatory dermatoses, including contact, nummular, and dyshidrotic dermatitis, and may exhibit psoriasiform hyperplasia during chronic phases. Spongiosis can be histologically characterised by the presence of microscopic vesicles in the epidermis.[7] Dyshidrotic dermatitis, contact dermatitis, and

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volar skin psoriasis may appear virtually identical; however, volar psoriasis usually has more mounds of parakeratosis with neutrophils. Other conditions described as 'psoriasiform dermatitis' include: pityriasis rubra pilaris, an idiopathic condition which presents with follicle-based papules, plaques, and as palmoplantar keratoderma; and lichen simplex chronicus which is associated with intense pruritus and hyperkeratotic erythematous patches.[8] Abramovits et al. reported on the occurrence of overlapping psoriasis and AD symptoms in their clinic and proposed an overlapping dermatologic entity called 'PsEma'.[9]

Distinct and overlapping pathogenic mechanisms are also evident between psoriasis and AD which drive the treatment approaches available today. The first systemic treatments were the nonspecific, broad-acting immunomodulators methotrexate and cyclosporin, which provided symptomatic control.[10-13] In recent years, however, systemic treatments have evolved considerably, mirroring our growing understanding of the T-cell driven pathologies of these diseases, including the dominance of the Th17/IL-17 pathway in psoriasis and Th2/IL-13 pathway in AD. Targeted biologic agents offer advantages over broad-acting immunomodulators, particularly in terms of safety profiles.[14] The evolution of targeted treatment for psoriasis started with approval of monoclonal antibodies against TNF-α, followed by approval of more targeted systemic agents that inhibit IL-12/23, IL-23, IL-17, and the IL-17 receptor subunit A (IL-17RA).[15] In contrast, targeted treatment for AD has only recently become available with the approval of monoclonal antibodies against IL-4/13, with targeted treatments against IL-13 currently in development.[16,17]

Personalised Therapy in Psoriasis with a Focus on IL-17

Professor Richard Warren

The interplay between environmental and genetic factors is implicated in the initiation of psoriasis and the activation of the psoriatic inflammatory cascade. There are three immune axes involved in this cascade, all of which are mediated by different subsets of T cells: Th1 cells which secrete TNF-α and interferon (IFN)-γ, Th22 cells which secrete IL-22, and Th17 cells which secrete IL-17.[18,19] All three T cell subtypes play an important role in the immunopathogenesis of psoriasis; however, Th17 cells have been shown to be the main driver of the disease phenotype. Activated dendritic cells release IL-23 which stimulates Th17 cells to produce IL-17 family cytokines. In psoriasis, expression of IL-17A, IL-17C, and IL-17F is increased; these cytokines activate IL-17RA complexes on keratinocytes and immune cells leading to inflammation and the clinical manifestations of the disease.[20-24] As multiple cell types can produce IL-17, inhibiting upstream cytokines such as TNF-α, IL-12, or IL-23 only partly attenuates IL-17 production.[25] This leaves other cytokines to synergise with residual levels of IL-17 contributing to the inflammatory response.[26,27] Inhibition of IL-17RA, however, directly blocks the action of multiple IL-17 cytokines (specifically IL-17A, IL-17C, IL-17E, IL-17F, and IL-17A/F). This rapidly and completely normalises the inflammatory response suggesting that IL-17RA plays a key role in the pathogenesis of psoriasis.[20,21,27]

Due to the importance of the IL-23/17 axis, targeting IL-23 or IL-17 should have great therapeutic potential in psoriasis.[28] Treatment of psoriasis has evolved considerably over recent years with the introduction of highly efficacious IL-17 and IL-23 inhibitors. To date, three IL-17 inhibitors are approved for moderate-to-severe plaque psoriasis: secukinumab and ixekizumab which selectively bind to IL-17A, and brodalumab which selectively binds to IL-17RA and thereby blocks activity of IL-17A, IL-17C, IL-17E, IL-17F, and IL-17A/F molecules (Figure 1).[29]

Approved Agents Targeting IL-17

Secukinumab was the first IL-17-specific biologic approved for psoriasis based on data from two registrational Phase III trials, ERASURE and FIXTURE.[30] Together, these studies investigated secukinumab (150 mg and 300 mg doses every 4 weeks [Q4W]) versus placebo and the TNF-α blocker, etanercept in 2,044 patients with refractory, moderate-to-severe plaque psoriasis.

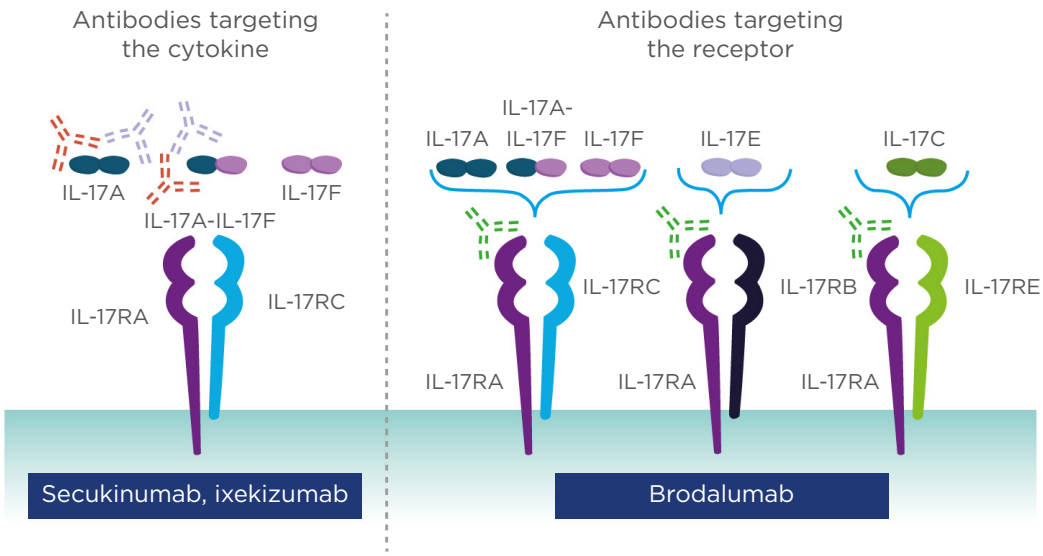

Figure 1: Approved IL-17 inhibitors target the cytokine or the receptor.

Adapted from Patel et al.[29]

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At Week 12, secukinumab was superior to placebo and etanercept for the co-primary efficacy endpoints of Psoriasis Area and Severity Index (PASI) 75 ($p<0.001$) and response of 0 or 1 on the modified Investigator's Global Assessment (IGA; $p<0.001$), and was also superior for other efficacy endpoints including PASI 90 and 100 at Week 12. The benefit with secukinumab was dose-dependent, with higher levels of response observed with the higher dose of 300 mg.[30] The SCULPTURE extension study demonstrated that PASI responses (PASI 75, 90, and 100) with secukinumab can be maintained for up to 5 years (observed analyses; small reductions were observed with multiple imputation and last observation carried forward analyses).[31] In the ERASURE and FIXTURE studies, the incidence of serious adverse events (AE) with secukinumab was low and comparable to placebo. The most common AE observed with secukinumab were nasopharyngitis, headache, and diarrhoea. There was a slightly higher incidence of candida infections in patients receiving secukinumab but this did not lead to discontinuation.[30] Crohn's disease and ulcerative colitis are other AE of special interest as IL-17 inhibitors were found to be ineffective for the treatment of these diseases and there were concerns that IL-17 treatment may exacerbate inflammatory bowel disease (IBD) in psoriasis patients; however, the incidence of IBD with secukinumab was low.[30] The long-term safety profile at 5 years was similar to the induction phase and no new safety signals were observed.[31]

European approval of ixekizumab for moderate-to-severe plaque psoriasis in 2017 was based on data from the UNCOVER-1, 2, and 3 Phase III studies. UNCOVER-2 and 3 assessed ixekizumab 80 mg every 2 weeks (Q2W) and Q4W versus placebo and etanercept in 1,224 and 1,346 patients, respectively. All patients treated with ixekizumab received an induction dose of ixekizumab 160 mg followed by 80 mg Q2W up to Week 12 followed by 80 mg Q2W or Q4W.[32] At Week 12, pooled data from these studies showed that ixekizumab was superior to etanercept and placebo for the co-primary endpoints of PASI 75 ($p<0.001$) and proportion of patients achieving static Physician's Global Assessment (sPGA) of 0 or 1 ($p<0.001$). This benefit was also observed with ixekizumab for PASI 90 and 100.[32] Among patients who received the recommended dose of ixekizumab (160 mg at Week 0, ixekizumab 80 mg Q2W up to Week 12, and Q4W thereafter) in the long-term extension of UNCOVER-3, clinical response was maintained up to Week 156.

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Long-term PASI response was assessed using observed and multiple imputation analyses, whereas long-term sPGA response was analysed using a modified non-responder imputation in which patients who discontinued due to AE, lack of efficacy, or relapse were considered non-responders, and as such, data was imputed as non-responder imputation.[33] The safety profile of ixekizumab across the three pivotal UNCOVER trials was manageable and the most common AE were nasopharyngitis and injection site reactions. A dose-dependent incidence of candida infections and low incidence of IBD were observed.[32] A similar safety profile was observed in the long-term extension at Week 156.[33]

Approved Agent Targeting the IL-17 Receptor

AMAGINE-1, 2, and 3 were the pivotal Phase III trials leading to approval of brodalumab: a human anti-IL-17RA monoclonal antibody. AMAGINE-2 and 3 were placebo-controlled, active comparator studies which recruited a total of 3,712 patients.[34]Patients received ustekinumab (anti-IL-12/23), placebo, or brodalumab (140 mg Q2W or 210 mg Q2W) during the 12-week induction phase. Individuals who received brodalumab induction were then re-randomised to receive brodalumab 210 mg Q2W or brodalumab 140 mg Q2W, Q4W, or Q8W during the 40-week maintenance phase. Patients randomised to placebo induction received maintenance brodalumab 210 mg Q2W. Individuals randomised to ustekinumab induction also received ustekinumab as maintenance therapy, and from Week 52 could receive brodalumab 210 mg Q2W in an open-label extension study.[34]

In both studies, at Week 12, the proportion of patients with PASI 75 (AMAGINE-2: p=0.08; AMAGINE-3: p=0.007), sPGA 0 or 1 score (AMAGINE-2 and -3: p<0.001), and PASI 100 (AMAGINE-2 and -3: p<0.001) was greater for brodalumab 210 mg Q2W versus ustekinumab.[34] Response to continuous brodalumab 210 mg Q2W was maintained throughout 120 weeks of treatment in AMAGINE-2 (using as observed analysis). Furthermore, switching from ustekinumab to brodalumab 210 mg Q2W at Week 52 resulted in improved outcomes, with similar levels of skin clearance response being achieved at Week 120 compared with patients who received brodalumab 210 mg Q2W from the start of the study.[35] In a pooled analysis of AMAGINE-2 and 3, brodalumab was associated with high rates of complete clearance over time (Week 0–52) compared with ustekinumab, regardless of prior therapy (systemic/biologic naïve, systemic treated, biologic treated with or without failure).[36] In AMAGINE-2 and 3, the incidence of AE was low and comparable to ustekinumab and placebo, and the most common AE were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. There was a low rate of candida infection, but no incidences of Crohn's disease were observed.[34] Long-term data demonstrated a similar safety profile, consistent with the induction phase, and no new safety signals.[35]

Given there are several biologics approved for moderate-to-severe psoriasis, comparing agents can be challenging due to limited head-to-head data to inform treatment decisions. Network meta-analyses (NMA) can be used to compare treatments using common comparators and are important in informing payors of differences between agents; however, they can include data from patients treated with unlicensed doses and analysis methodologies can vary across different NMA. A recent NMA compared the efficacy of available biologic and non-biologic systemic therapies for patients with moderate-to-severe plaque psoriasis, analysing data from 77 trials involving 34,816 patients.[37] This large-scale analysis revealed IL-17-targeted agents were among the top performing drugs, with brodalumab and ixekizumab outperforming secukinumab in terms of PASI responses and demonstrating similar efficacy to the IL-23 inhibitor risankizumab.[37] It should be noted however, that NMA provide only indirect evidence and may be influenced by the methodology employed; randomised comparator trials are needed to robustly compare the efficacy of the IL-17-targeted agents both with themselves and other agents.

Optimising Treatment for Personalised Care

An important aspect of personalising care in order to optimise treatment is consideration of the patient's perspective of their own treatment goals. When using a 'treat-to-target' approach, several clinical measures should be

incorporated: efficacy, safety, tolerability, and patient-reported outcomes (PRO).[38] PRO are particularly important because achieving complete clearance (PASI 100 or sPGA 0) is associated with improved HRQoL in the clinical trial setting and in real-world clinical practice.[39,40] Caution should be exercised when reviewing these data as not all patients achieving complete clearance experience this benefit in HRQoL and this may be due to the insensitivity of the PRO used or a residual impact on patients' wellbeing.

Predictors of Response to Biologic Treatment

Despite the availability of several effective biologic treatments, some patients are still unable to achieve an adequate response; therefore, a better understanding of the predictors of response may be beneficial. Studies from the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) study group have demonstrated that serum drug levels of adalimumab and ustekinumab taken around Week 4 may be predictive of PASI 75 response at 6 months.[41,42] Genetic biomarkers such as *HLA-C*06:02*, a susceptibility allele for psoriasis, may also be important when predicting differing responses to adalimumab and ustekinumab.[43]

The future of personalised care in psoriasis will integrate 'multi-omic' data, including drug levels, genetic biomarkers, and the proteome, to allow clinicians to predict response to treatment and effectively manage care. These approaches to personalised care are highly relevant to AD as it is a very heterogeneous disease with several underlying immunological pathways, including some involvement of IL-17.[1]

Atopic Dermatitis: A Th2 Dominant Disease with Greater Molecular Heterogeneity

Professor Stephan Weidinger

AD is a common inflammatory skin disease associated with a high disease burden, including a negative impact on mental health and QoL, frequent sleep disturbances, infections, and comorbidities such as asthma, rhinitis, and food allergies.[44,45] AD is triggered by a complex immune pathophysiology pathway in which epidermal barrier dysfunction and Type 2 inflammation are thought to play an important role.

In AD, decreased expression of epidermal barrier proteins, including filaggrin and hornerin, contribute to skin barrier dysfunction which affects the composition of the skin microbiome, including decreased bacterial diversity and distinct bacterial colonisation patterns such as increase in the presence of *Staphylococcus aureus.*[46,47] Filaggrin deficiency has also been found to increase epidermal permeability in animal models, which may contribute to enhanced antigen penetration and sensitisation.[48,49] Epidermal barrier disruption promotes inflammation by stimulating keratinocytes to release skin alarmins such as thymic stromal lymphopoietin, IL-33, and IL-25.[50,51] These mediators activate skin-resident Group 2 innate lymphoid cells to stimulate secretion of IL-13 and IL-5 which activate and recruit further immune cells to the skin, creating a positive feedback loop.[50,52] Th2 lymphocytes are also activated leading to the secretion of IL-13 and IL-4.[50]

IL-13 is a Key Driver of Chronic Inflammation in Atopic Dermatitis Skin

While AD and psoriasis share several clinical features and pathogenic mechanisms, they are molecularly distinct diseases. A recent study of messenger RNA (mRNA) levels in AD and psoriatic skin lesions revealed that, despite common dysregulated genes, the AD genetic skin signature is dominated by Th2 cytokines (IL-13 being the most distinctive marker), while psoriasis is dominated by the IL-17 family of cytokines. Furthermore, *IL13* mRNA expression was detected in all AD lesional skin samples analysed in this study, whereas *IL4* mRNA expression was only detected in 40% of samples, suggesting that AD is predominantly IL-13 driven. The authors also reported a positive correlation between *IL13* mRNA expression and disease severity in AD patients.[53]

Data presented by Prof Weidinger at EADV 2019 further supported the key role of IL-13 in driving the pathogenesis of AD.

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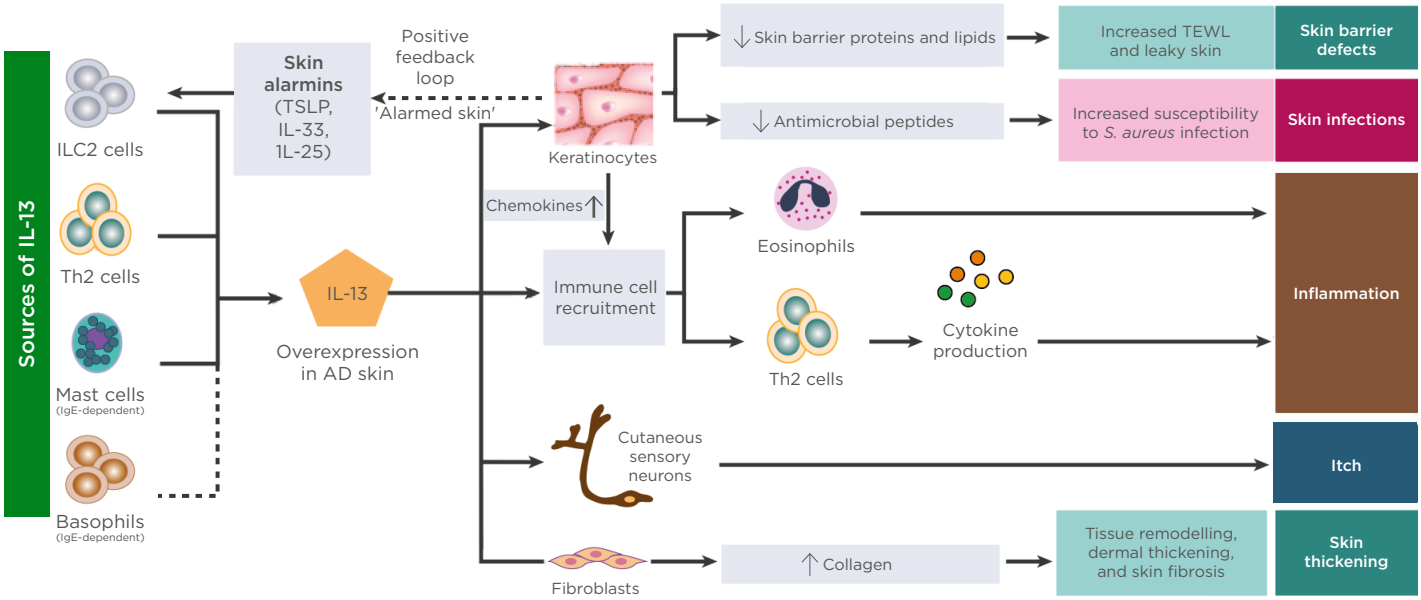

Figure 2: Sources and impact of IL-13 in atopic dermatitis skin.

AD: atopic dermatitis; ILC: innate lymphoid cells; *S. aureus: Staphylococcus aureus*; TEWL: transepidermal water loss; TSLP: thymic stromal lymphopoietin.

Adapted from Bieber T.[52]

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IL13 mRNA expression in *in vitro* skin cultures from AD patients was shown to positively correlate with the expression of key inflammatory chemokines and negatively correlate with skin barrier biomarkers;[54] furthermore, addition of an IL-13 inhibitor to these skin cultures restored the expression of genes central to epithelial barrier function, including filaggrin.[54] Together, these findings support the concept that IL-13 is the dominant cytokine in AD, with downstream effects on epithelial barrier function, susceptibility to infection, inflammation, itch, and skin thickening (Figure 2).[52]

Targeting IL-13 Pathways

Dupilumab is the first licensed biologic for AD and elicits its effects by binding to the shared IL-4Rα subunit of the Type I and Type II receptors blocking both IL-4 and IL-13-mediated signalling.[16] Approval of dupilumab was based on two Phase III monotherapy trials (SOLO 1 and SOLO 2 [N=1,379]) and a Phase III trial investigating concomitant administration with topical corticosteroids ([TCS] CHRONOS). Pooled Week 16 monotherapy data from SOLO 1 and 2 showed that dupilumab 300 mg Q2W resulted in a greater proportion of patients achieving IGA response (score 0 or 1 and ≥2 point reduction from baseline) versus placebo (37.0% versus 9.3%; p<0.0001) and a greater proportion of patients with Eczema Area and Severity Index (EASI)-75 (47.7% versus 13.3%; p<0.0001).[55] Similar outcomes were observed with dupilumab 300 mg Q2W in combination with TCS at Week 16 in the 917 patients enrolled in the CHRONOS study (IGA response: 38.7% versus 12.4%, p<0.0001; EASI-75: 68.9% versus 23.2%, p<0.0001).[56] Real-world data from the TREATGermany registry indicate that dupilumab is well-tolerated in routine clinical practice, with conjunctivitis being the most frequently reported AE.[57]

Specific inhibition of IL-13 is currently under investigation in AD, and data from Phase IIb studies of tralokinumab and lebrikizumab have recently been reported.[58,59] Tralokinumab binds to the IL-13 cytokine at an epitope overlapping the IL-13Rα receptor binding site, preventing IL-13 from binding to the IL-13Rα1 subunit of the Type II receptor.[52] At Week 12 of the

placebo-controlled Phase IIb study, tralokinumab 300 mg Q2W in combination with TCS was associated with a greater proportion of patients achieving IGA response (26.7% versus 11.8%; p=0.06) and EASI-75 (42.5% versus 15.5%; p=0.003) compared with placebo plus TCS. A low level of serious AE was reported, and the most common treatment-emergent AE were upper respiratory tract infection and headache.[58] Lebrikizumab binds to the IL-13 cytokine at an epitope overlapping the IL-4Rα receptor binding site to prevent IL-4Rα/IL-13Rα1 heterodimerisation of the Type II receptor.[52] At Week 16 of a placebo-controlled Phase IIb study, a higher proportion of patients treated with lebrikizumab 250 mg Q2W monotherapy achieved an IGA response (44.6% versus 15.3%; p=0.0023) and EASI-75 (60.6% versus 24.3%; p=0.0005) compared with placebo. The most frequent AE reported were upper respiratory tract infection and nasopharyngitis.[59] Efficacy and safety data from Phase III trials for tralokinumab and lebrikizumab are required to further inform the potential utility of IL-13-specific inhibition as a therapeutic approach for AD.

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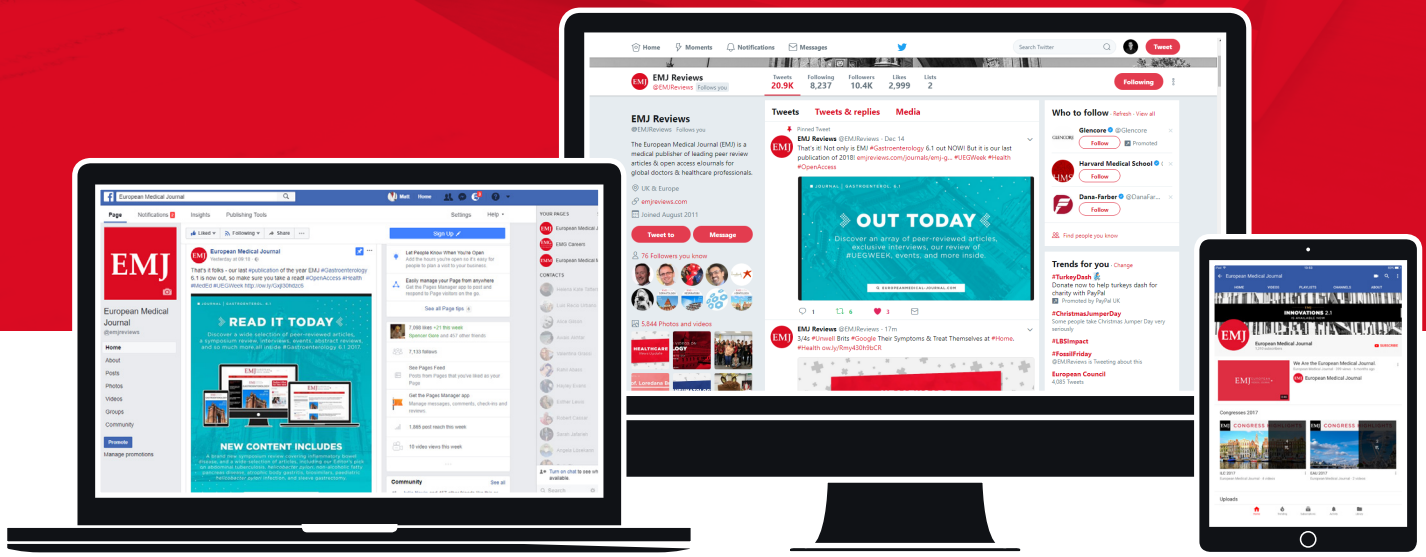

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Considering Tomorrow in Today's Treatment Choice of Women Living with Psoriasis

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Chairperson: Matthias Augustin[1]

Speakers: Matthias Augustin,[1] Alexander Egeberg,[2] Sandy McBride[3]

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Certolizumab pegol (CZP, CIMZIA®, a trademark from the UCB group of companies) is licensed in the European Union (EU) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. CZP, in combination with methotrexate (MTX), is also indicated for the treatment of active psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate or as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. **CZP Safety information**: in plaque psoriasis, the safety profile of CZP 400 mg every 2 weeks and CZP 200 mg every 2 weeks were generally similar. During controlled clinical trials through Week 16, the proportion of patients with serious adverse events was 3.5% for CZP and 3.7% for placebo. The proportion of patients who discontinued treatment due to adverse events in the controlled clinical studies was 1.5% for patients treated with CZP and 1.4% for patients treated with placebo. The most common adverse reactions reported through Week 16 belonged to the system organ classes Infections and infestations, reported in 6.1% of patients on CZP and 7% of patients on placebo, General disorders and administration site conditions, reported in 4.1% of patients on CZP and 2.3% of patients on placebo, and Skin and subcutaneous tissue disorders, reported in 3.5% of patients on CZP and 2.8% of patients on placebo. **CZP information regarding pregnancy and lactation:** data from more than 500 prospectively collected pregnancies exposed to CZP with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of CZP. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with CZP administration during pregnancy. CZP should only be used during pregnancy if clinically needed. Nonclinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of CZP (no Fc region). Clinical data based on CRIB, a pharmacokinetic study of women ≥30 weeks pregnant (n=16; last dose ≤35 days prior to delivery) receiving commercial CZP (n=15, CZP 200 mg Q2W; n=1, CZP 400 mg Q4W), and on CRADLE, a pharmacokinetic study of lactating mothers (n=17) receiving commercial CZP (n=16 received CZP 200 mg Q2W; n=1 received CZP 400 mg Q4W), for a locally approved indication (RA, axSpA/AS, PsA, and CD*) and at an approved dose at the time the study was conducted. The CRIB and CRADLE study did not include any patients receiving CZP 400 mg dose Q2W. The clinical significance of low levels of certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last CZP administration during pregnancy before administration of live or live-attenuated vaccines (e.g., BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Click here to view CZP prescribing information (CIMZIA®, certolizumab pegol label) on EMA website.

Citation: EMJ Dermatol;7[1]:34-43.

Meeting Summary

This symposium explored the challenges of plaque psoriasis that are more prevalent in, or specific to, women, in terms of burden, treatment needs, and treatment options. This theme was introduced by Prof Augustin who described the social and emotional burden of plaque psoriasis and gender differences in relation to its impact and treatment expectations. Many areas, such as relationships, sexual activity, childbearing, and educational and career prospects can be affected in women, and as well as possible disease progression, need to be considered when discussing therapeutic options with the patient. Dr Egeberg outlined the certolizumab pegol (CZP) plaque psoriasis clinical trial programme. Three-year treatment results from the CIMPASI 1 and 2, and CIMPACT Phase III trials, showed that the clinical responses previously reported for moderate-to-severe plaque psoriasis with CZP 200 mg every other week (Q2W) or 400 mg Q2W for up to 48 weeks were well maintained over 3 years, with no new safety signals observed, underpinning the durability of the efficacy profile

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of CZP. Aligned with the unique Fc-free structure of CZP, clinical findings of no-to-minimal transfer of CZP from mother to infant or into breast milk, mean that CZP could be used during pregnancy if clinically needed and post-partum. Dr McBride described the profound life-impact of plaque psoriasis specifically in women and why it is essential to understand their needs and life goals when exploring treatment options. She discussed the importance of reviewing family planning and conception plans at every visit in case of changes in treatment needs. Immediate and future life plans, including the impact of pregnancy, childbirth, and the postpartum period, need to be considered when exploring treatment options with the patient. Women with plaque psoriasis face significant challenges and there is a need for long-term, effective treatments that are compatible with pregnancy and breastfeeding.

Introduction

Professor Matthias Augustin

The objectives of this symposium were to understand the importance of planning treatment addressing the specific needs of women living with moderate-to-severe plaque psoriasis throughout their life journey, and to discuss the importance of shared decision making early in the management of plaque psoriasis in women, as well as to identify any particular issues or helpful tools that could aid this decision-making process. A further objective was to share data on the durable efficacy of the TNF inhibitor CZP and its consideration for treating plaque psoriasis in women.

Meeting the Expectations of Patients Living with Plaque Psoriasis

Professor Matthias Augustin

The emotional and social burden of plaque psoriasis is considerable. One in four patients believe that their psoriasis makes it harder to find work and has stopped them following their chosen career.[1] Approximately one-fifth of patients are affected by depression, with suicidal ideation reported for between 2.5% and 9.7%.[2-5] Most patients reported feeling stigmatised and isolated and many fear passing on their psoriasis.[6] Patients with plaque psoriasis are also more likely than the general population to be affected by other chronic and serious diseases including psoriatic arthropathy, anxiety and depression, metabolic syndrome, cardiovascular disease, and inflammatory bowel disease.[2,3,7-13] Quality of life across a range of emotional and physical components is negatively affected, with 94% of psoriasis and psoriatic arthropathy patients reporting that their condition was a problem in daily life, 88% that it affected their emotional wellbeing, and 82% that it interfered with their enjoyment of life (n=5,604 patients).[14] The emotional impact also increases with disease severity,[14] and mental illness, including disorders due to substance abuse, mood and stress-related disorders, is also more frequent in patients with plaque psoriasis.[15] In one survey of the burden of skin manifestations of plaque psoriasis, patients (n=17,434) reported negative effects on a number of aspects of their lives including sleep, working life, and sexual activity; in another, 79% of the respondents (n=40,350) reported that their daily life was disrupted for 10% of the time.[16]

Psoriatic lesions in the abdominal, genital, buttock, and lumbar areas have been associated with an increased likelihood of sexual dysfunction, independent of anxiety or depression.[17] Patients with genital lesions had higher Dermatology Life Quality Index (DLQI) scores (mean 8.5 versus 5.5 without; n=487).[18,19] Genital lesions are experienced by >60% of patients at some time,[18] significantly impacting quality of life across a range of areas, including symptoms and feelings, personal relations, sexual difficulties, daily activities, and leisure.[18,19]

The emotional and social burden is clearly apparent when looking at patients' treatment expectations beyond skin clearance and control, with gender differences in the burden experienced also reflected in these expectations. Women express a greater need to be free of pain and discomfort and to feel more in control of their disease and treatment, particularly with respect to emotional and social wellbeing (Figure 1).[20] Furthermore, in a Swedish Registry study (n=2,450), although more men than women had Psoriasis Area and Severity Index (PASI) 75 scores >10 (35% versus

27%), more women had DLQI scores >10 (38% versus 28%).[21] In this same registry, only one-third of patients receiving treatment with a biologic agent (n=589) were women, in spite of the higher impact on quality of life.[21]

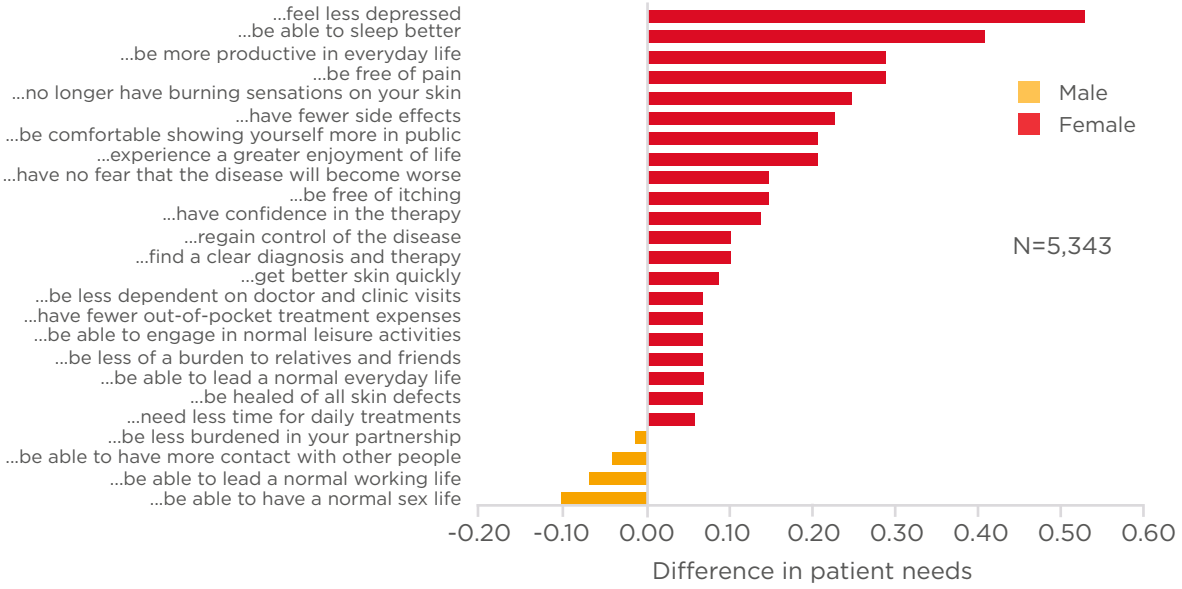

Figure 1: Differences in patients' plaque psoriasis treatment needs by gender.

Patients were recruited from the German and Swiss psoriasis registries PsoBest (n=4,894) and Swiss Dermatology Network of Targeted Therapies (SDNTT) (n=499).

Adapted from Maul et al 2019.[20]

Looking further at what drives gender-specific psoriasis experiences and treatment expectations, the 2017 World Psoriasis Happiness Report (n=121,800) found that women with plaque psoriasis experience a greater happiness gap from the general population than affected men, and were more likely to experience stress (>60% versus 42%) and loneliness than men (25–28% and 19–24%, respectively).[22] Women experience greater stigmatisation because of their psoriasis than men, reporting significantly greater anticipation of rejection, feelings of being flawed, sensitivity to others' opinions, and secretiveness.[23] Women also reported a greater degree of suffering associated with genital lesions than affected men, including itch, pain, stinging, burning, and dyspareunia, as well as less frequent sex as a result of the lesions.[18]

Hormonal fluctuations during a woman's lifetime can affect disease activity.[24] A study of >150,000 women with plaque psoriasis illustrated clearly the various ways in which the disease can affect their life and disease journeys,[25] with irregular versus regular menstrual cycles and a surgical menopause rather than a natural menopause being more likely in women with plaque psoriasis; whereas, women without plaque psoriasis were likely to breastfeed their infants for longer and showed a nonsignificant trend towards a higher likelihood of multiple births.[25] While it is often stated that plaque psoriasis improves with pregnancy, in a prospective study of pregnant women (n=47), 44% had no change or worsening, and, strikingly, postpartum, 65% experienced worsening.[26]

In summary, there are gender differences in how patients experience plaque psoriasis. Female patients have different expectations and needs from therapy compared with men. Many areas, such as relationships, sexual activity, childbearing, and educational and career prospects,[27-31] can be impacted by the disease or can cause worsening. These need to be considered when discussing therapeutic options with the patient.

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Achieving Long-term Impact in Patients Living with Plaque Psoriasis with Certolizumab Pegol

Doctor Alexander Egeberg

The TNF inhibitor CZP differs in molecular structure from other antibody-based anti-TNF and anti-IL biologic therapies, as it is a PEGylated humanised anti-TNF Fab' fragment without an Fc region.[32-35]

The Certolizumab Pegol Plaque Psoriasis Clinical Development Programme

A Phase III efficacy and safety programme in patients with moderate-to-severe plaque psoriasis was conducted across 11 countries in North America, western Europe, and eastern Europe. The three randomised, double-blind, parallel group Phase III trials (CIMPASI 1, CIMPASI 2, and CIMPACT) included >1,000 patients and comprised blinded, maintenance, and open-label periods.[36-39] A Phase III study has also been completed in Japan.[40]

In CIMPACT, patients were randomised to either CZP 400 mg Q2W; CZP 200 mg Q2W, preceded by a CZP 400 mg loading dose at Weeks 0-2-4; etanercept (50 mg twice-weekly); or placebo. The primary endpoint was a 75% reduction in PASI 75 at Week 16. This was followed by a maintenance period up to Week 48, and then open-label treatment with possible dose adjustment (see CIMPASI-1 and 2) up to Week 144 .[38,39] From Week 16, patients who had responded with a PASI reduction ≥75% were rerandomised to CZP 200 or 400 mg to explore dose optimisation. Patients with a PASI reduction <75% in all treatment groups received 'escape' treatment with CZP 400 mg Q2W.[38,39]

In CIMPASI 1 and 2, patients were randomised to CZP 400 mg, CZP 200 mg preceded by 400 mg loading dose at Weeks 0-2-4 or placebo (all Q2W). The primary endpoint was PASI 75 or a Physician's Global Assessment (PGA) score of 0 or 1 at Week 16.[37] From Week 16, patients who had responded on placebo with a PASI reduction ≥50–75% were re-randomised to CZP 200 mg. Nonresponders (PASI reduction <50%) were switched to 'escape' treatment as above in all treatment groups. From Week 48, open-label CZP 200 mg Q2W was continued to Week 144, but with the option of the higher dose if PASI reduction was <50%. During the open-label phase, dose adjustment between 200 mg to 400 mg Q2W could occur, and escalation was either mandated if patient response was <PASI 50 or permitted at the clinician's discretion if the response was between PASI 50 and 75. De-escalation was also permitted for a response >PASI 75.[37,39]

Across CIMPACT and CIMPASI 1 and 2 (n=850), patients had quite severe plaque psoriasis at baseline (PASI ~20; mean affected BSA ~25%) and 25–30% had previously been treated with another biologic. Demographic and baseline characteristics of the pooled patients were well-balanced between CZP treatment arms and placebo.[41]

What May We Expect of a Biologic in the Treatment of Plaque Psoriasis?

There were consistent clinical responses (PASI 75) in the Phase III trials after 16 weeks' treatment with CZP 200 mg (<75%; n=351) or 400 mg (<80%; n=342) Q2W.[37,38] In the long-term analysis of CIMPASI 1 and 2, the PASI 75 response rate was approximately 70% (n=186) after one year's treatment with 200 mg Q2W, and the PASI 90 rate was approximately 50%. These rates remained stable over the remainder of the study up to Week 144, with most patients staying on 200 mg Q2W.[39,42]

With the 400 mg Q2W dose, >60% of patients had a PASI 90 response after 1 year (PASI 75 84%; n=175). When the dose was lowered to 200 mg Q2W, response rates decreased slightly, but stabilised at >70% for PASI 75 and >40% for PASI 90.[39,42] For patients originally randomised to placebo, but who crossed over to 400 mg Q2W, PASI 75 at 1 year was 83% and PASI 90, 60% (n=72). Most patients (63%) then continued on the 400 mg dose, but the remainder switched to the lower dose; similarly, response rates remained stable over the remainder of the study.[39] These findings show that dose adjustment could be practical in real-life clinical practice. Evaluating quality of life impact, more than 50% of patients (n=361) treated with CZP had a DLQI of 0 or 1 after 1 year (>60% with 400 mg Q2W [Figure 2]), demonstrating that they were effectively normalised with respect to DLQI.[39] No new or unexpected safety signals

were identified during long-term treatment when compared to previously reported data for CZP in psoriasis and in other indications as well as other TNFi agents approved for psoriasis. The most frequently reported adverse events were nasopharyngitis (IR 14.2) and upper respiratory Infections (IR 7.9) with an overall similar profile and discontinuation rate for both doses. There was no sign of an increased risk of infections with continued exposure over time.[39]

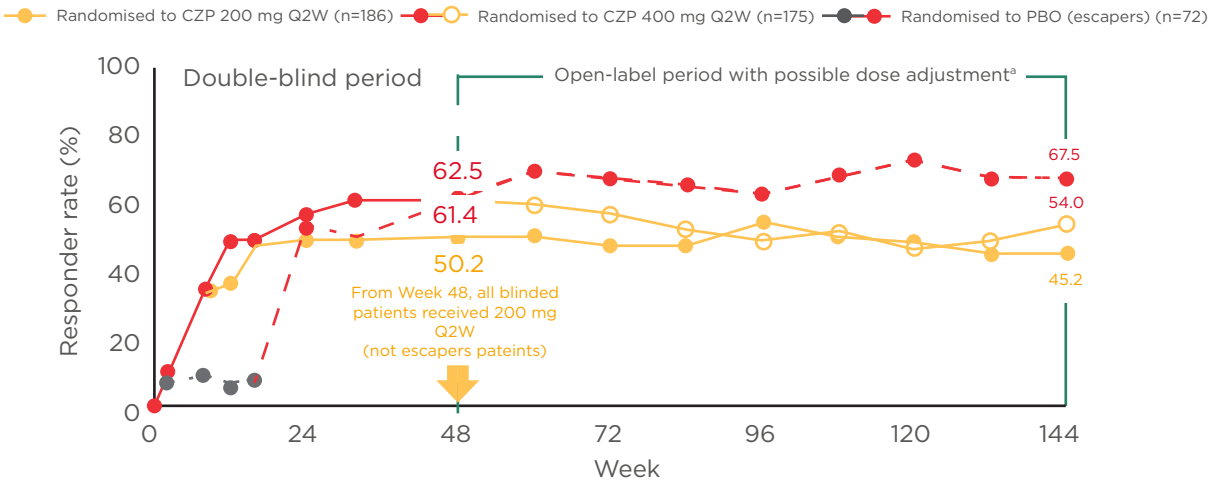

Figure 2: Percentages of patients with mild-to-moderate plaque psoriasis who had Dermatology Life Quality Index scores of 0 or 1 when treated with certolizumab pegol 400 mg every other week for up to 144 weeks.[39]

Markov Chain Monte Carlo imputation. Missing values were imputed based on all data available for a given patient. This was repeated several times, and logistic regression applied to generate a single estimated responder rate for each visit. Results for the escape arm patients and the certolizumab pegol-randomised patients originate from two independent models.

[a]Dose adjustments were mandatory in patients with Psoriasis Area and Severity Index (PASI) <50 and at the investigator's discretion in patients with PASI 50–74. Patients who received 12 weeks certolizumab pegol 400 mg every other week could dose-reduce at the investigator's discretion if they achieved PASI 75 and were withdrawn if they did not achieve PASI 50. PASI 75/90: ≥75/90% improvement from baseline in PASI.

CZP: certolizumab pegol; PBO: placebo; Q2W: every other week.

Other Elements to Consider in Clinical Practice

There are several reasons why patients with plaque psoriasis may switch between biologics, including life events and lack of response to treatment. In patients who were responsive to etanercept (n=74), responsiveness was maintained after switching to CZP (200 mg Q2W), with an increase in PASI 90 from 30% to 78%.[43] Nonresponsive patients who were switched to CZP (400 mg Q2W), had improvements in PASI 75, PASI 90, and PGA 0/1.[44] In psoriatic arthritis patients with plaque psoriasis (BSA ≥3%) treated with CZP, improvements in PASI 75 scores and complete resolution of nail disease were sustained over 216 weeks.[45] Patients treated with CZP also showed stable response rates across a range of BMI subgroups.[46]

The expectation that the unique Fc-free structure of CZP prevents its active placental transfer[32-35] aligns with pharmacokinetic findings of no-to-minimal (<0.1%) transfer from mother to infant;[47] similarly, there was minimal transfer of CZP in breast milk.[48] Unlike several other biologic agents, CZP treatment can therefore be considered during pregnancy if clinically needed and in breastfeeding mothers.[49]

In summary, CZP showed durable efficacy over 3 years in plaque psoriasis. Responder rates were higher with 400 mg Q2W and gradually

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decreased with dose reduction to 200 mg Q2W, suggesting that continued treatment at 400 mg Q2W may be needed to maintain optimal response. No new or unexpected safety signals were revealed in the long-term study. There was also no-to-minimal placental transfer of CZP from mother to infant or into breast milk.

Unique Patient Challenges and How to Address Them

Doctor Sandy McBride

The everyday reality for many women with plaque psoriasis is very far from the aspirational images of female beauty promoted in the media. In a study in which women with severe plaque psoriasis wrote postcards to express their feelings towards their disease, many expressed feelings of distress, such as feeling separated from other women and alone because of their psoriasis, as well as low self-esteem and self-denigration.[50] Women have also been reported to experience higher stigmatisation than men because of their psoriasis.[23]

When analysed by gender, World Psoriasis Happiness Surveys data for >50,000 women and >35,000 men with plaque psoriasis, showed that affected women had lower life satisfaction than affected men and the general population. They were also more likely to experience feelings of loneliness and higher levels of stress, with differences greatest in younger women.[51]

For women with plaque psoriasis, anxiety and depression can be an everyday occurrence throughout their lifetime.[50]

Women usually develop Type 1 psoriasis when they are at the age of child-bearing potential, generally from their late teens to early 30s, with 75% of cases presenting before age 40 years (Figure 3).[52,53] It is an everyday reality of clinical practice that almost half of pregnancies are unplanned or are unintended,[54] which presents a considerable challenge when treating plaque psoriasis in women of childbearing age. Questions to the symposium audience showed that while most participants asked their patients about family planning before initiating treatment, this was rarely asked about again after treatment initiation. Furthermore, although family planning partnership with their dermatologist is critical to successful outcomes,[22] in a USA study of 141 women with plaque psoriasis, 88% sought advice from the internet, 7% reported that their dermatologist initiated family planning discussions, and 21% did not even inform their dermatologist they were pregnant.[55] A snapshot clinic audit found that family planning was discussed with 62.5% of patients before treatment, but with only 12.5% at subsequent visits (Dr McBride and colleagues, through personal communication). These findings led to the introduction in the clinic of a brief questionnaire for completion by female and male patients at every clinic visit on pregnancy, fathering a child, and contraception use, so that patients' needs could be reviewed and addressed if they had changed (Dr McBride and colleagues, through personal communication).

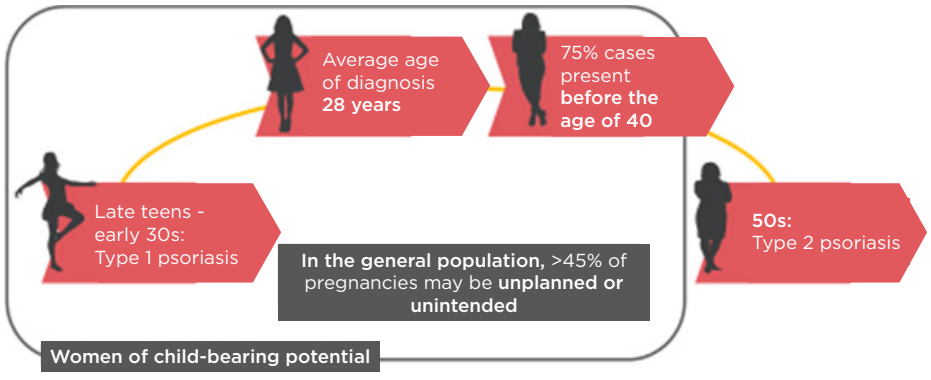

Figure 3: Plaque psoriasis: A woman's journey.

Onset and diagnosis frequently occur when women are of child-bearing age. The patient's wishes to plan for a family and also the high risk of unintended pregnancy therefore need to be considered when planning treatment.[52–54,56]

Plaque psoriasis impacts pregnancy and its outcomes. Women <35 years of age with plaque psoriasis (n=7,400) have a 22% lower likelihood of pregnancy than the general population,[56] with those with moderate-to-severe plaque psoriasis having ≤50% fewer children.[57] The risk of complications such as gestational hypertension and diabetes, pre-eclampsia, and the need for caesarean section are increased in moderate-to-severe plaque psoriasis, which has also been linked to increased likelihoods of preterm birth and low birth weight.[58] Women with psoriatic disease may suffer Koebnerization at their nipples from infant suckling and may therefore be less likely to breastfeed.[59] Dr McBride also referred to findings that almost half of women with plaque psoriasis reported no change or worsening during pregnancy, and post-partum, two-thirds experienced worsening.[26] It is therefore important that women are followed up closely after giving birth. Dr McBride suggested that a lack of treatment options during pregnancy and breastfeeding leads to treatment being stopped during pregnancy, which may result in disease flares and effects on psychological wellbeing. For example, the prevalence of depression in women with plaque psoriasis is doubled during pregnancy.[60,61] Treatment and support for women with plaque psoriasis during and after pregnancy therefore needs to improve. In summary, plaque psoriasis has a profound life-impact in women. Women with plaque psoriasis face unique challenges and there is a need for long-term, effective treatments that are compatible with pregnancy and breastfeeding.

AUDIENCE QUESTION AND ANSWER SESSION

The panel were asked if they treat men and women with plaque psoriasis differently. Dr McBride replied that in their clinic they now ask their patients about their plans for conception and pregnancy at every visit. When biologic therapies are discussed with women, their long-term treatment journey and pregnancy plans should be considered. Dr Egeberg commented that this should be the case as men and women with plaque psoriasis have differing expectations of treatment and are affected differently by the condition; additionally, some treatments such as acitretin should not be used in fertile women. It was also asked if male and female dermatologists treat their patients differently. Dr McBride suggested that from personal experience she might have a better understanding of pregnancy and breastfeeding, and therefore post-partum treatment needs, than a male colleague, and also might be more likely to consider the likelihood of pregnancy during treatment. Dr Egeberg concurred, commenting that everyone has their own reference points, for example, a male dermatologist may not fully appreciate how risk averse pregnant women might be when thinking about treatment. Prof Augustin added that it is important that male and female colleagues learn from each other.

Dr McBride was asked about the implementation of the family planning and pregnancy questionnaire in clinical practice and if these have been helpful. She explained that these questionnaires are given to all patients for completion and review before the patient is seen by the dermatologist. They have been found to be very helpful. The panel also noted the value of telephone clinics as an aid to extending the intervals between clinic visits.

It was asked if DLQI was useful in clinical practice. Dr Egeberg described how, in their practice, a system of colour coding patient records by DLQI score was used to track changes in wellbeing and helped dermatologists focus on managing specific issues before they arise or worsen. Asked about stopping and restarting CZP treatment, Dr Egeberg commented that in his opinion he would prefer that CZP was not stopped during pregnancy if clinically needed; however, if it is stopped, it would be the patient's decision to restart. He added that after a long pause in treatment, it may be difficult to regain control of symptoms. The panel agreed that there was a need to ensure that the obstetrics and gynaecology team caring for the patient during pregnancy are aware of their psoriasis and CZP treatment.

It was asked if unconscious gender bias and inequality affected the treatment of plaque psoriasis in women. Dr McBride replied that she wished that both women and men with plaque psoriasis were more able to talk to others about their condition. Dr Egeberg added that dermatologists needed opportunities for reflection and supervision on how gender might impact their practice. It was asked if the CZP

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clinical trial and registry data have been analysed by gender. Dr Egeberg replied that the 3-year data have not yet been analysed, but registry data are being evaluated. After the meeting, it was noted that analysis of pooled 16-Week Phase III data found no significant difference in efficacy between male and female patients.[62]

CONCLUSION

It is essential to understand the needs and life goals of women with plaque psoriasis, and clinicians should ask them how they think their lives would be different without the condition. Treatment should be chosen with the patient after considering both their immediate and future needs. Family planning and conception plans need to be reviewed at every visit to ensure that current treatment is aligned with the patients' life plans. The long-term clinical data for CZP in plaque psoriasis showed a durable efficacy following dose adjustment, which will aid effective treatment in real-world clinical practice. All biologics are, however, not the same, and CZP has particular characteristics and promising clinical data that physicians may wish to consider early in the treatment journey of their female patients. Women's and men's requirements and expectations from treatment differ in many areas and clinicians need to be aware of the specific and changing needs of women with plaque psoriasis throughout their life.

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Epithelial Barrier Dysfunction in Type 2 Inflammatory Diseases

This satellite symposium took place on 19th September 2019 as part of the 49th European Society for Dermatological Research (ESDR) Annual Meeting in Bordeaux, France

Chairperson: Ignacio Dávila

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Meeting Summary

This satellite symposium took place during the 49th annual meeting of the European Society for Dermatological Research (ESDR). Prof Dávila began the symposium by describing the immunology behind Type 2 inflammation as a complex interaction between environmental factors, immune response, and barrier dysfunction. He explained that the principal cells participating in innate Type 2 immunity are Type 2 innate lymphoid cells (ILC2), eosinophils, basophils, and mast cells, and that Th2 lymphocytes, dendritic cells (DC), and their main cytokines (IL-4, IL-5, and IL-13) comprise the adaptive arm of the Type 2 immune response and are essential in IgE-mediated reactions. Prof Seneschal followed by explaining that Type 2 inflammation in atopic dermatitis (AD) is a combination of immune and epidermal barrier components influenced by genetic and environmental factors. Epidermal barrier proteins are expressed in lower levels in AD, and other proteins are also dysregulated, disrupting tight junctions. Both lesional and nonlesional skin in patients with AD show

epithelial barrier dysfunction, and inflammation can lead to a vicious cycle of itching and damage. Prof Dahlén concluded the meeting by explaining that airway inflammation is one of the major factors involved in Type 2 asthma, and this can be driven by an allergic route, involving mast cells, or a nonallergic route, involving ILC2. Inflammatory cytokines also increase mucus production, one of the main causes of asthma-related death. Recent studies of asthma immunology have suggested that ILC2 are subject to feedback modulation by prostaglandin D2 (PGD2), and that both IL-4 and IL-13 are involved in hyper-responsiveness in asthmatic lung tissue.

The Immunology of Type 2 Inflammation

Professor Ignacio Dávila

Type 2 immunity evolved from a dialogue between the immune system and microbes. This form of immunity confers protection against bacteria, viruses, and parasites such as helminths, but also promotes allergic inflammation, forming the basis of AD.

Type 2 immunity involves the activation and recruitment of immune cells, and the release of inflammatory cytokines.[1] Helminths trigger the 'alarmins' IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which activate Type 2 innate lymphoid cells (ILC2). ILC2 activate and amplify other Type 2 cells such as Th2 cells and eosinophils, and release Type 2 cytokines (for example, IL-4, IL-5, and IL-13).[1]

Inflammation resulting from Type 2 immunity is a complex interaction between environmental factors, immune response (both innate and acquired), and barrier dysfunction.[2] Barrier dysfunction is a core feature of Type 2 inflammatory diseases; in asthma, respiratory viruses and allergens penetrate the epithelium causing an infiltration of immune cells and release of IL-4, IL-5, and IL-13, which disrupt bronchial epithelial tight junction proteins further.[3-5] In AD, environmental allergens pass through the dermal barrier, encouraging the infiltration of immune cells to the area, and subsequent disruption of the stratum corneum and/or tight junctions.[3]

Proteases, endotoxins, and β-glucans can destroy tight junctions, leading to the production of NF-kβ and reactive oxygen species, and the release of IL-33, IL-25, and danger signals such as uric acid.[6] These signals can act on immature DC (iDC) and ILC2 cells, causing inflammation. Some nonproteolytic allergens and genetic polymorphisms in genes such as *SPINK5* can also induce barrier defects, facilitating the penetration of allergens and giving them increased access to DC, as well as the sensitisation of Th2 cells.[6]

Early immune responses are driven by ILC2. Following activation from the epithelium, they release IL-9, IL-13, and IL-5, causing goblet-cell hyperproliferation, subepithelial fibrosis, migration of eosinophils, and subsequent TGF-β production, and smooth muscle remodelling.[6-9] ILC2 cells work through complex networks to stimulate the activation and proliferation of diverse immune cells, including macrophages, eosinophils, B cells, DC, and T cells, resulting in the production of prostaglandin D2 and other cytokines.[10] Alarmins can also activate DC, which in turn are able to capture allergens and migrate to regional lymphatic nodes. There, they present antigens to naïve T cells, inducing a Th2 response.

Eosinophils are produced in the bone marrow, and display receptors for Ig, IL, and many other cytokines. These cells can produce molecules that affect nerves, such as prostaglandins, chemokines, and growth factors.[11,12] Eosinophils also perform multiple immunomodulatory functions, including the activation of natural helper cells (NHC), macrophages, and Th2 cells, and the proliferation of T cells and neutrophils, resulting in the release of histamine and mast cell mediators.[12]

Mast cells and basophils both express receptors for IgE (high-affinity IgE receptor [FcεRI]), but priming factors differ, with mast cells primed by IL-4 and IL-6, and basophils primed by IL-3, IL-5, and IL-33. Each cell produces its own mediators, including IL-5 from mast cells, and IL-4 from basophils, as well as some common mediators, such as histamine and granzyme B.[13] The mast cell network is very important for the Type 2 immune response. It connects mast cells with nerves, where they have a bidirectional influence through TNF and PGD2, causing irritation. The

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release of mast-cell granules recruits leukocytes to the endothelium, and secretion of TNF stimulates proliferation of T cells causing lymph node hypertrophy.[14] The role of basophils in the Type 2 immune response was long ignored, but peripheral basophils produce IL-4, facilitating Th2 differentiation following stimulation through the major histocompatibility complex class II. Basophils can also display the major histocompatibility complex class II molecules on their surface through trogocytosis, to stimulate Th2 differentiation.[15] Mast cells and basophils perform different roles in allergic inflammation, with basophils particularly significant in IgE-mediated chronic allergic inflammation and IgE-independent asthma.[16]

Asthma is a condition caused by Type 2 inflammation in the airways.[17] Epithelial cells release IL-25 which stimulates DC, activating Th2 cells through IL-4.[17] Th2 cells activate B cells, releasing IgE, which later occupies mast cell receptors inducing the release of histamine and cytokines, causing smooth muscle contraction.[17] Th2 cells also activate eosinophils through the release of IL-5, resulting in activation of the epithelium and consequent mucus production.[17] Some types of Th1 cells are also involved in asthma, through the TNF-α/interferon gamma (IFN-γ)-mediated activation of neutrophils.[17] The major Type 2 cytokines involved in asthma are IL-4, IL-5, and IL-13, all produced by Th2 and ILC2 cells.[18] The release of these cytokines produces a multitude of effects on the airways, including smooth muscle contraction, hyperproduction of mucus, barrier disruption, tissue remodelling, and fibrosis.[18]

AD is a result of Type 2 inflammation in the skin, involving the activation of ILC2 cells through cytokines IL-25 and IL-33, followed by itching produced by IL-31 from Th2 cells.[19] In the acute stage there is an increase in DC and Th2 activation, along with dilation of the vasculature, which leads to Th1 involvement and the release of IL-17, IL-22, and IFN-γ.[19] The major cytokines involved in AD are IL-4 and IL-13, which together result in Th2 expansion, B cell class-switching and IgE production, increased vascular adhesion and permeability, production of chemoattractants, and stimulation of the itch-scratch cycle.[20-26]

In summary, Type 2 immunity has important functions in the body, such as defence against parasites and venoms. It has three main components: the epithelial barrier, innate immunity, and acquired immunity. The principal cells participating in innate Type 2 immunity are ILC2 cells, eosinophils, basophils, and mast cells. Th2 lymphocytes, dendritic cells, and their main cytokines (IL-4, IL-5, and IL-13) comprise the adaptive arm of the Type 2 immune response and are essential in IgE-mediated reactions.

Epithelial Barrier Dysfunction and Type 2 Inflammation in Atopic Dermatitis

Professor Julien Seneschal

Healthy skin functions as a physical, permeability, and antimicrobial barrier against exogenous molecules or antigens, and maintains the internal environment.[27,28] The terminally differentiated layer of the skin, the stratum corneum, consists of corneocytes embedded in a water-repellent, lipid-rich matrix that prevents transepidermal water loss and allergen absorption.[27,29-31] Antimicrobial peptides, including β-defensin and cathelicidin, prevent colonisation and invasion by pathogenic microbes.[32] Tight junctions form a structural barrier by sealing intracellular spaces and are often disrupted in AD.[27,31,32] The plasma membrane of corneocytes is replaced by an insoluble protein structure known as the cornified cell envelope, and this forms a scaffold for lipid matrix attachment.[29,33] Filaggrin, involucrin, and loricrin are important structural proteins in the cornified cell envelope, with filaggrin binding intracellular keratin fibres, and degrading into natural moisturising factor to maintain skin hydration and low pH.[32,34-36]

The pathophysiology of AD has a multifactorial aetiology of immune and epidermal barrier components influenced by genetic and environmental factors.[37] Genetic factors can predispose individuals to AD, and include dysregulations of thymic stromal lymphopoietin (TSLP), IL-4/IL-13, toll-like receptor 2 (TLR2), IgE/FcεRI, filaggrin, serine protease inhibitor of the Kazal type (SPINK), and hornerin. Environmental factors can include allergy sensitisation, dryness, scratching, phototoxicity, and exposure to microbes or toxins which disrupt the skin barrier.

AD histology is characterised by marked spongiosis, which is vesicle formation from intraepidermal fluid, parakeratosis, the retention of nuclei in the stratum corneum, and subtle vacuolar and dermal–epidermal interface changes.[38,39] Epidermal barrier proteins such as filaggrin are expressed in lower levels in AD. Although mutations in filaggrin have been observed, they are neither necessary nor sufficient for the development of AD, suggesting that other factors are involved.[36,40] AD is associated with defects in the stratum corneum which result from filaggrin deficiency, including fewer keratohyalin granules, downregulated filaggrin degradation enzymes, dysregulated acidification pathways, and higher exposure to *Staphylococcus aureus*, herpes simplex virus Type 1 (HSV-1), and other allergens.[41] Dysregulation of claudin-1 in AD causes disruption to tight junctions, which results in the elongation of Langerhans cell dendrites into the epidermal layer, encouraging antigen sensitisation.[27]

In patients with AD, even normal-appearing skin has barrier defects, making these individuals more sensitive to environmental factors, *S. aureus,* and scratching.[8,18,19] One of the characteristics of AD is the abnormal microbiome of the skin, with increased colonisation with *S. aureus*.[42] *S. aureus* induces epithelial barrier disruption through toxin production and inflammation, resulting in increased protease activity. A recent study by Williams et al.[43] found that the introduction of *S. hominis* to the skin can inhibit *S. aureus* activity, preventing skin barrier disruption and inflammation.

The genetic expression profile in patients with AD, the 'AD transcriptome', shows that genes associated with Type 2 inflammation are upregulated in AD. However, since the transcriptome is similar in both lesional and nonlesional skin, there must also be a molecular aspect to the inflammation in lesional skin.[44] Inflammation in AD involves CD4+ and CD8+ T cells in both the dermis and epidermis, with the CD4+ cells secreting Type 2 cytokines IL-4 and IL-13, but again, this profile is similar between lesional and nonlesional skin.[45] AD is associated with increased expression of IFNγ, IL-13, and IL-22 in the skin compared to healthy individuals, and these cytokines are most abundant in lesional skin.[44] The expression levels of Type 2 cytokines IL-4, IL-5, IL-10, IL-13, and IL-31, in particular, correlate with disease activity in skin biopsies patients with AD.[46] These Type 2 cytokines have been shown to downregulate epidermal barrier proteins filaggrin and hornerin,[47] and increase TSLP production, inducing spongiosis.[48] Type 2 inflammation induces defects in the epidermal barrier, increasing skin permeability and the cutaneous innate immune response. IL-4 and IL-13 result in epidermal thickening and disturb the expression of tight junction proteins such as occluding,[49] as well as exacerbating the itch-scratch cycle by sensitising neurons to pruritogens IL-31, TSLP, and histamines.[25]

In summary, alteration of the epidermal barrier is an important feature of AD, promoting inflammation in both lesional and nonlesional skin associated with increased Type 2 proinflammatory cytokines IL-4 and IL-13. These cytokines induce defects in the epidermal barrier, leading to a vicious cycle that needs to be blocked.

Epithelial Barrier Dysfunction and Type 2 Inflammation in Asthma

Professor Sven-Erik Dahlén

It is an exciting time for asthma and respiratory disease, with many new therapeutic treatment strategies coming to market, and many more in the pipeline. In addition to new biologics, there are also new molecular targets and drug combinations, some with remarkable effects. Treatments for asthma have evolved over the last 100 years; from adrenaline, oral steroids, theophylline, and inhaled β2-agonists, through inhaled anticholinergics and steroids, long-acting drugs, and sodium cromoglycate, to anti-IgE, antileukotrienes, anti-IL-5, and anti-IL-4Rα.[50]

Asthma Pathobiology

Asthma can be described as a condition whereby airways constrict too much, too often, and too easily, resulting in impaired lung physiology and quality of life. A bronchoscopy of patient with asthma, 3 hours after a bronchoprovocation challenge, will show that although lung function may have recovered, severe inflammation and oedema remain, and the airway is still quite narrow due to smooth muscle constriction. Pathologically, asthma has four components:

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airway hyper-responsiveness, airway remodelling, airway inflammation (often eosinophilic with increased fractional exhaled nitric oxide [FENO]), and bronchoconstriction.

Airway hyper-responsiveness can be measured by airway reactivity (lung function) to inhaled methacholine, or histamine. In patients with severe asthma, lung function decreases significantly after a bronchoprovocation challenge with even low doses of methacholine/histamine, and these patients can be described as 'super responders'. Current treatments for asthma are poorly effective against this problem. Airway remodelling in asthma includes epithelial dysfunction; furthermore, asthmatic airways demonstrate increasing thickness of the epithelium and reticular basement membrane, and goblet cell hyperplasia as asthma severity increases.[51] In asthmatic patients, external factors such as viruses, pollutants, and allergens are able to cross the dysfunctional epithelial barrier and trigger a Type 2 response. There are two major routes to Type 2 eosinophilic inflammation in the airway: the allergic route, which involves mast cells; and the nonallergic (innate) route, which involves ILC2 cells rarely seen in healthy lung tissue.[2] As well as eosinophilic inflammation, mucus production is stimulated by IL-13 and IL-9, and many asthma deaths are caused by mucus suffocation.[52]

Bronchoconstriction in asthma can be triggered by antigens, which bind to IgE receptors on the surface of mast cells and induce secretion of histamine, cysteinyl leukotrienes, and prostanoids, causing contraction of smooth muscle in the airway.[53] In isolated human small bronchi, challenge with anti-IgE can mimic allergen exposure and result in bronchoconstriction. This reaction can be blocked with a combination of the thromboxane receptor antagonist SQ-29,548, the H1 antagonist mepyramine, and the leukotriene synthesis inhibitor MK-886.[53] This shows the dependence on the mast cell mediators for the immediate IgE-dependent reaction.

Biomarkers of Type 2 Asthma

The main biomarkers of Type 2 inflammation in asthma are eosinophils in the blood and sputum, FENO, IgE, and periostin. Dr Morrow Brown identified the important role of eosinophils in chronic asthma in 1958, and this association has become more firmly established in the past 25 years.[54] Monitoring the eosinophilic content of sputum to guide treatment choices has been shown to reduce the severity of cumulative asthma exacerbations.[55]

FENO levels relate to eosinophilic inflammation and can be used as another marker of Type 2 inflammation.[56,57] When FENO is measured during repeated low-dose allergen challenges, it shows a clear sensitivity to steroid treatment.[58] A recent Phase III trial of dupliumab, a monoclonal antibody that inhibits IL-4 and IL-13, used FENO to predict patient response, demonstrating that patients with higher levels of FENO responded better to treatment.[59] U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) is a large, ongoing study which aims to identify novel biomarkers in severe asthma. A specialised 'breathomics' device is being used to recognise organic compounds in exhaled air of patients with severe asthma or mild/moderate asthma, and in healthy controls.[60] IgE still has a role as a biomarker of asthma, but periostin is being used less due to variable research findings.

Pivotal Role for Prostaglandin D2 in Type 2 Innate Lymphoid Cell Function

The nonallergic (innate) route to eosinophilic airway inflammation involves the stimulation of ILC2 cells.[2] ILC2 cells stimulated by alarmins such as IL-2, IL-25, IL-33, and TSLP secrete PGD2, and inhibition of PGD2 synthesis by either an nonsteroidal anti-inflammatory drugs or an experimental drug results in reduced production of IL-5 and IL-13, suggesting that endogenously produced PGD2 is necessary for ILC2 cytokine production.[61] This suggests ILC2 cells are subject to feedback modulation by PGD2 via the chemoattractant receptor-homologous molecule receptor.[63]

In summary, the pathobiology of Type 2 asthma is driven by the inflammatory cytokines IL-4, IL-5, and IL-13 that are secreted in reactions involving Th2 cells, mast cells, eosinophils, and ILC2 cells. Although Type 2 asthma responds to inhaled steroids, this is not sufficient to provide optimal control in more severe cases. Eosinophils, FENO, and total IgE are currently used to indicate Type 2 inflammation in patients with asthma, and urinary LTE4 and PGD2 metabolites show promise as novel biomarkers.

Knowledge Gaps in Type 2 Inflammatory Diseases (Panel Discussion)

Professor Ignacio Dávila, Professor Julien Seneschal, and Professor Sven-Erik Dahlén

Q: Is Th2 inflammation equally important in both asthma and atopic dermatitis, and does it occur before or after the development of barrier defects?

Prof Dahlén indicated that 30 years ago, damaged epithelium was considered to be critical in the development of asthma, but that more recently it has been considered to be more of a functional consequence of increased levels of alarmins and PGE2 rather than damage per se. Prof Seneschal said that for AD, both biological defects and inflammation are important, and promote each other. The epidermal layer is important for the production of alarmins and many other cytokines. He noted that smooth muscle contraction is one of the main symptoms in asthma but not in AD, so perhaps the response of smooth muscle to specific cytokines may explain the differences between asthma and AD. Prof Seneschal replied that in asthma, 2–3 days' incubation of airways with IL-4 and IL-13 can transform the epithelium into an asthmatic phenotype. Many cytokines are important to modify immune cells and affect smooth muscle, but the main effectors of the contraction are histamine and prostaglandins.

Q: Would restoring the epithelial barrier in atopic dermatitis be useful in the prevention of atopic dermatitis, for example, through moisturisation?

Prof Dahlén said that healthcare providers try to educate patients to apply moisturising creams. There has been some encouraging data for the use of creams in the prevention of AD in new-born babies, but in general, skin moisturisation is important to prevent new skin defects and flares in AD patients, in combination with anti-inflammatory medication.

Q: Type 2 inflammation is prominent in atopic dermatitis, but other types of inflammation are also important. In asthma, are Th2 cells more prominent than they are in atopic dermatitis?

Prof Dahlén replied that the Th2 paradigm is a huge simplification, and that severe asthma does seem to involve some neutrophilic inflammation, though it is unclear whether this is steroid-induced, or the result of bacteria. Efforts are being made through molecular phenotyping to identify new biomarkers; many different inflammatory subtypes for asthma can now be identified, but it is unclear how many are clinically relevant and can be independently targeted. Prof Seneschal said that in AD, patients could be grouped as IgE sensitive or insensitive, but the reasons for these differences can be very hard to understand.

CONCLUDING REMARKS

Professor Ignacia Dávila

In regard to the presented discussion, it would appear that although there is a Type 2 inflammatory basis to both AD and asthma, these conditions are not always associated, and do not always respond to the same treatments. The Type 2 Innovation Grant,[64] established in 2018, supports independent, novel, and innovative research projects designed to advance knowledge in the field of Type 2 immune-mediated diseases, with relevance to clinical practice. It targets not-for-profit organisations established in the European Economic Area and provides grants to research that is not related to investigational or marketed medicines. Applications are reviewed according to predefined criteria by independent international experts. Prof Seneschal is part of the expert dermatology panel established in 2019, and Prof Dahlén is on the respiratory panel. This innovation grant is proving a successful initiative, with 502 users, 252 active applications, 81 applications submitted to experts for review, and 8 selected projects thus far.

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Rosacea: The Patient Experience is Now 'CLEAR'

These 'Meet the Expert' sessions took place on 10th and 11th October 2019, as part of the 28th Congress of the European Academy of Dermatology and Venereology (EADV) in Madrid, Spain

Speaker: Martin Schaller

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Meeting Summary

These 'Meet The Expert' sessions took place during the 28th Congress of the European Academy of Dermatology and Venereology (EADV). Prof Schaller introduced the many faces of rosacea and explained that this disease can present as a single phenotype, but more often presents as a combination of phenotypes, including transient erythema (flushing), persistent erythema, telangiectasia, inflammatory papules/pustules, phymas, or ocular abnormalities, and is not easy to diagnose or classify. The most commonly used classification system for rosacea is that of the National Rosacea Society (NRS); however, this classification does not reflect the everyday clinical situation. Patients with rosacea have a high burden of disease. Correct diagnosis and effective treatment, which should continue until the patient is 'clear', is required to lower the burden of rosacea. Prof Schaller emphasised that achieving 'clear' is clinically meaningful for the patient, with benefits including improved quality of life, longer time to relapse, reduced social and productivity burden, and increased overall happiness. Prof Schaller introduced ROSCO, the Rosacea Consensus panel, which defined the most important clinical phenotypes of rosacea to form the basis of diagnosis and effective treatment of the disease. The ROSCO treatment algorithm enables healthcare providers to make a clear diagnosis and aim treatment towards, and achieve, a 'clear' goal. No two rosacea patients are the same, so treatment needs to be individualised, as shown in the three presented case studies. Prof Schaller concluded that the ROSCO classification, treatment algorithm, and recommendations have simplified the task of effective diagnosis and treatment of rosacea by addressing the multiple features and aiming for 'clear'. A phenotype-based approach could improve patient outcomes to 'clear', with 'clear' versus 'almost clear' being the primary objective because of the extended relapse time and the patient quality of life benefits.

Rosacea: The Patient Experience is Now 'CLEAR'

Professor Martin Schaller

The Many Faces of Rosacea

Prof Schaller posed the question "what makes rosacea so special?" and explained that the manifestations of rosacea are very varied, including papules, pustules, oedema, and erythema. Rosacea can present with multiple features, alone or simultaneously; therefore, it is not easy to diagnose and classify this disease.

The most commonly used classification system for rosacea is that of the NRS in which the condition is classified by subtype: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, or ocular.[1] The NRS classification system is used worldwide in clinical studies and forms the basis of treatment algorithms; however, this classification does not reflect the everyday clinical situation.

Rosacea can sometimes present as a single phenotype[2] and patients with such presentation are appropriate for the NRS classification (e.g., patients with only erythema fit into ETR, patients with only papules and pustules fit into PPR). Most patients, however, have an overlap of subtypes, e.g., papules, pustules, and erythema or papules, pustules, and ocular rosacea.

The problem with the NRS classification system as a basis for treatment of patients with rosacea is clearly demonstrated with ETR. If a patient is classified as having ETR, it is important to know whether this takes the form of erythema or telangiectasia because these conditions are treated very differently. Erythema can be successfully treated with some topical treatments, e.g., brimonidine, whereas the use of topical treatments does not improve telangiectasia, which requires laser treatment. To combine these two subtypes in the same classification does not make sense when diagnosing and treating rosacea; it would make more sense to define certain phenotypes of rosacea.

Prof Schaller explained that rosacea presents more often as a combination of phenotypes: transient erythema (flushing), persistent erythema (mainly induced by vasodilation or inflammation), telangiectasia, inflammatory papules/pustules, phymas, or ocular abnormalities.[2] For example, a patient with a combination of different phenotypes, such as papules, pustules, erythema, and ocular rosacea, requires treatment for each of these signs, and it would not make sense to classify the patient's rosacea purely as PPR because this would miss all the other signs and preclude their treatment.

Prof Schaller introduced ROSCO, which defined the most important clinical phenotypes of rosacea to form the basis of diagnosis and effective treatment of the many types of rosacea.

The Burden of Disease

According to Prof Schaller, it is important to understand the burden of disease beyond visible features. Rosacea is a disease of the face and is visible to everybody; therefore, patients with rosacea have a high burden of disease. The best way to measure burden of disease for a patient is to measure their quality of life. The Dermatology Life Quality Index (DLQI) scores from no impact on life at all (score 0 or 1) to extremely large impact on life (score 21–30).

The results of a global survey, in which 710 rosacea patients were asked about the effect of rosacea on their quality of life (using the DLQI), showed that almost one-third of the patients (31%) reported that rosacea had at least a very large impact on their lives (score 11–20; 22%) or an extremely large impact (score 21–30; 9%).[1] Furthermore, a total of 86% of patients had changed their daily activities or lives to avoid triggers and over half of patients reported that their condition had affected their work or study.[3] These results show how the daily lives of patients with rosacea are very much affected by this disease.

Aiming for 'Clear': How Long Should the Rosacea Patient be Treated for?

To lower the burden of rosacea requires correct diagnosis and effective treatment. Prof Schaller emphasised that it is most important to not stop treatment when the patients are 'almost clear' of rosacea signs (Investigator's Global Assessment [IGA] score 1), but to continue treatment until the patients are completely 'clear' (IGA 0), which is time consuming. Figure 1 shows that the transition from 'almost clear' to 'clear' can take another 10 weeks of treatment, but it is important for the patient to have no remaining signs and to receive the treatment to enable this success criterion.

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Figure 1: How long should the rosacea patient be treated?

A) shows that the patient was 'almost clear' at 14 weeks and the last step from 'almost clear' to 'clear' was 10 weeks. **B)** shows that the patient was 'almost clear' after 12 weeks but a further 9 weeks of treatment were required for the patient to be completely 'clear'.

IGA: Investigator's Global Assessment.

Images provided by Prof Schaller, Tübingen University, Tübingen, Germany, with informed consent from the patients.

Does 'Clear' Versus 'Almost Clear' Make a Difference for the Patient?

Prof Schaller queried whether it makes a difference for the patient if their signs are 'clear' or 'almost clear'. A study using DLQI, comprising 341 patients who achieved 'clear' and 1,003 patients who achieved 'almost clear', showed that achieving 'clear' is clinically meaningful for the patient and their quality of life. Of the patients who achieved 'clear', 84.2% reported that rosacea no longer had any negative effects on their quality of life (DLQI score 0 or 1), compared with 66.0% of the 'almost clear' patients ($p<0.001$).

Achieving 'clear' (IGA 0) can also extend the time to disease relapse. The time to relapse after stopping treatment at the end of a 16-week treatment period was compared for 'clear' and 'almost clear' patients in a pooled analysis of different studies.[5] Patients who achieved 'clear' had at least 5 months' increased treatment free time and twice as many patients were treatment free after 8 months compared with 'almost clear' patients (54% compared with 23%, respectively). Furthermore, the median time to relapse in 'almost clear' patients was 85 days and in 'clear' patients was >252 days ($p<0.0001$).[5]

The social burden of rosacea is also reduced by achieving 'clear'. A survey showed that patients who achieved 'clear' were statistically significantly less likely to adapt their behaviour because of rosacea than 'almost clear' patients (21/21 patients versus 16/19 patients, respectively; $p\leq0.05$).[3,4]

In addition, achieving 'clear' can reduce the productivity burden of disease compared with achieving 'almost clear', but the difference is not statistically significant. A survey showed that of the patients who achieved 'clear', 72% reported no impact of rosacea on their productivity in the previous 7 days of work compared with 56% of 'almost clear' patients ('almost clear' n=71; 'clear' n=57; p=not significant).[3,4]

Once patients with rosacea are correctly diagnosed, aiming for 'clear' can lead to better patient outcomes. Prof Schaller summarised the benefits of achieving 'clear' as improved quality of life, longer time to relapse, reduced social burden, reduced productivity burden, and happier patients.[3,5,]

Rosacea Consensus: A Clear Diagnosis With a 'Clear' Goal

Prof Schaller posed the question: "How can we as healthcare providers better diagnose our patients and treat them to be 'clear'?" The ROSCO classification, treatment algorithm, and recommendations enable healthcare providers to make a clear diagnosis and aim treatment towards, and achieve, a 'clear' goal.[2]

The ROSCO panel used a phenotypic approach to rosacea diagnosis by representing the individual mix of clinical features of this disease.[7] Diagnosis according to phenotype aligns rosacea management to the patient's experience. The ROSCO panel used phenotypes or signs to define major and minor diagnostic features of rosacea. According to Prof Schaller, the idea behind this classification, to define signs or features to enable diagnosis of disease, is perhaps not so important for experienced healthcare providers but provides a good approach for healthcare providers who are less experienced in this therapeutic area.

Defined diagnostic features are individually diagnostic (presentation of only one of these features is required for diagnosis of rosacea): persistent centrofacial erythema intensified by triggers or phymatous changes.[2] Major features are only diagnostic in combination (presentation of two of these features is required for diagnosis of rosacea): flushing/transient centrofacial erythema, inflammatory papules and pustules, telangiectasia, or ocular manifestation (lid margin telangiectasia, blepharitis, keratitis/conjunctivitis, sclerokeratitis).[2] Minor features include burning, stinging, or dry sensation of the skin and oedema.[2]

The ROSCO panel used the diagnostic and major features of rosacea to produce a treatment algorithm (Figure 2)[6,] in which these features are divided into mild, moderate, and severe categories. First-line treatment options for each of these features are presented.

Mixed Phenotype Rosacea

At least half of the rosacea patients seen by healthcare providers are considered by Prof Schaller (and the meeting audience) to have a mixed phenotype. Patients with a mixed phenotype, e.g., papules and erythema, should be asked what their perceived worst problem is and which is the most important phenotype to treat first. A patient based (rather than physician based) decision aligns with the patient's experiences and wishes. The physician can then discuss how long they expect to treat for the patient to be 'clear'; usually this requires ≤6 months because short-term treatment does not necessarily achieve this goal.

Prof Schaller described how he often sees patients with papules and pustules who have used doxycycline for 4 weeks, switched to metronidazole for 4 weeks, then switched to azelaic acid for 4 weeks and they say nothing helped to improve their rosacea. All these treatments help, but they require time. In some cases, it can take a long time for treatment to be effective, e.g., 10 months with doxycycline to achieve 'clear'.

In practice, patients can present with multiple phenotypes simultaneously (Figure 3).[2]

No Two Rosacea Patients are the Same: Three Case Studies

No two rosacea patients are the same, so treatment needs to be individualised. Here follows a description of the experiences of three rosacea patients.

Prof Schaller first focussed on the patient in Figure 1A, who was previously treated with azelaic acid for 5 years (a very long time in Prof Schaller's opinion), then switched to metronidazole gel 4 weeks before consultation.

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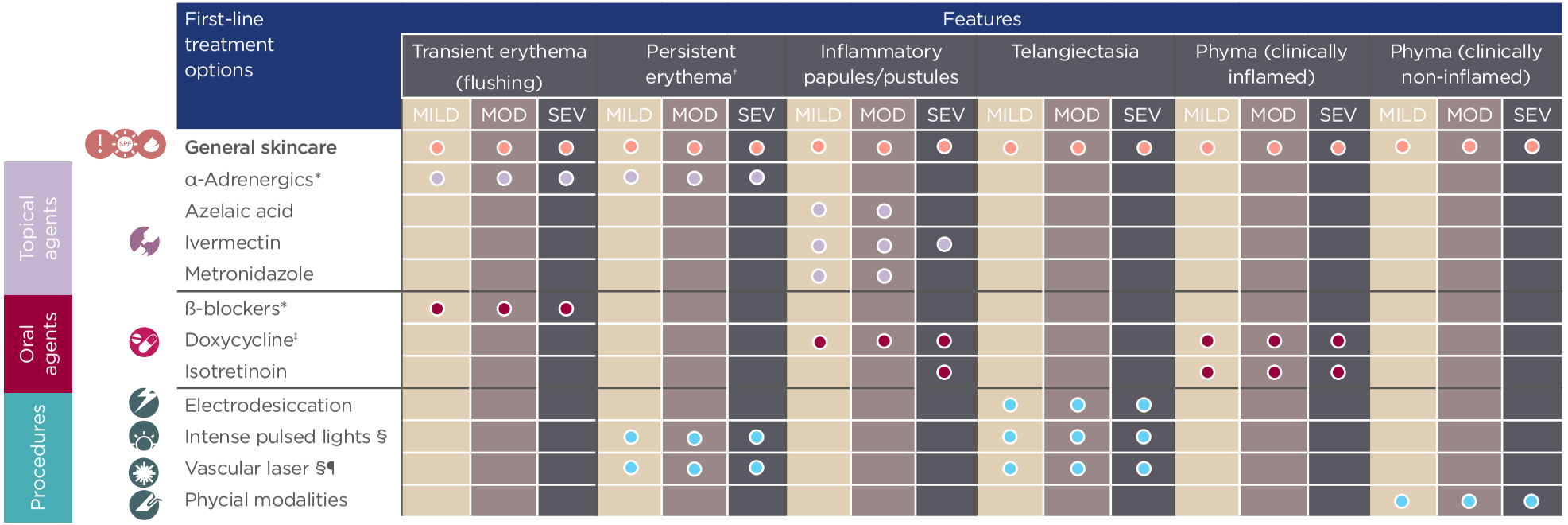

Figure 2: The Rosacea Consensus treatment algorithm.

*There is limited evidence to support the use of topical α-adrenergic modulating agents or oral β-blockers for treatment of flushing/transient erythema. However, clinical experience indicates they could be considered in certain situations. †Persistent centrofacial erythema associated with periodic intensification by potential trigger factors. ‡Doxycycline 40 mg modified-release superior to placebo; doxycycline 40 mg modified-release noninferior to doxycycline 100 mg. No inference possible from indirect comparison. §Use of intense pulsed light and vascular lasers in darker skin phototypes may require consideration by a healthcare provider with experience in this situation. ¶e.g., pulsed-dye laser and 532-nM KTP laser.

MOD: moderate; SEV: severe.

Adapted from Schaller et al.[6] and Schaller et al.[7]

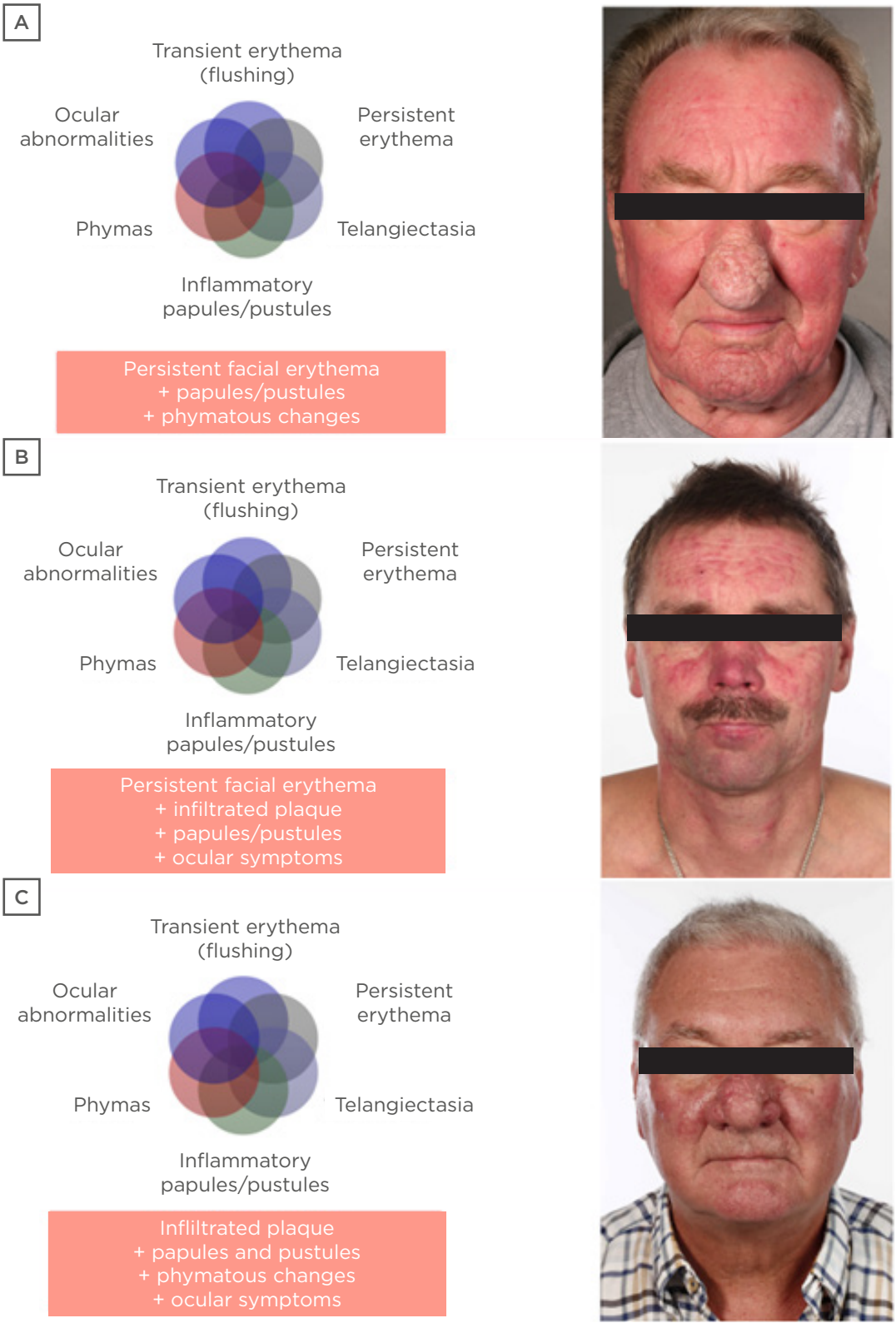

Figure 3: Patients presenting with multiple phenotypes simultaneously.

In each case, the patient was asked which sign they wanted treated first. **A)** Patient indicated their nose was the main problem; therefore, the patient was prescribed very low dose isotretinoin to treat the phymatous rosacea. After 3–4 months, a discussion would take place about the option to operate to excise the sebaceous glands of the nose. Prof Schaller recommended brimonidine to treat the persistent facial erythema, and ivermectin or metronidazole to treat the papules and pustules. **B)** Patient had persistent facial erythema for 3–4 months, infiltrated plaque, papules at the lip edges, pustules, blepharitis, and dry eyes. This patient required a combination of different treatments, particularly for the ocular signs. **C)** Patient had infiltrated plaque, papules, pustules, phymatous changes, and ocular signs and also required a combination of different treatments.

Images provided by Prof Schaller, Tübingen University, Tübingen, Germany, with informed consent from the patients.

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At this point the patient felt hopeless about her disease. Using the ROSCO treatment algorithm (Figure 2), Prof Schaller classified the patient's disease as moderate inflammatory papules/pustules, with azelaic acid, ivermectin, metronidazole, doxycycline, and isotretinoin as the treatment options. Prof Schaller asked the audience which would be their treatment of choice for this patient. He explained that every answer is correct because any of these treatments can be used, although he did not recommend azelaic acid because this cream had been used for 5 years without success. As the audience proposed, the patient was prescribed ivermectin and the expectations of treatment and the time required to achieve 'clear' (≤6 months) were discussed with the patient.

The treatment aim was 'clear' and the treatment plan comprised ivermectin 1% cream monotherapy and a routine skincare regimen. At Week 6, the patient had significantly improved, further improvement was seen at 14 weeks, when the patient was 'almost clear', and at Week 24 the patient was 'clear' (Figure 1A). Maintenance therapy for this patient is ivermectin 1% cream twice a week. Prof Schaller clarified that he always recommends a maintenance therapy at a reduced frequency compared with active treatment to help the patient in the long term.

Prof Schaller then described a young female patient (aged 18 years) who presented with severe ocular manifestations (confirmed severe blepharoconjunctivitis), persistent erythema, papules, and pustules. Ocular signs are more often seen in younger patients, particularly children, with cases of undiagnosed severe ocular rosacea more severe in children than in adults. The patient had a 4–5-year history of facial skin problems, had undergone multiple operations for chalazia, and had received systemic antibiotics (specifics unknown) and a variety of creams (including cortisone). Chalazia represents the beginning of ocular rosacea in patients.

Using the ROSCO treatment algorithm (Figure 2), Prof Schaller diagnosed severe inflammatory lesions and moderate persistent erythema. With the treatment aim of 'clear', oral doxycycline at 100 mg/day for 3 months followed by 40 mg modified release capsules once daily (QD) was prescribed to treat ocular signs, ivermectin 1% cream QD for inflammatory lesions, and brimonidine as required for erythema (the latter was also the maintenance treatment). At Month 10, the patient was completely 'clear' of ocular signs, with papules and pustules completely clearing before then.

Prof Schaller then considered the patient in Figure 1B, who had rosacea with skin and eye involvement since 2014 and had tried many topical treatments with little or no success. The last treatment the patient had tried was doxycycline 50 mg twice daily plus metronidazole from November 2015 to July 2016. Using the ROSCO treatment algorithm (Figure 2), Prof Schaller diagnosed the patient as having severe papules and pustules. Isotretinoin was recommended at the initial consultation but the patient refused, fearing the side effects (Prof Schaller highlighted that at low dosage, these side effects are not likely to be present), and they also refused systemic treatment with doxycycline, but the patient was desperate for a solution.

Again, the treatment aim was 'clear' (IGA 0) and ivermectin 1% cream monotherapy QD was prescribed for 12 weeks because this is the only topical treatment that would improve severe inflammatory lesions. As shown in Figure 1B, there was improvement by Week 4, with further improvement at Week 8 and the patient was 'almost clear' at Week 12. The patient was asked again at 12 weeks if they wanted doxycycline and this time they agreed. Combination therapy with topical ivermectin and doxycycline 40 mg modified release capsules QD (which has shown superior results to ivermectin plus placebo in a randomised Phase IIIb/IV study) was taken from 12 weeks and complete lesion clearance was seen at Week 21. The patient had not expected a large improvement and was happy with his treatment. Maintenance therapy for this patient is ivermectin 1% cream QD.

The Target is 'Clear': Rosacea Consensus Can Help

Prof Schaller concluded that the ROSCO classification, treatment algorithm, and recommendations have simplified the task of effective diagnosis and treatment of rosacea by addressing the multiple features and aiming for 'clear'.[6] A phenotype-based approach could improve patient outcomes to 'clear', with 'clear' versus 'almost clear' being the primary objective because of the extended relapse time and patient quality of life benefits.[6,7]

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Abstract Reviews

These abstract summaries are provided by the very authors who shared their latest research at Congress this year.

Anxiety and Depression in Family Members and Caregivers of Preschool Children with Atopic Dermatitis

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Keywords: Anxiety, atopic dermatitis (AD), caregivers, depression, family members, psychological distress.

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BACKGROUND

Anxiety and depression are often overlooked and underdiagnosed in both patients with atopic dermatitis (AD) and their family members and preschool caregivers. The clinical spectrum of AD often includes insomnia, anxiety, and psychosocial distress in patients. There is also a serious burden on the parents who are actively participating in the management of their child's disease and are therefore also highly psychosocially affected.

METHODS

The Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HAM-A), and a 7-item questionnaire were used for evaluation of the symptoms of depression and anxiety in 83 family members and caregivers of 35 patients with AD aged 1–6 years. The severity of AD was measured by the scoring atopic dermatitis (SCORAD) index.

RESULTS

A total of 61 (73.5%) participants presented with depression. The average score on the HAM-A scale was 12.9±4.8 (lowest score 6.7, highest score 20.0). The highest HAM-A and HAM-D score was not associated with highest SCORAD values in patients, but with the most persistent long-term clinical presentation of AD. The major concerns of caregivers and family members was

the information given to them regarding the nature of the disease itself, because it is a long-term condition which requires complex and costly therapeutic regimens.

CONCLUSION

AD is a serious disease with high impact on the quality of life, not only of patients but of family members and caregivers as well. The chronicity and complexity of the disease often leads to overlooked anxiety and depression in family members and caregivers, and therefore addressing this might offer a wholesome view of the situation, tracking a widened approach to the management of AD, not only in the patients but in their families as well.

Although AD is not considered a lethal disease *per se*, the first information parents are given is that it is a genetically determined disease that, despite new promising medications, cannot be cured and is only managed. The pressure the parents perceive is even higher when faced with new medications, because even though they could have good results with the symptom control of AD, they tend to have side and adverse effects that could potentially outweigh the offered benefits.[1] This typically starts a guilt, shame, and anxiety cycle, and the process of dealing with this information can result in a search for a 'responsible person' to advise them on the situation their child is facing.

The treatment choosing process develops in multiple ways as the care for the child demands physical, mental, and financial engagement from the parents, as well as a continuous dedication of time.[2] Parents must control their child's food consumption, clothes, and activities, though they must avoid micromanaging too much of their child's lifestyle and habits. Knowing they must find the 'perfect equilibrium' between protecting their child and being an overbearing parent is an additional burden to parents.

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Alternative Medicine use in Hidradenitis Suppurativa

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Keywords: Complementary and alternative medicine (CAM), hidradenitis suppurativa (HS), turmeric.

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BACKGROUND

Hidradenitis suppurativa (HS) is a chronic, incurable disease of apocrine gland-bearing skin, which presents with painful nodules and scarring most commonly in the axillae, inguinal, and inframammary folds. Comorbidities associated with HS often include increased rates of depression and anxiety, and patients tend to come from lower socioeconomic backgrounds with higher rates of unemployment.[1,2] There is a paucity of highly effective therapies available for HS patients, with no proven therapeutic basis for complementary and alternative medicine (CAM).[3] This study investigated CAM use in a cohort of patients with HS attending a monthly tertiary specialist HS clinic over a 4-month period (N=139; 107 completed questionnaires).

Patients were asked to respond to nine questions on previous CAM use, concerning rationale, duration, cost, treatment success, duration of HS, and previous HS-related hospital admissions.

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Table 1: Alternative therapies reported and reasons for use.

Alternative therapies reported	n (%)
Turmeric	7 (33)
Reiki	6 (29)
Acupuncture	4 (19)
Aromatherapy	3 (14)
Nutritional supplements	3 (14)
Herbal ointment	3 (14)
Chinese medicine	2 (10)
Iodine	1 (5)
Pantothenic acid	1 (5)
Blood purifier	1 (5)
Aloe vera liquid	1 (5)
Apple cider vinegar	1 (5)
Homemade body scrub	1 (5)
Magnesium stones	1 (5)
Osteopathy	1 (5)
Tea tree oil	1 (5)
Zinc paste	1 (5)
Reason for use	**n (%)**
Dissatisfaction with conventional treatment	7 (33)
Intrigue	7 (33)
Recommended	5 (24)
Waiting for specialist input	1 (5)
Was told no cure	1 (5)

RESULTS

Results showed that 20.0% of patients had previously used a CAM, with an extensive range of treatments reported including turmeric, reiki, acupuncture, and aromatherapy (Table 1). A number of reasons were reported for CAM use in the patient population, the most common being curiosity and dissatisfaction with conventional treatment (Table 1). One patient believed CAM had no potential to cause adverse effects while another patient was employed as a complementary therapist themselves. Eight patients reported a decrease in symptoms and an increase in quality of life with CAM use (38.1%). Patients had spent between €0.00 and €5,200.00 on CAM treatment, with an average cost of €413.55, and therapy duration range from 1 week to 2 years. Acupuncture (€50.00/session), reiki (€30.00/session), and aromatherapy (€25.00/session) were the most expensive treatments, while turmeric was the cheapest costing a maximum of €5.00. The mean duration of HS was 13.1 years and almost 50% of patients had been admitted to hospital for HS treatment (n=40). Only three patients had been questioned previously by a doctor regarding CAM use.

CONCLUSION

In the cohort of patients with HS, use of CAM was lower than reported in the general population.[4] This under-representation in the patient population was potentially due to the accessibility of conventional treatments at this specialist HS clinic. The practice of alternative medicine is increasingly endorsed by celebrities and influencers on social media platforms, with turmeric labelled a 'wonder drug' in the media.[5]

There is, to date, little legislation regarding use of social media to promote treatments without proven therapeutic effect as 'instagrammers' with millions of followers promote controversial products.[6] As HS is a disease characterised by lower socioeconomic status and increased comorbidity burden, the use of expensive, ineffective, and dangerous treatments should be discouraged. Patients most commonly reported CAM use due to curiosity and one patient believed alternative medicine had no side effects when compared to conventional HS treatments. Most dermatologists do not enquire about alternative therapies but given that negative outcomes and serious adverse events are widely reported in the literature,[7] routine questioning for all patients with HS should be encouraged.

Dermatologists should familiarise themselves with alternative treatments so that open and honest dialogue can enable patients to make an informed decision regarding their ongoing CAM use in the age of Instagram, social media influencers, and sponsored celebrity endorsements.

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Dermatomyositis Revealing Bladder Cancer Recurrence

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Keywords: Bladder, dermatomyositis, paraneoplastic.

Citation: EMJ Dermatol. 2019;7[1]:63-65. Abstract Review No: AR3.

There is a well-recognised association between inflammatory dermatomyopathy, dermatomyositis, and underlying visceral malignancy in adults. It is most commonly associated with malignancies arising in the lungs, breasts, and stomach. This is a report of a case found in association with transitional cell carcinoma of the bladder, a site which has only featured in a handful of previous reports.[1-8]

A 68-year-old man, with several weeks history of frequent micturition and haematuria under urological investigation, presented with a history of 3-months' general illness with muscular pain and weakness, causing him difficulty arising and walking up or down stairs. Physical examination revealed photo-distributed poikiloderma with flagellate erythema of the posterior trunk and nailfold changes (includes ragged cuticles, cuticular hypertrophy, nail-fold telangiectasia) associated with proximal scapular muscular deficit with deltoid amyotrophy (Figure 1). Routine laboratory analysis revealed that creatine phosphokinase levels had reached 1,430 UI/L (normal; 24–195 UI/L), serum lactate dehydrogenase levels were at 544 UI/L, and aldolase A reached 32 UI/L.

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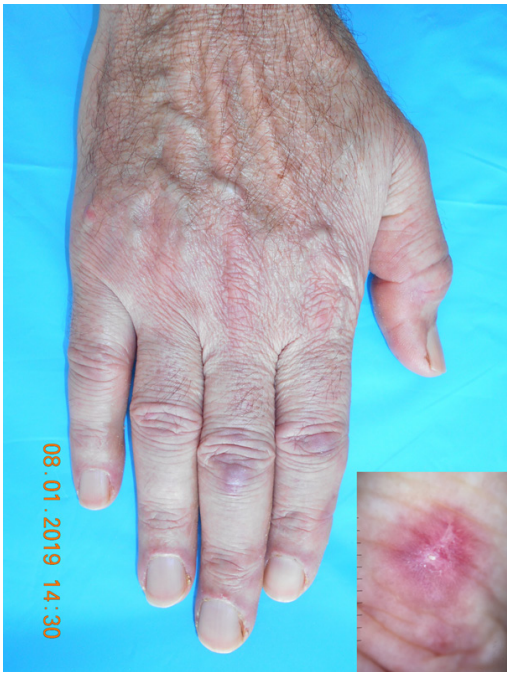

Figure 1: Erythematous bands on the back of hands with Gottron's papules. Upon dermoscopy (lower-right), surface scales and dotted vessels on a homogenous pink background can be seen.

Immunological tests such as the antinuclear antibody test (titer: 320 with speckled nuclear fluorescence), and the anti-TIF1-γ antibody test, were both positive. Electromyography showed increased insertional activity and spontaneous fibrillations with abnormal myopathic low-amplitude, short-duration polyphasic motor unit potential, and complex repetitive discharges in both deltoid muscles. Transurethral cystoscopic examination of the bladder additionally revealed a solid tumour on the left lateral wall of the bladder, which was resected. Histological examination of this lesion revealed poorly differentiated malignant cells, with various transitional cell differentiation, indicative of a primary urothelial bladder neoplasm, without invasion of the muscle in the specimen. The paraneoplastic dermatomyositis association with bladder cancer was retained and the patient was started on intravenous methylprednisolone bolus for 3 consecutive days with relay by oral prednisone 1 mg/kg daily. The patient showed both clinical and biological improvement, including decreased muscular enzyme levels, and surgery was planned 1 week later. However, a month after admission the patient succumbed to urinary infection with gram-negative septic shock and massive bladder bleeding.

Dermatomyositis is an acquired inflammatory dermatomyopathy.[1,2] It is characterised by erythematous and oedematous changes in the skin and is associated with muscle weakness and inflammation. The muscular symptoms usually predate the skin lesions and include aching and weakness, particularly in the proximal muscle groups. Patients therefore often experience difficulty in standing up from a chair, walking up stairs, and raising their arms up above their head. The skin lesions include the characteristic purple-red heliotrope rash over the eyelids, upper cheeks, forehead, and temples. There are also small, red, flat papules, known as Gottron's papules, and small plaques over the knuckles. Other symptoms include general malaise, fever, and, occasionally, nasal speech and regurgitation.[3-5] Management of malignancy-associated dermatomyositis involves steroids, or azathioprine as an alternative, steroid-sparing agent.[6] The activity of the dermatomyositis can be reflected in the state of underlying malignancy.[7] Effective antitumour treatment may be accompanied by regression of the inflammation, or conversely, it may deteriorate with progressive malignant disease.[8]

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Autoimmune Bullous Skin Disorder Induced by PD-1 Inhibitors

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Keywords: Bullous disease, melanoma, PD-1 inhibitor.

Citation: EMJ Dermatol. 2019;7[1]:65-66. Abstract Review No: AR4.

Immune checkpoint inhibitors are important therapeutic modalities not only against metastatic melanoma, but in other malignant disorders, including metastatic squamous cell carcinoma, lung, and urogenital carcinomas.[1] Albeit the most commonly reported cutaneous toxicities are mild, a subset may persist and can lead to severe or even life-threatening toxicity. Autoimmune bullous disorders belong to the rare adverse events of checkpoint inhibitors, and in a study by Siegel J et al.[2] the incidence was found to be approximately 1%. In June 2018, the U.S. Food and Drug Administration (FDA) warned about adverse events of bullous pemphigoid (BP) to be associated with pembrolizumab use. According to a recently published pharmacovigilance analysis of real-world adverse events (including published case reports and reports to the FDA), PD-1 inhibitors, pembrolizumab, and nivolumab were found to have a statically significant signal with BP.[3]

The authors report two cases of BP which began shortly after the initiation of PD-1 inhibitor therapy. One of the patients presented with metastatic melanoma and received nivolumab therapy (case 1), while the other one was treated with pembrolizumab for his urothelial carcinoma (case 2). In both cases, the diagnosis of BP was based on clinical symptoms and confirmed by histopathological and direct immunofluorescence findings. At the time of diagnosis, elevated BP antibody titers were only present in case 2 (elevated serum levels of BP180). In case 1, during the nivolumab treatment palliative radiotherapy was initiated for the metastatic lesions of the right leg with mild symptoms of BP present at that time. In both cases, methylprednisolone (0.5–1.0 mg/kg) was eventually administered and resulted in complete healing of the skin lesions (Figure 1). In case 1, BP flare was seen after steroid taper; therefore, her regular oral antidiabetic drug (a gliptin derivate) was switched to metformin and an oral corticosteroid was readministered. After cessation of oral steroids, a challenge with nivolumab was initiated. After the second cycle of nivolumab vesicles appeared again, and increased levels of BP230 were detected by ELISA. Symptoms resolved with topical clobetasol propionate therapy, and after complete regression pembrolizumab was started. Until now, the patient has received a total of nine cycles of pembrolizumab, and no blisters have occurred, while her melanoma is in stable condition. In case 2, BP reoccurred despite the slow tapering of the corticosteroid therapy. Methylprednisolone was reintroduced, but unfortunately his tumour progressed and the patient deceased in September 2018.

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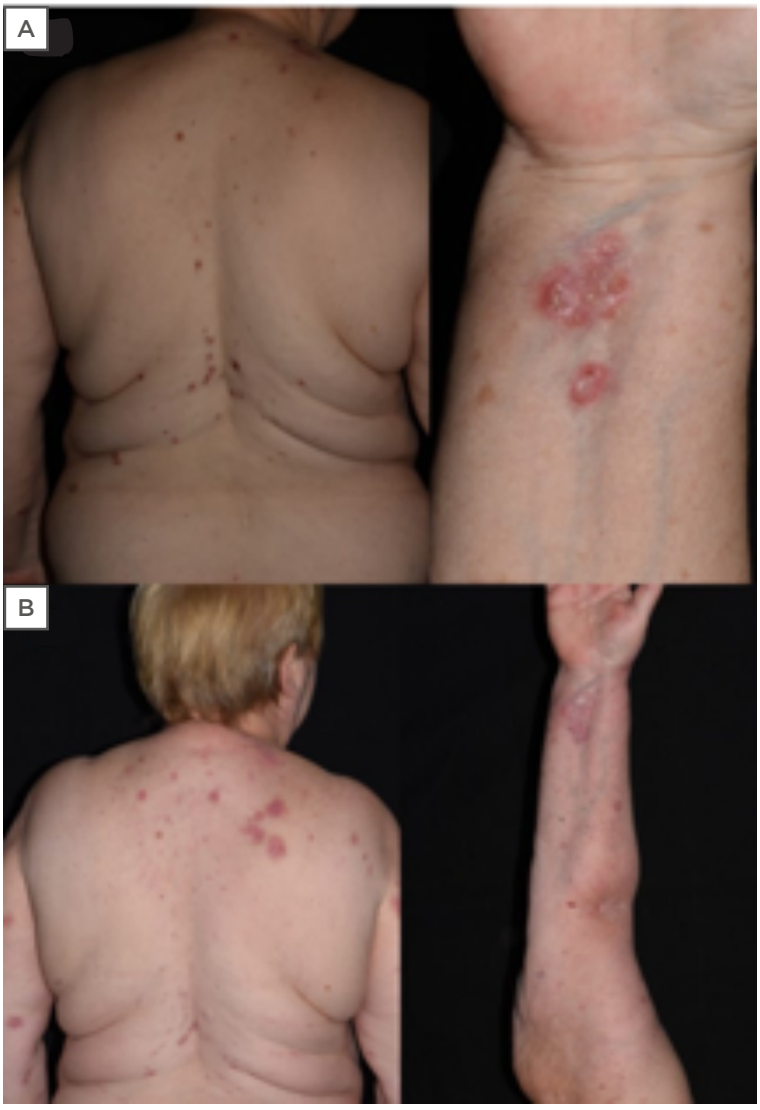

Figure 1: A) Clinical images of bullous pemphigoid (case 1). Extensive pruritic skin lesions, erythematous plaques with erosions. B) Healing of the lesions on methylprednisolone therapy.

In summary, in both presented cases skin symptoms occurred early during the course of PD-1 inhibitor treatment (9 weeks and 12 weeks), which is in line with current literature data. Systemic steroid therapy resulted in complete clearance of the skin lesions; however, even after slow tapering and discontinuation of PD-1 inhibitor therapy, flares of BP were seen. In case 1, concurrent radiation therapy might have aggravated the course of BP, and the regularly taken gliptin derivate may have potentiated the risk of BP. Interestingly, ELISA was negative in case 1 and upon challenging with nivolumab she became positive for BP230, which has been reported in PD-1 inhibitor induced BP less commonly. The results suggest the possibility of an epitope spreading phenomena. Overall, patients on checkpoint inhibitors should be carefully monitored for any subtle skin symptoms of BP, and the risks and benefits of PD-1 inhibitors weighted when deciding on whether to continue the medication.

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Analysis of Methods of the Demodex Mites Diagnosis

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Keywords: Demodex mites, *in vivo* confocal laser scanning microscopy (CLSM), standardised skin surface biopsy.

Citation: EMJ Dermatol. 2019;7[1]:67-68. Abstract Review No: AR5.

INTRODUCTION

Demodex mites are microscopic arthropods that present in the pilosebaceous units of the human skin.[1,2] Demodex mites support the severity of the inflammatory process in dermatoses such as acne, rosacea, seborrheic dermatitis, perioral dermatitis, and can also cause an independent disease called demodicosis.[3] Among different methods for the detection of Demodex mites, one of the easiest and most informative is a standardised skin surface biopsy (SSSB).[4,5] In practical medicine, it is relevant to search for informative, high-tech, and noninvasive diagnostic methods. Demodex mites can also be detected by *in vivo* confocal laser scanning microscopy (CLSM) on the facial skin,[6] as well as in the terminal bulbs of the eyelashes in ocular demodicosis diagnosis.[7] The aim of the study was to compare and analyse the data of *in vivo* CLSM with SSSB in rosacea patients for the identification of Demodex mites.

MATERIALS AND METHODS

The study recruited 30 participants (12 males [40%] and 18 females [60%]) >18 years old with a diagnosis of rosacea. All patients undertook a SSSB to detect for the presence of Demodex mites and CLSM (VivaScope 1500® Lucid Inc., Rochester, New York, USA). A SSSB was performed in a 1 cm^2 area and studied under light microscopy with a magnification of ×40 and ×100. CLSM was carried out at three positions (both cheeks and forehead), in two modes of operation of the VivaBlock and VivaStack. The results of examinations were considered positive if >5 Demodex mites per 1 cm^2 were present.

RESULTS

The Demodex mites were found in 24 patients (80.0%) by the SSSB method; 10 patients (33.3%) had <5 mites per 1 cm^2 (2.3±1.2 mites on the average). Fourteen patients (46.7%) had >5 mites per 1 cm^2, which makes it possible to diagnose demodicosis. The Demodex mites were detected in all patients by CLSM. The mean number of mites found in the follicle was 5.4±3.9 (minimum:1.0; maximum:16.0). Demodex mites were defined as round or long conical formations in the hair follicles, as well as excretory ducts of the sebaceous glands with peripheral hyper contouring (Figure 1).

CONCLUSION

CLSM is an alternative research method for Demodex mite detection, performed noninvasively in a real-time system. This method makes it possible to detect mites in deeper parts of the sebaceous glands that are inaccessible to SSSB. This makes it possible to count the number of mites not only per unit area but also directly in the follicles themselves, and also to analyse the condition of the surrounding skin, underlying structures, and pathomorphological changes.

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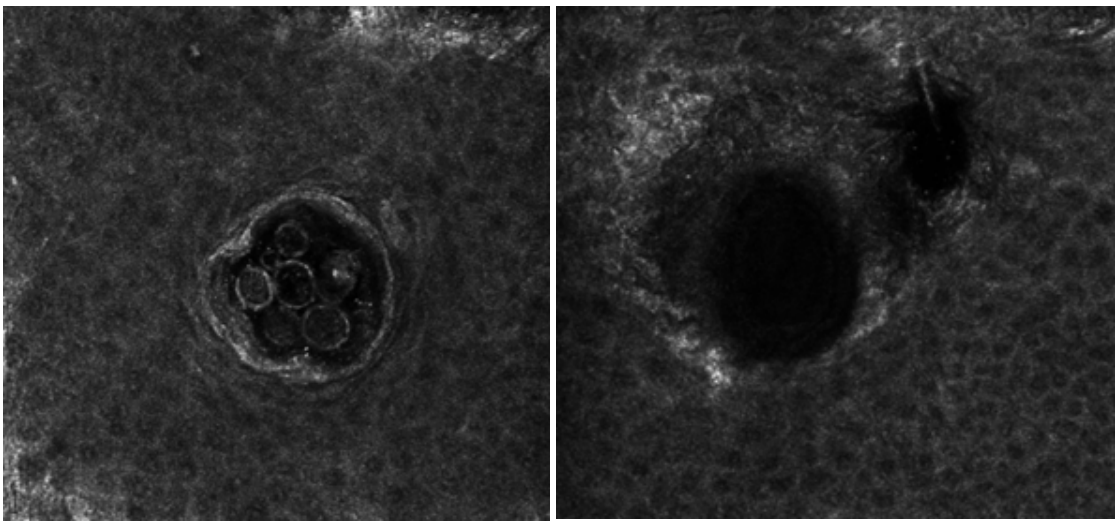

Figure 1: Images obtained with a VivaScope 1500® confocal laser scanning *in vivo* microscope.

Hair follicles and sebaceous glands with the presence (left) and the absence (right) of Demodex mites.

Apulian Experience with the Innovative Drug for Atopic Dermatitis: Dupilumab

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Apulian experience, atopic dermatitis (AD), dupilumab, therapy.

Citation: EMJ Dermatol. 2019;7[1]:68-69 Abstract Review No: AR6.

BACKGROUND AND AIM

Four patients with long-standing atopic dermatitis (AD) with elevated Eczema Area and Severity Index (EASI) and nonresponders to common therapies have been treated with the innovative drug for AD, dupilumab. Dupilumab is a fully human monoclonal IgG4 antibody targeting the α-subunit of the IL-4 receptor (IL-4Rα).[1-4] IL-4Rα is a part of Type I and Type II IL-4 receptors and the IL-13 receptor; therefore, blocking it inhibits the downstream signaling of IL-4 and IL-13. IL-4 and IL-13 are both crucial cytokines of the Th2 pathway. The aim of the study was to bring the authors' experience with this new drug to patients from southern Italy.

MATERIALS AND METHODS

The study involved 4 patients, the male to female ratio was 1:1, and the mean age was 36.25 years.

Table 1: Quantitative indexes score.

	Itch-VAS T0	Itch-VAS T1	EASI T0	EASI T1	DLQI T0	DLQI T1
28-year-old male	10.0	0.0	24.3	3.0	25.0	0.0
40-year-old female	9.0	1.0	23.2	5.0	20.0	3.0
48-year-old male	10.0	0.0	14.7	0.0	26.0	2.0
29-year-old female	10.0	1.0	27.0	2.0	30.0	0.0

DLQI: dermatology life quality index; EASI: eczema area and severity index; Itch-VAS: itch-visual analogue scale; T0: before treatment; T1: after 3 months of therapy.

All the patients had AD from infantile age that had been treated over time with topical corticosteroids, topical calcineurin inhibitors, and also oral cyclosporine without significant improvement of the pathology. One patient had to stop cyclosporine because of increased blood pressure. All patients had AD in severe form with dry skin, and red-to-brownish patches on the hands, ankles, wrists, and neck with lichenification of the folds. One patient presented with pityriasis alba in face and limbs with important psychological implications on his social life. To evaluate the effectiveness of dupilumab, the authors used the following scores: EASI, itch-visual analogue scale (VAS), and dermatology life quality index (DLQI). The patients were revalued after 3 months of therapy (T1) with iconographic documentation.

RESULTS

Significantly positive results of the scores were obtained at 3 months of observation without any adverse effect (Table 1). All patients showed rapid clinical improvement of cutaneous lesions and no other new lesions were reported during treatment. From T0 to T1, EASI showed a reduction of -7.7% in the first patient, -78.4% in the second patient, -100.0% in the third patient, and -92.6% in the fourth patient. The average value for the reduction of EASI in all patients was 89.675. Reduction of daily itching was reported after the first month of treatment. From T0 to T1, VAS showed a reduction of -100.0% in the first patient, -88.9% in the second patient, -100.0% in the third patient, and -90.0% in the fourth patient. The average value in the reduction of VAS of all patients was 94.725. All aspects of AD regressed; the quality of life improved, as can be seen from the value of DLQI; and patients had fewer problems dealing with others and in their manual and work activities. From T0 to T1, DLQI showed a reduction of -100.0% in the first patient, -85.0% in the second patient, -92.3% in the third patient, and -100.0% in the fourth patient. In the average value of all patients the reduction of DLQI was 94.325.

CONCLUSIONS

The data obtained show that the biologic drug for AD notably improves the patients quality of life, acting initially on the itching, and subsequently on the clinical picture of the disease opening a new era in the treatment of AD in chronic and severe patients.

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Cutaneous Adverse Effects Induced by Nivolumab

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Keywords: Adverse event, nivolumab, psoriasiform reaction, subacute cutaneous lupus erythematosus.

Citation: EMJ Dermatol. 2019;7[1]:70-71. Abstract Review No: AR7.

BACKGROUND

Nivolumab is a humanised IgG4 monoclonal antibody that binds the programmed cell death protein 1 (PD-1) receptor and blocks interaction with its ligand (PD-L1), preventing the inhibition of T lymphocytes by tumour cells. It is approved for the treatment of various cancers such as melanoma, squamous cell carcinoma of the head and neck, and nonsmall cell lung cancer, among others. The authors report two cases of nivolumab-induced cutaneous toxicity, which has been scarcely reported in the literature.

CASE STUDY

A 66-year-old male with no dermatological history of interest, diagnosed with a Stage IV squamous cell carcinoma of the floor of the mouth, under treatment with nivolumab, presented with a progressive cutaneous eruption on the hands, feet, and scalp (Figures 1A-B). Physical examination revealed erythematous, desquamative, hyperkeratotic lesions on the scalp, fingers, and toes, with intense nail and periungual involvement associated with enthesitis symptoms. Given the suspicion of psoriasiform reactions triggered by nivolumab, topical treatment was initiated, which led to a slight improvement.

A 66-year-old female with a history of cervical carcinoma *in situ*, ductal carcinoma *in situ* of the left breast, and invasive lobular carcinoma of the right breast, who was diagnosed with Stage IV lung adenocarcinoma, presented with a 2-month history of a pruritic cutaneous eruption. The patient was under treatment with nivolumab due to disease progression despite having received chemotherapy for a total of 24 cycles. Physical examination showed annular papulosquamous and crusted plaques on the upper torso, limbs, and face (Figures 1C-D). Histopathology showed pseudoepitheliomatous hyperplasia, a lymphoid inflammatory infiltrate in the upper dermis, basal vacuolar change, and abundant apoptotic keratinocytes. The patient tested positive for antinuclear autoantibodies (1/320) and anti-Sjögren's syndrome-related antigen A (anti-SSA/Ro60). The overall clinical presentation was consistent with a diagnosis of nivolumab-induced subacute cutaneous lupus erythematosus. Nivolumab was discontinued and treatment with topical betametasone dipropionate or gentamicin sulfate, and 1 mg/kg/day oral prednisone was initiated, with resolution. Nivolumab treatment was resumed, but the patient subsequently presented with pneumonitis, leading to discontinuation of the drug indefinitely.

The most common patterns of cutaneous toxicity caused by PD-1 inhibitors are lichenoid dermatoses, pruritus, and vitiligo.[1,2] Other dermatoses such as bullous pemphigoid, or the psoriasiform reactions[3] and subacute cutaneous lupus erythematosus[4,5] that were presented, are much less frequent. In the case of psoriasiform reactions, the differential diagnosis with paraneoplastic acrokeratosis can be complicated, as was the case for this patient. It is therefore important for dermatologists to know the cutaneous adverse effects of these new generation of oncological therapies such as nivolumab. A multidisciplinary approach to the cutaneous toxicities of these drugs facilitates early diagnosis and effective management, which allows patients to remain on these survival-prolonging treatments. It is expected that, given its increasing use, other adverse effects will be described in the future.

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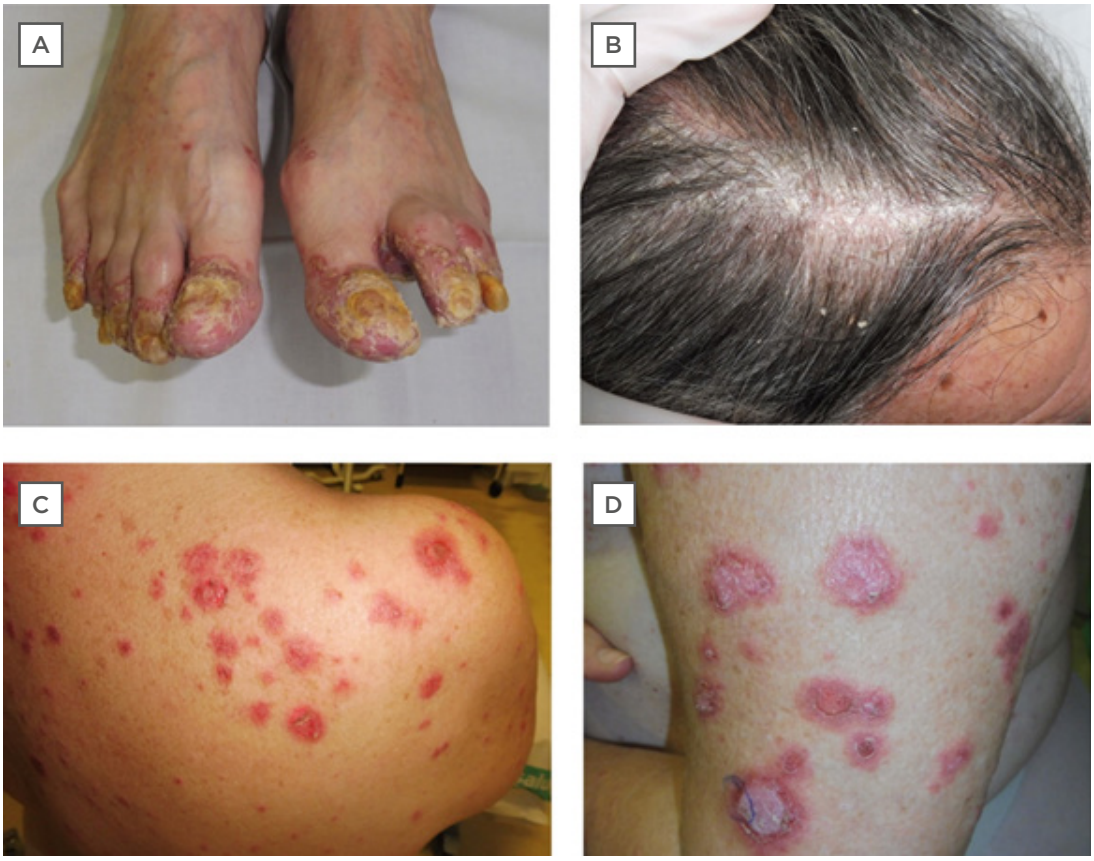

Figure 1: A-B) Erythematous, desquamative, hyperkeratotic lesions on scalp and toes, with intense nail and periungual involvement in a patient with a psoriasiform reaction triggered by nivolumab. C-D) Annular papulosquamous and crusted plaques on the upper trunk and limbs in a patient with a nivolumab-induced subacute cutaneous lupus erythematosus.

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Erythema Multiforme: A Clinical Study of Thirty-Two Patients

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Keywords: Erythema multiforme (EM), herpes simplex virus (HSV), *Mycoplasma pneumoniae.*

Citation: EMJ Dermatol. 2019;7[1]:72. Abstract Review No: AR8.

Erythema multiforme (EM) is an acute, immune-mediated skin condition that infection or medication can trigger. It occurs most frequently in young adults, particularly male, and is categorised into major (with mucosal involvement) and minor forms.[1] Usually the rash ameliorates by itself over several weeks; however, sometimes treatment may be required depending on the severity of the outbreak.[1] Thus, the aim of this study was to describe the epidemiological, clinical, and therapeutic features of EM among a sample of a Tunisian hospital's patients.

This was a retrospective study based on medical records of patients diagnosed with EM who presented to the authors' dermatology department between 2008 and 2018. The study group consisted of 32 patients (21 females and 11 males) with a mean age of 26.3 years (age range: 16.0 months to 59.0 years). Thirty percent of patients were children. Typical targetoid lesions with acral distribution were observed in 18% of patients. The eruptions were mostly located on the upper limbs (83%), followed by the lower limbs (66%), trunk (20%), and face (16%). Bullous EM was observed in 6 patients, in whom the presence of target lesions and skin biopsy allowed the distinction of EM from other bullous dermatoses. Only 11 patients had major EM. Oral mucosa was affected in the 11 cases, genital lesions were found in 3 cases, and ocular lesions in 6 cases. Nine patients (30%) had recurrence of the disease, of whom 50% reported a history of previous herpes simplex virus (HSV) infection. Two patients received prophylactic treatment with acyclovir to treat recurrent EM caused by HSV. In two cases, an infection with *Mycoplasma pneumoniae* was incriminated, with severe mucosal involvement and pulmonary infection; one case was diagnosed by serology and the other by PCR. Drug-associated EM was reported in 12% of cases (the underlying drugs were amoxicillin in 3 cases and oxacillin in 1 case). In 21% of patients, the authors could not identify a possible aetiology. Nine patients were treated with systemic steroids. Seven patients diagnosed with EM were hospitalised.

EM is a rare skin condition easily diagnosed based upon clinical appearance, but sometimes hard to distinguish from other dermatoses such as Stevens–Johnson syndrome, fixed drug eruption, urticaria, and Rowell's syndrome. In some cases, skin biopsy is needed to confirm the diagnosis. EM continues to present many unanswered questions, especially in determining the causal agent. In the present study, HSV was incriminated in almost half of the cases (47%) and was seen to influence recurrence of this disease (50%). EM caused by *M. pneumoniae* seems to be characterised by severe manifestations with prominent mucosal involvement, leading to its consideration in some recent publications as a new syndrome.[2] Antibiotics (particularly amoxicillin) were associated with some cases of EM in this analysis, whereas other drugs were reported in previous studies including nonsteroidal anti-inflammatory drugs, sulfonamides, and antiepileptics.[1] The management of minor EM involves symptomatic treatment with topical steroids, and recurrent EM associated with HSV may be treated with prophylactic antiviral therapy.[1] Hospitalisation and treatment with oral corticosteroids and antibiotics were required to treat EM due to *M. pneumonia*.[1,2] It has also been suggested that steroids can be used to treat major EM to decrease the duration and severity of symptoms.[1]

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Combined Treatment of Acneiform Rash Involved in Epidermal Growth Factor Receptor Inhibitors Therapy

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Keywords: Acneiform rash, betamethasone valerate, doxvcvcline, epidermal growth factor receptor (EGFR) inhibitors, fusidic acid, ivermectin, metronidazole.

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INTRODUCTION

Acneiform rash has a great influence on patient quality of life. Such severe dermatologic reactions are induced by epidermal growth factor receptor (EGFR) inhibitors in antineoplastic therapy, which may lead to its future replacement as a treatment. Acneiform rash is based on specific underlying inflammation,[1] and the severity of the skin reaction is based on the drug dosage and level of antitumour activity.[2-4] Management of this side effect is therefore particularly significant.

METHODS

This study analysed 35 patients with Grade I-II acneiform rash, divided into 2 groups. All the participants received oral doxycycline (100 mg) twice a day for 10 days, and a local combination of fusidic acid and betamethasone valerate (20 mg/g and 1 mg/g cream) for 3 days in the morning, as well as various topical treatments in the evening for 3 months. Group 1 were treated with metronidazole 1% gel, while Group 2 were treated with ivermectin 1% cream. The Acne Dermatology Index (ADI) and Dermatology Life Quality Index (DLQI) were used to evaluate treatment results.

RESULTS

After the first week of oral doxycycline treatment with fusidic acid and betamethasone valerate, both groups showed evident regression to acneiform rash eruption. Group 1, who were treated with metronidazole 1% gel, subsequently showed a moderate response to treatment. Group 2, treated with ivermectin 1% cream, later showed a more rapid regression of both ADI and DLQI (Figure 1), with regression to acneiform rash eruption.

CONCLUSIONS

Treatment with oral doxycycline at the early stages of Grade I-II acneiform rash led to significant clinical impact by preventing further dermatological aggravation and eruption. A combined treatment method of oral doxycycline with simultaneous application of 1% ivermectin cream, alongside fusidic acid and betamethasone valerate cream, appears to result in a faster clinical effect in comparison to combination treatment of oral doxycycline, fusidic acid and betamethasone cream, and 1% metronidazole gel. Combined treatment of Grade I-II acneiform rash with 1% ivermectin appears optimal for rapid improvement of clinical presentation and patient quality of life, whilst also allowing continuation of a patient's main treatment scheme without interruption and dosage reduction. The increasing use of EGFR inhibitors in clinical practice highlights the importance of research into dermatologic toxicity, possible complications, and differential diagnosis, ensuring the right treatment is used. Prevention and early treatment in this group of patients is of great importance as it results in a greater chance of patient compliance in treatment of oncological diseases, and significantly improves patient quality of life.

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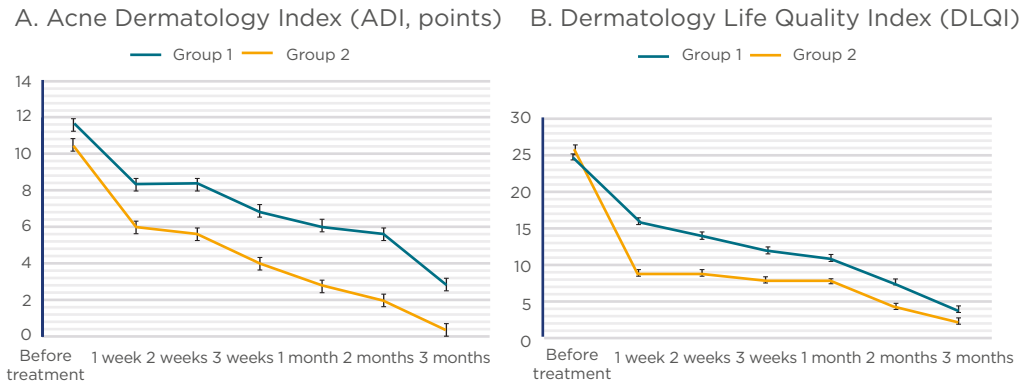

Figure 1: Dynamics in patients with acneiform rash before and after various methods of skin toxicity therapy.

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Editorial Board Interviews

Introducing key insights from two members of our valued editorial board: Dr Jaishree Sharad and Prof Alin Tatu.

Dr Jaishree Sharad

Director of Skinfinti Aesthetic Skin and Laser Clinic;
International Mentor, American Society of Dermatologic Surgeons;
Board of Director, International Society of Dermatologic Surgeons,
Mumbai, India

Q1

What inspired or influenced you to become a dermatologist? What continues to inspire you in your job?

After completing my MBBS, I completed a 1-year internship, rotating from one department in the hospital to another. During my internship in the department of dermatology, I found the subject to be extremely interesting. Cosmetic issues were not that common at that time, but acne, leukoderma, vitiligo, and many other disorders could be physiologically very disturbing and to cure them was gratifying and rewarding; and of course, there were hardly any emergencies in this field. This was the initial reason that I took up dermatology, but by the time I finished my post-graduate degree, dermatologic surgery had become popular and we were doing chemical peels, lasers, and dermatologic surgeries. Botulinum toxin and fillers were just beginning to become known in India and I found it intriguing. I went ahead and did my fellowship in injectables in the USA and in Bangkok. The concept of recreating youthfulness was exhilarating and rewarding; recreating natural beauty and sculpting faces is something that I am extremely passionate about. To help somebody to become scar-free, to make somebody look more gorgeous, to instil that confidence in someone is something I look forward to every single day and there is nothing more gratifying than the feeling of making someone feel happy and confident.

Q2

Within your 20 years of practising cosmetic dermatology, what are the most common skin disorders that you came across? Furthermore, in your expert opinion what basic advice would you give to the population to prevent these disorders from arising?

In my 20 years of practice, the most common skin problem that I have come across in India is pigmentation. People have all kinds of pigmentary disorders due to sun exposure, oil use, herbal supplements, and powders that have a lot of heavy metals. Hair dye and perfume allergies causing pigment contact dermatitis or Riehl melanosis is very common. People tend to use a lot of pumice stones, scrubs, and loofahs which causes friction melanosis and macular amyloidosis. I would advise people to start using an adequate quantity of sunscreen every single day whether it is raining, snowing, hot, or cloudy, and if they are outdoors for >2 hours they must learn to reapply the sunscreen, and, of course, moisturise well. I also urge individuals to eat healthily, exercise every day, and make sure they get at least get 7–8 hours of sleep. I would advise them to stay away from habits such as smoking, alcohol, and excessive sugar intake.

Q3

During your education and career, you have worked in various countries including the USA, Thailand, and Germany. How has travelling and meeting medical experts from different countries influenced your career and did you notice any differences in research and treatment focusses compared to India?

I think I have been extremely fortunate to have had the opportunity to travel all over the world and to observe a lot of my mentors practising in their clinics. I have always learnt a lot from them, from newer techniques, to the art of managing complications, and fine-tuning the skills for injectables, lasers, or any aesthetic procedure for that matter. I think that in India, we have the right facilities, but people need to be more open to aesthetic procedures or even basic skincare. People tend to ignore their skin all the time and take it for granted. The awareness has begun in metropolitan cities, but India is a country with more towns and villages, and this message must seep in everywhere.

Q4

From a clinical viewpoint, what dermatological disorder fascinates you the most and stands out from the rest?

I am an aesthetic dermatologist, so for me, ageing is very fascinating. The fact that it is not just your collagen that degrades, but that also your deep fat pockets are disappearing, there is bone resorption, and the superficial fat hypertrophies and sags down, changing the way you look. The fact that you can turn back the clock non-surgically with the help of fillers, certain lasers, and skin tightening devices, and make people look confident in their own skin is amazing.

Q5

Following your ethos of making people feel confident in their own skin, you have authored two books: 'Skin Rules' and 'Skin Talks' and edited one textbook. Could you please summarise the main take-home messages from these publications?

In my first book, 'Skin Talks', I described the anatomy of skin and its different layers; the process of skin ageing; the harmful enemies of skin including smoking, alcohol consumption, lifestyle, and diet; how to take care of your skin by using the right cleansers, moisturisers, sunscreens, and anti-ageing creams; and the difference between skincare in summer, winter, and in monsoons. The book is more of a 'skin bible,': it has got a very detailed descriptions on skincare.

'Skin Rules' on the other hand is more of a fun book. It is easy to read and contains simple tips and pictorials. The things I discuss in 'Skin Rules' include the ideal skincare ritual; how one should acquaint oneself with different labels that are seen in shops; how to deal with acne; hyperpigmentation; different 'skin myths' that exist; the difference between serums, creams, and lotions; the importance of exfoliation, food, and exercise; the right kind of lifestyle; and when should one see a dermatologist. By and large, both books will tell you that you should not ignore your skin and a lot of time the skin is trying to tell you something that is happening within your body. For example, you may have dry skin, pigmentation, or hair loss in hyperthyroidism; you may have acne, hair loss, or hair growth with polycystic ovarian syndrome; and you may have acanthosis nigricans and infections in diabetes.

I am the chief editor of the cosmetic dermatology textbook called 'Aesthetic Dermatology: Current Perspectives.' I have written about 12 chapters in it and the others have been written by esteemed dermatologists from India and abroad. There are

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sections on cosmeceuticals, botulinum toxin, soft tissue augmentation, lasers, and devices. It is a handy book for dermatologists, plastic surgeons, and aesthetic physicians.

Q6 As an active member of various organisations and journals, could you indulge us on your current tasks as a Board of Director within the International Society of Dermatologic and Aesthetic Surgery (ISDS) and the aims and scope of the organisation?

As a member of the Board of Directors of ISDS, it is my duty to see that more dermatologists, plastic surgeons, and aesthetic physicians become members, as well as exchange ideas from various parts of the globe and learn and innovate newer techniques. It is important to explore new talent and bring out the best in every doctor in order to be able to give excellent cosmetic results to our patients. At ISDS, we conduct workshops and conferences in dermatologic surgery and aesthetic dermatology in order to be able to teach more students. We also plan to have mentors across the globe so that it becomes easy for students to learn not just the basics, but also the latest developments in the field.

Q7 The rise of pollution and the thinning of the ozone layer are contributing to increased levels of environmental factors that affect the health of skin and may lead to nonmelanoma skin cancer. In your expert opinion, what safety precautions would you recommend, and do you believe these merits wider global attention?

Pollution is on the rise all over the world. In India, it is due to road dust, soot from vehicles, fuel from industries, and kitchen fires. It is becoming a perpetual problem because of the construction of new roads, metros, and buildings, which has been an ongoing process. The rise in pollution is not harmful for human beings alone, but also for the flora and fauna. In humans, apart from causing damage to the lungs, there is also an increase in free radicals which may lead to skin cancer. Free radicals increase in the skin, leading to allergic rashes, itching, blotchy and dry skin, increased skin sensitivity, acne, fine lines, wrinkles, premature greying of hair, premature hair loss, pigmentation, and increased incidence of rosacea, all because of pollution.

Aside from having basic skincare in the form of cleansing, moisturising, and using a sunscreen, one must pick a moisturiser which protects the lipid barrier layer of the skin; and, antipollution creams should be used. Maximum effort should be made to avoid adding to pollution. Those who work outdoors should wear masks which not only cover the nose and mouth, but the entire face, excluding the eyes. It is important to drink enough water and have a lot of antioxidants in the diet. Supplements and vitamin C, E, and A help, and in extreme conditions, air purifiers can be kept in the home. One can take oral supplements of antioxidants or have organic food (especially brightly coloured berries and fruits) in order to help the body to fight the toxins caused by pollution.

Q8 Holding numerous awards to your name, such as winner of the 'Best Skin Expert' at Vogue Beauty Awards 2016 and Elle Beauty Awards 2016, and winner of the '50 Outstanding Women in Healthcare 2017' at the World Health and Wellness Congress, what advice would you give to aspiring dermatologists and cosmetic dermatologists?

My advice to young dermatologists is to dream big; even the sky is not the limit, and everything is possible if you work towards it sincerely and honestly. Make sure you work hard and keep upgrading your knowledge all the time. There is no end to learning. Also, never forget to keep your integrity, your respect, and your ethics. We are doctors, and what we must have is empathy and compassion. We should be able to help our patients to make right decisions, rather than just carry out a lot of treatments to make money. Keep the hunger for learning alive. And most importantly, stay happy.

Prof Alin Tatu.

Medical and Pharmaceutical Research Unit, ''Dunărea de Jos'' Integrated Interdisciplinary Research Platform (ReForm-UDJG), Dermatology, Faculty of Medicine and Pharmacy, Pharmacology Sciences and Clinical Department, ''Dunărea de Jos'' University of Galati, Galați, Romania

Q1

Have you always had a passion for dermatology, and why? Did you ever consider following other paths in scientific research?

I have always had always a passion for dermatology. It started in the last year of the medical school at the Carol Davila University of Medicine and Pharmacy in Bucharest, Romania, in Colentina Hospital. I considered following other paths in scientific research when collaborating with colleagues from pharmaceutical departments, such as pharmacists or chemical researchers, to better explain some of the alternative treatments for common diseases such as vitiligo or acne.

Q2

You have a particular interest in skincare and are currently working on the 'FACE Project'. Could you explain a bit more about the project and the algorithm you are developing as part of this project?

This was an idea from some of my friends and colleagues. The goal is to develop an algorithm for facial health and beauty according to age, lifestyle, and associated diseases. We wanted to study the clinical factors of these criteria by collecting data and observing correlations between the factors.

Q3

Last year, you published a paper entitled: 'Butterfly Effect – the Concept and the Implications in Dermatology, Acne, and Rosacea'. Could you give a brief explanation about the 'Butterfly Effect,' and its use in dermatology? How does future treatment of rosacea compare to the current treatment options for this condition?

The 'butterfly effect' (in chaos theory) is the sensitive dependence on initial conditions, that is, a very small change in one state of a deterministic nonlinear system is associated with large differences in a later stage. Edward Lorenz coined the term, which derives from the metaphorical example in which the details of a tornado were influenced by minor perturbations such as flapping of the wings of a distant butterfly. The pathophysiology of rosacea continues to remain unclear, but it is believed that genetic factors, immune system dysregulation, abnormal neurovascular signalling, and dysbiosis of commensal skin organisms may be the key promoters of rosacea. Triggers of rosacea include sun exposure, hot temperatures, exercise, feelings of embarrassment or anger, spicy foods, and alcohol consumption. Endosymbionts of *Demodex spp.* have been identified as triggers of inflammation in rosacea, specifically *Bacillus oleronius*. My team and I have previously described other types of *Bacillus spp.*: *Bacillus simplex*, *Bacillus pumilus*, and *Bacillus cereus*. Future therapies for the condition need further validation and large populational studies to improve the disease control.

Q4

Do you find that there any challenges working in the field of dermatology? What has been the greatest challenge you have faced in your career?

The 'butterfly effect' (in chaos theory) means there are a lot of challenges in the field of dermatology, such as comorbidities in hospitalised patients and their management. These are potential future directions to investigate in the field of complementary and alternative medicine. The greatest challenge of my career has been to simultaneously manage three patients with acute urticaria who arrived at the hospital at the same time.

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Q5 Do you think there are any areas of dermatology that currently require more attention within medicine?

As I have previously mentioned, I believe future directions of complementary and alternative medicine in dermatology requires more attention. There is a need for physicians to have informed discussions about the options of complementary and alternative medicine with their patients, and greater focus must be placed on this as there are data indicating the positive effect of complementary and alternative medicine on psoriasis. There is data to suggest that 34.5% of patients use CAM, however 42.3% of patients do not report using it to doctor. The reasons for patients not informing their doctor of this include the clinician not asking the patient, or the doctor not needing to know about it. This kind of data is extremely important and requires our attention because it suggests there is a 'trust deficit' between clinicians and their patients. Our patients trust us with their health and their lives, and it is vital that they are able to disclose such important information. The data suggests that patients did not want to discuss their use of CAM with their doctor based on the belief that physicians have a general lack of openness, interest, and respect; furthermore, the patients did expect their physician to have information about CAM sufficient to refer them for this. We, as physicians, need to ensure we are engaging patients and refer them to the appropriate healthcare professionals for CAM. By doing this, we will meet the needs of patients, maintain their trust, and protect them from dangerous practice.

Q6 You have recently attended EADV 2019. Which sessions resonated with you the most? Have any taken you by surprise?

I particularly enjoyed the sessions about rosacea, the microbiome, and biologics in psoriasis treatments. I was interested in the rosacea session because this is one of my fields of research. There were discussions about *Demodex spp.* and dermatoscopy in rosacea; new treatments for Morbihan disease, such as the off-label uses of omalizumab; experiences with oxymetazoline and brimonidine; and the improvement of transepidermal water loss in rosacea by doxycycline and other medications. The microbiome is now in the centre of research involved in almost all dermatologic diseases, so the new data presented improved our perception about preserving it. The sessions about psoriasis included the latest data about safety and efficiency in psoriasis, and new studies about better selection of certain biologics for individuals.

I was taken by surprise in the session which presented the possibility of using omalizumab as a treatment for Morbihan disease in the future. I was also taken by surprise to learn that doxycycline decreased transepidermal water loss in rosacea, revealing that the barrier function in this disease is not influenced just from a sebaceous perspective but also by diminishing inflammation.

Q7 Why are annual meetings such as EADV so important? Considering the key, take home messages from EADV 2019, what do you think will be the key focusses in dermatology over the next year?

The EADV annual meeting is an opportunity to discover new information about our speciality, to explore new and interesting places in Europe, and to meet friends, old or new, working in our field. I think that the key focusses next year will include new data on the efficiency of the new therapies or biologics for psoriasis, atopic dermatitis, computer assisted dermatology, clinical updates in the field, and breaking news in dermatology.

Acne Therapy Across Time in the USA

EDITOR'S PICK

Acne remains a rather mysterious skin and hair follicle disorder, with a significant level of morbidity in severe cases. While there has been some progress in dissecting its aetiology and pathomechanism, treatments are still frustratingly suboptimal for most patients. In this edition, my Editor's Pick is an update review by Dr Valeria De Debout, which assesses the current state of the art in treatments for acne used in the USA in terms of their relevance, efficacy, tolerability, and safety.

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Abstract

Acne vulgaris is the most common skin condition affecting the American population. The present review evaluates the topical and systemic therapies available in the USA for the management of acne reporting their relevance, efficacy, tolerability, and safety. This review also discusses alternative treatments such as light therapy, diet, and probiotics. Further research on acne therapy is needed given the high prevalence, and thus, the immense economic burden that the condition poses in our society.

INTRODUCTION

Acne is the most common skin condition in the USA, affecting over half of its population.[1] It is an inflammatory skin disease that predominantly affects adolescents and young adults. Multiple factors are involved in the pathogenesis of acne including skin hyperkeratinisation around the follicular infundibulum, increased sebum production, colonisation of *Cutibacterium acnes*, and activation of the innate immune system leading to an inflammatory response.[2] Acne represents a significant economical and psychological burden for our society, and thus, the relevance of understanding its pathogenesis and seeking an adequate treatment that is cost-effective, safe, and widely accepted by patients is extremely important. This review will discuss the different available options for the treatment of acne across time, focussing on agents and modalities currently used and their level of evidence and safety. An English language search for literature on PubMed using the key terms "acne", "treatment", and each of the individual therapies was included according to personal experience. Relevant articles were reviewed pertaining to these treatments used in daily practice in the USA and are presented here.

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TREATMENTS

Over the last century, new treatment options have emerged for the management of acne. Figure 1 illustrates how topical and systemic agents have advanced over time.[3] There is a vast number of current available treatment options for this condition and the success of such treatments relies upon the use of an individualised approach focussing on the severity of acne presentation, treatment side effects, patient preferences, patient education, and establishing realistic expectations to treatment.[4] The treatment of acne can be divided in three major categories, which include topical agents, systemic agents, and miscellaneous or complementary treatments.

TOPICAL AGENTS

Sulphur

Sulphur has been used for the treatment of acne since Ancient Egypt due to its antimicrobial and keratolytic properties.[5] It is currently used mainly as an adjuvant to other therapies such as sodium sulfacetamide, which is also approved as a monotherapy treatment for acne in the form of washes, leave-on lotions, creams, masks, and foams in concentrations of 1–10%.[5]

Topical sulphur is tolerated very well with few side effects that may include skin dryness and malodour. Sulphur is a Category C medication; therefore, it should be only used in pregnant women when the benefits outweigh the risks.[5]

Resorcinol

Topical resorcinol for the treatment of acne has been used for centuries in low concentrations of 1–2% combined with other agents, such as a keratolytic agent. In higher concentrations of up to 40%, it has been used as a chemical peel for the treatment of hyperpigmentation, erythema, and scars.[6]

Topical Antibiotics

Efficacy of clindamycin and erythromycin is limited over time. Increased antibiotic resistance is reported with long-term treatments, particularly with erythromycin.[7,8] The clinical guidelines for the treatment of acne in 2016 classified topical antibiotics as Grade A with a level of evidence of I–II.[9]

Such guidelines established the level of evidence of treatments according to the quality of selected studies that evaluated each therapy; similarly, the strength of recommendation was defined according to the best available evidence.[9]

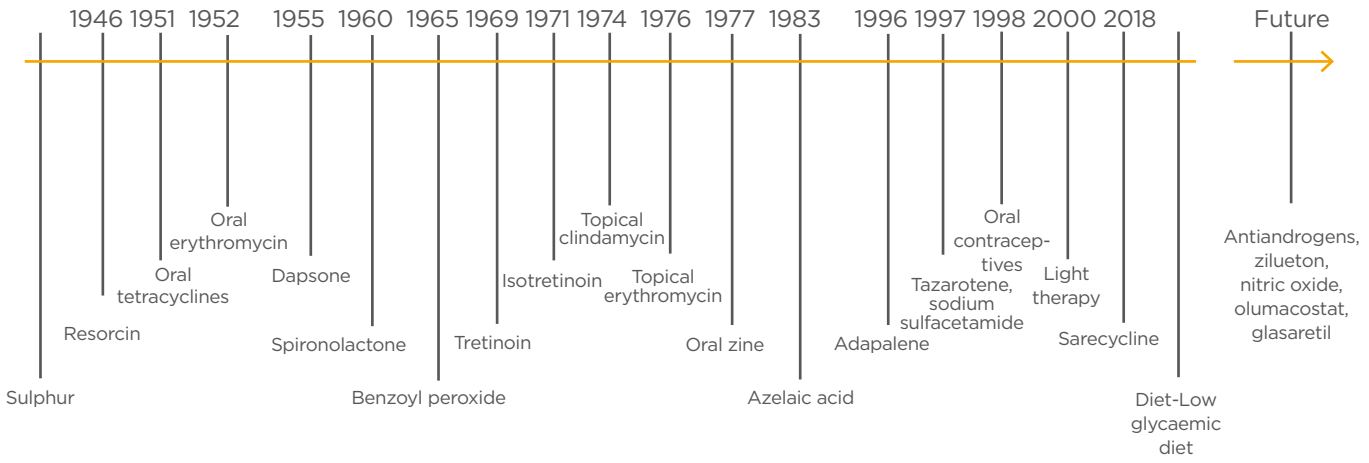

Figure 1: Treatment across time.

Acne treatment over the last 50 years.

TETRACYCLINES

Topical minocycline is a relatively new alternative for the treatment of acne lesions. Two randomised placebo-controlled Phase III studies evaluated the efficacy of minocycline for the treatment of acne during a 12-week period in 961 patients and concluded that treatment with minocycline was significantly superior in reducing the inflammatory lesion count ($p<0.05$).[10]

Benzoyl Peroxide

Topical benzoyl peroxide is a comedolytic and antibiotic that effectively works against *C. acnes*.[5] It has been used as an adjuvant medication to other topical antibiotics to reduce resistance to medication.[11,12] Multiple studies have addressed its effectiveness alone or in combination with other agents such as topical antibiotics and retinoids. Shalita et al.[13] evaluated the efficacy of benzoyl peroxide 6.0% wash and tretinoin 0.1% gel compared to tretinoin alone for the treatment of acne vulgaris in 87 patients during a 12-week period. They concluded that patients using the combination therapy had a significant reduction in the acne papule count ($p=0.037$) from Week 2, compared to patients in the monotherapy group who did not show a significant improvement in their acne until Week 12.[13] Side effects were minimal and included local skin irritation.[5] The clinical guidelines for the treatment of acne in 2016 classified it as Grade A with a level of evidence of I–II.[9]

Topical Retinoids

Topical retinoids include tretinoin, adapalene, and tazarotene. Their use in the treatment of acne has demonstrated satisfactory outcomes.[14] An analysis of two multicentre, randomised, vehicle-controlled, Phase III studies evaluated the efficacy of topical tretinoin for patients with moderate-to-severe acne and demonstrated a significantly higher efficacy of tretinoin 0.05% in reducing acne lesion count compared to vehicle alone in 154 patients ($p=0.001$).[14] U.S. Food and Drug Administration (FDA)-approved in 1996, adapalene has mainly been reported as a combined regimen with benzoyl peroxide with mean percentage changes of comedonal acne being superior than for those patients treated with adapalene as a single agent.[15,16] Topical tazarotene was first approved in 1997 for the treatment of acne. A review of five Phase I studies in normal controls and two Phase III studies in patients with moderate-to-severe acne reported on the safety and efficacy of tazarotene 0.1% foam for acne vulgaris.[17] Reported side effects are mainly limited to dryness and irritation.[5] The clinical guidelines for the treatment of acne in 2016 classified them as Grade A with level of evidence of I–II.[9]

Salicylic Acid and Azelaic Acid

Both salicylic and azelaic acid are used as a topical keratolytic for the treatment of acne.[5] Both agents have mild side events which are limited to local irritant reactions. The clinical guidelines for the treatment of acne in 2016 classified them as Grade B with a level of evidence II and Grade A with level of evidence I, respectively.[9]

Dapsone

Dapsone was first approved in 1955, and later its higher concentration (5%) was FDA-approved in 2008 for the treatment of acne.[18] Topical dapsone 5.0% and 7.5% gel is used especially among female adults. In controlled studies, it significantly reduced the noninflammatory and total lesion counts in adult patients when compared to adolescents. Two double-blind, randomised Phase III studies evaluated the efficacy of dapsone 5.0% gel applied twice daily for the treatment of acne. At Week 12, patients on the dapsone group were found to have a significant reduction in their acne lesion count, particularly the adult patients compared to adolescents ($p<0.001$).[18] In clinical studies, it has demonstrated a safety and efficacious profile including in patients with glucose-6-phosphate dehydrogenase deficiency.[19] Adverse events are minimal and include local reactions such as dryness and pruritus. The clinical guidelines for the treatment of acne in 2016 classified it as Grade A with a level of evidence of I–II.[9]

Nicotinamide

Recent reports and studies have investigated the efficacy of topical nicotinamide for the treatment of acne, but the current available data is too limited to create formal recommendations. Upon testing, either as single agent or in combination with antibiotics, nicotinamide has demonstrated an improvement of acne lesions.[20,21] No major side effects have been reported. Future topical agents

currently undergoing Phase II–III clinical trials include nitric oxide[22] and olumacostat glasaretil.[23]

SYSTEMIC AGENTS

Birth Control Pills

Birth control pills reduce acne lesion counts and severity of lesions.[24-26] Lucky et al.[24] compared the efficacy of drosperinone 3 mg and ethinyl estradiol 20 µg for the treatment of acne vulgaris in a randomised, placebo-controlled study, and found that the therapy group had a significant improvement in the investigators overall improvement rating scale compared to those patients in the placebo group ($p<0.001$). Norgestimate-ethinyl estradiol, drospirenone-ethinyl estradiol, norethindrone acetate-ethinyl estradiol, and ethinylestradiol/drospirenone/levomefolate calcium are FDA-approved for the treatment of acne.[24-26] The most common side effects associated with them include weight gain, breast tenderness, mood changes, and vaginal bleeding;[27] although rarely, thromboembolism and stroke have also been reported.[27] Patients with uncontrolled high blood pressure or migraines with neurologic signs should not be started on birth control pills.[28] The clinical guidelines for the treatment of acne in 2016 classified it as Grade A with level of evidence of I.[9]

Spironolactone

Spironolactone was first approved by the FDA in 1960. Spironolactone at doses 50–100 mg daily displays favourable results for the treatment of acne vulgaris through its antiandrogenic effects and reduction of sebum production.[29-31] The most common reported side effects include menstrual irregularities, hyperkalaemia, and central nervous system symptoms such as lethargy, fatigue, dizziness, and headache.[29,30] Physicians should be careful when prescribing this medicine concomitantly with potassium supplements, angiotensin-converting enzyme inhibitors, other potassium-sparing diuretics, digoxin, lithium, corticosteroids, and nonsteroidal anti-inflammatory drugs. Flutamide is a pregnancy Category C medication. The clinical guidelines for the treatment of acne in 2016 classified it as Grade B with a level of evidence of II–III.[9]

Systemic Antibiotics

Systemic antibiotics have been widely used for the treatment of acne vulgaris because of their antimicrobial and anti-inflammatory properties. Despite the increased risk of acquired antibiotic resistance, it is recommended to maintain a regimen of 6–8 weeks with a total duration of 3–6 months of therapy. The most commonly used antibiotics for the treatment of acne vulgaris include tetracyclines and macrolides.

Tetracyclines, including doxycycline, minocycline, tetracycline, and sarecycline, have been used for a long time with favourable results for the treatment of acne.[32-34] Doxycycline is considered as first-line therapy for acne among systemic antibiotics. The most common side effects include gastrointestinal upset, photosensitivity, and hyperpigmentation.[4,35] The clinical guidelines for the treatment of acne in 2016 classified them as Grade A with level of evidence of I–II.[9] Tetracyclines are pregnancy Category B medications, and as such they are teratogenic.

Macrolides, including azithromycin, erythromycin, and clarithromycin, are a safe alternative to doxycycline for the treatment of acne, especially in those patients with poor tolerance or resistance to the treatment with doxycycline.[36] A meta-analysis of randomised controlled trials was performed to analyse the efficacy of azithromycin compared to oral doxycycline in patients with moderate-to-severe acne vulgaris. Six studies were included and found no significant difference between the two groups in terms of lesion count improvement after therapy ($p=0.27$).[36] Special consideration should be given to long-term antibiotic resistance where macrolides have a higher risk than clindamycin.[37] The 2016 clinical guidelines for the treatment of acne classified them as Grade A with a level of evidence I.[9] Trimethoprim has been used as an alternative in some patients. The 2016 clinical guidelines for the treatment of acne classified it as Grade B with a level of evidence of II.[9]

Isotretinoin

Isotretinoin is an FDA-approved oral retinoid for the treatment of acne vulgaris. Its mechanism of action covers the four major pathogenic factors involved in the development of acne and it is superior in disease control when compared with other medications in randomised clinical

trials.[9,39-41] Peck et al.[39] performed a double-blind placebo-controlled study comparing the effects of isotretinoin initiated with 0.5 mg/kg/day with placebo over a 4-month period and reported a significant difference in acne improvement for the therapy group compared to placebo ($p<0.001$ at 1 month and $p<0.008$ at 2 months). Patients are commonly treated with 0.5–1.0 mg/kg/day until a cumulative dose of 120.0–150.0 mg/kg is reached.[41] Reaching the cumulative dose is necessary for patients to see a long-lasting effect with less risk of recurrence. Relapses have been described more commonly in those who were treated in their early teens.[42] More recently, a newer form of isotretinoin, called isotretinoin-lidose, has been released.[43] This newer form increases the absorption levels of isotretinoin independently of the patient's fasting status, thus maintaining the same safety and efficacy properties as the previous form.[43,44] As a Category X medicine, isotretinoin is teratogenic and thus contraindicated in pregnancy, lactation, and in patients with severe hepatic and renal dysfunction.[45] It should always be prescribed concomitantly with a reliable birth control method in females with child-bearing potential and everyone should be registered in the iPLEDGE program.[9] Although caution should be taken in patients with suicidal tendencies and mental illness, studies have been inconclusive for a clear association among them.[41,46-49] The clinical guidelines for the treatment of acne in 2016 classified it as Grade A with a level of evidence of I–II.[9]

Flutamide

Flutamide is a nonsteroidal antiandrogen medication infrequently used in dermatology for the treatment of acne. A randomised study compared the effects of flutamide with cyproterone acetate-ethinyl estradiol during a 6-month period and concluded that both treatments significantly decreased the acne severity scores ($p<0.001$).[50] The clinical guidelines for the treatment of acne in 2016 classified it as Grade C with a level of evidence of III.[9]

Zinc

Since 1977, zinc has been used for the treatment of acne after finding low levels of zinc in patients with the disease.[51] The data on the efficacy of zinc for the treatment of acne has since been mixed.[52-54] Zinc acts through several mechanisms such as regulation of protein, lipid, and nucleic acid metabolism and gene transcription; maintenance of an adequate immune activity; antimicrobial effects against *C. acnes*; and suppression of sebum production.[55] Another systemic therapy currently undergoing Phase II–III clinical trials is zileuton.[56]

LIGHT THERAPY

Both photodynamic therapy (PDT) and lasers have demonstrated promising effects for the treatment of acne vulgaris, yet no long-term data from rigorous clinical studies is available. Their mechanism of action is mainly attributed to bactericidal and anti-inflammatory effects secondary to a reduction in the production of macrophage cytokines and a decreased sebum production due to thermic effects on the sebaceous glands.[57]

Photodynamic Therapy

The use of PDT for the treatment of acne has been recently described.[58] Studies have compared its efficacy with oral antibiotics and a significantly higher improvement has been shown in the PDT group. A randomised study performed by Nicklas et al.[59] in 46 patients reported that patients treated with PDT had a significant reduction in the noninflammatory lesion count ($p=0.013$) and total lesion count ($p=0.038$) after 6 weeks of therapy compared to those treated with doxycycline 100.0 mg/day plus adapalene gel 0.1%. A small clinical trial demonstrated improvement of acne lesions after PDT therapy with minimal side events, decreased sebum production, and decreased inflammatory markers on the lesions.[58] Different photosensitisers (aminolevulinic acid, methyl aminolevulinate, and indole-3-acetic acid) and light sources (red light, pulsed-dye laser, intense-pulsed light, long-pulsed dye laser, and green light) could be used. The best outcomes are with the combination of aminolevulenic acid and red light.[58]

Laser Therapy

Laser therapy was previously limited to post acne scarring, but since the early 2000s some lasers have been FDA-approved for active acne lesions demonstrating success in the treatment of inflammatory acne, especially with nodular

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lesions ($p<0.05$).[60] The 1,550 nm erbium glass fractional laser, 1,450 nm diode laser, and 800 nm diode lasers have had promising results in clinical trials.[61-63] The most commonly reported side effect included mild erythema of the treated area.[60] Gold-plated, silica-core, light-absorbing microparticles with light and laser therapy have recently been an area of special interest because of their antisebum effects. Vacuum-assisted light therapy is also gaining interest for the treatment of acne, claiming to improve light penetration and thus allowing for a better outcome when performed prior to light therapy.

CHEMICAL PEELS

The use of superficial and medium-depth chemical peels for acne is very popular in the dermatological practice because of its favourable results, low-cost, and safety.[64,65] Exfoliation, keratolysis, decreased sebum production, anti-inflammatory and antibacterial properties, and comedolytic effects are all mechanisms of action attributed to chemical peels.[66] The most popular chemical peels used for acne therapy are salicylic acid, glycolic acid, lactic acid, and trichloroacetic acid. The clinical guidelines for the treatment of acne in 2016 classified them as Grade B with a level of evidence of II–III.[9] A special consideration should also be taken for patients undergoing treatment with tetracyclines, birth control pills, and isotretinoin, in whom there may be a higher risk of side effects.

ALTERNATIVE TREATMENTS

In the search for more natural therapy with less side effects, increased use of complementary and alternative medicine, probiotics, and diet have been emerging in society. Such approaches still lack strong evidence-based recommendations. Tea tree oil, green tee derivates, and resveratrol are some of the most common natural products used for acne displaying anti-inflammatory and sebo-suppressive properties.[67,68] The clinical guidelines for the treatment of acne in 2016 classified complementary and alternative therapies (tea tree oil, herbal, and biofeedback) as Grade B with level of evidence of II.[9] Diet and probiotics have also gained attention for acne treatment.[9,69,70] A Cochrane review concluded that a low glycaemic load diet, although only supported by small trials with low-quality evidence, had positive results in the treatment of acne.[69] A clinical trial examined skin samples of acne lesions and similarly concluded that the sebaceous glands were smaller and less inflammation was present in patients with a low glycaemic diet, resulting in improvement of their acne.[71] Dairy, and dairy-derived products such as whey supplements, are also associated with increased risk of acne. A systematic review and meta-analysis described an increased odds ratio for acne in patients with a high dairy-based diet.[72] Evidence-based data is still limited with regards to the impact of diet and acne, and results should be analysed very carefully because of small samples, lack of long-term follow-up, heterogeneity, and bias among studies. Probiotics also play a role in therapy of acne by reducing inflammation, sebum content, and *C. acnes* colonisation.[70]

CONCLUSION

Acne is one of the most common medical conditions in the USA and a very common reason of consult in dermatology. Treatment should be guided according to the severity of presentation and the patient's expectations. Topical and oral antibiotics along with topical retinoids and/or benzoyl peroxide for mild-to-moderate acne, and isotretinoin as the standard of care for severe lesions, are in use to reach remission, but also to prevent scarring and other complications. Hormonal therapy for female patients should be considered with every case, but may not be suitable for all. Alternative or less-used treatments present us with options to refine care for the acne patient, but most often have to be used with more traditional therapies. More research is needed given the existent gaps in knowledge. When to start, which agent to choose, and duration of treatment are often questions both the practitioner and the patient have when considering acne therapy. Treatment challenges for transgender patients, pregnant women, and patients of differing ethnicities; more long-term safety data for systemic agents; and additional options for men are the biggest gaps in the current knowledge. It is mandatory for practitioners to continuously seek for a more efficacious, safe, and cost-effective therapeutic option for their patients.

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Treatment of Atopic Dermatitis Using JAK Inhibitors: A Systematic Review

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Abstract

Background: The advent of JAK inhibitors (JAKi) has significantly modernised the treatment of atopic dermatitis (AD), offering a novel approach to treating this recalcitrant dermatological condition. Although topical treatment is shown to be effective, oral formulations are yet to be widely utilised in the treatment of AD.

Objectives: To review the efficacy, safety, and tolerability of JAKi in the treatment of AD.

Methods: A PRISMA systematic review of several databases was conducted: Cochrane Skin Specialised Register, Cochrane Central Register of Controlled Trials, Ovid Medline and Embase, LILACS, and Global Resource of EczemA Trials. Five clinical trial archives were also consulted. The following resources were manually searched: conference proceedings of the American Academy of Dermatology (AAD), FDA.gov, the European Medicines Agency (EMA), and Epistemonikos.

Results: Of the 34 articles meeting inclusion criteria, 6 were chosen for final qualitative review. A total of 827 patients were pooled from 5 randomised controlled trials and 1 cohort study. Improvements in objective and subjective scoring indices were observed in patients receiving topical or oral JAKi. Overall safety and tolerability were satisfactory in JAKi treatment.

Limitations: Due to the scarcity of randomised controlled trials and the small sample sets in the studies, a meta-analysis was not conducted.

Conclusions: Preliminary investigations show promising results for patients with AD treated with oral or topical JAKi. However, existing gaps should be addressed with more extensive and long-term trials before JAKi become a standard treatment for AD.

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INTRODUCTION

Atopic dermatitis (AD) is one of the most common and debilitating chronic inflammatory skin diseases, often greatly affecting physical, economical, and psychological quality of life (QoL).[1] It affects approximately 20% of children and 3–10% of adults,[2] with mean lifetime prevalence increasing in recent decades.[3,4] In 60% of cases, onset occurs in the first year of life; however, AD can present at any age.[5] The course of AD ranges from chronic to relapsing-remitting, with 44% of cases spontaneously resolving in late childhood.[6]

AD is a clinical diagnosis with no definitive laboratory or histological findings. The hallmark of this condition is a disturbance of epidermal-barrier function due to recurrent skin inflammation, leading to dry skin, pruritis, and IgE-mediated allergen sensitisation.[7] Skin lesions may then lead to increased risks of secondary bacterial and viral infections. Histologically, AD is characterised by skin infiltration with inflammatory cells, predominantly lymphocytes, eosinophils, and mast cells.[8] AD is strongly associated with other atopic disorders, such as allergic rhinitis and asthma, with 50–80% of children exhibiting concurrent atopic manifestations.[1] Other comorbidities of AD include cardiovascular disease, sleep disturbances, and cutaneous/systemic infections and malignancies, all of which highlight the correlation between inflammatory processes and atopic diatheses.

Treatment of AD is aimed at continuous epidermal-barrier repair through the use of emollients and avoidance of personal triggering factors.[9,10] Topical corticosteroids, calcineurin inhibitors, and nonsteroidal topical phosphodiesterase-4 inhibitors are considered preliminary therapies for acute exacerbations. However, topical therapeutics for AD face many challenges, including imperfect efficacy, difficulty with application, adverse effects (AE) with long-term topical steroid regimens, and local site reactions.[11] For severe cases of AD (modified Eczema Area and Severity Index [mEASI] score >10 with Investigator Global Assessment [IGA] >3 and >10% Body Surface Area [BSA] affected), phototherapy and systemic immunosuppressants (prednisone, cyclosporin, azathioprine, mycophenolate mofetil, or methotrexate) can be attempted. However, access to phototherapy is limited for many patients. Furthermore, side effect profiles for certain systemic immunosuppressants can decrease overall compliance.[12] In 2017, dupilumab, an injectable monoclonal anti-IL-4Rα antibody, was successfully trialled in the USA for the treatment of moderate-to-severe AD.[13] However, long-term data on its efficacy and safety are still pending.

The aetiology of AD is not yet fully clarified, but it is likely a multifactorial disease involving genetic and environmental components. Mutations in the filaggrin gene have been associated with AD and are thought to lead to epidermal barrier dysfunction.[14] This dysregulation stimulates release of chemokines by keratinocytes[15] causing subsequent immune cell infiltration, particularly Th2 cells and epidermal dendritic cells.[16-18]

Recently, JAK inhibitors (JAKi) have emerged as a novel therapeutic intervention for inflammatory diseases. JAK are intracellular secondary messengers that transmit extracellular cytokine signalling to the STAT pathway.[19] There are four members of the JAK family: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Cytokines that activate JAK have been implicated in lymphocyte activation and proliferation.[20] Moreover, inhibition of the JAK–STAT pathway can suppress inflammation and inhibit immune-cell activation in T cell-mediated disorders.[21] Currently, three JAKi have been approved in the European Union (EU): ruxolitinib and baricitinib (JAK1/2 inhibitors) are approved for myeloproliferative disorders (including polycythaemia vera) and rheumatoid arthritis (RA), respectively. Tofacitinib, a JAK1/3 inhibitor, is approved for RA, psoriasis, and ulcerative colitis. Novel selective JAK1 inhibitors, such as filgotinib, have also been efficacious in Phase IIa trials for RA.

Given the limited treatment arsenal for AD and the challenges posed by traditional topical and systemic agents, many patients are unable to achieve disease remission.[22] Novel topical agents for AD have been absent for the past decade, making topical JAKi a promising option for recalcitrant disease. Although dupilumab is effective in the treatment of AD, its injectable formulation makes it prohibitive for certain patients. Given the optimistic safety profiles of oral JAKi and inconsistent compliance with topical agents, novel oral JAKi provide a

meaningful alternative for patients afflicted with refractory AD.

METHODS

A search strategy was created on the basis of the Cochrane Handbook for Systematic Reviews of Interventions[23] and the PRISMA statement.[24] The authors' review included randomised controlled trials (RCT), cohort studies, case reports and series, conference proceedings, and clinician-based experiences. Exclusion criteria included review articles, commentary pieces, patient-reported outcome studies, ongoing clinical trials, and preclinical investigations. No limitations were placed on language or publication status. The search strategy was peer reviewed by two independent librarians. The literature's level of evidence was evaluated using The Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence Grading scale[25] (Table 1).

Electronic Searches

The following electronic databases were systematically searched:

- Cochrane Skin Specialised Register (CRS)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE via Ovid (from 1946 to 22nd June 2018) (Table 2)
- EMBASE via Ovid (from 1980 to 22nd June 2018) (Table 2)
- Latin American and Caribbean Health Science Literature (LILACS) Information database (from 1982 to 22nd June 2018)
- Global Resource of EczemA Trials (GREAT)

Table 1: Overview of current investigations in the treatment of atopic dermatitis with JAK inhibitors.

Author (year)	Therapy	Study design / CEBM Level of evidence* Limitations	Results	Safety
Nakagawa H et al.,[26] 2018	JAK inhibitor (JTE-052)	• Phase I / CEBM Level 1b. • Single-centre, 2-part study, randomised (n=66), intraindividual. • QBX1-1 (dermal safety): double-blind study (n=22): JTE-052 ointment BID for 7 days (0.03%, 0.10%, 0.30%, 1.00% or 3.00%) versus placebo and negative control. • QBX1-2 (pharmacokinetics/ efficacy): 3-part, single-blind (n=44): JTE-052 ointment BID for 7 days (1% or 3%) versus placebo and negative control. • Small sample size. • Short dosing duration.	• QBX1-1: No photoallergy and phototoxicity range of 4.5–9.1. • QBX1-2: no systemic accumulation of JTE-052. • EASI improvements (%): 32/53/52 for placebo/1.00%/3.00%. • IGA improvements: 0;-1/0;-1;-2/0; -1;-2;-3 for placebo/1.00%/3.00%. • NRS Day 8 (day;night): -1;-1.5/-1.4;-1.0/-2.7;-2.5 for placebo/1.00%/3.00%.	• QBX1-1: proteinuria (n=1). • QBX1-2: leukopenia (n=2), glucosuria (n=1), erysipelas (n=2 with 1 from drug reaction). • No photoallergy. • Minimal systemic drug accumulation. • Good overall tolerability with no SAE.

Table 1 continued.

Nakagawa H et al.,[27] 2018	JAK inhibitor (JTE-052)	• Phase II / CEBM Level 1b. • Multicentre, randomised, vehicle controlled (n=327), intergroup (n=6). • JTE-052 ointment BID for 4 weeks (0.25%, 0.50%, 1.00%, or 3.00%) versus vehicle versus tacrolimus (0.10%, open label). • Tacrolimus group was nonblinded. • Short dosing duration. • Rescue medications readily available.	• mEASI improvements (%): 12/42/57/55/73/62 for vehicle/0.25%/0.50%/ 1.00%/3.00%/ tacrolimus. • IGA 'clear' or 'almost clear': 23% for 3.00% ointment versus 3.00% for vehicle. • NRS scores improved in all groups with large reduction at Night 1.	• AE: 16% in vehicle versus 19% in JTE-052 versus 43% tacrolimus. • Nasopharyngitis (4%), furuncle (1%), acne (2%), folliculitis (n=1), erysipelas (n=1), herpes simplex (n=1), contact dermatitis (n=1). • Minimal systemic drug accumulation in all groups. • Good overall tolerability with no SAE.
Gooderham M et al.,[28] 2018	JAK inhibitor (PF-04965842)	• Phase IIa / CEBM Level 1b. • Multicentre, randomised, double-blind (n=327). • PF-04965842 PO daily (10, 30, 100, or 200 mg) versus placebo.	• SCORAD and EASI improvements (%): 40% and 47% in 100 mg group, respectively. • 100 mg and 200 mg groups reached EASI 50, 75, or 90 more than placebo. • Pruritis decreased by 25% and 20% in 200 mg and 100 mg groups, respectively.	• AE: 68.0% in total with 3.4% SAE. • Thrombocytopenia in 200 mg and 100 mg groups with return to normal by Week 4. • Good overall tolerability.
Guttman-Yassky E et al.,[29] 2018	JAK/SYK dual oral inhibitor (ASN002)	• Phase I / CEBM Level 2b. • Single centre, randomised, double-blind (n=36). • ASN002 20 mg, 40 mg or 80 mg QD – 4 weeks. • Biomarkers studied (Th1, Th2, and Th22).	• mEASI improvements: 40 mg and 80 mg groups at 2 weeks (57%) and 4 weeks (79%). • Reduction of inflammation biomarkers (especially Th2 and Th22) in 40 mg group.	• Good overall tolerability with no SAE.
Bissonnette R et al.,[30] 2016	Tofacitinib	• Phase IIa / CEBM Level 1b. • Randomised, double blinded, vehicle controlled (n=69). • 2% tofacitinib versus vehicle ointment BID for 4 weeks. • Small sample size and short dosing. • Small range of AD severities. • Biomarkers not studied.	• mEASI improvements: tofacitinib (82%) versus vehicle (30%). • PGA 'clear' or 'almost clear': 73% tofacitinib versus 22% vehicle. • BSA improvements: tofacitinib 76% versus vehicle 31%. •ISI improvements: 6.5 tofacitinib versus 5.5 vehicle.	• AE: 44% total (89% mild). • Infections (13%): nasopharyngitis (n=2), furuncle (n=1), bronchitis (n=1), gastroenteritis (n=1). • Application site reaction (n=1). • Minimal systemic drug accumulation. • Good overall tolerability with no SAE.

Table 1 continued.

Levy LL et al.,[31] 2015	Tofacitinib	• Cohort study / CEBM Level 2b. • Nonrandomised (n=6). • 2% tofacitinib 5 mg BID or 5 mg QD for 29 weeks. • Small sample size with possible bias, no placebo.	• SCORAD improvements: 54.8% then 66.6% at 29 weeks. • Pruritus/sleep loss scores improvements: 69.9%/71.2% at 14 weeks then 76.3%/100.0% at 29 weeks.	• No infection, cytopenia or decreased renal function. • Good overall tolerability with no SAE.

*The literature's level of evidence was evaluated using The Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence Grading scale.[25]

AD: atopic dermatitis; AE: adverse event; BID: twice daily; BSA: body surface area; CEBM: Oxford Centre for Evidence-based Medicine; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; ISI: Itch Severity Item; JAK/SYK: JAK/spleen tyrosine kinase; mEASI: modified Eczema Area Severity Index; NRS: Numeric Rating Scale; PGA: Physician Global Assessment; PO: by mouth; QD: once daily; SAE: serious adverse event; SCORAD: Scoring Atopic Dermatitis.

Complementary Resources

Clinical trial registers were manually searched (until 23rd June 2018), using the search terms "atopic dermatitis", "eczema", "neurodermatitis", "Janus Kinase", "JAK", "Janus Kinase inhibitor":

- International Standard Randomised Controlled Trials Number (ISRCTN) registry
- ClinicalTrials.gov
- Australian New Zealand Clinical Trials Registry (ANZCTR)
- World Health Organization (WHO) International Clinical Trials Registry Platform
- EU Clinical Trials Register

Conference Proceedings

- The American Academy of Dermatology (AAD)

Organisational Websites

- National Eczema Association (NEA)[32]
- U.S. Food and Drug Administration (FDA)[33]
- European Medicines Agency (EMA)[34]
- Epistemonikos[35]

RESULTS

A comprehensive search yielded a total of 34 articles. Of these, six met the established inclusion criteria (Figure 1). A total of 827 patients were pooled from the 5 RCT and 1 cohort study identified. There were no case reports or case series singled out. A synthesis of the results was completed (Table 1).

Phase I Trial: Topical JTE-052 (JAK inhibitor)

Nakagawa et al.[26] conducted a Phase I, single-centre RCT studying the efficacy, safety, and pharmacokinetics of a novel JAKi, JTE-052 (a JAK1/2/3 and TYK2 inhibitor), in the treatment of adult patients (18–65 years old) with AD. This RCT was divided into two subset studies: QBX1-1 and QBX1-2.

QBX1-1 investigated the cutaneous safety of JTE-052 ointment in 22 patients. A double-blind, randomised, intraindividual approach compared JTE-052 (0.03%, 0.10%, 0.30%, 1.00%, or 3.00% ointments) to placebo, white petrolatum ointments, and negative controls. Ointments were applied twice daily (BID) for 7 days (maximum of 5 g daily on any affected areas). Patch testing and photopatch testing were used to assess dermal safety at 60 minutes, 24 hours, then daily for 4 days. There were no positive photoallergy reactions in any of the 22 patients. The phototoxicity index ranged from 4.5 to 9.1 for the JTE-052 group compared to 4.5 for placebo, white petrolatum, and control groups. JTE-052 ointments up to 3.00% therefore

Table 2: Search strategies.

Search Strategies	
MEDLINE via Ovid	EMBASE via Ovid
1. exp Eczema/ or eczema.mp.	1. eczema.mp. or exp eczema/
2. exp Dermatitis, Atopic/	2. exp dermatitis/ or dermatitis.mp.
3. neurodermatitis.mp. or exp Neurodermatitis/	3. exp atopic dermatitis/
4. exp Dermatitis/ or dermatitis.mp.	4. neurodermatitis.mp. or exp neurodermatitis/
5. or/1-4	5. or/1-4
6. randomized controlled trial.pt.	6. janus kinase 1.sh.
7. controlled clinical trial.pt.	7. janus kinase 2.sh.
8. randomized.ab.	8. janus kinase 3.sh.
9. placebo.ab.	9. (jak1* or jak-1*).ti,ab.
10. clinical trials as topic.sh.	10. (jak2* or jak-2*).ti,ab.
11. randomly.ab.	11. (jak3* or jak-3*).ti,ab.
12. trial.ti.	12. (jakafi* or jakavi*).ti,ab.
13. janus kinase 1/	13. (jak* adj3 inhibit*).ti,ab.
14. janus kinase 2/	14. (janus* adj2 kinas*).ti,ab.
15. janus kinase 3/	15. (incb-018424 or incb018424).ti,ab.
16. (jak1$ or jak-1$).tw,kf,ot.	16. ruxolitinib/
17. (jak2$ or jak-2$).tw,kf,ot.	17. tofacitinib/
18. (jak3$ or jak-3$).tw,kf,ot.	18. upadacitinib/
19. (jak$ adj3 inhibit$).tw,kf,ot.	19. (INC-424 or INC424).ti,ab.
20. (janus$ adj2 kinas$).tw,kf,ot.	20. or/6-19
21. (INCB-018424 or INCB018424).tw,kf,ot.	21. random$.mp.
22. ruxolitinib$.tw,kf,ot.	22. factorial$.mp.
23. tofacitinib$.tw,kf,ot.	23. (crossover$ or cross-over$).mp.
24. upadacitinib$.tw,kf,ot.	24. placebo$.mp. or placebo/
25. (INC-424 or INC424).tw,kf,ot.	25. (doubl$ adj blind$).mp.
26. or/13-25	26. (singl$ adj blind$).mp.
27. or/6-12	27. (assign$ or allocat$).mp.
28. (animals not (humans and animals)).sh.	28. volunteer$.mp. or volunteer/
29. 27 not 28	29. Crossover Procedure/
30. 5 and 26 and 29	30. Double Blind Procedure/
	31. Randomized Controlled Trial/
	32. Single Blind Procedure/
	33. or/21-32
	34. (animal or animal experiment or nonhuman).sh.
	35. human.sh.
	36. 35 not 34
	37. 36 and 33
	38. 5 and 20 and 37

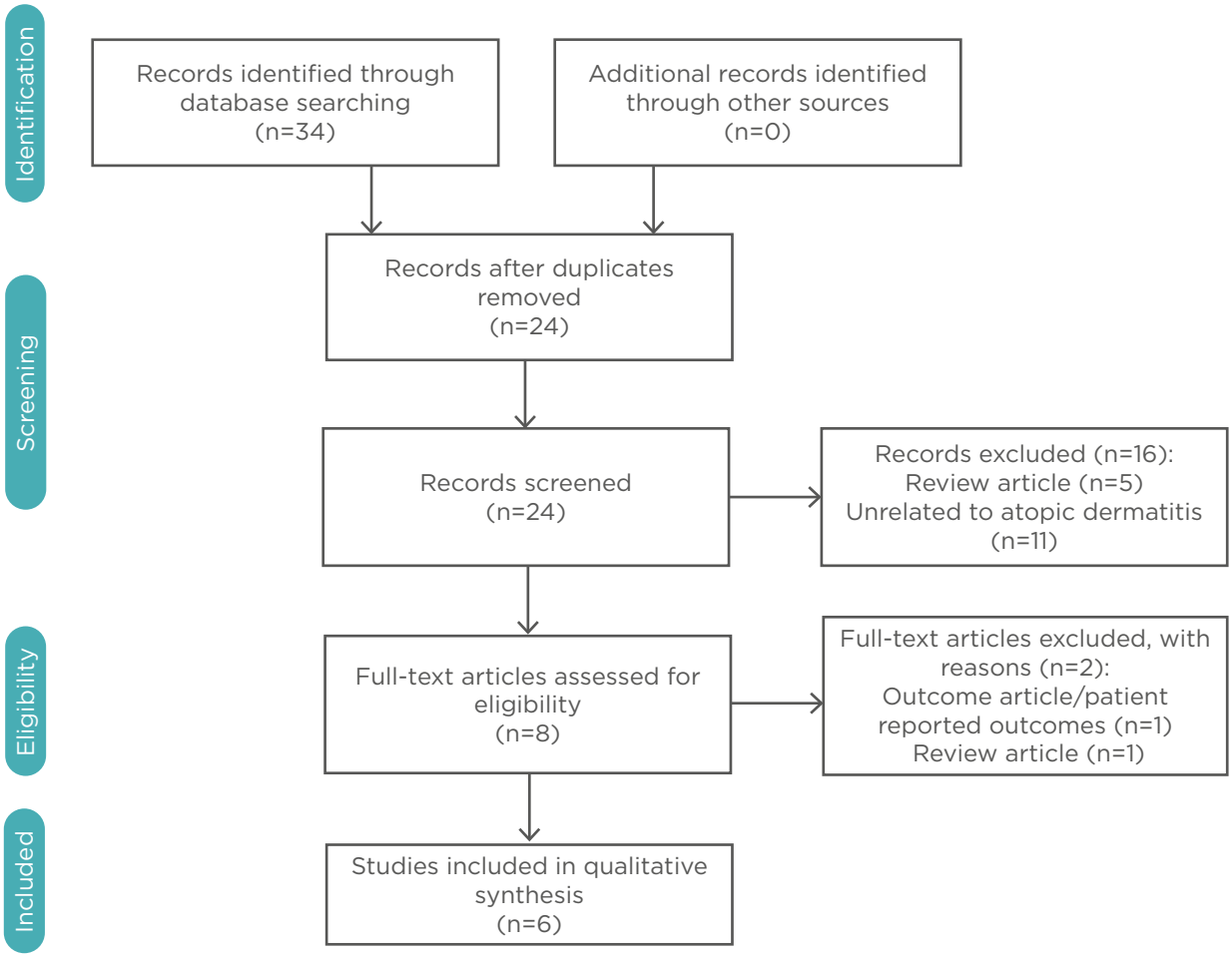

Figure 1: PRISMA flow diagram: Study search and selection criteria.

showed a low potential for phototoxicity and no potential for photoallergy. The ointments were well tolerated with no serious AE or adverse drug reactions noted.

QBX1-2 studied the pharmacokinetics, efficacy, and safety of JTE-052 ointment in a single-blind, randomised analysis of 44 patients. JTE-052 ointment (1.00% or 3.00%) was applied BID for 7 days on patients with AD and healthy subjects. In Part 1, serial urine and plasma concentrations showed low systemic exposure and no systemic accumulation when 1.00% or 3.00% JTE-052 ointment was utilised. Exploratory efficacy was confirmed through improvements in several indices. Changes in EASI scores on Day 4 and Day 8 were 10.71%/32.71% in placebo, 30.99%/53.12% with 1.00% JTE-052, and 17.27%/52.26% with 3.00% JTE-052, respectively. Absolute changes in IGA on Day 8 were increased (improved) with 1.00% JTE-052 and 3.00% JTE-052 when compared to placebo. Absolute changes in pruritus Numeric Rating Scale (NRS) on Days 4 and 8 improved to -1.0/-1.0 (sleep) and -1.0/-1.5 (daytime) in placebo, -1.3/-1.4 (sleep), and -0.4/-1.0 (daytime), with 1.00% JTE-052 as well as -2.2/-2.7 (sleep) and -2.5/-2.5 (daytime) with 3.00% JTE-052. Overall tolerability and safety were good, with one case each of glucosuria (placebo group), leukopenia (3.00% JTE-052), and erysipelas (1.00% JTE-052).

Phase II Trial: Topical JTE-052 (JAK inhibitor)

A Phase II multicentre, intergroup, vehicle-controlled RCT was conducted by Nakagawa et al.[27] as a follow-up to their Phase I trial. This study was not double-blinded in both groups; however, site personnel handled all samples with both investigators and patients unaware of the appearance of the ointments. The efficacy,

safety, and pharmacokinetics of JTE-052, a novel JAKi, were investigated across 38 centres in 327 patients with moderate-to-severe AD.

JTE-052 ointment (0.25%, 0.50%, 1.00%, or 3.00%), the vehicle ointment, or tacrolimus (0.10%) ointment was applied BID for 4 weeks (6 groups total). There were no baseline differences in the severity of AD amongst patients. At end of treatment in Week 4 (or at study discontinuation), all groups showed a decrease in mEASI ($p<0.001$ for JTE-052 at all concentrations). Reduction in mEASI was dose-dependent, with mean changes of -12.2%, -41.7%, -57.1%, -54.9%, and -72.9% for vehicle 0.25% and 0.50%, 1.00%, and 3.00% JTE-052, respectively. The mean change in mEASI for the tacrolimus group was -62.0%. Improvements in IGA, pruritus NRS, and percentage BSA were also noted in all JTE-052 groups over time. The proportion of patients achieving an IGA score of 'clear' or 'almost clear' was higher in 3.00% JTE-052 group (23%) compared to the vehicle group (3%) ($p=0.039$). Of note was the rapid antipruritic effect of 0.5% JTE-052 (with improvements proportional to dosage concentration) from the first night of application versus vehicle ($p=0.001$). No statistical comparisons between tacrolimus and JTE-052 were performed in regard to antipruritic effects. At Weeks 2 and 4, plasma concentrations of JTE-052 were highest in the 1.00% and 3.00% JTE-052 groups. Minor AE (mostly skin infections) were reported in 16.0% of patients in the vehicle group compared to 19.2% in the JTE-052 groups. The tacrolimus group was associated with the highest proportion of application site reactions. Overall tolerability of application was good in all groups.

Phase IIb Trial: Oral PF-04965842 (JAK inhibitor)

A Phase IIb trial was conducted by Gooderham et al.[28] to examine the secondary efficacy and safety of PF-04965842, a novel oral JAK1 inhibitor. This double-blind, multicentre RCT followed 323 patients over 12 weeks. Patients were administered 10, 30, 100, or 200 mg of PF-04965842 versus daily placebo by mouth (PO). Scoring of AD index (SCORAD) and EASI scores improved by 40.7% ($p=0.0017$) and 47.4% ($p=0.0091$) in the 100 mg group compared to placebo, respectively. Patients in the 100 mg and 200 mg groups achieved EASI 50, 75, or 90 more often than with placebo (EASI50: 78.5% and 55.3% versus 27.4% [$p=0.0042$]; EASI75: 63.7% and 41.6% versus 15.6% [$p=0.0043$]; EASI90: 51.6% and 26.8% versus 10.3% [$p=0.0354$]). Placebo-adjusted percentage change from baseline for pruritus severity was 25.4% ($p=0.0034$) in the 200 mg and 20.7% ($p=0.0172$) in the 100 mg group. PF-04965842 was generally well tolerated, with 68.9% AE and 3.4% serious AE (thrombocytopenia).

Phase I Trial: Oral ASN002 (JAK/spleen tyrosine kinase inhibitor)

A Phase I trial was conducted by Guttman-Yassky et al.[29] to investigate the tissue response, safety, and clinical efficacy of ASN002, a novel dual oral inhibitor of JAK/spleen tyrosine kinase (JAK/SYK) signalling. JAK/SYK (including TYK2) signalling controls AD related Th2 and Th22 cytokine production (suppressing IL-6 and IgE stimulation). This double-blind RCT followed 36 patients with moderate-to-severe AD. ASN002 20 mg, 40 mg, 80 mg doses, or placebo were administered daily (QD) for 4 weeks. Skin biopsies were evaluated at baseline, 2 weeks, and 4 weeks for biomarkers. Overall, amongst the 40 mg and 80 mg ASN002 groups, optimal mEASI score improvement occurred at 2 weeks (57% change) and 4 weeks (79% change). Reductions in inflammation, T-cell activation, hyperplasia, Th2/Th22, and Th1 were noteworthy in the 40 mg ASN002 group ($p<0.004$). A correlation was also noted between improvements in EASI and Th2/Th22 biomarkers. Overall, there was adequate tolerability and safety for product administration in all groups.

Phase IIa Trial: Topical Tofacitinib (JAK inhibitor)

Bissonnette et al.[30] completed a Phase IIa, double-blind, parallel-group, vehicle-controlled, multicentre RCT in 69 adults with moderate-to-severe AD. The efficacy, safety, and pharmacokinetics of 2% tofacitinib ointment (JAKi) was evaluated via a BID regimen over 4 weeks. After 4 weeks, improvement in mEASI was greater in the tofacitinib group (81.7%) compared to the vehicle group (29.9%) ($p<0.001$). Similarly, the proportion of patients with a Physician Global Assessment (PGA) of 'clear' or 'almost clear' at Week 4 was 73%

in the tofacitinib group compared to 22% for the vehicle group (p<0.05). At 4 weeks, a 76% improvement from baseline BSA was seen in the tofacitinib group compared to 31% in the vehicle group (p<0.001). Improvements in the baseline Itch Severity Item (ISI) score were greater in the tofacitinib group (6.5) versus the vehicle group (5.5) (p<0.001). Overall, 44% of the patients experienced AE, of which 89% were mild. The tofacitinib group included 12 AE (in 11 patients) compared to 26 AE (in 19 patients) for the vehicle group. Two patients in the vehicle group discontinued treatment because of AE. The most frequent AE were infections and infestations (13%). Postadministration plasma tofacitinib concentrations in Weeks 2 and 4 were only slightly higher than pre-dose concentrations, indicative of a flat concentration curve. Concentrations increased with higher treated percentage BSA at Week 2 but not Week 4.

Cohort Trial: Oral Tofacitinib (JAK inhibitor)

Levy et al.[31] evaluated the efficacy of oral tofacitinib citrate (a JAK1/3 inhibitor) in 6 consecutive patients (18–55 years old) with refractory AD. Moderate-to-severe AD was established with a baseline SCORAD of >20. Over 29 weeks, 5 patients received 5 mg (PO) BID and 1 patient received 5 mg (PO) QD (since QD dose was sufficient to elicit remission). Assessments were conducted at 4 to 14 weeks then 8 to 29 weeks. In all six patients, tofacitinib treatment resulted in reduced dermatitis and oedema BSA score. Composite SCORAD index decreased by 54.8% from Weeks 4 to 14 and decreased by 66.6% compared to baseline at Week 29 (p<0.05 for all comparisons). At Week 14, the pruritus and sleep loss scores decreased by 69.9% and 71.2%, respectively (p<0.05). These scores diminished by 76.3% and 100.0% from baseline at Week 29. Oral tofacitinib was well tolerated overall, with few AE reported.

DISCUSSION

Recent developments in the study of topical and oral JAKi have greatly advanced the understanding of AD and its response to novel treatment alternatives. The authors' review bridges the gap between previous knowledge and current concepts addressing the use of JAKi in AD. The majority of the studies captured in this review describe Phase I[26,28] or Phase II[27,29] clinical trials. Completed Phase III data is currently unavailable, although multiple adult and paediatric clinical trials studying novel JAKi (including oral baricitinib, topical tofacitinib, and oral upadacitinib) are under way in the USA and Europe.[36-43] Both topical and oral JAKi resulted in reductions in AD disease severity compared to placebo/vehicle. Marked and rapid reductions were observed for most pruritus scores,[26,30] sometimes within 1 day of initiating treatment. Overall, safety, tolerability, and systemic accumulation of JAKi (via measurement of urine and plasma concentrations) were well within acceptable ranges. Aggregate findings therefore suggest that both oral and topical JAKi are safe and efficacious in the treatment of AD.

The success of JAKi in controlling AD also confirms the importance of the JAK–STAT pathway in the pathogenesis of the disorder. Cytokines such as IL-4, which increase in AD, make use of JAK for signalling.[44,45] IL-4 promotes differentiation of Th2 cells, and subsequent production of other inflammatory cytokines (IL-4, IL-5, IL-10, and IL-13). Given that AD is overwhelmingly a Th2 focussed disorder, JAKi are a promising treatment option for AD.

Of the JAKi that were examined in this present review, tofacitinib was most extensively studied in major inflammatory conditions, including immune-mediated dermatologic conditions.[42-44] Tofacitinib preferentially blocks signalling through JAK1 or JAK3 which are paired with JAK2.[49,50] Several cytokines, including IL-4, signal through this pathway[21] whereas IL-13 signals through JAK1/TYK2. The authors identified a Phase IIa study using topical tofacitinib[30] and a cohort study using oral tofacitinib.[27] Though topical tofacitinib has conflicting efficacy for plaque psoriasis,[51,52] the Phase II trial included in this present review showed it to be superior to placebo[29] for the treatment of AD. Oral tofacitinib can also safely lead to clearance of moderate-to-severe AD.[30] However, in this study, success was demonstrated in a small, noncontrol cohort study (n=6), which may limit extrapolation to the general population.

Three novel JAKi were also efficacious in the treatment of AD. *In vitro*, JTE-052 inhibited JAK1, JAK2, and JAK3.[53] In animal dermatitis models, activation of inflammatory cells was inhibited,

consequently supressing skin inflammation.[54] JTE-052 also successfully inhibited keratinocyte production of filaggrin,[55] a contributor to the pathogenesis of AD. Accordingly, Phase I and Phase II studies[26,27] showed that topical JTE-052 was superior to placebo in reducing disease severity and pruritis. Finally, PF-04965842 (oral JAK1/2 inhibitor) and ASN002 (oral dual JAK/SYK inhibitor) showed promising results in Phase I and Phase II RCT, respectively.[28,29] ASN002 also manifests strong antitumour properties, suppressing haematological malignancies in preclinical studies.[56]

Pruritis is a major feature of AD and leads to a significant reduction in QoL,[57] often analogous to the discomfort experienced in chronic pain syndromes. IL-31 plays a lead role in the pruritis pathway for patients with AD.[21] Previous studies demonstrated that tofacitinib and JTE-052 may suppress IL-31.[58-60] This was supported by the rapid and significant reduction in pruritis observed during the Nakagawa et al.[26,27] Phase I/II trials.

JAKi are also involved in pathways that are important for immunity. This has led to concerns regarding the effects of JAKi in immune and haematopoietic development.[61] The JAKi that the authors reviewed exhibited a low incidence of AE, most of which were mild in severity. There was no clear dose-related association to AE; additionally, incidence and severity of AE were not attributed to particular JAKi or formulations (oral versus topical). Of note, one study showed higher rates of AE in vehicle groups when compared to JAKi groups.[29] Most AE were infectious in nature (nasopharyngitis, bronchitis, furuncle, gastroenteritis, and viral upper respiratory tract infections). An event of erysipelas (outside of the application area) with 1% JTE-052 ointment[26] was deemed a drug-related AE, potentially attributable to JAK inhibition. Given short study durations and limited samples size, inferences regarding the long-term safety of JAKi cannot be presently established. One of the limitations of this review was therefore the inability to conduct a meta-analysis because of the shortage of RCT and the small sample sets in the studies. The exposure histories were not thoroughly investigated between study groups in each trial; however, the efficacy and safety of tofacitinib is evident in other inflammatory diseases such as RA[62,63] and ulcerative colitis.[64] Murine models are at risk of latent tuberculosis reactivation[61] with cases reported in trials of tofacitinib in RA patients.[66] Therefore, the efficacy of JAKi should be weighed against black box warnings such as serious infections and malignancies. In RA trials, tofacitinib treatment was associated with dose-dependent decreases in mean neutrophil counts and haemoglobin, with normalisation of blood counts during the treatment period without intervention.[67] In psoriasis, alterations in blood lipid profiles were also seen in some patients using tofacitinib.[68,69] Although the short-term safety profiles of tofacitinib and other JAKi reported in this review were acceptable, data should be interpreted with caution, especially if extrapolating to long-term treatment regimens.

CONCLUSION

JAKi remain a promising new therapeutic modality for patients with AD. Traditional topical agents, such as corticosteroids and calcineurin inhibitors, have historically poor adherence and a higher incidence of application site reactions. Given their established efficacy, low rate of AE, and rapid relief of pruritis, continued investigations into topical JAKi for the treatment of AD should be thoroughly undertaken. Although only two studies in this review examined the efficacy and safety of oral JAKi, the convenience and potential improved adherence of oral agents make them a realistic alternative in the treatment of AD. However, continued explorations into the efficacy and long-term safety of JAKi should be addressed by means of more extensive Phase III/IV clinical trials.

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Near Circumferential Invasive Proliferative Gelatinous Mass in the Calf: An Unusual Presentation of Hidradenitis Suppurativa

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Abstract

Hidradenitis suppurativa, or acne inversa, is a chronic, recurrent inflammatory disease of the skin and subcutaneous tissue, and is characterised by painful, recurrent nodules that results in abscesses and formation of chronic draining sinus tracts and scarring. It has been traditionally described as a disease of the apocrine gland. Present evidence, however, suggests it is a disease of the follicular epithelium and the pathogenesis is complex and multifactorial, implicating genetics, microbiome, physiological, and environmental factors. Recently, several cases of apparent hidradenitis suppurativa have been reported in the literature in areas of the body that defy Dessau's typical topographic criteria. Herein, the authors described an unusual case of a 69-year-old female who presented with hidradenitis suppurativa in her calf post-thermal injury. This case will add to the sparse literature on hidradenitis suppurativa in apocrine-devoid sites and lends credence to the argument that the pathogenesis of hidradenitis suppurativa is multifactorial and complex in nature.

INTRODUCTION

Hidradenitis suppurativa, or acne inversa, is a chronic, recurrent inflammatory disease of the skin and subcutaneous tissue characterised by painful, recurrent nodules that results in abscesses, scarring, and the formation of chronic draining sinus tracts. It was historically described as a disease of the apocrine gland affecting the intertriginous skin of the axillary, inguinal, inframammary, and anogenital region. Present evidence, however, suggests that it is a disease of the follicular epithelium and the pathogenesis is complex and multifactorial, implicating genetic, microbiome, physiological, and environmental factors. Hidradenitis suppurativa is currently diagnosed using the modified Dessau definition that was adopted by the 2nd International Conference on Hidradenitis Suppurativa in San Francisco, California, USA.[1] It comprises three criteria:

1. Typical lesions: deep-seated painful nodules or blind boils in early stages that may develop into abscesses with draining sinuses, bridging scars, and 'tombstone' double-ended pseudo-comedones as disease progresses.

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2. Typical topography: axillae, groins, perineal and perianal region, buttocks, and infra and intermammary folds.

3. Chronicity and recurrences.

All three criteria must be met for establishing the diagnosis, as such the diagnosis of hidradenitis suppurativa is made predominantly on the basis of its typical clinical presentation and there is no pathognomonic test, it still remains a diagnostic challenge for physicians with a reported mean delay to reach diagnosis of 7 years.[2] In recent years, several cases of apparent hidradenitis suppurativa have been reported in the literature in areas of the body that defy Dessau's typical topographic criteria suggesting that rarer variants may exist outside of diagnostic criteria. Presented herein is a report on a case of a 69-year-old female who presented with hidradenitis suppurativa-like lesions in the lower extremity many months post-thermal insult, on a background of limb swelling from chronic venous insufficiency.

CASE REPORT

The patient is a 69-year-old Indian female with no past medical history of note who had previously received treatment elsewhere after scalding her left calf. Her recovery was complicated by recurrent skin and soft tissue infections, requiring 2 months of antibiotic therapy. She was subsequently referred 8 months post-injury to the authors' service for calf swelling and a presumed chronic venous insufficiency ulcer. The ulcer was 2x3 cm in size, located over the distal third of the left medial calf, moderately deep and sloughy, and had been present since the initial insult. Her ipsilateral dorsalis pedis and posterior tibial pulses were strong, and toe pressures were excellent at 124 mmHg on the right and 133 mmHg on the left. Venous duplex confirmed venous insufficiency of the left long saphenous vein. She was initially scheduled for elective VenaSeal™ (Medtronic plc, Minnesota, USA) ablation of her long saphenous vein and wound debridement but returned to the emergency department after a vein in the ulcer edge ruptured with copious bleeding requiring oversewing and admission for more expedient surgery.

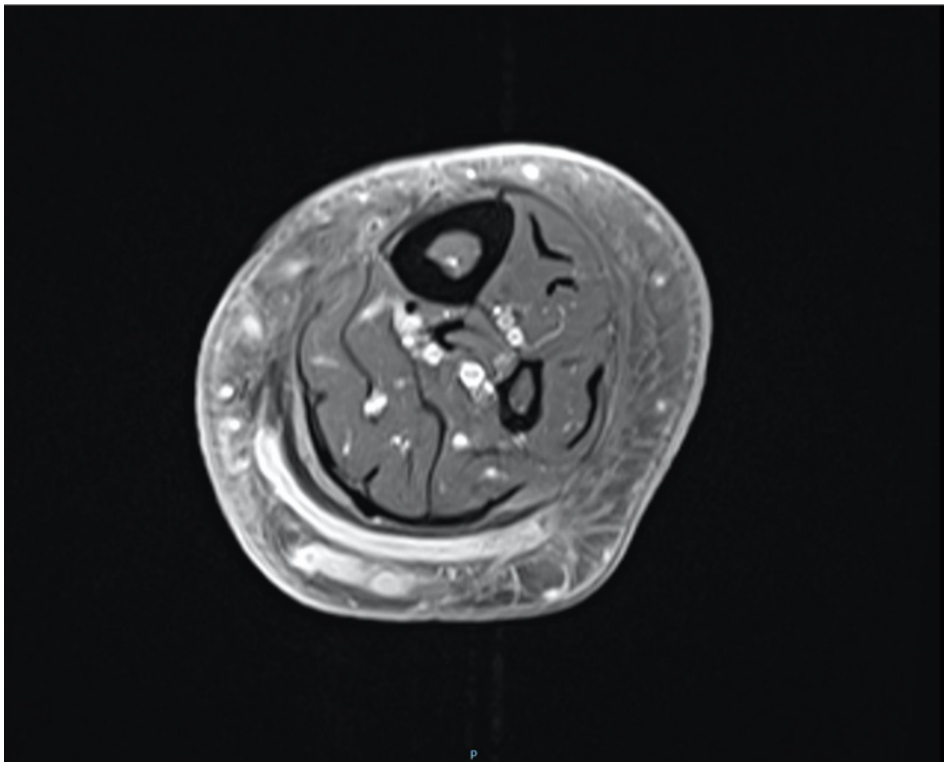

Figure 1: Axial T1-weighted MR image showing a sinus tract that crosses the midline to the lateral aspect of the left calf.

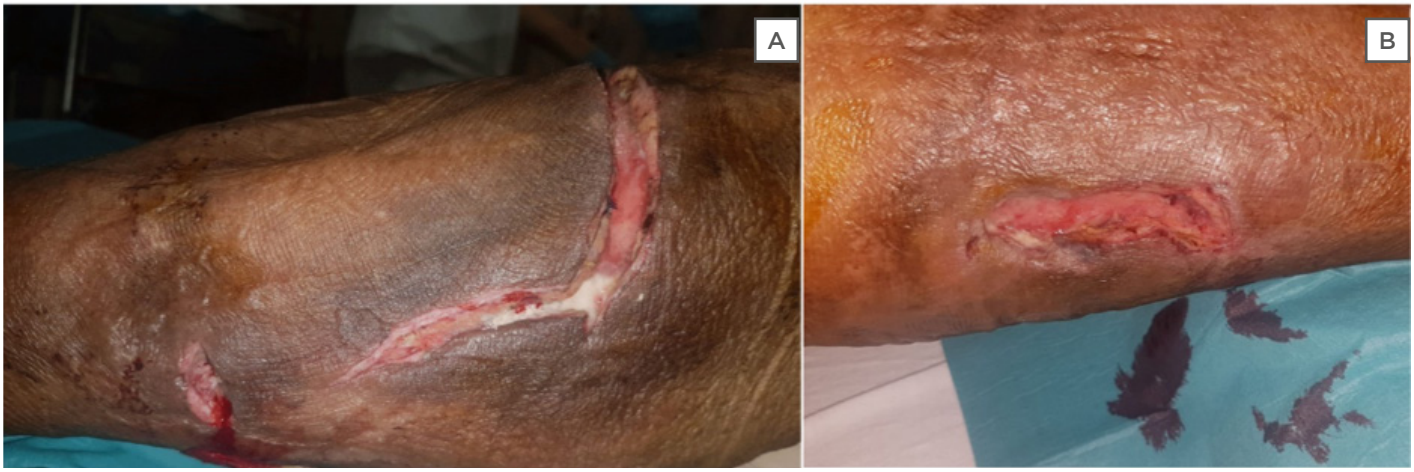

Figure 2: A) lateral calf wound in continuity with B) the medial calf wound via a posterior tract ascending superiorly up the calf towards the knee and then transversely across the shin where it had ruptured superficially.

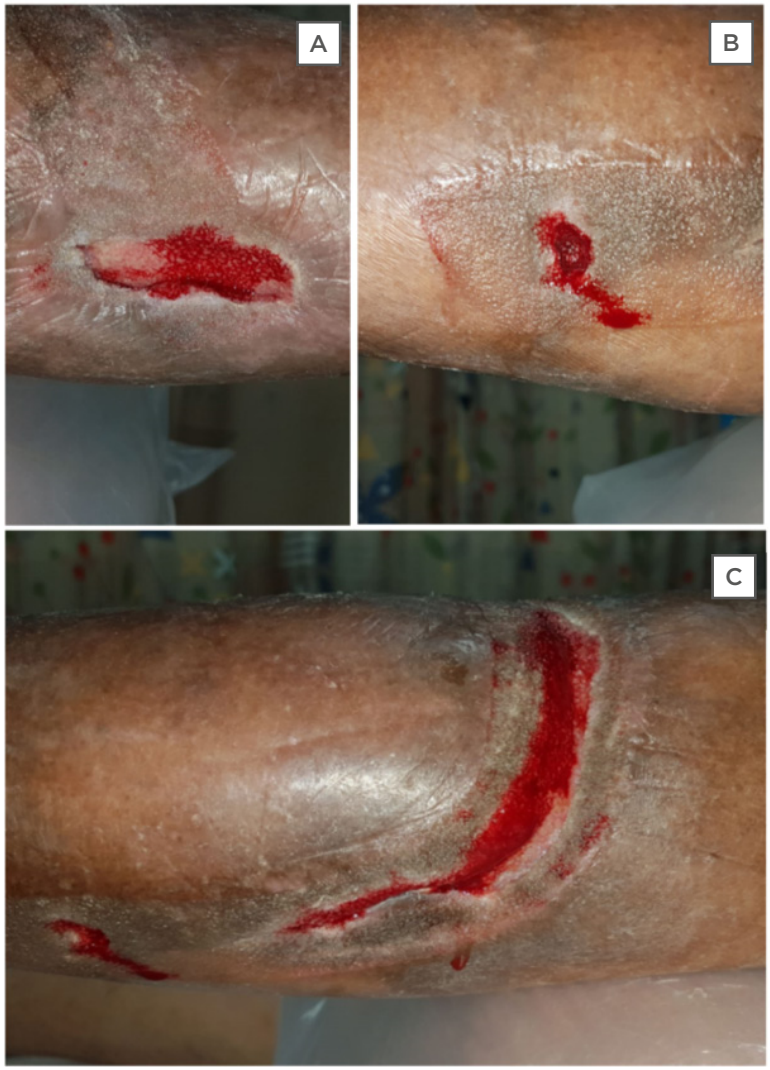

Figure 3: A) medial shin wound; B) lower lateral shin wound; C) and ascending calf wound across the shin, granulated nearly flush with sealing of the posterior tunnel.

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During debridement, the ulcer was noted to be unusually deep, nearly 2 cm, for its size (2x1 cm). She was discharged with daily povidone-iodine gauze packing of the wound. Follow-up duplex ultrasound confirmed complete ablation of the long saphenous vein.

The ulcer remained static over the following month; furthermore, at follow-up she had developed a bullous lesion high on the proximal contralateral aspect of her calf which ruptured and discharged clear fluid when expressed. This was deroofed in clinic revealing an underlying 2.5 cm diameter superficial cavity tunnelling caudally for some 15.0 cm. An MRI was performed to exclude osteomyelitis, which revealed an unusual horseshoe-shaped tract within the subcutaneous fat starting at the superolateral wound above, tunnelling caudally then making a turn to tunnel transversely across the posterior calf to the medial aspect of the calf, then ascending superiorly to exit at the original wound. There was no evidence of osteomyelitis (Figure 1). She underwent formal operative deroofing and debridement of the entire tract. Intraoperatively, a long, 1.5cm deep, subcutaneous tract that was approximately 0.7–0.8 cm wide was found connecting both wounds in continuity (Figure 2), which filled with pink amorphous gelatinous tissue highly reminiscent of the invasive proliferative gelatinous mass (IPGM) found in hidradenitis suppurativa wounds.

Aerobic tissue culture grew group B beta-haemolytic strep (*Streptococcus agalactiae*) and *Staphylococcus aureus*. Acid-fast bacilli smear was negative. Histopathology of the tissue reported ulceration with granulation tissue formation, mixed inflammatory infiltrates, and reactive nuclear changes with hyperkeratosis of the epithelium, in keeping with previous descriptions of hidradenitis suppurativa.[3] There was no evidence of dysplasia or invasive malignancy. The wounds were treated with Vacuum Assisted Closure® (VAC) therapy in combination with Grade 2 graduated compression stockings. A month later, the wounds had granulated flesh and VAC therapy had been ceased (Figure 3).

DISCUSSION

Hidradenitis suppurativa was historically assumed to be attributable to entrapment of secretions from apocrine glands with secondary bacterial infection and the intertriginous areas are commonly affected. It is postulated that these sites predispose to friction, shearing forces, and pressure or other physical irritation from clothing and undergarments.[4] In recent decades, contemporary opinion has shifted and it is now believed that hidradenitis suppurativa is caused by inflammatory obstruction of the follicular portion of the folliculopilosebaceous unit (FPSU) in patients with a predisposition to rupture of the FPSU.[5,6] To date, only three cases of hidradenitis suppurativa of the lower extremity have been reported in the literature, making this an unusual presentation in a site devoid of apocrine glands.[3,4,7] One of the cases described was hidradenitis suppurativa of a lower limb amputation stump, which the authors postulated was attributable to recurrent mechanical friction against the ambulatory prosthesis resulting in follicular trauma and secondary bacterial infection.[7] None of the previous cases detailed scalding as the precipitant. In the authors' opinion, the initial thermal injury directly damaged the FPSU at the site of contact of her medial calf causing follicular occlusion which in turn triggered the chronic inflammatory process leading to the spreading IPGM-filled sinus tract across her posterior calf and ascending up the contralateral side of her calf where it subsequently ruptured through the relatively thin skin of her shin. This hypothesis is consistent with the three-stage sequence of events in the pathogenesis of hidradenitis suppurativa proposed by Vossen et al.,[8] who suggested that the initial event is triggered by follicular occlusion and dilation, which is driven by endogenous and exogenous factors. This is followed by rupture of the dilated follicle, triggering a cascade of inflammatory pathways. The third event is chronic inflammation with development of sinus tract resulting from the presence of epithelial strands, imbalance between matrix metalloproteinases and tissue inhibitors of metalloproteinase, and elevated activity of tissue growth factor.[8]

CONCLUSION

This case adds to the sparse literature of hidradenitis suppurativa in apocrine-devoid sites and lends credence to the argument that the pathogenesis of hidradenitis suppurativa is multifactorial and complex in nature. In

this current case, the lesion was successfully treated using VAC therapy in conjunction with therapies, VenaSeal, and graduated compression stockings, to manage tissue swelling from chronic venous insufficiency.

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Serum Sickness-Like Reaction in Children: Review of the Literature

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Abstract

Serum sickness-like reaction (SSLR) is an acute inflammatory condition affecting children and adults characterised by the development of erythematous skin lesions and joint swelling with or without fever. Although these features resemble the ones seen in patients with classic serum sickness, the precise pathophysiology of SSLR remains unclear. It is considered that drugs, usually β-lactam antibiotics, and some infectious agents can trigger an immunologic reaction that leads to these clinical manifestations. This condition is usually under-recognised or mistakenly diagnosed as other conditions (e.g., urticaria, urticaria multiforme, reactive arthritis, erythema multiforme) and therefore infrequently reported. Until now, there was no standardised treatment for this condition and controversy regarding the use of antihistamines, nonsteroidal anti-inflammatory drugs, and oral corticosteroids remains. Most of the current literature on SSLR is based on occasional case reports series. The main objective of this manuscript is to offer an organised and updated review of the clinical features and current treatment options for paediatric SSLR, useful for physicians and other health professionals with interest in paediatrics and adverse drug reactions.

DEFINITION AND AETIOLOGY

Serum sickness-like reaction (SSLR) is an immunological condition characterised by skin rash and arthralgia, with or without fever. It can present in both adult and paediatric populations, although it is seen more often in children. Unlike classic serum sickness (SS), which also presents with similar clinical characteristics, SSLR is mainly triggered by drugs, mostly β-lactam antibiotics; however, vaccines and infectious agents have also been implicated in SSLR development.[1]

Classical SS was originally described at the beginning of the 20th century in patients who had received heterologous serum as antitoxins to treat diphtheria.[2,3] Later, this condition was classified as a Type III immune hypersensitivity reaction, which is mediated by antigen-antibody complex formation. The accumulation of these complexes on small blood vessels from different tissues leads to complement activation and cytokine release, resulting in severe inflammation.[4] Although the precise pathophysiology has not yet been elucidated, the mechanism by which drugs or other agents trigger SSLR appears to

be different from the classic SS, because SSLR is not associated with antigen-antibody complex formation and the blood levels of complement are usually normal.[5] Some theories consider the possibility that drugs, or their metabolites, may act similarly to haptens that bind plasma proteins and subsequently induce an abnormal immunologic response.[6,7] Other studies have suggested that drug metabolites by themselves have a direct toxic effect on the lymphocyte affected patients.[8,9] More recently, Zhang et al.[10] reported that in children, antibiotics such as cefaclor may increase the intestinal mucosal permeability by damaging its integrity, which leads to the passing of antigens to the blood circulation favouring the development of SSLR. Likewise, other studies have demonstrated that the biotransformation of the parent drug in patients that develop SSLR induced by antibiotics, such as cefaclor, may be secondary to an inherited defect in the metabolism of reactive intermediates.[8]

Since its original description at the end of the last century, SSLR has been associated mostly with the use of antibiotics.[11] Among these, β-lactams are the most commonly reported triggers, with one of the first drugs associated with SSLR in children being cefaclor.[3,12] However, a great variety of other drugs have been reported to trigger SSLR: sulfonamide drugs, anticancer agents, anticonvulsants, anti-inflammatory agents, griseofulvin, metronidazole, bupropion, and more recently, biological agents such as rituximab, infliximab, and efalizumab, among others.[13-16] Initial studies estimated that the incidence of SSLR in children caused by cefaclor was an estimated 0.4–0.5% of all antibiotic courses.[12] Subsequent studies reported that SSLR represents 4.0% of all adverse drug reactions associated with amoxicillin.[2] Other authors have reported that the risk of developing SSLR cefaclor is higher than amoxicillin.[17] Overall, data regarding cross-reactivity among β-lactam antibiotics in children with SSLR are scarce, although it is considered that patients with SSLR attributable to cefaclor usually do not have to avoid other cephalosporins or penicillin because this reaction appears to be more compound-specific than class-specific.[9]

To the authors' knowledge, there is no estimated incidence for SSLR caused by infections; although, infectious agents have also been reported as potential triggers of SSLR. To date, there is no literature available regarding studies that evaluate their role on its pathogenesis. In the past, vaccines were also associated with the development of SSLR; however, the current literature in paediatric patients is outdated and limited. A 1987 report by Milstien et al.[18] described ten cases of paediatric patients that developed SSLR after exposure to *Haemophilus influenzae* Type B vaccination; nevertheless, the criteria used to diagnose SSLR are questionable as many of them did not consider joint involvement or associated skin rash.[19] No further cases of SSLR associated to vaccines have been reported in children, but a a small number of case reports and series in adult populations have suggested an association between H1N1 influenza vaccination and SSLR.[20,21]

Currently, paediatric SSLR is considered an uncommon adverse drug reaction; however, its precise prevalence is unknown. This is mostly because of the lack of knowledge of some health professionals regarding this condition and its clinical presentation; therefore, SSLR is usually unrecognised or easily mistaken by other cutaneous entities such as urticaria, urticaria multiforme, erythema multiforme, infectious rashes, or other drug reactions.

CLINICAL FEATURES

Initial reports of patients with SSLR described presentation of skin rash associated with joint inflammation or arthralgia with or without a fever.[22,23] The morphology of the skin rashes reported in the literature varies widely including morbilliform rash, urticarial and annular plaques with central clearing, or erythema multiforme-like lesions (erythematous annular converging plaques with purplish/dusky centre) (Figure 1A). It is also reported that, unlike acute urticaria, skin lesions in SSLR are not migratory, but are fixed. Once skin lesions develop, they stay in the same area until they resolve, and occasionally leave a bruise-like postinflammatory hyperpigmentation behind that may last for several days.[6,24] The skin lesions usually start as small erythematous papules or plaques on the trunk and then enlarge and progressively spread to the rest of the body. With regard to facial impact, periorbital or lip swelling may present resembling angioedema; however, these patients do not develop tongue swelling or respiratory compromise as seen in other allergic reactions.

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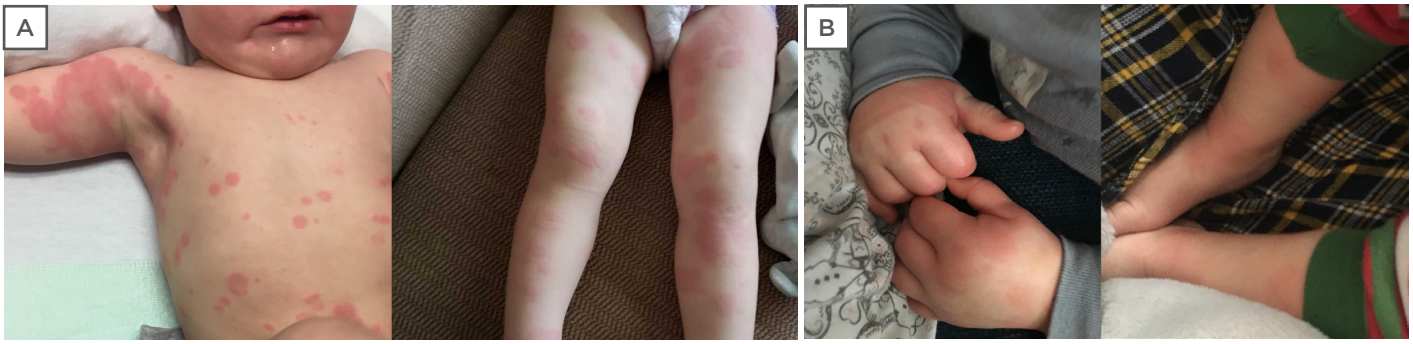

Figure 1.

A) Erythematous papules and annular lesions, some of them with a polycyclic arrangement, central clearing and purplish discolouration.

B) Painful inflammation of hands and feet (notice erythema and oedema overlaying the joints.

Unlike classical urticaria, itchiness in SSLR is mild or nonexistent; however, skin soreness or burning sensation may present instead. Given the common presence of knowledge gaps in dermatology, other health professionals often misdiagnose SSLR with erythema multiforme because skin lesions in SSLR may present with a violaceous centre that simulate target lesions. Unlike erythema multiforme, SSLR lesions do not have three rings (typical target lesion), do not blister, and have no involvement of mucous membranes.[3]

Alongside skin rash, the presence of joint involvement, characterised by joint swelling and arthralgia, is also necessary to make the diagnosis of SSLR. Joints are usually affected bilaterally but may present on only one side. Joints in the hands and feet are the most commonly involved, followed by knees, and then elbows. Purple discolouration and oedema may also be seen on the skin overlaying the joints[5] (Figure 1B). Although oedema of the hands and feet (without arthralgia) could also present in other conditions such as urticaria multiforme and urticaria, joint inflammation in children with SSLR lasts for several days and the associated pain is disabling: parents usually report that children with SSLR avoid walking or move abnormally.[9,23]

Unlike classic SS, fever in children with SSLR may not be present. Concomitant fever ranges from 30% to 75% in these patients.[6,23,25] Likewise, paediatric SSLR seldom presents with lymphadenopathy or systemic involvement; however, malaise and irritability lasting several days or weeks even after the rash has resolved has been reported.[26]

The development of skin rash and arthralgia in children with SSLR can present several days after exposure of the trigger, ranging from a couple of days up to several weeks. In the case of SSLR induced by antibiotics, the clinical features typically appear after the course has been completed (approximately 7–10 days).[7,23] There are several studies that have confirmed up to 80% of paediatric patients with SSLR exposed to the same drug at least once show no previous reaction. There are no studies which have established the recurrence rate for SSLR in these patients; although, evidence has suggested those who had experienced an event of SSLR and were then re-exposed to the same medication presented with early and more severe symptoms than the previous reaction.[3,9,17] As it stands, there is a need for more robustly conducted studies to determine the risk of recurrence in these patients.

Finally, formal diagnostic criteria and scales for the severity of SSLR in children are lacking. Thus, a formal evidence-based consensus is needed in addition to well-controlled prospective studies to develop these. A summary of a series of cases of paediatric SSLR are shown in Table 1.

Table 1: Summary of series of cases of paediatric serum sickness-like reaction.

Author/year of publication	Main trigger drug	Number of cases M/F	Age	Time to onset	Reaction duration	Skin rash morphology	Main joints affected	Fever	Treatment	Main laboratory abnormalities
Kunnamo/1986[22]	Penicillin (60.0%)	15 9/6	3.1–13.6 years Median: 6.4 years	3–33 days Mean: 12.8 days	5.9 days***	Urticarial like, erythema multiforme like	Ankles, metacarpophalangeal	33.3%	N/A	Elevated ESR (40.0%), leukocytosis (20.0%) +CIC (80.0%)†
Heckbert/1990[17]	Antibiotics Cefaclor (41.0%)	12	<6.0 years	7–11 days	A few days–4.0 weeks***	Urticarial rash, erythema multiforme like, angioedema	N/A	N/A	N/A	N/A
Kearns/1998[9]	Cefaclor	10	1.3–4.8 years Median: 1.6 years	3–5 days Median: 6.3 days	Median: 14.0 days	Urticarial, erythema multiforme like	Wrists, ankles, knees	100.0%	N/A	N/A
King/2003[3]	Cefaclor (84.1%)	32** 20/10	5.0–11.0 years Median: 2.6 years	1–13 days Median: 6 days	1.0–120.0 days Median: 5.0 days	Urticarial like, erythema multiforme like	N/A	N/A	Combinations of steroids and antihistamines	N/A
Patel/2009[24]	Amoxicillin (76.0%)	19	6.0–24.0 months††	7–13 days†††	7.0–13.0 days	Urticarial, purplish annular plaques	N/A	77.0%	Antihistamines/NSAID, corticosteroids (59.0%)	N/A
Shiari/2011[7]	Antibiotics Furazolidone (18.0%) Cefexime (14.0%)	28 11/17	15.0 months–9.0 years Mean: 3.5 years	1–3 weeks	1.0–5.0 days* Median: 3.0 days	Urticarial like, erythema multiforme like, angioedema	N/A	75.0%	Conservative treatment (80.0%), corticosteroids (20.0%)	Leukocytosis (46.0%); thrombocytosis (11.0%); ESR elevation (76.0%); low C3, C4, CH50 (80.0%)
Yorulmaz/2018[6]	Antibiotics (62.0%)	29 15/14	8.3±4.4 years	8–14 days	5.14±3.20 days*	Urticarial like, erythema multiforme like	Elbows, knees, wrists	34.5%	Systemic corticosteroids (methylprednisolone)	Leukocytosis (34.4%), elevated ESR (58.6%)

CIC: circulating immune complexes; ESR: erythrocyte sedimentation rate; M/F: male/female; NSAID: non-steroidal anti-inflammatory drug; N/A: data not available.

*Duration of hospital stay. ** In this study 44 patients were diagnosed with serum sickness-like reaction, but the data only refers to 32 patients with serum sickness-like reaction induced by cefaclor. *** Duration of joint symptoms.
† positive CIC. †† 59% of patients were in this range of age. ††† 53% of patients were in this range of days.

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INVESTIGATIONS

Currently, the diagnosis of SSLR is primarily based on history and clinical features because the laboratory profile is usually nonspecific and in some cases seems contradictory. Shiari et al.[7] reported a series of cases of 29 children with SSLR, of whom 46.0% showed leukocytosis on the complete blood test, 76.0% had high erythrocyte sedimentation rate, and 83.3% (20/24) had low levels of complement (C3, C4, and CH50); however, in other cases, levels of complement have been reported as normal or slightly elevated. A previous study performed in children with arthritis attributable to SSLR showed the presence of circulating immune complexes; however, no other study has replicated the findings.[23] More recently, Yorulmaz et al.[6] reported that, in addition to leukocytosis and elevated erythrocyte sedimentation rate, some patients presented with mild proteinuria or haematuria. Other studies also reported abnormal liver function tests and elevated creatinine.[2] Skin testing and radioallergosorbent test were usually negative because SSLR does not appear to be an IgE-mediated reaction. Other *in vitro* tests, such as the lymphocyte toxicity assay, were used to evaluate the toxic effect of specific drugs on T cells from patients with adverse drug reactions, including SSLR. This test is not currently validated for the diagnosis of SSLR because the lack of a gold standard test means its predictive value remains difficult to define. Several studies, however, have demonstrated that T cells from SSLR patients have a higher sensitivity to specific medications compared to T cells from healthy controls.[9,27]

Skin biopsies are rare in children with SSLR because of their invasive nature; however, sometimes the histological features could help rule out other pathologies that share clinical features similar to SSLR. Some of these differential diagnoses include rheumatic fever, urticarial vasculitis, systemic lupus erythematosus, drug-induced lupus, Still's disease, and Henoch-Schönlein purpura, among others.[2,24] Histopathology is characterised by perivascular and mid-dermal inflammatory infiltrate with admixed neutrophils, eosinophils, and lymphocytes, usually without leukocytoclastic vasculitis.[16,28]

PROGNOSIS AND TREATMENT

Although SSLR is usually a self-limiting condition with no sequelae, complete resolution of the symptoms can take several days and even weeks. Additional to the immediate withdrawal of the causal drug when this is the case, medical treatment may be necessary. The latter focusses on the elimination and/or improvement of the symptoms and reduction of the disease course. Antihistamines and nonsteroidal anti-inflammatory drugs are used to control joint pain and itchiness. When symptoms are more severe and prolonged, the use of a short course of oral corticosteroids such as prednisone (0.5–1.0 mg/kg/d for 3–5 days) or intravenous methylprednisolone (10.0 mg/kg/d for 3 days) is recommended.[1,6] Until now, there are no current guidelines for medical treatment of children with SSLR because there are no studies evaluating the effectiveness and safety of these therapies, so dosage and length of treatment are usually based on the severity of the symptoms and the experience of the healthcare professionals.[5] The prognosis of children with SSLR is typically favourable because they have a mean recovery time of 5–7 days with no evidence of sequalae, even if they do not receive any treatment. Moreover, as previously stated, the rate of recurrence in children with SSLR is unknown but suspected to be high; therefore, avoidance of the trigger drug is highly recommended to prevent severe recurrences. Additionally, classical desensitisation does not appear to have a role in patients with SSLR because protocols for desensitisation were designed to treat Type 1 (IgE-mediated) mast cell reactions. There is no current evidence supporting this management in non-IgE-mediated and non-immune-mediated processes.[29]

CONCLUSION

SSLR in children is an immune reaction characterised by the development of skin rash and arthralgia with or without fever, and it is mainly associated with antibiotics from the β-lactam class. Skin lesions are characterised by fixed erythematous and oedematous patches/plaques and annular lesions with central clearing and/or purplish discolouration. Joint inflammation more frequently affects wrists and

ankles bilaterally (hands and feet), but other joints can also be affected. Symptoms of SSLR usually develop several days after exposure to the trigger drug. Patients may have been exposed to the same drug previously without any complications. Although the prognosis of patients with SSLR is usually good, in some patients, the resolution of the symptoms may take several weeks. Laboratory studies are usually nonspecific; however, they may be useful to rule out other conditions. Treatment with antihistamines, nonsteroidal anti-inflammatory drugs, and/or systemic corticosteroids may reduce the recovery time and improve the symptoms but the use of these medications remains controversial and avoidance of the trigger drug is recommended. Further prospective and well-organised studies are needed to create more accurate diagnostic criteria which will help clinicians to better recognise the condition and establish a safe and effective treatment to reduce the morbidity associated with SSLR in children.

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IL-23 Inhibitors for Moderate-to-Severe Plaque Psoriasis: A Review of Clinical Efficacy, Safety, and Tolerability

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Abstract

Psoriasis is a chronic, immune-mediated skin condition with systemic involvement, frequently requiring long-term treatment. At present, there are 11 biologic agents available for the treatment of moderate-to-severe psoriasis, which target specific inflammatory cytokines involved in the immunopathogenesis of the disease. Among these, three monoclonal antibodies specifically inhibit the p19 subunit of IL-23. IL-23 is a heterodimeric cytokine consisting of two subunits: IL-23p19 and IL-23p40. IL-23 plays a key role in the immunopathogenesis of psoriasis by activating Th17 cells, leading to stimulation of downstream cytokines involved in the systemic inflammation and keratinocyte hyperproliferation observed in psoriasis. Overall, the anti-IL-23 agents demonstrate rapid clinical improvement along with a favourable safety profile. This review has analysed data on the clinical efficacy, safety, and tolerability of the three IL-23 agents (tildrakizumab, guselkumab, and risankizumab) in the treatment of moderate-to-severe plaque psoriasis.

INTRODUCTION

Psoriasis is a common, chronic, immune-mediated skin disease affecting approximately 2–3% of the global population.[1,2] Characteristic signs and symptoms of psoriasis include well-demarcated erythematous plaques with silvery scales, and significant pruritus and discomfort, which often impacts psychosocial function and reduces quality of life amongst patients.

Table 1: Pivotal Phase III trials for guselkumab.

Trial	N	Study arms	Primary outcomes	Secondary outcomes
Guselkumab Phase III (VOYAGE 1)[3]	837	Placebo (placebo at Weeks 0, 4, 12, and guselkumab 100 mg at Weeks 16, 20, and every 8 weeks thereafter) Guselkumab (guselkumab 100 mg at Weeks 0, 4, and 12, and every 8 weeks thereafter) Adalimumab (adalimumab 80 mg at Week 0, 40 mg at Week 1, and every 2 weeks thereafter)	(Week 16) guselkumab versus placebo PASI 90: 73.3 versus 2.9% IGA 0/1: 85.1 versus 6.9%	(Weeks 16, 24, 48) guselkumab versus adalimumab IGA 0 (Week 24; 48): 52.6 versus 29.3%; 50.5 versus 25.7% IGA 0/1 (Week 16; 24; 48): 85.1 versus 65.9%; 84.2 versus 61.7%; 80.5 versus 55.4% PASI 100 (Week 16; 24; 48): 37.4 versus 17.1%; 44.4 versus 24.9%; 47.4 versus 23.4% PASI 90 (Week 16; 24; 48): 73.3 versus 49.7%; 80.2 versus 53%; 76.3 versus 47.9% PASI 75 (Week 16): 91.2 versus 73.1%
Guselkumab Phase III (VOYAGE 2)[4]	992	Placebo (placebo at Weeks 0, 4, 12, and guselkumab at Weeks 16, 20, and every 8 weeks thereafter) Guselkumab (guselkumab 100 mg at Weeks 0, 4, 12, 20, and every 8 weeks thereafter) Adalimumab (adalimumab 80 mg at Week 0, 40 mg at Week 1, and every 2 weeks thereafter)	(Week 16) guselkumab versus placebo PASI 90: 70.0 versus 2.4% IGA 0/1: 84.1 versus 8.5%	(Weeks 16, 24, 48) guselkumab versus adalimumab IGA 0 (Week 24): 51.8 versus 31.5% IGA 0/1 (Week 16; 24): 84.1 versus 67.7%; 83.5 versus 64.9% PASI 90 (Week 16; 24): 70.0 versus 46.8%; 75.2 versus 54.8% PASI 75 (Week 16): 86.3 versus 68.5%
Guselkumab Phase III (NAVIGATE)[5]	268	Guselkumab (guselkumab 100 mg at Weeks 16, 20, and every 8 weeks thereafter) Ustekinumab (ustekinumab 45 mg ≤100 kg or 90 mg ≥100 kg body weight, at Week 16 and every 12 weeks thereafter)	(Weeks 28–40) guselkumab versus ustekinumab: mean number of visits to IGA 0/1 and ≥2 grade improvement from Week 16 (among patients with inadequate response to ustekinumab): 1.5 versus 0.7	(Week 28) guselkumab versus ustekinumab: IGA 0/1 and ≥2 grade improvement: 31.1 versus 14.3% PASI 90: 48.1 versus 22.6% (Weeks 28–40) mean number of visits to PASI 90: 2.2 versus 1.1

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Standardised scoring systems used to evaluate these signs and symptoms of psoriasis can be found in Table 1. Comorbid conditions linked to psoriasis include cardiovascular disease, metabolic syndrome, psychosocial disorders, and psoriatic arthritis.[6-8]

The role of T lymphocytes in psoriatic disease has long been acknowledged. More recently, Th17 cells and the associated IL-23/IL-17 pathway have emerged as central to the immunopathogenesis of psoriasis. IL-23 is a heterodimeric cytokine consisting of two subunits: IL-23p19 and IL-23p40. IL-23 is produced by dendritic cells and keratinocytes, among others, causing the proliferation and survival of Th17 cells, as well as the production of IL-17A and IL-22, which are key drivers of the keratinocyte proliferation central to psoriasis.[9,10] Clinical trials for psoriasis treatments have successfully used monoclonal antibodies against IL-17 and IL-23, supporting the current evidence of these cytokines as key drivers of psoriasis.

Three IL-17 antagonists, secukinumab, ixekizumab, and brodalumab have been approved for the treatment of psoriasis, with additional IL-17 inhibitors under development. In addition, ustekinumab is a combined IL-12 and IL-23 blocker approved for the treatment of moderate-to-severe plaque psoriasis (MTSPP), psoriatic arthritis, and Crohn's disease. Ustekinumab binds to the p40 subunit common to IL-12 and IL-23, preventing its interaction with the IL-12 receptor β1 subunit present on IL-12 and IL-23 receptor complexes.[11]

Most recently, increasingly specific therapeutic agents targeted to the p19 subunit of IL-23 to inhibit the release of proinflammatory cytokines have been developed and approved. As a result of their specificity, favourable safety profiles and efficacies have been observed. Three p19 IL-23 inhibitors are approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). This report focusses specifically on these inhibitors, summarising the results of Phase III clinical trials for guselkumab, tildrakizumab, and risankizumab (Table 2). Their clinical efficacy, safety, and tolerability in the treatment of MTSPP will be reviewed.

GUSELKUMAB

Guselkumab is a fully human immunoglobulin G1 (IgG1)λ monoclonal antibody that selectively binds to the p19 subunit of IL-23. Guselkumab decreases levels of IL-17A in both the serum and skin lesions of psoriasis patients.[13] By targeting the p19 subunit, guselkumab is able to specifically inhibit IL-23, in contrast to ustekinumab which targets both IL-12 and IL-23 via binding to the shared p40 subunit. As a result, guselkumab leaves the IL-12/Th1 axis undisturbed, leaving an important regulator of immune function intact.[14] Guselkumab was first approved by the FDA in July 2017 and the EMA in November 2017, making it the first in the IL-23 class to be approved in adults with MTSPP in the USA and Europe.

Dosage

The recommended dosage of guselkumab for adult patients with MTSPP is 100 mg by subcutaneous injection at Weeks 0 and 4, and every 8 weeks thereafter.

Clinical Efficacy

Several clinical trials have assessed the clinical efficacy and safety of guselkumab. VOYAGE 1 and VOYAGE 2 were randomised, double-blind, pivotal Phase III clinical trials performed with guselkumab, placebo, and a comparator, adalimumab (a TNF-α inhibitor) for the treatment of MTSPP.[3,4] Both were 48-week studies, comparing guselkumab to placebo and adalimumab. Patients were randomised at baseline to receive either a placebo at Weeks 0, 4, and 12, followed by guselkumab 100 mg at Weeks 1 and 20, and then every 8 weeks; guselkumab 100 mg at Weeks 0, 4, and every 8 weeks thereafter; or adalimumab 80 mg at Week 0, adalimumab 40 mg at Week 1 and adalimumab 40 mg every 2 weeks thereafter.[15] Additionally, VOYAGE 2 investigated the maintenance of efficacy of guselkumab after withdrawal.

Guselkumab was significantly superior to placebo and to adalimumab in both VOYAGE trials at 16 weeks for its 2 primary outcomes: the Investigator's Global Assessment (IGA) scale of 0 or 1 (VOYAGE 1/2: 85.1/84.1% guselkumab versus 6.9/8.5% placebo) and the Psoriasis Area and Severity Index (PASI) 90 response (VOYAGE 1/2: 73.3/70.0% guselkumab versus 2.9/2.4% placebo).[3,4]

Table 2: Pivotal Phase III trials for tildrakizumab.

Trial	N	Study arms	Primary outcomes	Secondary outcomes
Tildrakizumab Phase III (reSURFACE 1)[12]	772	Placebo (placebo at Weeks 0 and 4, then rerandomised to tildrakizumab at Weeks 12 and 16) Tildrakizumab (tildrakizumab 100 mg by SCI [at Weeks 0, 4, 16, and subsequently every 12 weeks]) Tildrakizumab (tildrakizumab 200 mg by SCI [at Weeks 0, 4, 16, and subsequently every 12 weeks])	(Week 12) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo PASI 75: 64.0 versus 62.0 versus 6.0% IGA 0/1: 58.0 versus 59.0 versus 7.0%	(Week 12) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo PASI 90: 35.0 versus 35.0 versus 3.0% PASI 100: 14.0 versus 14.0 versus 1.0% (Week 28) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo → tildrakizumab 200 mg versus placebo → tildrakizumab 100 mg PASI 75: 77.0 versus 79.0 versus 78.0 versus 73.0% IGA 0/1: 63.0 versus 67.0 versus 64.0 versus 72.0% PASI 90: 49.0 versus 57.0 versus 47.0 versus 55.0% PASI 100: 22.0 versus 31.0 versus 24.0 versus 30.0%
Tildrakizumab Phase III (reSURFACE 2)[12]	1,090	Placebo (placebo at Weeks 0 and 4, then rerandomised to tildrakizumab at Weeks 12 and 16) Tildrakizumab (tildrakizumab 100 mg by SCI [at Weeks 0, 4, 16, and subsequently every 12 weeks]) Tildrakizumab (tildrakizumab 200 mg by SCI [at Weeks 0, 4, 16, and subsequently every 12 weeks]) Etanercept (etanercept 50 mg by SCI twice a week until Week 12, then weekly)	(Week 12) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo versus etanercept PASI 75: 61.0 versus 66.0 versus 6.0 versus 48.0% IGA 0/1: 55.0 versus 59.0 versus 4.0 versus 48.0%	(Week 12) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo versus etanercept PASI 90: 39.0 versus 37.0 versus 1.0 versus 21.0% PASI 100: 12.0 versus 12.0 versus 0.0 versus 5.0% (Week 28) tildrakizumab 100 mg versus tildrakizumab 200 mg versus placebo → tildrakizumab 200 mg versus placebo → tildrakizumab 100 mg versus etanercept 50 mg PASI 75: 73.0 versus 73.0 versus 69.0 versus 55.0 versus 54.0% IGA 0/1: 65.0 versus 69.0 versus 64.0 versus 48.0 versus 45.0% PASI 90: 55.0 versus 57.0 versus 46.0 versus 38.0 versus 29.0% PASI 100: 22.0 versus 26.0 versus 18.0 versus 13.0 versus 11.0%

Compared to adalimumab, guselkumab was also found to be significantly superior as measured by the proportion of patients achieving IGA 0 or 1 (VOYAGE 1/2: 85.1/84.1% guselkumab versus 65.9/67.7% adalimumab) and PASI 90 (73.3/70.0% guselkumab versus 47.9/46.8% adalimumab) at Week 16. Significantly better responses to guselkumab compared with

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adalimumab were also maintained at Week 24. At Week 48 of VOYAGE 1, the rates comparing guselkumab against adalimumab for IGA 0, IGA 0/1, and PASI 90 were 50.5% versus 25.7%, 80.5% versus 55.4%, and 76.3% versus 47.9%, respectively.[3]

Additionally, VOYAGE 2 investigated the efficacy of guselkumab after withdrawal.[4] Patients with ≥90% PASI improvement from baseline were re-randomised to a withdrawal group at Week 28. Patients received either placebo or maintenance therapy at this point.

The guselkumab withdrawal group restarted Guselkumab either upon loss of ≥50% of Week 28 PASI improvement or by Week 72. VOYAGE 2 reported superior maintenance of response from Weeks 28 to 48 in patients maintained on guselkumab compared to those who underwent withdrawal (88.6% versus 36.8%; *p*<0.001).

Additionally, in the adalimumab nonresponders who were switched to guselkumab, 66.1% achieved PASI 90 at Week 48, with 28.6% achieving PASI 100.[4] When compared to the maintenance group sustained through Week 72, the efficacy in the guselkumab withdrawal group had diminished (11.5% versus 86.0%).

After 20 weeks of retreatment, 80.4% of guselkumab withdrawal patients achieved PASI 90 responses compared to baseline.[16] Furthermore, PASI improvements correlated with improvement in anxiety (r=0.27; p<0.0001) and depression (r=0.25; p<0.0001) scores in patients with baseline Hospital Anxiety and Depression Scale (HADS) of ≥8. Greater improvements in HADS were also observed at Week 16 in guselkumab-treated versus placebo-treated patients using a stricter cut-off of 11 on the HADS.[17] In addition, considerably greater improvements from baseline were observed at Weeks 8 and 16 in the guselkumab group compared to placebo when using the Dermatology Life Quality Index (DLQI). Guselkumab showed significantly greater improvement over adalimumab at Week 24 using the DLQI (p<0.001). The proportion of patients achieving DLQI 0 or 1 (indicating no impact) at Week 24 was higher with guselkumab compared to adalimumab (58.9 versus 40.2%; p<0.001).[18]

Pooled analysis of both VOYAGE trials evaluating the effect of guselkumab on psoriasis in specific body regions revealed that guselkumab was superior to placebo in the treatment of scalp psoriasis, traditionally a region 'difficult to treat'.[19] The proportion of patients achieving a scalp specific-IGA score of 0 or 1 was 81.8% for guselkumab versus 12.4% for placebo at Week 16. When compared to adalimumab (68.5%), guselkumab was also superior (85.0%) at Week 24 (p<0.001). Furthermore, a greater percentage of the guselkumab group versus the adalimumab group achieved a scalp specific-IGA score of 0 (69.9% versus 56.3%; p<0.001). Palmoplantar psoriasis, another difficult-to-treat area, was also evaluated. The Physician's Global Assessment of the Hands and Feet (hf-PGA) score of 0 or 1 was achieved by 75.5% in the guselkumab group versus 14.2% in the placebo group at Week 16, and 80.4% in the guselkumab group versus 60.3% in the adalimumab group at Week 24. A greater percentage of the guselkumab group versus the adalimumab group achieved a hf-PGA score of 0 (75.0% versus 50.3%; p<0.001). The difference in finger-PGA score of 0 or 1 was also statistically significant between guselkumab and placebo at Week 16 (46.7% versus 15.2%; p<0.001), but was not when compared to adalimumab at Week 24 (60.0% versus 64.3%; p=0.11).

Three-year long-term efficacy data for continuous treatment with guselkumab has been reported from the Phase III VOYAGE 1 trial.[20] Clinical responses for guselkumab were maintained through Week 156 in the open-label extension. The proportions of patients who achieved PASI 75, PASI 90, PASI 100, IGA 0/1, and IGA 0 at Week 156 were 96.0%, 82.8%, 50.8%, 82.1%, and 53.1%, respectively. Psoriasis Symptoms and Signs Diary (PSSD) responses were maintained at Week 100 and Week 156 with 40.2% and 40.4% of patients reporting a PSSD score of 0 in both instances, respectively.[21]

A Japanese study with 192 patients reported similar results.[5] At Week 16, a significantly higher proportion of patients receiving guselkumab 50 mg or 100 mg versus placebo achieved IGA 0 or 1 (92.3%, 88.9%, and 7.8%, respectively) and PASI 90 (70.8%, 69.8%, and 0.0%, respectively). Patients in the guselkumab 50 mg and 100 mg groups achieved significant improvements in PASI 75 compared to placebo at Week 16 (89.2%, 84.1%, and 6.3%, respectively). Improvements were maintained through Week 52.

NAVIGATE was a Phase III randomised, double-blind trial that evaluated the efficacy and safety of guselkumab in 268 patients with MTSPP who had a previous inadequate response to ustekinumab.[22] All enrolled patients initially received ustekinumab 45 mg or 90 mg (weight-based dosing) at Weeks 0 and 4. Patients were then assessed for IGA response at Week 16. Those with a continued IGA score ≥2 at Week 16 were randomised either to continue ustekinumab (every 12 weeks) or to switch to guselkumab 100 mg (at Weeks 16, 20, and then every 8 weeks thereafter). Those with an IGA ≤1 continued to receive ustekinumab every 12 weeks. The primary endpoint, the mean number of visits at which patients achieved IGA of 0 or 1 and at least a 2-Grade improvement, was significantly greater in the guselkumab group compared to those who were maintained on ustekinumab (1.5 versus 0.7; p<0.001). Greater proportions of patients in the guselkumab group achieved IGA 0 or 1 and at least a 2-Grade improvement at Week 28 compared to ustekinumab (31.1% versus 14.3%; p=0.001) and Week 52 (36.3% versus 17.3%; p<0.001).[21] At Week 52, a significantly greater proportion of patients who transitioned to guselkumab (51.1%) achieved PASI 90 compared to those who continued on ustekinumab (24.1%).

A head-to-head comparison between guselkumab and secukinumab (ECLIPSE) randomised 1,048 psoriasis patients to 1 of 2 groups: 100 mg guselkumab at Weeks 0, 4, and every 8 weeks thereafter; or 300 mg secukinumab weekly for 5 weeks and every 4 weeks thereafter.[23] The primary endpoint of PASI 90 response showed guselkumab patient response to be superior at Week 48 (84.5% guselkumab versus 70.0% secukinumab; p<0.001). Secondary endpoints were PASI 75 and IGA 0 responses at Weeks 12 and 48. In guselkumab patients, 84.6% achieved PASI 75 at Week 48 compared to 80.2% of those taking secukinumab, showing noninferiority (p<0.001) but not superiority (p=0.062). IGA 0 at Week 48 was achieved by 62.2% of patients on guselkumab and 50.4% on secukinumab. Complete clearance (PASI 100) was reported in 58.2% of guselkumab patients compared to 48.4% of those on secukinumab at Week 48.

A study evaluating the utility of guselkumab in the treatment of generalised pustular psoriasis and erythrodermic psoriasis revealed a 77.8% and 90.9% treatment success rate in both sets of patients at Week 16, respectively.[24] Furthermore, treatment with guselkumab consistently showed improvement in response for secondary endpoints such as PASI, IGA, Japanese Dermatological Association (JDA) severity index, and improvement in body surface area.

Case reports suggest that guselkumab therapy could be effective for paradoxical psoriatic alopecia induced by adalimumab or brodalumab.[25] It has also shown effectiveness in patients with concomitant Crohn's disease who achieve remission while undergoing treatment for psoriasis.[25,26] Future therapeutic indications of guselkumab include palmoplantar pustulosis, psoriatic arthritis, and hidradenitis suppurativa, with early studies showing promising treatment responses.[27-29]

Adverse Reactions

The most common adverse events (AE) reported in the VOYAGE trials included nasopharyngitis, upper respiratory tract infection, erythema at the injection site, and headache.[3] Serious infections requiring antibiotic treatment occurred in similar rates across both the guselkumab and adalimumab groups. Serious AE, including those that led to study agent discontinuation, occurred infrequently and in similar proportions of patients for each treatment group. Incidence rates of candidiasis and neutropaenia were low and also comparable between groups.[3] In the NAVIGATE trial, infection was the most common AE.[22] Of the patients given guselkumab, 77.9% reported at least 1 AE compared to 81.6% of those administered secukinumab. In the ECLIPSE trial, serious AE were reported in 6.2% of guselkumab patients and 7.2% of secukinumab patients. At 44 weeks, 5.1% of the patients on guselkumab had discontinued therapy compared to 9.3% on secukinumab.[23] There has also been a reported case of nummular dermatitis associated with guselkumab treatment for palmoplantar psoriasis, as well as a report of a patient developing multiple lentigines following treatment of psoriasis with guselkumab.[30,31]

TILDRAKIZUMAB

Tildrakizumab is a high-affinity, humanised, IgG1κ monoclonal antibody that targets the p19 subunit of IL-23. It received FDA approval in March 2018

and EMA approval in September 2018 for the treatment of MTSPP.

Dosage

The recommended dose for tildrakizumab for adult patients with MTSPP is a 100 mg, subcutaneous injection at Weeks 0, 4, and every 12 weeks thereafter.

Clinical Efficacy

Several studies have evaluated the efficacy and safety of tildrakizumab. Both of the pivotal Phase III reSURFACE trials were three-group, parallel, double-blind, randomised, placebo-controlled studies.[12] In reSURFACE 1, 772 patients with moderate-to-severe chronic plaque psoriasis were randomised to receive tildrakizumab 100 mg, tildrakizumab 200 mg, or placebo (2:2:1) at Weeks 0, 4, and 16. At Week 12, the placebo patients crossed over to receive tildrakizumab at 100 mg or 200 mg for Weeks 12 and 16. At Week 12, the proportion of patients on either dose of tildrakizumab achieving PASI 75 compared to placebo was significantly greater (64.0% on 100 mg, 62.0% on 200 mg, and 6.0% on placebo). When comparing PGA responses in the tildrakizumab groups compared to placebo, 58.0% in the 100 mg group, 59.0% in the 200 mg group, and 7.0% in the placebo group achieved a PGA score of 0 or 1, with ≥2 Grade reductions from baseline at 12 weeks ($p<0.0001$). Long-term extension data from reSURFACE 1 at Week 160 showed that patients on tildrakizumab 100 mg and 200 mg achieved high and durable PASI 75/90/100 response rates of 84.4%, 57.6%, and 24.9%, and 75.4%, 50.8%, and 25.4%, respectively.

In reSURFACE 2, 1,090 patients were divided into 4 treatment groups: tildrakizumab 200 mg; tildrakizumab 100 mg at Weeks 0, 4, and 16; placebo; or etanercept 50 mg twice weekly until Week 12, then once a week until Week 28 (2:2:1:2).[32] At Week 12 of reSURFACE 2, 66.0% in the 200 mg group, and 61.0% in the 100 mg group achieved PASI 75, compared to 6.0% in the placebo group and 48.0% in the etanercept group. A total of 59.0% in the 200 mg and 55.0% in the 100 mg tildrakizumab groups achieved a significant PGA response, compared to 4.0% in the placebo group and 48.0% of patients receiving etanercept.[32] At Week 148 in the reSURFACE 2 extension study, tildrakizumab again demonstrated sustained clinical response with PASI 75, 90, and 100 achieved by 89.0%, 64.0%, and 35.0% of patients, respectively. [33]

Pooled analysis from 3 clinical trials revealed that at Week 12, PASI and PGA responses to tildrakizumab versus placebo were numerically greater in patients with lower versus higher bodyweight, and that responses were better on 200 mg compared to 100 mg of tildrakizumab for those with higher bodyweight.[34] At Week 12, the proportion of patients achieving PASI 75 on tildrakizumab 100 mg or 200 mg was higher compared to placebo in patients both with and without prior exposure to biologic therapy for psoriasis. The proportions of patients with PASI 90 and PGA responses on both tildrakizumab 100 mg and 200 mg versus placebo were greater in biologic naïve patients compared to those with prior biologic exposure.

Pooled analysis from the reSURFACE 1 and 2 trials investigating long-term outcomes found that at Week 148, the tildrakizumab 200 mg responder group (≥75% improvement in PASI) and partial responder group (≥50 to <75% improvement in PASI) had a higher percentage of responders achieving a PASI of 75, 90, and 100, compared to the tildrakizumab 100 mg group.[35]

Adverse Reactions

The most common adverse reaction reported in both Phase III reSURFACE trials up to Week 28 was nasopharyngitis. The incidence of severe infection, malignancies (including non-melanoma skin cancer), and major cardiovascular AE were low and similar across all treatment groups.[32] Furthermore, analysis of the adverse events reported from Phase IIb and two Phase III (reSURFACE 1 and reSURFACE 2) trials suggested that the IL-23 inhibitor tildrakizumab does not induce or worsen inflammatory bowel disease (IBD) in patients with psoriasis, in contrast to the IL-17 class of inhibitors.[36-39]

Safety and tolerability up to 64 weeks of tildrakizumab therapy using pooled data from 3 randomised controlled trials showed that in the full trial period, exposure-adjusted rates (patients per 100 patient-years), treatment-emergent serious AE, and discontinuations due to AE with tildrakizumab 100 mg and 200 mg, were lower than or comparable with the placebo rates, and lower than with etanercept.[40] Pooled analysis

from the reSURFACE 1 and 2 trials for the rates of discontinuation of tildrakizumab due to AE, major cardiovascular AE, severe infection, and malignancy were low, and tildrakizumab efficacy was well maintained in Week 28 responders who continued tildrakizumab treatment for 3 years.[35]

RISANKIZUMAB

Risankizumab is a humanised IgG1 monoclonal antibody that binds to the p19 subunit of IL-23, working similarly to both guselkumab and tildrakizumab. It received FDA and EMA approval in April 2019 for the treatment of MTSPP, making it the most recently approved IL-23p19 inhibitor. Risankizumab is currently being investigated for its utility in Crohn's disease, whereas other studies have revealed its lack of efficacy in the treatment of ankylosing spondylitis (AS).[41-43]

Dosage

The recommended dosage for risankizumab for the treatment of MTSPP is 150 mg administered by subcutaneous injection at Weeks 0, 4, and every 12 weeks thereafter.

Clinical Efficacy

In a Phase II clinical trial, 77.0% of patients treated with risankizumab achieved a PASI 90 response at Week 12, compared to 40.0% of patients on ustekinumab (p<0.001).[44] Furthermore, risankizumab has been evaluated in two pivotal, identical, Phase III, double-blind, randomised controlled trials (UltIMMa-1 and UltIMMa-2).[45,46] Patients were randomised to 1 of 3 groups: risankizumab (150 mg), ustekinumab (45 mg or 90 mg depending on weight), or placebo at Weeks 0 and 4. At Week 16, patients in the placebo group were switched to risankizumab, administered at Weeks 16, 28, and 40. In UltIMMa-1, PASI 90 was achieved by 75.3% of patients receiving risankizumab by Week 16, compared to 42.0% receiving ustekinumab and 4.9% receiving placebo (p<0.001). Static PGA of 0 or 1 was achieved by 87.6% of patients receiving risankizumab by Week 16, compared to 63.0% receiving ustekinumab and 7.8% receiving placebo (p<0.001).[45] In UltIMMa-2, 83.7% of patients receiving risankizumab versus 5.1% receiving placebo (placebo-adjusted difference 78.5% [95% CI; 72.4–84.5]) and 61.6% receiving ustekinumab achieved static PGA 0 or 1 at Week 16 (ustekinumab-adjusted difference 22.3% [12.0–32.5]; p<0.0001).[46] In UltIMMa-1 and UltIMMa-2, 81.9% and 80.6% of patients treated with risankizumab achieved PASI 90 at 52 weeks, compared to 44.0% and 50.5% in the ustekinumab groups, and 78.4% and 85.1% in the crossover groups, respectively. PASI 100 was achieved at Week 16 by 36.0% and 51.0% of patients treated with risankizumab in UltIMMa-1 and 2, respectively, compared to 12.0% and 24.0% of ustekinumab patients. At Week 52, 56.0 % and 60.0% of patients treated with risankizumab achieved PASI 100 in UltIMMa-1 and 2, respectively, compared to 21.0% and 30.0% of patients treated with ustekinumab.[46]

A Japanese Phase II/III, double-blinded, placebo-controlled study (SustaIMM) stratified 171 patients with MTSPP by bodyweight and concomitant psoriatic arthritis.[47] Patients were randomised to risankizumab 75 mg, 150 mg, or placebo at Weeks 0, 4, 16, 28, and 40 (with placebo crossover to 150 mg occurring at Week 16). Primary endpoints were PASI 90 at Week 16 for risankizumab 75 mg, 150 mg, and placebo, with significantly higher response rates for patients receiving risankizumab 75 mg and 150 mg compared to placebo (75.9% versus 74.5% versus 1.7%, respectively; p<0.001). Week 16 PASI 90 response was seen in 72.7%, 100.0%, and 0.0% of patients with psoriatic arthritis receiving risankizumab 75 mg, risankizumab 150 mg, and placebo, respectively. Patients weighing ≤90 kg (without psoriatic arthritis) and those >90 kg were also compared at the same dosages, with PASI 90 response seen in 80.0%, 69.8%, and 2.3%, and 57.1%, 85.7%, and 0.0% of the patients, respectively. Secondary endpoints included PASI 75, PASI 100, and IGA 0/1 responses which were significantly higher for both risankizumab doses (75 mg and 150 mg) compared to placebo (PASI 75: 90.0%, 95.0%, 9.0%; PASI 100: 22.0%, 33.0%, 0.0%; IGA 0/1: 86.0%, 93.0%, 10.0%, respectively). PASI and IGA response rates were maintained or improved through Week 52. The American College of Rheumatology (ACR)20 responses were measured in 11 patients at select study sites, with ACR20 higher in those on risankizumab versus placebo at Week 16. Sustained efficacy was confirmed in 55% of patients at Week 52.

More recently, risankizumab was compared with adalimumab in patients with MTSPP in an active comparator-controlled, Phase III trial.

Table 3: Pivotal Phase III trials for risankizumab

Trial	N	Study arms	Primary outcomes	Secondary outcomes
Risankizumab Phase III (UltIMMA 1)[41]	603	Placebo (placebo at Weeks 0 and 4, then switched to risankizumab at Weeks 16, 28, and 40) Risankizumab (risankizumab 150 mg at Weeks 0, 4, 16, and 40) Ustekinumab (ustekinumab 45 mg or 90 mg [weight-based])	(Week 16) risankizumab versus ustekinumab versus placebo PASI 90: 75.3 versus 42.0 versus 4.9% IGA 0/1: 87.8 versus 63.0 versus 7.8%	(Week 12) risankizumab versus ustekinumab versus placebo PASI 75: 86.8 versus 70.0 versus 9.8% IGA 0/1: 82.2 versus 65.0 versus 8.8% (Week 16) risankizumab versus ustekinumab versus placebo IGA 0: 36.8 versus 14.0 versus 2.0% PASI 100: 35.9 versus 12.0 versus 0.0% (Week 52) risankizumab versus ustekinumab versus placebo → risankizumab PASI 90: 81.9 versus 44.0 versus 78.4% PASI 100: 56.3 versus 21.0 versus 54.6% IGA 0: 57.6 versus 21.0 versus 54.6%
Risankizumab Phase III (UltIMMA 2)[41]	585	Placebo (placebo at Weeks 0 and 4, then switched to risankizumab at Weeks 16, 28, and 40) Risankizumab (risankizumab 150 mg at Weeks 0, 4, 16, and 40) Ustekinumab (ustekinumab 45 mg or 90 mg [weight-based])	(Week 16) risankizumab versus ustekinumab versus placebo PASI 90: 74.8 versus 47.5 versus 2.0% IGA 0/1: 83.7 versus 61.6 versus 5.1%	(Week 12) risankizumab versus ustekinumab versus placebo PASI 75: 88.8 versus 69.7 versus 8.2% IGA 0/1: 82.3 versus 64.6 versus 9.2% (Week 16) risankizumab versus ustekinumab versus placebo IGA 0: 51.0 versus 25.3 versus 3.1% PASI 100: 50.7 versus 24.2 versus 2.0% (Week 52) risankizumab versus ustekinumab versus placebo → risankizumab PASI 90: 80.6 versus 50.5 versus 85.1% PASI 100: 59.5 versus 30.3 versus 67.0% IGA 0: 59.5 versus 30.3 versus 67.0%

IMMvent randomised patients 1:1 to risankizumab 150 mg at Weeks 0 and 4, or to adalimumab 80 mg at Week 0 and then adalimumab 40 mg at Weeks 1, 3, 5, and every other week thereafter until Week 16 (the end of the double-blind treatment period).[48] During Weeks 16–44, adalimumab intermediate responders either continued on adalimumab or switched to risankizumab (1:1). Randomisation was stratified by weight and prior TNF-inhibitor exposure. The primary endpoints were PASI 90 and IGA 0/1 at Week 16 and PASI 90 in intermediate responders at Week 44. Risankizumab showed significantly greater efficacy than adalimumab for all primary endpoints: PASI 90: 72.0% risankizumab versus 47.0% adalimumab and IGA 0/1: 84.0% risankizumab versus 60.0% adalimumab.

At Week 44, PASI 90 response among adalimumab intermediate responders was reached by 66.0% of those switched to risankizumab versus 21.0% of those who continued adalimumab.

IMMhance was another Phase III, randomised, double-blind, placebo-controlled study including randomised withdrawal and retreatment. Initially, 507 patients were assigned to receive either 150 mg risankizumab or placebo (4:1).

Of the patients receiving risankizumab, 73.2% achieved PASI 90 at Week 16, compared to 2.0% of patients receiving placebo ($p<0.001$). Furthermore, 83.5% of patients on risankizumab achieved sPGA scores of 0 or 1, compared to 7.0% of patients on placebo. Patients on placebo were switched to active drug at Week 16. At Week 28, patients who had achieved sPGA of 0 or 1 were either re-randomised to continue on risankizumab or switch to placebo. At Week 52, 52.4% of those re-randomised to the placebo group achieved PASI 90 compared to 85.6% of those who continued on risankizumab, with sPGA 0/1 scores achieved by 61.3% and 87.4% of patients, respectively.[49]

Adverse Reactions

In the Phase II trials with risankizumab, rates of serious AE in the 18 mg and 90 mg risankizumab groups, and the ustekinumab group were 12.0%, 15.0%, and 8.0%, respectively. Serious AE included 2 basal cell carcinomas and 1 major cardiovascular AE; there were no serious AE in the 180 mg risankizumab group.[44] In the Phase III UltLMMa trials, the frequencies of AE in the risankizumab, ustekinumab, and placebo groups were similar during the first 16 weeks. The most commonly reported AE were upper respiratory tract infection, headache, fatigue, injection site reactions, and tinea infections.[45,50] No additional, unexpected safety concerns for risankizumab emerged during the SustaIMM or IMMvent trials (including for those patients who switched from adalimumab to risankizumab) compared to previous Phase III trials. AE in these trials were also comparable to those of the UltLMMa trials.[47,48]

CONCLUSION

This review of the IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab) illustrates the significant clinical efficacy and safety of these agents for MTSPP. The development and approval of these agents has expanded psoriasis treatment with increasingly effective biologic options,[51] validating the importance of IL-23 as a key cytokine in psoriasis pathogenesis and establishing PASI 90 and 100 as new specific endpoints in clinical trials, compared to the prior PASI 75 standard. Clinical trials with IL-23 agents have also yielded favourable safety data in the treatment of MTSPP.

In this review, the main results from Phase III clinical trials have been summarised. For all three agents, the most common adverse effects reported in the IL-23 clinical trials were similar to other psoriasis biologics, i.e., nasopharyngitis and upper respiratory infection, with rates of serious AE comparable to placebo. Selectively targeting the p19 subunit of IL-23 is of importance to avoid side effects seen with other classes of biologics (for example, risk of tuberculosis reactivation with TNF-α inhibitors, fungal infections with IL-17 inhibitors, etc.). Although data from clinical trials are extremely promising showing impressive clinical efficacy and no new safety signals to date, long-term safety of this relatively new class of biologics is yet to be determined. Thus, long-term safety data from open-label extension studies and registries, as well as head-to-head comparison amongst these biologic agents, is important to further elucidate long-term safety and efficacy profiles of the three current IL-23 inhibitors in the treatment of MTSPP.

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