EMJ DERMATOLOGY

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+ EADV 2020 VIRTUAL CONGRESS

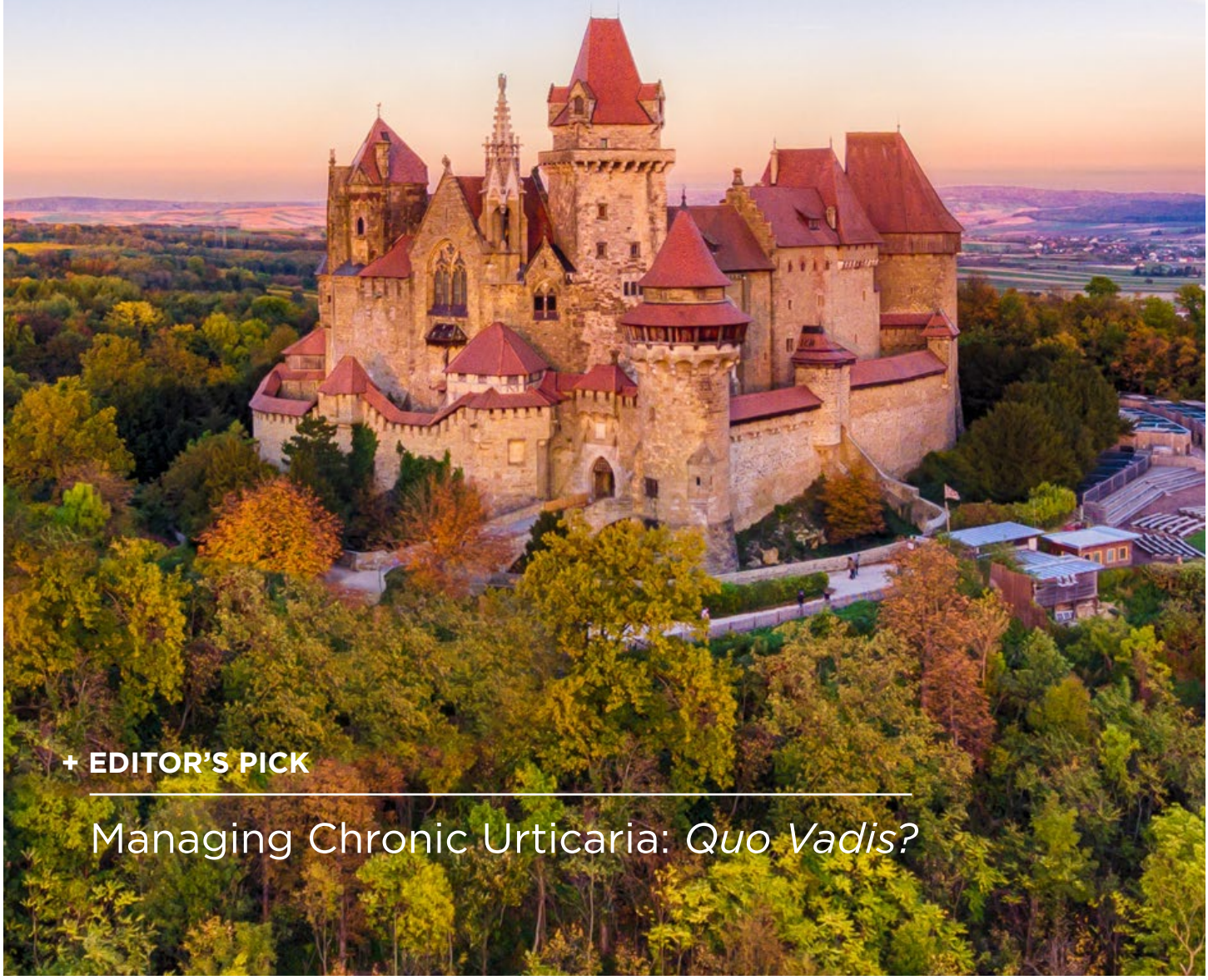
Reviewed

+ INTERVIEWS

A conversation with EADV President Prof Alexander Stratigos is followed by a roundtable interview with EADV Committee members.

+ ABSTRACT REVIEWS

Summaries of abstracts presented at the 29th EADV 2020 Virtual Congress, covering topics such as PD-1 and mTOR inhibitors, inflammatory bowel disease, and metformin, in skin disease.



+ EDITOR'S PICK

Managing Chronic Urticaria: *Quo Vadis?*

SHARED RESULTS

SHARED RELIEF

FOR ADULTS AND ADOLESCENTS (12 YEARS AND OLDER) WITH ATOPIC DERMATITIS WHO ARE INADEQUATELY CONTROLLED ON TOPICAL THERAPIES*

- First and **only targeted immunomodulator to specifically inhibit IL-4 and IL-13 signaling**, thereby reducing persistent underlying type 2 inflammation[1,2]
- **Rapid and sustained improvement** in lesion extent and severity, pruritus intensity, and quality-of-life measures[1,3–6]
- **Long-term safety profile** established up to **3 years in adults** and **52 weeks in adolescents**[1,7] — No monitoring for organ toxicities required[1]
  - Most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes[1]

*DUPIXENT is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Abbreviated Prescribing Information can be found **here.**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspectedadverse reactions.

References: 1. DUPIXENT summary of product characteristics. 2019. 2. Gandhi NA et al. Nature Rev Drug Disc 2016; 15:35–50. 3. Blauvelt A et al. Lancet 2017; 389:2287–2303. 4. de Bruin-Weller M et al. Presentation at the 27th European Academy of Dermatology and Venereology Congress; 2018; September 12–16; Paris, France. 5. Simpson EL et al. JAMA Dermatol 2020; 156(1):44–56. 6. Paller AS et al. Am J Clin Dermatol 2020; 21:119–131. 7. Thaci D et al. Poster presented at the 17th Winter Clinical Dermatology Conference; 2020; January 17–22; Kohala Coast, HI, USA.

SANOFI GENZYME REGENERON

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DUPIXENT® (dupilumab)
CONTINUOUS CONTROL

Contents

"At EMJ we strive to ensure uninterrupted access to research and hope that our continuous contribution of quality content, including EMJ Dermatology 8.1, will encourage trailblazing studies in the future."

Spencer Gore, CEO

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kyntheum®▼

Brodalumab

CONFIDENCE STARTS WITH CLEARANCE

Kyntheum® (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.[1] Kyntheum® is a fully human monoclonal antibody and the only biologic that selectively targets the IL-17 receptor subunit A.[1–4]

PSORIASIS

Is PASI 100 worth fighting for?*

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:** *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* Cases of new or exacerbations of inflammatory bowel disease have been reported with IL-17 inhibitors. Therefore, Kyntheum is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, Kyntheum should be discontinued and appropriate medical management should be initiated. *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. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been reported in the post-marketing setting. In the event of an anaphylactic reaction, or any other serious allergic reaction, administration of Kyntheum should be discontinued and appropriate therapy initiated. *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. *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 of 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), 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), neutropenia, conjunctivitis. *Rare (≥1/10,000 to <1/1,000):* anaphylactic reaction. **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:** July 2020

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

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References:
1. Kyntheum® (brodalumab) EU Summary of Product Characteristics. July 2020. **2.** Brembilla NC et al. *Front Immunol* 2018;9:1682.
3. Pappu R et al. *Immunology* 2011;134:8–16. **4.** Baker KF and Isaacs JD. *Ann Rheum Dis* 2018;77:175–87. **5.** Lebwohl M et al. *N Engl J Med* 2015;373:1318–28.

October 2020
MAT-38367

*PASI 100 at 12 weeks with Kyntheum®: 44% in AMAGINE-2 (N=612) and 37% in AMAGINE-3 (N=624). In the statistical analysis, missing data were imputed as nonresponses (NRI).[5]

LEO

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VIEW IN FULL ←

Aims and Scope

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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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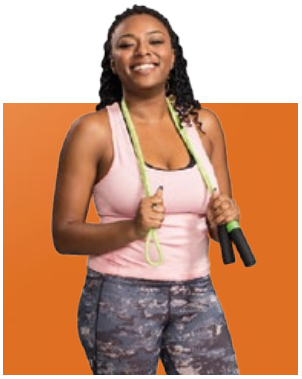
cimzia®
(certolizumab pegol)

Durable efficacy
FOR HER skin and beyond[1-3]

Data published in June/July 2020 confirming durable efficacy (Week 144) and long-term safety of **CIMZIA®** up to 3 years[1,2]



+10 Years

experience across PSO, PsA, axSpA and RA[4]

*CIMZIA® is indicated for treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy and for the treatment of active psoriatic arthritis in adults in combination with MTX when the response to previous DMARD therapy has been inadequate. CIMZIA® can be given as monotherapy for psoriatic arthritis in case of intolerance to MTX or when continued treatment with MTX is inappropriate.[4]

AxSpA, axial spondyloarthritis; DMARD, Disease-modifying anti-rheumatic drugs; MTX, methotrexate; PsA, psoriatic arthritis; PSO, psoriasis; RA, rheumatoid arthritis.

References
1. Gordon K, et al. *Br J Dermatol*. 2020; doi:10.1111/bjd.19393. 2. Blauvelt A, et al. *Br J Dermatol*. 12 June 2020; doi:10.1111/bjd.19314. 3. van der Heijde D, et al. RMD Open. 2018;4(1):e000582.
4. CIMZIA® Summary of Product Characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/cimzia-epar-product-information_en.pdf. Acessed December 2020

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. After at least 1 year of treatment with Cimzia, in patients with sustained remission, a reduced maintenance dose of 200 mg every 4 weeks may be considered. ***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 patients with axial spondyloarthritis (including ankylosing spondylitis and non-radiographic axial spondyloarthritis) in a clinical study for up to 96 weeks, which included a 48-week open-label run-in phase (N=736) followed by a 48-week placebo-controlled phase (N=313) for patients in sustained remission (C-OPTIMISE), 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 3 years. The long-term safety profile of Cimzia® 400 mg every 2 weeks and Cimzia® 200 mg every 2 weeks was generally similar and consistent with previous experience with Cimzia®. Please refer to the full Prescribing Information in your country before prescribing. **Legal Classification:** Medical product subject to medical prescription. **Date of revision:** October 2020. **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.

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

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Date of Preparation: December 2020

GL-P-CZ-PSO-2000017

Welcome

Dear Readers,

It is with great pride that I welcome you to our final journal of this year, *EMJ Dermatology*, a brilliant compilation of major breakthroughs in the field. 2020 has been a year like no other; the coronavirus disease (COVID-19) pandemic continues to be a societal challenge, making the dissemination of information even more crucial. At EMJ we strive to ensure uninterrupted access to research and hope that our continuous contribution of quality content, including *EMJ Dermatology 8.1*, will encourage trailblazing studies in the future.

This year's 29th European Academy of Dermatology and Venereology (EADV) 2020 Virtual Congress lived up to expectations and provided the usual cutting-edge scientific content, coupled with novel ways to virtually interact in light of the current situation. Our independent Congress Review provides an account of all the highlights and latest research trends including foot odour prevention through nanoparticles, bacterium therapeutics in psoriasis, and dermatological symptoms presented in 'long' COVID-19 patients.

Don't miss our interview with EADV President, Prof Alex Stratigos, who shared his personal clinical experiences and the focus of his upcoming presidential term. In a round table interview with EADV committee members and this year's congress spokespeople, we discussed how recent advancements in technology have influenced patient care, as well as providing key recommendations for clinicians to provide expert care for their patients during the COVID-19 era.

As always, we also provide a fine assortment of abstract summaries from this year's EADV meeting, with topics ranging from skin toxicity, severe drug allergy, and more. Our superb, hand-picked, peer-reviewed articles in this issue will provide thought-provoking and essential information for all dermatologists. I hope you enjoy reading these as much as I did!

Finally, I would like to thank all collaborators, contributors, and the Editorial Board members for their continued support now and always. I would also like to extend a special thank you to the entire EMJ team for their perseverance this year. We have provided many innovative, multidisciplinary journals in 2020 and strive to provide high-quality content in 2021 again.

Spencer Gore

Chief Executive Officer, EMG-Health

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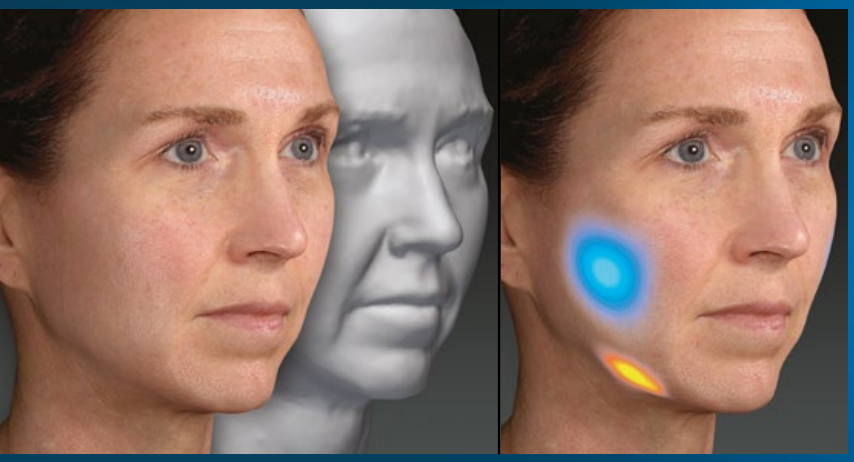

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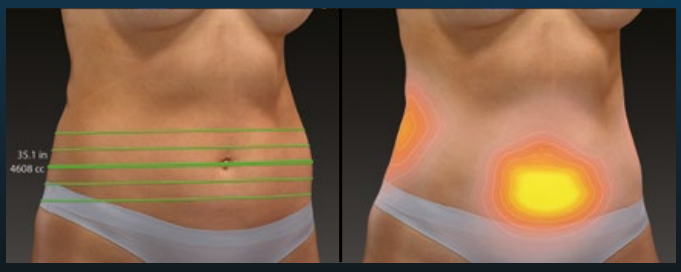

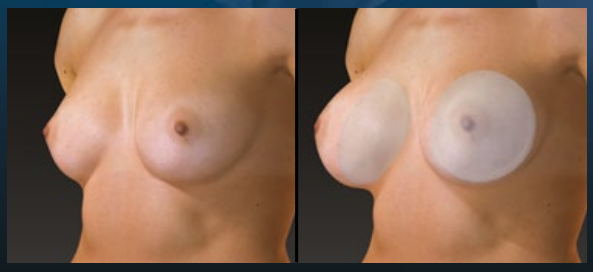

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Foreword

Dear Colleagues and Readers,

It is my pleasure to extend to you a very warm welcome to *EMJ Dermatology*, your thorough report of research and review, made open access to facilitate a faster and unrestricted pathway to the latest medical research in dermatology.

The latest issue of *EMJ Dermatology* is also home to the independent review of the 29th European Academy of Dermatology and Venereology (EADV) Virtual Congress. The annual meeting was rescheduled and made into a fully virtual learning experience after the coronavirus disease (COVID-19) pandemic caused incomparable disruption to the meeting, and all walks of life, this year. Upon entering the meeting, the visible hard work and dedication that had gone into the virtual platform ensured spirits remained high, proven by the fact that each day saw record-breaking numbers of attendees. The theme of the congress was 'New Frontiers in Dermatology and Venereology,' meaning the scientific programme featured a wealth of cutting-edge and innovative research, including highlights such as improving the patient–doctor relationship and addressing patient needs in the aftermath of COVID-19.

This issue features a wide variety of topics discussed at the congress. I would like to draw your attention in particular to contributions from EADV 2020 abstract presenters who have provided summaries of their abstracts herein, on topics including dermatology and mental health, melanoma, and skin reactions to metformin. My Editor's Pick from the selection of peer reviewed articles included in this year's journal is 'Managing Chronic Urticaria: *Quo Vadis*?,' the review by Petkova and Staevska in which the authors provide a thorough and extensive write-up on the allergic skin condition chronic urticaria.

I hope that you will enjoy this latest issue, and I look towards the future where we will meet to celebrate the 30th year of the EADV Congress in Berlin, Germany in 2021.

Prof Desmond Tobin

University College Dublin, Dublin, Republic of Ireland

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Congress Review

European Academy of Dermatology and Venereology (EADV) 2020 Virtual Congress

Location: EADV 2020 Virtual Congress

Date: 28th October–1st November 2020

Citation: EMJ Dermatol. 2020;8[1]:14-22.

VIENNA, Austria, is a city with unquestionable spirit, influence, and grandiosity, and would have been a spectacular host to this year's European Academy of Dermatology and Venereology (EADV) 29th Congress. In light of the restrictions on travel and large gatherings during the coronavirus disease (COVID-19) pandemic, and valuing the safety of their members, the EADV took the hard decision to make the congress fully virtual this year for the first time in its history. We bore witness to the effects of the hard work that made this congress a success as it proudly provided an outstanding educational learning experience in a marvellous all-virtual framework. Creative strokes of genius allowed EADV to cross borders as we were greeted with a virtual welcome to the platform by Prof Carle Paul, EADV President (2020), University of Athens, Athens, Greece, upon first entering.

The congress began on 29th October, which coincided with World Psoriasis Day 2020. This befitting occurrence acted as a reminder that the mission of EADV is "to help and empower the millions of individuals who are living and suffering with skin diseases," shared Prof Paul. The main theme for the congress was 'New Frontiers in Dermatology and Venereology', and "the EADV team has taken forward the EADV mission while supporting innovation and new ways of thinking," according to the EADV President. The congress drew in more than 12,000 participants, 750 speakers, and 170 exhibitors from over 100 countries across the world. Not only did it push boundaries with its visual representation, but also with the scientific information and knowledge it delivered.

With 170 sessions, more than 500 experts, over 1,600 abstracts, and 28 virtual booths, participants were granted access to 3 days' worth of interactive sessions. Up-to-date scientific data presented by experts worldwide were hand-picked by EADV Scientific Committee leaders. Presentation topics spanned across the discipline and included inflammatory

skin diseases, improving the patient–doctor relationship, cutaneous oncology, infectious diseases, dermoscopy, hair and nail disorders, and paediatric dermatology, as well as a special address from Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), who delivered the latest news on the COVID-19 pandemic. EADV provided novel ways to connect, and the participants were invited to enjoy a series of mini-breaks and social media masterclasses to further improve communication, bringing the interaction and sense of global community to physicians, nurses, and patient representatives through the screen.

A strong online presence was observed on Day 1 of the congress and new audiences were reached with an astounding 10,923 online attendees, almost as high as the face-to-face congress. Media engagement was high across social platforms and ground-breaking news stories on the topics of dermatology and COVID-19, vitamin B3 and ultraviolet exposure, and increased sexually transmitted infections during national lockdowns attracted much attention. Attendance of the virtual meeting of the congress remained strong across the weekend and 10,945 attendees saw the congress draw to a close on Day 3. At the congress, Prof Alex Stratigos was announced as the newest President-elect and was warmly encouraged by Prof Paul to further the success of EADV in extending the frontiers of knowledge of skin diseases.

EADV considers education as the main foundation for continuing professional development. The information delivered at the congress left healthcare professionals with a wealth of evidence to help better manage skin diseases in their clinical practice. As Prof Paul shared in his welcome, "Keeping ahead of the curve is essential for EADV... This has enabled us to continue to grow in strength, effectiveness, and wisdom and in so doing, better serve our members."

"Keeping ahead of the curve is essential for EADV... This has enabled us to continue to grow in strength, effectiveness, and wisdom and in so doing, better serve our members."

EADV 2020 REVIEWED →

"While completing an internship as a naval officer in the medical department, I saw a high number of foot infections in military personnel. "

Nanoparticle Technology Can Prevent Foot Odour

SOCKS that have been coated in nanoparticles of zinc oxide have been shown to thwart bromodosis (foot odour) and pitted keratolysis (the bacterial infection that causes feet to smell). This is according to a study presented at EADV Virtual Congress and a press release dated 30th October 2020.

Antibacterial efficacy, safety, and compatibility with human skin are all properties of zinc oxide nanoparticles that have been found to make them a suitable compound for textiles, including socks, by researchers from the Royal Thai Airforce, Bangkok, Thailand. In a double-blind, randomised controlled trial enrolling 148 cadets at the Thai Naval Rating School, the team sought to prevent the development of bromodosis and pitted keratolysis, which occur in over one-third of naval cadets in Thailand (38.5%), by using zinc oxide nanoparticle-coated socks.

Significantly, those wearing the coated socks had less foot malodour than at baseline (p=0.009), compared with the uncoated sock group, who experienced a greater level of food odour (p=0.04). Additionally, those not wearing the coated socks were more likely to develop pitted keratolysis compared with those wearing the nanoparticle socks (p=0.05).

Bromodosis is a common complaint among military personnel and negatively impacts their daily lives. Dr Punyawee Ongsri, lead study author and final year resident at the Siriraj Hospital, Bangkok, Thailand, was motivated to find a solution to this problem after encountering it first-hand: "While completing an internship as a naval officer in the medical department, I saw a high number of foot infections in military personnel. I wanted to find a way to prevent and treat these fungal and bacterial infections and those conditions associated."

Dr Ongsri is optimistic about the results of the study, and is continuing the research with additional materials, hoping to treat and prevent other bacterial and fungal infections.

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Long COVID and Sustained Skin Symptoms

LONG-LASTING dermatological symptoms in patients who have had coronavirus disease (COVID-19) have been found to vary according to the type of COVID-19 skin rash. This is according to research presented at the EADV Virtual Congress in a press release dated 29th October 2020.

The International League of Dermatological Societies (ILDS) and the American Academy of Dermatology (AAD) have created a large registry, the International COVID-19 Dermatology Registry, which involves 990 COVID-19 patients with skin symptoms from 39 countries. Data from the registry has subsequently been analysed, revealing that a subset of patients with 'long COVID' have presented with prolonged dermatological symptoms lasting >60 days.

On average, all skin symptoms endured for 12 days, with several lasting for >150 days. Hives (urticaria) was shown to last for a median of 5 days, pernio/chilblains lasted for a median of 15 days, and papulosquamous eruptions were present for a median of 20 days.

It is thought that these COVID-19 patients with dermatological symptoms that have persisted after the initial phase of COVID-19 could aid the understanding of the long-lasting inflammatory response observed in some cases postinfection. Additionally, these findings could help to predict COVID-19 severity, as 100% of the patients with retiform purpura experienced severe COVID-19 and were hospitalised. In contrast, just 16% of those who developed pernio/chilblains were admitted to hospital.

Principal Investigator of the registry Dr Esther Freeman, Massachusetts General Hospital, Boston, Massachusetts, USA, summarised the findings: "This data adds to our knowledge about how COVID-19 can affect multiple different organ systems, even after patients have recovered from their acute infection. The skin can provide a visual window into inflammation that may be going on elsewhere in the body."

"The skin can provide a visual window into inflammation that may be going on elsewhere in the body"

Bacterium Therapeutic Shows Promise for Mild-to-Moderate Psoriasis

CROSSTALK between the small intestine and the immune system is well established, making this an attractive therapeutic target for immune conditions such as psoriasis. Researchers from Evelo Biosciences investigated whether the oral administration of a bacterium could interfere with this crosstalk to improve psoriasis symptoms; the results from the study were presented at EADV Virtual Congress and in a press release dated 29th October 2020.

The gut–body network relays immunomodulatory messages throughout the body, and specific bacterial strains have been identified to modulate the small intestinal axis and induce systemic inflammation resolution without immunosuppression, a key mechanism that leads to severe side effects. In the Phase Ib study, a non-living single strain of the bacterium *Prevotella histicola* was isolated from the duodenum of a human donor and was administered to two cohorts of patients with mild-to-moderate psoriasis (low-dose n=12; high-dose n=18) for 28 days. The microbe was given orally, but it is not absorbed into the body; instead, it interacts with the gut–body network to induce a systemic therapeutic immune response.

A significant reduction in Psoriasis Area Severity Index (PASI) score at Day 28 was seen in both the microbe cohorts versus placebo (16% versus 1%). This trend continued to the end of the 14-day follow-up, with PASI reductions being 21% in the high-dose group compared with 3% in placebo; however, the improvements in PASI in the low-dose group subsided, with the PASI reduction being 10% at Day 42. When assessing the Lesion Severity Scores (LSS), it was observed at Day 28 that the LSS in the high-dose and low-dose groups decreased by 15% and 23%, respectively, compared with an increase of 1% in the placebo group. Finally, a further reduction to 24% was seen in the high-dose group.

Lead author of the study Dr Douglas Maslin, Addenbrooke's Hospital in Cambridge, UK, and Evelo Biosciences, London, UK, commented: "It is a real breakthrough, especially as we have seen from the preclinical and Phase I trials that it was well tolerated with no overall difference from placebo and with no severe side effects reported."

"It is a real breakthrough, especially as we have seen from the preclinical and Phase I trials that it was well tolerated with no overall difference from placebo and with no severe side effects reported"

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Can Vitamin B3 Protect Skin Against Ultraviolet Exposure?

VITAMIN B3 treatment has been shown to protect skin cells against ultraviolet (UV) exposure-related oxidative stress, in a study shared at the EADV Virtual Congress and in a press release dated 31st October 2020.

UV radiation exposure is the main risk factor for nonmelanoma skin cancers because exposure leads to DNA damage, increased production of reactive oxygen species, local inflammation activation, and depletion of cellular energy; these processes lead to genomic instability and cell death. The incidence of nonmelanoma skin cancers is increasing worldwide; these cancers are already the most common malignancy among the Caucasian population.

Researchers from the dermatological unit of AOU Maggiore della Carità, Novara, Italy, pretreated human primary keratinocytes from the skin of patients with nonmelanoma skin cancers. They compared three concentrations of a form of vitamin B3, nicotinamide, which they treated the isolated skin cells with for 18, 24, and 48 hours prior to exposure to UVB.

Pretreatment with 25 µmol of nicotinamide 24 hours before irradiation with UVB was shown to protect against UV-induced oxidative stress and DNA damage. The nicotinamide enhanced repair of DNA, as expression of the DNA repair enzyme OGG1 decreased; decreased expression of antioxidants; and blocked local inflammation, as evidenced by reduced release of nitric oxide release, production of reactive oxygen species, and expression of inducible nitric oxide synthase.

The translation of these research findings to clinical practice was outlined by Lara Camillo: "Our study indicates that increasing the consumption of vitamin B3, which is readily available in the daily diet, will protect the skin from some of the effects of UV exposure, potentially reducing the incidence of nonmelanoma skin cancers. However, the protective effect of vitamin B3 is short-acting, so it should be consumed no later than 24 to 48 hours before sun exposure."

"increasing the consumption of vitamin B3, which is readily available in the daily diet, will protect the skin from some of the effects of UV exposure, potentially reducing the incidence of nonmelanoma skin cancers"

Anti-inflammatory Moisturiser Enjoyed by 97% of People with Dry Skin

XEROTIC and extremely dry skin can be treated with a novel allergen-depleted and anti-inflammatory fragrance. This is according to the results of a new study, which was presented at EADV Virtual Congress and reported as part of a press release on 31st October 2020.

After cell testing, researchers from Beiersdorf AG, Hamburg, Germany, who developed this new fragrance, found that the anti-inflammatory ingredients of the allergen-depleted fragrance composition reduced expression of both prostaglandin E2 and IL-8 after a stress response. The fragrance was added to a moisturiser and applied to the forearm of volunteers who shaved their skin on 3 consecutive days to monitor skin irritation. The study found that redness of skin was significantly reduced in people who used the moisturiser. Dr Julia Gallinger, senior scientist at Beiersdorf AG's Research, spoke of the benefits of the new product: "A moisturiser containing our novel fragrance could provide an improved treatment option for people with dry skin conditions. It would be both pleasant to use due to its scent, enhancing patients' treatment adherence, and actively soothing inflammation."

"The long-standing paradigm of fragranced moisturisers considered as allergenic risk in the treatment of xerotic dermatoses may soon become obsolete"

Fragrances are one of the most frequent causes of allergic contact dermatitis; the novel fragrance was innovatively developed without the addition of any of the 26 established allergens, or, remarkably, without any of the 60 potential allergens currently under evaluation. Patient treatment adherence to this moisturiser was enhanced, owing to its pleasant scent and thus improved cosmetic acceptability. In a patient preference study, 86 people with dry skin used the fragranced moisturiser for 2 weeks. The results showed that 97% of the participants agreed that application of the moisturiser did not feel burdensome or like a compulsory task but actually enjoyed the action of it. The scent in the lotion made care routines more pleasurable for 91% of participants and 71% confirmed that they preferred the scented moisturiser to their usual unscented moisturiser. "The long-standing paradigm of fragranced moisturisers considered as allergenic risk in the treatment of xerotic dermatoses may soon become obsolete," explained Dr Gallinger.

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"The results of this study highlighted the importance of ongoing screening for STI and the benefits of making screening services available and open during the pandemic"

COVID-19 Pandemic Did Not Deter Risky Sexual Behaviour

ADVICE on social distancing during the coronavirus disease (COVID-19) pandemic did not inhibit risky behaviour, and acute sexually transmitted infections (STI) increased during this time. This is according to the results of a new study presented at EADV Virtual Congress and reported in a press release dated 31st October 2020.

Despite restrictions and lockdown measures implemented by national and international organisations, the prevalence of STI such as gonorrhoea, secondary syphilis, and mycoplasma genitalium increased, compared with the number of diagnoses made over the same period of time in 2019 in two main STI centres in Milan, Italy. The study group for this research investigated the number of confirmed diagnoses of the most common STI in patients with symptoms from 15th March to 14th April 2020 after measures were put in place to control the ongoing pandemic.

The number of attendances to the clinic reduced by one-third over the course of the study but the number of acute bacterial infections, most associated with males who have sex with males, increased during the observational period, including secondary syphilis and gonorrhoea. Cases fell, however, in the nonacute cases, such as genital warts and molluscum contagiosum.

Dr Marco Cusini, study author, La Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano Policlinico, Milan, Italy, commented on the unexpected results: "It was assumed that the lockdown would reduce the opportunity for sexual encounters and STI. However, I was surprised by the number of new acute infections diagnosed in this short period of time."

The greater morbidity and mortality of COVID-19 observed in the elderly may have led younger people to believe they were more protected against this novel virus. Dr Cusini explained that, typically, gonorrhoea and syphilis are more prevalent in people aged 30–40 years old, and infection transmission may have increased in this cohort because of the reduced inhibitions of young people who thought they had lower risk of COVID-19 and continued to break physical distancing rules. Dr Cusini shared that it is "unrealistic to prevent people from having sex," but the close contact does lead to increased risk of COVID-19 infection. The results of this study highlighted the importance of ongoing screening for STI and the benefits of making screening services available and open during the pandemic.

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The Other Side of the Moon: A Clinical Dialogue on the IL-23 Pathway

This symposium took place on 29th October 2020, as part of the 29th Academy of Dermatology and Venereology (EADV) Virtual Congress

Speakers: Kenneth B. Gordon,[1] Kristian Reich,[2] Peter C. Taylor[3]

1. Department of Dermatology, Froedtert Hospital and the Medical College of Wisconsin, Milwaukee, Wisconsin, USA
2. Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
3. Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford and St Peter's College, Oxford, UK

Disclosure: Prof Gordon has received consultation fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Janssen, Novartis, and Pfizer; and has received research grants from AbbVie, Amgen, Celgene, and Janssen. Prof Reich has been an advisor and/or paid speaker for and/or participated in clinical trials for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Covagen, Dermira, Eli Lilly, Forward Pharma, Fresenius, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medac, Miltenyi Biotec, MSD, Novartis, ocean pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and Xenoport. Prof Taylor has received consultation fees from AbbVie, Biogen, Bristol Myers Squibb, Eli Lilly, Fresenius, Galapagos, Gilead, GlaxoSmithKline, Janssen, Nordic Pharma, Pfizer, Roche, Sanofi, and UCB; and has received research grants from Celgene, Galapagos, Gilead, and Eli Lilly.

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Meeting Summary

The symposium, "The Other Side of the Moon: A Clinical Dialogue on the IL-23 Pathway", took place during the European Academy of Dermatology and Venereology (EADV) Virtual Congress on 29th October 2020. Distinguished experts Prof Gordon, Prof Reich, and Prof Taylor highlighted how the IL-23 pathway has emerged as a promising target in the management of psoriatic diseases. The expert faculty provided virtual attendees with updates on the newest developments from both dermatological and rheumatological perspectives, offering invaluable insights into psoriasis and psoriatic arthritis (PsA), as well as clinical guidance on managing these conditions in everyday practice.

Around the World in 15 Minutes: Recent Insights into IL-23 in Psoriasis

Professor Kristian Reich

Prof Reich began by highlighting how insights into the pathophysiology of psoriasis have led to the development and expansion of cytokine-targeted therapies, beginning with anti-TNF therapies in the early 2000s, and evolving to therapies targeting the IL-12, IL-17, and IL-23 pathways in the past decade. Now, with the introduction of treatments that block the p19 subunit of IL-23, therapies are available that solely block IL-23.

Biopsies from psoriatic skin have revealed that T cells are activated by dendritic cells, which requires the presentation of antigens to T cells, costimulatory signals given by cell-surface molecules, and signals received from 'educational cytokines' released by dendritic cells to determine functional Th cell subsets.[1,2] The current model of psoriasis immunopathogenesis emphasises the role of the IL-23 pathway in the production of IL-17 by T cells, thus inducing the hyperproliferation of keratinocytes and a psoriatic phenotype. Prof Reich also emphasised the role of keratinocytes in the production of a multitude of cytokines, and the interplay between keratinocytes and T cells, representing a cycle of disease perpetuation.[3] The evolution of the treatment landscape has resulted in a sharper focus on IL-12/23 inhibition, with emphasis on the inhibition of IL-23 and the p40 subunit (IL-23p40). Results of trials with briakinumab and ustekinumab have revealed that these therapies result in swift improvements in Psoriasis Area and Severity Index (PASI) 75, 90, and 100 scores after 12 weeks of treatment.[4-6] Further examination has revealed a critical role of IL-23, as seen in a study of IL-23 subunit p19 and p40 expression in paired samples of uninvolved and lesioned skin from patients with psoriasis.[7]

The breakthroughs in the past decade have led to a re-examination of the psoriasis disease model, with a greater focus on the pathways associated with innate immunity, synergistic proinflammatory effects, and keratinocyte proliferation.[3] The results of the Phase III UltIMMa-1 and -2, IMMvent, and IMMhance trials have shown that treatment with risankizumab resulted in significant improvements in static Physician's Global Assessment (sPGA) 0/1 and PASI 90 scores at Week 16, compared with placebo, adalimumab, and ustekinumab.[8-10] Furthermore, a network meta-analysis that assessed the probability of achieving PASI 90 or 100 scores at the primary endpoint at Weeks 10–16 of treatment, and at the end of the maintenance period at Weeks 44–60, revealed that a significant proportion of patients achieved these scores when receiving treatment with ixekizumab, brodalumab, risankizumab, and guselkumab at both time points, and additionally, secukinumab during the maintenance period.[11] Treatment with guselkumab has also been shown to result in long-term efficacy, with 86.2% of patients (as observed) maintaining a response over 5 years.[12]

Insights from patients with a genetic deficiency of IL-17 point to a role of the cytokine in protecting from *Candida* spp. infection.[13] Interestingly, targeting IL-23 appears to leave the physiological role of the IL-17 pathway intact (Figure 1).[14,15]

Results from the IMMhance and VOYAGE 2 trials with risankizumab and guselkumab, respectively, showed that treatment response can be maintained after treatment withdrawal, indicating a possible 'disease reprogramming' in patients with sustained responses.[16,17] Parameters predictive of the maintenance of PASI 90 responses to guselkumab following treatment withdrawal included shorter disease duration and lower BMI at baseline, and PASI 100 and Investigator's Global Assessment (IGA) 0 responses at Week 28 of treatment.[18] Underlying the maintenance of response are tissue-resident memory (Trm) cells, which remain elevated in clinically nonactive psoriatic lesions, produce IL-17, and may drive disease recurrence.[19]

Biopsy data from the ECLIPSE trial were used to examine T-cell frequency in psoriatic lesions and skin of patients treated with guselkumab or secukinumab to further differentiate between the effects of IL-23 and IL-17 blockade on psoriasis outcomes. The results showed that, at Week 24 of treatment, significant differences in the frequency of cluster of differentiation (CD)8$^+$ Trm cells within CD3 T cells were observed between treatments, with reduced numbers of Trm cells in patients who received guselkumab treatment, compared with secukinumab.[20]

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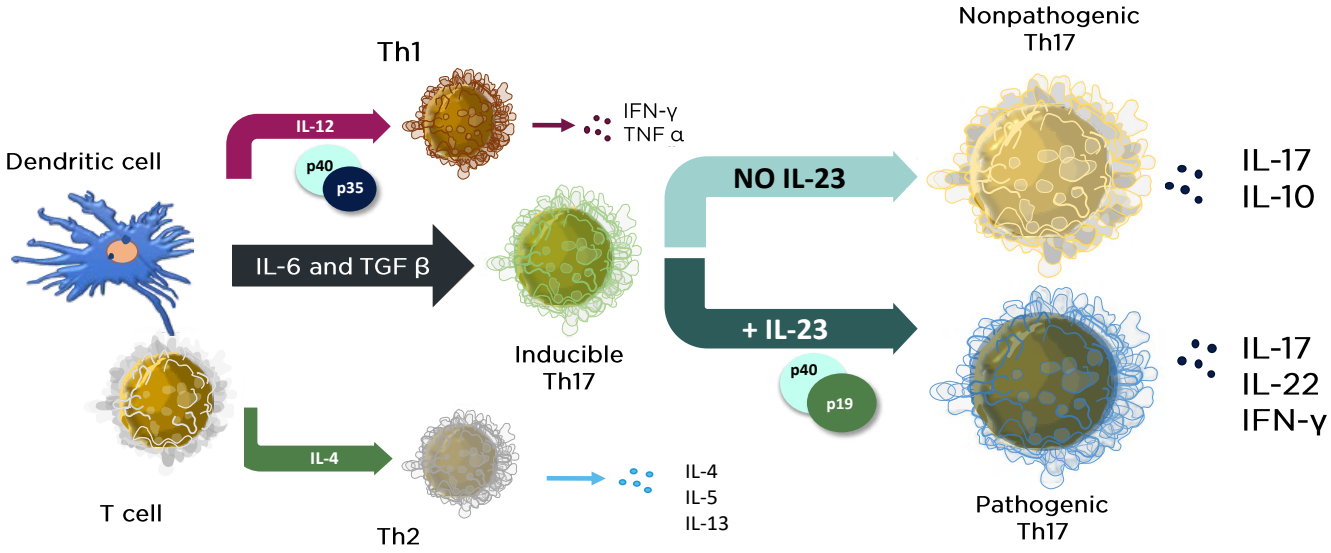

Figure 1: The cytokine environment regulates lymphocyte differentiation into functional subsets.

Adapted from Zhu J et al.[15]

Safety analyses of biologic therapies for psoriasis have revealed that there were low absolute numbers of safety events of interest, and no target-specific safety observations for IL-23 inhibitors (Reich, personal communication).

Prof Reich concluded that IL-23 is a key mediator in psoriatic skin inflammation, though the exact role of IL-23 in PsA domains (for example, enthesitis) is unclear. Inhibition of IL-23 appeared to be very safe and induced a high level of stable and sustainable clinical response in most patients with psoriasis.

The Translational Journey of IL-23 Pathway Inhibitors in Psoriasis

Professor Kenneth B. Gordon

There is much to be learnt from IL-23 inhibitors in the treatment of psoriasis, including information about the long-term efficacy of these treatments and use in special populations, as well as information regarding treatment withdrawal and retreatment, patient-reported outcomes (PRO), and long-term safety implications. In order to better understand the efficacy of IL-23p19 inhibition on psoriasis outcomes, the VOYAGE 1 and VOYAGE 2 trials examined the impact of treatment with guselkumab 100 mg, given every 8 weeks (q8w), compared with adalimumab, given at 40 mg every 2 weeks, on PASI outcomes in patients with mild-to-moderate psoriasis.[21,22] In VOYAGE 2, patients who received placebo from Weeks 0 to 16 crossed over to guselkumab 100 mg at Week 16.[21,22]

Results from the VOYAGE 1, UltIMMa-1 and -2, and reSURFACE 2 trials demonstrated the high clinical efficacy of IL-23p19 inhibitors, and high proportions of patients achieved PASI 90 responses after treatment with guselkumab, risankizumab, or tildrakizumab.[21,23,24] High levels of PASI responses were also maintained through Week 252 and Week 148 with guselkumab and tildrakizumab treatment, respectively.[12,25] A recent post hoc analysis showed that 88 of 494 (17.8%) patients treated with guselkumab from Week 0 or 16 in the VOYAGE 1 trial maintained PASI 0 scores at all visits for a period of 3 years.[26]

Furthermore, PASI 90 responses were maintained in 11.5% of patients 52 weeks after withdrawal from guselkumab, and response was regained in up to 85.7% of patients after treatment reinitiation.[17] These results further underscored the hypothesis that complete elimination of Trm cells may be required to achieve a long-term treatment response. Similarly, PASI 90 responses were maintained in sPGA 0/1 responders to

risankizumab after withdrawal.[27] Pooled data from the VOYAGE 1 and 2 trials showed that patients who received guselkumab treatment showed comparable IGA 1/0 responses to treatment, regardless of body weight, while patients with higher body weights who received adalimumab showed decreased IGA 1/0 responses.[28]

The PRO tended to mirror the clinical outcome results; patients who received guselkumab and adalimumab reported significant improvements in the Dermatology Life Quality Index (DLQI), achieving 0/1 scores at Weeks 8 and 16 of treatment, compared with placebo (p<0.001). At Week 24 of treatment, 58.9% of patients who received guselkumab achieved DLQI 0/1 scores, compared with 40.2% of patients who received adalimumab (p<0.001).[29] Similarly, in the reSURFACE 1 and 2 trials, a numerically higher proportion of patients who received tildrakizumab with high PASI scores (90–100) achieved DLQI 0/1 scores, compared with patients with PASI scores 75–89 or 50–74.[30] In the UltIMMa-1 and -2 trials, a significant proportion of patients who received risankizumab achieved DLQI 0/1 scores, compared with ustekinumab (p<0.0001).[8] Prof Gordon emphasised that psoriasis is a disease that impacts quality of life and highlighted how the elimination of the disease impacts the patient's daily life as a major treatment goal. The Psoriasis Symptoms and Signs Diary (PSSD) is an alternative PRO assessment tool, in which patients can assess and record the severity of their psoriasis symptoms and signs using a scale of 1 to 10. The assessed symptoms include itch, burning, stinging, skin tightness, and pain; the assessed signs include skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding. Scores can range from 0 to 100, with a score of 0 representing symptom- and sign-free status. Notably, in a combined analysis of the VOYAGE 1 and 2 studies, a higher proportion of guselkumab-treated patients achieved a PSSD symptom or sign score of 0 at Week 24, compared with adalimumab-treated patients (Figure 2).[31] Of the patients who received continuous guselkumab, 94.4% of patients with PSSD symptom scores of 0 achieved DLQI 0/1 scores at Week 24.[29] Furthermore, 79.4% of patients who achieved PASI 100 also achieved DLQI 0/1 at Week 24, compared with only 65.8% of patients who received adalimumab. For patients achieving PASI <100, there was no notable difference between the two treatments.[29]

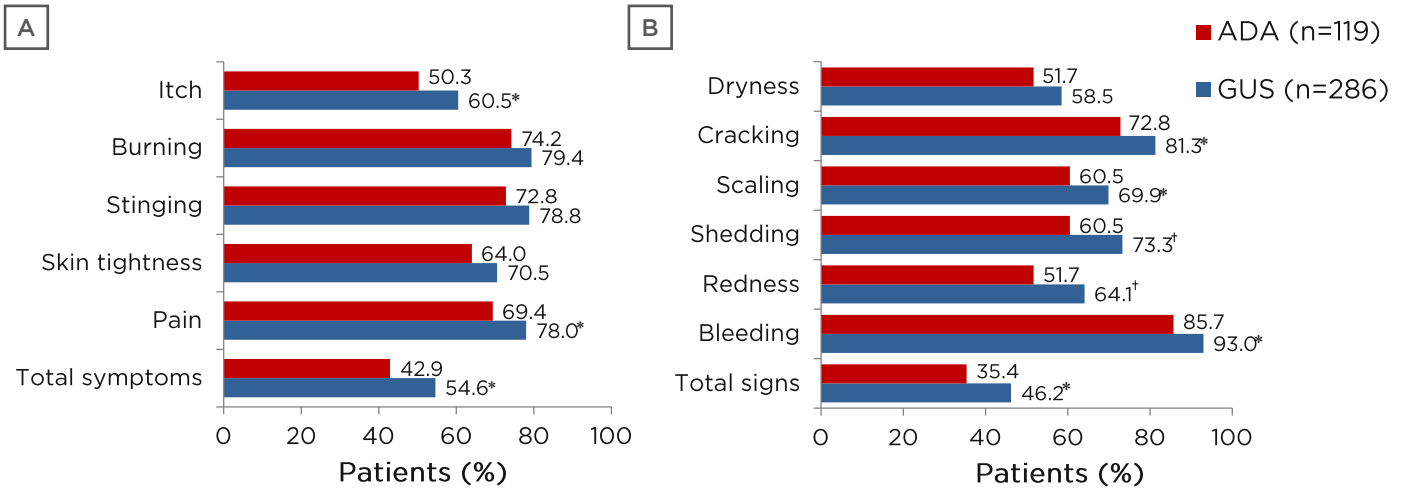

Figure 2: Proportions of patients achieving A) symptom-free or B) sign-free status at Week 24.

*p<0.05

†p<0.01

Combined analysis of PASI 100 responders from VOYAGE 1 and 2 studies.

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

Adapted from Blauvelt A et al.[31]

Data from a transcriptomic study suggested that the patients who achieved clearance (PASI 100) of their skin symptoms with guselkumab also demonstrated a normalisation of previously dysregulated genes in cleared lesional skin, whereas biopsies from cleared lesional skin of adalimumab-treated patients showed that the majority of genes had persistent dysregulated expression. This may partly account for the lower percentage of DLQI 0/1 scores in patients treated with adalimumab.[31]

Safety analyses of IL-23 inhibitors have revealed no new safety signals; a study examining tildrakizumab revealed no novel or unexpected safety signals through Week 148 of treatment,[25] while studies with guselkumab showed no new safety signals and none that increased with exposure over time.[32]

Prof Gordon concluded that clinical trial results have demonstrated consistent, high-level efficacy, and good DLQI responses that can be well maintained for years after treatment initiation. The VOYAGE trials have identified specific mechanisms driving the re-emergence of psoriasis after treatment cessation, creating unique and exciting possibilities for furthering the understanding of psoriasis signs and symptoms during treatment.

Transferring Orbits: IL-23 in Psoriatic Arthritis

Professor Peter C. Taylor

The spectrum of spondyloarthritis (SpA) encompasses both axial and peripheral manifestations, including nonradiographic axial SpA, ankylosing spondylitis, and PsA.[33] Several clinical trials have examined possible treatments for PsA, including TNF, IL-17, and IL-23 inhibitors.[34] In particular, IL-23 seems to be the main unifying factor in SpA; IL-23 sensitivity is associated with psoriasis and inflammatory bowel disease, and IL-23 overproduction is associated with SpA development.[35] Research has also shown that IL-23-responsive entheseal cells drive SpA, and that IL-23 and resident T cells promote enthesitis and osteoproliferation.[36,37]

Results from recent clinical trials have shown that several treatments, including TNF, IL-17, IL-12/23, and IL-23 inhibitors, all have an impact on American College of Rheumatology 20% (ACR 20) responses in patients with PsA.[38-41] However, a shifting focus on the p19 subunit of IL-23 has revealed that this specific inhibition resulted in significant proportions of patients achieving ACR 20 scores at Week 24 of treatment with guselkumab 100 mg every 4 weeks (q4w) and q8w, compared with placebo, in the DISCOVER-1 and -2 trials ($p<0.0001$ for both dosages in DISCOVER-2; $p<0.001$ for both dosages in DISCOVER-1) (Table 1).[41,42] Furthermore, in DISCOVER-1, significant proportions of patients who received either dosage of guselkumab also achieved ACR 50 scores at Week 24 of treatment, compared with placebo ($p<0.001$ for both dosages). A significant proportion of patients who received the guselkumab q4w dosage also achieved ACR 70 scores at Week 24, compared with placebo ($p<0.001$) (Table 1).[42]

The q4w and q8w dosages of guselkumab treatment also resulted in significant improvements in PASI 75, 90, and 100 scores, compared with placebo, at Week 24 of treatment in both the DISCOVER-1 and -2 trials.[41,42] The proportions of patients with minimal disease activity at Week 24 were higher with guselkumab than with placebo in the DISCOVER-1 and -2 trials, and response rates continued to rise through 1 year (Table 1).[43,44]

An analysis of treatment-emergent adverse events through Week 52 in DISCOVER-2 revealed no opportunistic infections or active tuberculosis, no inflammatory bowel disease, and no deaths associated with guselkumab treatment;[41,43] this was similar to the safety findings through the end of DISCOVER-1.[42,44]

Studies with several dosages of tildrakizumab have revealed that patients who received treatment also showed increased ACR 20 response rates, with significant improvements in PASI scores at Week 52 of treatment in patients with PsA.[45,46] Similarly, there were favourable ACR 20, 50, and 70 responses with risankizumab, compared with placebo, in a Phase II open-label extension study in patients with PsA.[47] In contrast to the effects in PsA, IL-23 inhibition failed to meet its primary endpoint in a study evaluating the efficacy of risankizumab in patients with

ankylosing spondylitis, with no observed improvements in Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, compared with placebo, at Week 12 of treatment.[48] However, pooled analyses from the DISCOVER-1 and -2 studies in a subgroup of patients with PsA with axial involvement revealed that treatment with guselkumab 100 mg q4w and q8w resulted in greater improvements in BASDAI scores ($p<0.001$), and significant improvements in ASDAS-related endpoints ($p<0.05$), compared with placebo, at Week 24 of treatment.[49]

Prof Taylor concluded that PsA is a progressive disease that is associated with significant disability. The diverse clinical characteristics associated with PsA have represented several challenges regarding therapies, though recent advances in the understanding of the pathobiology of PsA have contributed to several therapeutic treatment options. Recent clinical trials have validated the IL-23 pathway as a therapeutic target in psoriasis and PsA, and treatments with IL-23 inhibitors, such as guselkumab, tildrakizumab, and risankizumab, have led to improved outcomes for patients with PsA.

Conclusions

The understanding of psoriasis pathophysiology has increased substantially in past years, allowing for the development of targeted therapies, such as IL-23p19 inhibitors. As such, it may be necessary to raise the bar regarding psoriasis treatment goals as achieving PASI 90 and PASI 100 scores have become attainable for more patients with the new therapies. Emerging evidence has underscored the need to eradicate Trm cells, which remain elevated in clinically nonactive psoriatic lesions and which may drive disease recurrence.

Table 1: DISCOVER-1 and DISCOVER-2 joint (ACR) and skin (PASI) outcomes at Week 24 of treatment, and minimal disease activity outcomes at Weeks 24 and 52 of treatment.[41-44]

	DISCOVER-1			DISCOVER-2		
	Placebo	q8w	q4w	Placebo	q8w	q4w
Patients achieving scores at Week 24 (primary endpoint; %)						
ACR 20	22	52*	59*	33	64*	64*
ACR 50†	9	30‡	36‡	14	31‡	33‡
ACR 70†	6	12§	20**	4	19‡	13††
PASI 75†	14	76‡	86‡	23	79‡	78‡
PASI 90†	12	50‡	63‡	10	69‡	61‡
PASI 100†	6	26**	45‡	3	45‡	45‡
Patients achieving MDA (NRI; %)						
At Week 24	11.4	22.8	30.5	6.1	25.0	18.8
At Week 52	25.4‡‡	29.9	39.1	29.7‡‡	31.0	34.3

*$p<0.0001$ (USA procedure adjusted)

†ACR 50 and 70 scores and PASI 75, 90, and 100 scores were not multiplicity controlled in the USA-specific procedure

‡$p<0.0001$ (unadjusted)

§$p=0.0069$ (unadjusted)

**$p=0.0005$ (unadjusted)

††$p=0.0004$ (unadjusted)

‡‡Patients who received placebo crossed over to guselkumab 100 mg q4w at Week 24.

ACR: American College of Rheumatology; MDA: minimal disease activity; NRI: nonresponder imputation; PASI: Psoriasis Area Severity Index; q4w: every 4 weeks; q8w: every 8 weeks.

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Recent studies have illuminated the role of PRO in assessing psoriasis management, emphasising the importance of quality-of-life scores and patient-reported improvements in psoriasis signs and symptoms. Furthermore, recent ground-breaking advances in the understanding of the pathobiology of PsA have contributed to several therapeutic treatment options. Treatment with IL-23 inhibitors, such as guselkumab, tildrakizumab, and risankizumab, has led to improved outcomes for patients with PsA, including improvements in ACR and minimal disease activity scores. Guselkumab treatment, in particular, led to enthesitis resolution, as well as improvements in ASDAS-CRP and BASDAI scores. Safety analyses for IL-23 inhibitors have revealed no new safety signals. Furthermore, no opportunistic infections or active tuberculosis, inflammatory bowel disease, or deaths were associated with long-term guselkumab treatment.

This symposium underlined the growing importance of the IL-23 pathway in the management of psoriatic diseases. The latest developments from dermatological and rheumatological studies highlighted the key role this pathway plays in the management of psoriatic disease conditions in everyday practice.

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Latest Highlights on Biologic Treatments for Psoriasis and Psoriatic Arthritis from EADV 2020

These poster presentations took place from 29th to 31st October 2020, as part of the 29th European Academy of Dermatology and Venereology (EADV) Virtual Congress

Presenters: Antonio Costanzo,[1] Melinda Gooderham,[2-4] Alice B. Gottlieb,[5] Kristian Reich[6]

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2. SKiN Centre for Dermatology, Peterborough, Canada
3. Queen's University, Kingston, Canada
4. Probity Medical Research, Waterloo, Canada
5. Icahn School of Medicine at Mount Sinai, New York City, New York, USA
6. Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Disclosure: Prof Costanzo has received research support and/or honoraria as a scientific advisory board member and/or speaker from AbbVie, Amgen, Celgene, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB. Dr Gooderham has been an investigator, speaker, advisor, and/or consultant for AbbVie, Amgen, Akros Pharma, Arcutis Biotherapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Coherus BioSciences, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, UCB, and Valeant/Bausch Health. Prof Gottlieb has received honoraria as an advisory board member and consultant for Avotres, Beiersdorf, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Incyte, Janssen, LEO Pharma, Novartis, Sun Pharma, UCB, and XBiotech; and has received research/educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, Sun Pharma, UCB, and XBiotech. Prof Reich has been an advisor and/or paid speaker for and/or participated in clinical trials for AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Covagen, Dermira, Eli Lilly, Forward Pharma, Fresenius, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medac, MSD, Novartis, Miltenyi Biotec, ocean pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant, and Xenoport.

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Meeting Summary

Recent studies have examined the potential efficacy and safety of treatments for psoriasis and psoriatic arthritis (PsA), including the monoclonal antibody guselkumab, which specifically binds to the p19 subunit of IL-23 (IL-23p19). The results of the Phase III VOYAGE 1, VOYAGE 2, DISCOVER-1,

and DISCOVER-2 trials with guselkumab showed that treatment was followed by sustained improvements in skin, joint, and soft tissue manifestations in adult patients with moderate-to-severe psoriasis and active PsA, with no new safety signals. The poster presentations in this review discussed the results of these trials at the 29th European Academy of Dermatology and Venereology (EADV) Virtual Congress.

Complete Skin Clearance Throughout 156 Consecutive Weeks of Guselkumab Treatment in Patients with Moderate-to-Severe Psoriasis: A Post Hoc Analysis of the VOYAGE 1 Trial

The VOYAGE 1 trial[1] was a placebo- and active-controlled Phase III study to evaluate long-term efficacy and safety of the IL-23p19 inhibitor guselkumab in patients with moderate-to-severe plaque psoriasis. The study demonstrated superior efficacy of guselkumab compared with the TNF inhibitor adalimumab through 48 weeks of therapy.[2] The trial consisted of an arm in which patients received guselkumab, an active comparator arm in which patients received adalimumab from Week 0 to Week 48, and a placebo arm in which patients who were randomised to placebo crossed over to guselkumab treatment at Week 16. After Week 16 or Week 48, all patients received guselkumab until the conclusion of the study.[1] The objective of this particular post hoc analysis was to examine the baseline clinical characteristics and demographics of patients who had achieved absolute Psoriasis Area and Severity Index (aPASI) scores of 0, indicating complete skin clearance, for at least 156 consecutive weeks.[1]

Data from 494 patients who had either received guselkumab from Week 0 or crossed over to guselkumab from placebo at Week 16 were combined, resulting in 178 patients with available aPASI data for at least 156 consecutive weeks. A total of 88 patients (17.8%) maintained an aPASI score of 0 over 3 years and were compared with 90 patients (18.2%) who did not achieve an aPASI score of 0 at any visit.

In the comparator group, median aPASI scores were 18.6 at baseline, 4.0 at Week 12, and 1.9 at Week 204, but median scores in the aPASI=0 group decreased from 18.3 at baseline to 0.0 at Week 12, maintained to Week 204. Notably, 51.1% of those patients achieved complete skin clearance by Week 12 of treatment and this proportion increased to 70.5% by Week 20.[1]

Patients in the aPASI=0 group had a numerically higher plasma concentration of guselkumab than those in the comparator group. Patients who achieved complete skin clearance also generally had more favourable baseline characteristics: they were younger, had a lower BMI, and had lower body weight. Importantly, they had less severe disease and a shorter disease duration. These results demonstrated the sustained response to biologic therapy using stringent aPASI=0 criteria for 156 consecutive weeks in patients with moderate-to-severe psoriasis.[1]

Long-Term Safety of Guselkumab in Patients with Moderate-to-Severe Plaque Psoriasis Through 4 Years of Continuous Follow-up in the VOYAGE 1 and 2 Trials

The cumulative safety experience with guselkumab was described using pooled data from the VOYAGE 1 and VOYAGE 2 trials through 4 years, to Week 204.[3] The safety outcomes evaluated included adverse events (AE), AE leading to discontinuation, serious AE, and other AE of special interest, such as serious infections, malignancies, and major adverse cardiovascular events (MACE). Three groups were included in the analysis: a guselkumab group, including patients who had received placebo and crossed over to guselkumab; a group of patients who had received adalimumab and crossed over to guselkumab; and a combined guselkumab group, which included all patients from the first two groups.[3]

Cumulative rates of AE, reported per 100 patient-years of follow-up, were generally comparable between groups, showing minor year-to-year variability without increasing trends. In

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the guselkumab–adalimumab crossover and combined guselkumab groups, pooled AE rates that led to discontinuation per 100 patient-years of follow-up through Week 204 were 1.66, 1.48, and 1.62, respectively. Rates of special interest AE, including serious infections and MACE, were low. Malignancy rates in all groups were similar to the observed level in the general population in the USA. Furthermore, there were no reports of tuberculosis, anaphylactic or serum-sickness-like reactions, or inflammatory bowel disease in patients receiving guselkumab.[3]

Overall, the long-term safety profile of guselkumab remained favourable in patients with psoriasis, and AE rates were generally low and stable over a 4-year period during continuous guselkumab treatment.[3]

Guselkumab, an IL-23 Inhibitor that Specifically Binds to the IL-23 p19 Subunit, in Biologic-Naïve Patients with Active Psoriatic Arthritis: Composite Week 24 Efficacy of the Phase III, Randomised, Double-blind, Placebo-Controlled Studies

The DISCOVER-1 and DISCOVER-2 studies were multicentre, randomised, double-blind, placebo-controlled studies in patients with active PsA who were either biologic-naïve (both studies), or who had previously received a TNF inhibitor (DISCOVER-1).[4] In both studies, patients were randomised 1:1:1 to subcutaneous guselkumab 100 mg every 4 weeks (q4w); guselkumab 100 mg at Week 0, Week 4, then every 8 weeks (q8w); or placebo. Both trials included patients who had active PsA and active plaque psoriasis, nail changes, or a history of plaque psoriasis despite standard therapies. The pooled primary endpoint results for the American College of Rheumatology 20% (ACR 20) response at Week 24 showed a significantly better outcome in both guselkumab treatment arms (nominal $p<0.001$ for guselkumab versus placebo), with 28.0% for placebo-treated patients (n=261), 63.2% for the guselkumab 100 mg q8w (n=258) group, and 64.8% for patients who received guselkumab 100 mg q4w (n=273).[4] The analysis presented in this review assessed the composite joint and skin efficacy of guselkumab in the treatment of PsA separately for each study, using ACR 50 and PASI 100 scores at Week 24.[4]

The DISCOVER-1 analysis included 82 patients who received guselkumab 100 mg q8w, 89 who received guselkumab 100 mg q4w, and 78 who received placebo. ACR 50 and PASI 100 responses were achieved by 9.8% of patients who received the q8w dosage (8.7% difference; 95% confidence interval [CI]: 1.8–15.6) and 19.1% of patients who received the q4w dose of guselkumab (17.9% difference; 95% CI: 9.5–26.3), compared with 1.3% of patients who received placebo.[4]

The DISCOVER-2 analysis included 176 patients who received guselkumab 100 mg q8w, 184 who received guselkumab 100 mg q4w, and 183 who received placebo. ACR 50 and PASI 100 responses were achieved at Week 24 by 18.2% of patients who received the q8w dosage (17.4% difference; 95% CI: 11.7–23.0), and 21.7% of patients who received the q4w dose (21.2% difference; 95% CI: 15.2–27.1), compared with 0.5% of patients who received placebo.[4]

In conclusion, analysis of both studies demonstrated that in patients with active PsA, both the q4w and q8w doses of guselkumab demonstrated greater composite efficacy on joint improvement and complete skin clearance at Week 24 compared with placebo, regardless of prior biologic exposure.[4]

Efficacy and Safety of Guselkumab, a Monoclonal Antibody Specific to the p19 Subunit of IL-23, Through Week 52 of a Phase III, Randomised, Double-Blind, Placebo-Controlled Study Conducted in Biologic-Naïve Patients with Active Psoriatic Arthritis

The DISCOVER-2 study[5,6] revealed that, in addition to improving joint and skin signs and symptoms in biologic-naïve adults with active PsA, guselkumab significantly inhibited structural damage progression with the

100 mg q4w dosage. The results presented in this review reported on the efficacy and safety of guselkumab through Week 52 of treatment.[5]

ACR responses were measured in the modified intent-to-treat population, based on nonresponder imputation for missing data. Additional endpoints included improvements in physical function and health-related quality of life through Week 52.[5]

The analysis included a total of 712 out of 739 (96.3%) randomised and treated patients who continued the study agent at Week 24; 689 of 739 (93.2%) completed 52 weeks of treatment.[5]

Continued improvement with guselkumab treatment was seen in all three joint-treatment responses (ACR 20, 50, and 70) through Week 52. Of patients in the guselkumab q4w group, 70.6% achieved ACR 20 responses, as did 74.6% of patients in the q8w group. ACR 50 responses were achieved by 45.7% of patients in the q4w group and by 48.4% of patients in the q8w group. ACR 70 responses were achieved by 26.1% of patients in the q4w group and 27.8% of patients in the q8w group.[5]

Skin responses, including PASI 90 and PASI 100 scores, improved from Week 24 to 52 in patients with PsA who received guselkumab; this was also seen in the group that crossed over to guselkumab from placebo. Continued improvement in physical function and dactylitis and enthesitis outcomes, as well as a notable improvement in health-related quality of life were achieved from Week 24 to Week 52 in both active-treatment groups.[5]

Guselkumab treatment offered a favourable benefit–risk profile in patients with PsA, with no increases in serious infection rates, cases of tuberculosis or opportunistic infections, additional malignancies, MACE, or inflammatory bowel disease, consistent with the safety profile in psoriasis.[5]

Conclusions

When considered together, these results underscored the potential of specific IL-23 inhibition in psoriasis management; treatment with guselkumab resulted in high clinical response rates in PASI scores, which were maintained over 4 years of continuous treatment. These results suggested that psoriasis management goals may be shifting toward more stringent targets, such as the achievement of complete skin clearance. Furthermore, results from long-term safety analyses have revealed no new safety signals for guselkumab. Finally, IL-23 inhibition has also emerged as a promising target in PsA management, as demonstrated by the results of the DISCOVER-1 and DISCOVER-2 studies.

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Bimekizumab Efficacy and Safety in Patients with Moderate-to-Severe Plaque Psoriasis

These poster presentations took place from 29th to 31st October 2020, as part of the virtual 29th European Academy of Dermatology and Venereology (EADV) Annual Congress

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Disclosure: Prof Strober has served as consultant (honoraria) for AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Equillium, GlaxoSmithKline, Janssen, LEO Pharma, Meiji Seika Pharma, Mindera, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma, and UCB Pharma; has been a speaker for AbbVie, Amgen, Eli Lilly, Janssen, and Ortho Dermatologics; has been a scientific director (consulting fee) for the Corrona Psoriasis Registry; has been an investigator for AbbVie, Cara, Corrona Psoriasis Registry, Dermavant, Dermira, and Novartis; and is Editor-in-Chief (honorarium) for the Journal of Psoriasis and Psoriatic Arthritis. Prof Warren has received research grants and/or consulting fees from AbbVie, Almirall, Amgen, Arena, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB Pharma. Prof Reich has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Centocor, Covagen, Dermira, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medac, MSD, Miltenyi Biotec, Novartis, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB Pharma, Valeant/Bausch Health, and Xenoport.

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Meeting Summary

Prof Strober introduced the Phase III BE VIVID trial in which the efficacy of bimekizumab (BKZ) was compared with that of ustekinumab (UST) and placebo (PBO) in patients with moderate-to-severe plaque psoriasis. He described how BKZ provided robust and durable complete skin clearance through 52 weeks of treatment, as shown by higher Psoriasis Area and Severity Index (PASI) 100 responses compared with UST, regardless of baseline demographics, disease characteristics, or prior treatment

exposure. Prof Warren discussed the results of the Phase III BE SURE trial that evaluated efficacy and safety of BKZ versus adalimumab (ADA) in patients with moderate-to-severe plaque psoriasis. He highlighted how BKZ was associated with superior levels of skin clearance compared with ADA, with durable clinical responses through Week 56, regardless of the BKZ maintenance dose. Switching from ADA to BKZ resulted in rapid increases in PASI 90, PASI 100, and Investigator's Global Assessment (IGA) 0/1 responder rates, with results comparable to BKZ-randomised patients at Week 56. BKZ was generally well tolerated, with treatment-emergent adverse events (TEAE) as expected for the mode of action and comparable with previous studies. Prof Reich summarised the pooled safety data from eight Phase II and III clinical trials in patients with moderate-to-severe plaque psoriasis and explained that BKZ was well tolerated across the psoriasis clinical programme. The majority of TEAE were mild-to-moderate and discontinuation rates were low. *Candida* infections with BKZ were expected considering the mode of action of this drug (IL 17 inhibition). All *candida* infections were mucocutaneous in origin; oral candidiasis was the most common. Oral candidiasis TEAE were predominantly mild-to-moderate, easily treated, and did not lead to discontinuation.

Bimekizumab Versus Ustekinumab Efficacy Across Subgroups of Patients with Moderate-to-Severe Plaque Psoriasis: Results from the Multicentre, Randomised, Double-Blinded Phase III BE VIVID Trial[1]

Professor Bruce Strober

Psoriasis is a Th17-driven disease, with both IL-17A and IL-17F playing a pivotal role in its pathogenesis.[2,3] BKZ is a monoclonal IgG1 antibody that selectively inhibits IL-17A and IL-17F by binding with high affinity to a similar site on both isoforms.[4,5]

Severity of psoriasis and response to psoriasis therapies can vary with patient age, weight, prior treatment exposure, and other factors.[6] Therapies that provide a consistent and durable response regardless of these variables are needed, and it is important to understand how the efficacy of psoriasis therapies on skin clearance may differ between patients.

BE VIVID[7] was a randomised, double-blinded, PBO- and active comparator-controlled, Phase III trial to compare the efficacy of BKZ with that of UST over 52 weeks of treatment in adult patients with moderate-to-severe plaque psoriasis. Patients were randomised 4:2:1 to BKZ 320 mg every 4 weeks (q4w) through Week 52, UST 45 mg/90 mg (by weight) every 12 weeks through Week 52, or PBO. Patients randomised to PBO switched treatment at Week 16 to receive BKZ 320 mg q4w through Week 52. Randomisation was stratified by prior biologic exposure and region.

The authors conducted post hoc analyses of the following subgroups including only those patients who were randomised to BKZ or UST: baseline weight (≤100, >100 kg), prior biologic exposure, prior anti-TNF exposure, prior anti-IL-17 exposure, prior anti-IL-23 exposure, age (<40, 40–<65, ≥65 years), psoriasis disease duration (<median [14.54 years] or ≥median), baseline disease severity (absolute PASI: <20 or ≥20), and baseline IGA 3 or 4. Proportions of BKZ- versus UST-treated patients who achieved PASI 90 and PASI 100 were calculated at Weeks 16 and 52.

The authors reported that baseline characteristics were well balanced in the BKZ (n=321) and UST (n=163) treatment groups: baseline mean ± standard deviation PASI was 22.0±8.6 and 21.3±8.3, and body surface area affected was 29.0±17.1% and 27.3±16.7%, respectively. The duration of psoriasis was 16.0±11.6 years and 17.8±11.6 years in the BKZ and UST groups, respectively, and just over one-third of patients had previously been exposed to biologic therapy (125/321 [38.9%] in the BKZ group and 63/163 [38.7%] in the UST group).

Overall, at Week 16, PASI 90 was achieved by 85.0% and 49.7% of patients randomised to BKZ and UST, respectively, with results at Week 52 of 81.9% and 55.8%, respectively. Results were consistent across the patient subgroups at both time points.

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At Weeks 16 and 52, respectively, 58.6% and 64.5% of patients who received BKZ and 20.9% and 38.0% who received UST achieved PASI 100. A high level of PASI 100 response to BKZ was seen across all subgroups at both Week 16 and Week 52 (Table 1). The proportion of patients who achieved PASI 100 at Week 16 was greater for patients randomised to BKZ compared with UST across all subgroups (44.1–63.6% for BKZ and 0.0–29.2% for UST). Among BKZ-treated patients at Week 16, 60.2% (136/226) weighing ≤100 kg and 54.7% (52/95) weighing >100 kg achieved PASI 100 (compared with 23.0% and 14.6%, respectively, with UST), as did 60.8% (76/125) with and 57.1% (112/196) without prior biologic exposure (compared with 22.2% and 20.0%, respectively, with UST). PASI 100 responses at Week 16 were further improved at Week 52, with 50.0–69.1% of patients across subgroups who received BKZ and 16.7–50.9% of patients across subgroups who received UST achieving PASI 100.

Table 1: Patients achieving PASI 100 among subgroups (nonresponder imputation).

	Week 16		Week 52	
	Bimekizumab (n=321) n/N (%)	Ustekinumab (n=163) n/N (%)	Bimekizumab (n=321) n/N (%)	Ustekinumab (n=163) n/N (%)
Weight at baseline (kg)				
≤100	136/226 (60.2)	28/122 (23.0)	143/226 (63.3)	47/122 (38.5)
>100	52/95 (54.7)	6/41 (14.6)	63/95 (66.3)	15/41 (36.6)
Prior biologic exposure				
Yes	76/125 (60.8)	14/63 (22.2)	83/125 (66.4)	25/63 (39.7)
No	112/196 (57.1)	20/100 (20.0)	123/196 (62.8)	37/100 (37.0)
Prior anti-TNF exposure				
Yes	30/51 (58.8)	7/24 (29.2)	29/51 (56.9)	9/24 (37.5)
Prior anti-IL-17 exposure				
Yes	45/76 (59.2)	8/38 (21.1)	52/76 (68.4)	17/38 (44.7)
Age (years)				
<40	77/123 (62.6)	13/57 (22.8)	85/123 (69.1)	29/57 (50.9)
>40–<65	96/164 (58.5)	19/88 (21.6)	103/164 (62.8)	29/88 (33.0)
≥65	15/34 (44.1)	2/18 (11.1)	18/34 (52.9)	4/18 (22.2)
PSO disease duration				
<median (14.54 years)	106/169 (62.7)	17/73 (23.3)	107/169 (63.3)	34/73 (46.6)
≥median (14.54 years)	82/152 (53.9)	17/90 (18.9)	99/152 (65.1)	28/90 (31.1)
Baseline disease severity				
PASI <20	92/170 (54.1)	19/102 (18.6)	108/170 (63.5)	38/102 (37.3)
PASI ≥20	96/151 (63.6)	15/60 (25.0)	98/151 (64.9)	24/60 (40.0)
Baseline IGA*				
3	120/201 (59.7)	22/96 (22.9)	133/201 (66.2)	42/96 (43.8)
4	67/119 (56.3)	12/66 (18.2)	73/119 (61.3)	20/66 (30.3)

Nonresponder imputation was used for all missing data.

* One patient in the bimekizumab group and one patient in the ustekinumab group had a baseline IGA=2 and are not included here.

IGA: Investigator's Global Assessment; PASI: absolute Psoriasis Area and Severity Index; PSO: moderate-to-severe psoriasis.

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Among BKZ-treated patients at Week 52, 63.3% (143/226) weighing ≤100 kg and 66.3% (63/95) weighing >100 kg achieved PASI 100 (compared with 38.5% and 36.6%, respectively, with UST), as did 66.4% (83/125) with and 62.8% (123/196) without prior biologic exposure (compared with 39.7% and 37.0%, respectively, with UST).

The authors concluded that BKZ provided robust and durable complete skin clearance in patients with moderate-to-severe plaque psoriasis through 52 weeks, regardless of baseline demographics, disease characteristics, or prior treatment exposure. At Week 16, a greater proportion of BKZ-treated patients achieved PASI 90 and PASI 100 compared with UST-treated patients in all subgroups. Responses were further improved or maintained for BKZ through Week 52 and remained higher than responses with UST. These results were considered by the authors to support BKZ as a psoriasis treatment suitable for a wide variety of patients, given its consistent efficacy across all subgroups analysed.

Bimekizumab Efficacy and Safety Versus Adalimumab in Patients with Moderate-to-Severe Plaque Psoriasis: Results from a Multicentre, Randomised, Double-Blinded Active Comparator-Controlled Phase III Trial (BE SURE)[8]

Professor Richard Warren

BE SURE[9] was a randomised, double-blinded, active comparator-controlled Phase III trial to evaluate the efficacy and safety of BKZ versus ADA in adult patients with moderate-to-severe plaque psoriasis, and to assess the maintenance of efficacy of BKZ dosed in two different regimens. Patients were randomised 1:1:1 to BKZ 320 mg q4w for 56 weeks, BKZ 320 mg q4w for 16 weeks followed by BKZ 320 mg every 8 weeks (q8w) to Week 56, or ADA 40 mg every 2 weeks (q2w) for 24 weeks followed by BKZ 320 mg q4w to Week 56. Co-primary endpoints were PASI 90 and IGA 0/1 versus ADA at Week 16. Secondary endpoints included PASI 90 and IGA 0/1 at Weeks 24 and 56, and PASI 100 at Weeks 16 and 24.

A total of 158, 161, and 159 patients were randomised to BKZ 320 mg q4w, BKZ 320 mg q4w/q8w, or ADA 40 mg q2w/BKZ 320 mg q4w, respectively. Baseline demographics and characteristics were comparable in the three groups. Disease duration was long, with mean ± standard deviation of 20.4±13.2, 17.3±10.9, and 16.2±11.9 years with BKZ 320 mg q4w, BKZ 320 mg q4w/q8w, and ADA 40 mg q2w/BKZ 320 mg q4w, respectively. Approximately one-third of patients in each group had prior biologic therapy (50/158 [31.6%], 50/161 [31.1%], and 53/159 [33.3%] in the BKZ 320 mg q4w, BKZ 320 mg q4w/q8w, and ADA 40 mg q2w/BKZ 320 mg q4w groups, respectively).

The authors reported that all primary and ranked secondary endpoints were achieved. At Week 16, significantly more patients achieved PASI 90 and IGA 0/1 with BKZ (86.2% and 85.3%, respectively) than with ADA (47.2% and 57.2%, respectively), and PASI 100 was achieved by 60.8% of patients who received BKZ versus 23.9% who received ADA (all comparisons: $p<0.001$) (Table 2).[8] PASI 90 and PASI 100 response rates within BKZ treatment arms were durable through Week 56, irrespective of maintenance dose. Notably, using a nonresponder imputation analysis, 71.2% of patients who received BKZ achieved the PASI 100 threshold at Week 56 (Table 2).

In patients randomised to ADA, PASI 90, PASI 100, and IGA 0/1 responder rates rapidly increased following the switch to BKZ 320 mg q4w at Week 24. At Week 56, responder rates were comparable with those in patients who received BKZ continuously from Week 0.

The authors explained that TEAE and serious TEAE were comparable for patients who received BKZ (71.5% and 1.6%, respectively) and those who received ADA (69.8% and 3.1%, respectively) during Weeks 0 to 24. A total of 81.4% and 5.1% of patients who received BKZ (including those who switched from ADA) experienced TEAE and serious TEAE, respectively, during Weeks 0 to 56.

There were no unexpected safety findings in patients who switched from ADA to BKZ compared with patients who received continuous BKZ treatment.

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Table 2: PASI 90, PASI 100, and IGA 0/1 responses in patients randomised to receive bimekizumab and adalimumab (switching to bimekizumab at Week 24) though Week 56 (nonresponder imputation).

	Bimekizumab 320 mg q4w (n=158)	Bimekizumab 320 mg q4w (Weeks 0–16)/ q8w (Weeks 16–56)* (n=161)	Bimekizumab total (n=319)	Adalimumab (Weeks 0–24) or bimekizumab 320 mg q4w (Weeks 24–56)† (n=159)
PASI 90, n (%)				
Week 16	138 (87.3)	137 (85.1)	275 (86.2)‡	75 (47.2)
Week 24	136 (86.1)‡	137 (85.1)‡	273 (85.6)‡	82 (51.6)
Week 56	134 (84.8)	133 (82.6)	267 (83.7)	130 (81.8)
PASI 100, n (%)				
Week 16	95 (60.1)	99 (61.5)	194 (60.8)‡	38 (23.9)
Week 24	107 (67.7)‡	106 (65.8)‡	213 (66.8)‡	47 (29.6)
Week 56	114 (72.2)	113 (70.2)	227 (71.2)	106 (66.7)
IGA 0/1, n (%)				
Week 16	138 (87.3)	134 (83.2)	272 (85.3)‡	91 (57.2)
Week 24	136 (86.1)‡	140 (87.0)‡	276 (86.5)‡	92 (57.9)
Week 56	130 (82.3)	134 (83.2)	264 (82.8)	128 (80.5)

* Patients received bimekizumab 320 mg q4w for 16 weeks followed by q8w through Week 16–56.

† Patients randomised to adalimumab switched to bimekizumab 320 mg q4w at Week 24 (10 patients randomised to adalimumab at Week 0 did not continue in the trial past Week 24 and never received bimekizumab).

‡ p value versus adalimumab p<0.001.

PASI 90/100: ≥90/100% improvement from baseline in PASI.

IGA assessed on a five-point scale.

Data shown include all randomised patients. Missing data were imputed as nonresponder imputation. p values for the comparison of treatment groups are based on the Cochran–Mantel–Haenszel test from the general association.

IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index; q4w: every 4 weeks; q8w: every 8 weeks.

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There was one death in the study in a patient who received ADA; this was unrelated to treatment. The most common TEAE in the study was nasopharyngitis (which is a common side effect in biologic studies), with generally comparable incidence in the different treatment groups (20.3%, 16.8%, and 23.9% in the BKZ 320 mg q4w, BKZ 320 mg q4w/q8w, and ADA 40 mg q2w/BKZ 320 mg q4w groups, respectively, at Weeks 0–24, and 11.8%, 10.1%, and 13.4%, respectively, at Weeks 24–56). Oral candidiasis occurred in approximately 10% of patients in the BKZ groups compared with 0% in the ADA group at Weeks 0–24; however, cases of oral candidiasis were mostly mild or moderate, localised, and easily treatable and did not lead to discontinuation. Over 56 weeks, there were no cases of suicidal ideation or behaviour, inflammatory bowel disease, serious hypersensitivity reactions, or major adverse cardiac events in BKZ-treated patients.

The authors concluded that BKZ q4w was associated with superior levels of skin clearance compared with ADA, with complete skin clearance (PASI 100) at Week 16 achieved by 61% of patients who received BKZ q4w versus 24% who received ADA. Clinical responses were durable through Week 56, regardless of the BKZ q4w or q8w maintenance dose. Switching from ADA to BKZ resulted in rapid increases in PASI 90, PASI 100, and IGA 0/1 responder rates, with results comparable to BKZ-randomised patients

at Week 56. There were no new safety signals with BKZ, which was generally well tolerated, and results were comparable with previous studies.

Bimekizumab Safety in Patients with Moderate-to-Severe Psoriasis: Analysis of Pooled Data from Phase II and III Clinical Trials[10]

Professor Kristian Reich

BKZ has a new mode of action: in addition to blocking IL-17A (like secukinumab and ixekizumab) it blocks IL-17F; therefore, it is important to assess the safety data associated with this new mode of action as early as possible. Furthermore, psoriasis is a chronic disease requiring long-term management, so it is of interest to ascertain the safety profile of therapies such as BKZ. Pooled data from eight Phase II and III clinical trials were analysed to derive short and longer-term safety data in BKZ-treated adult patients with moderate-to-severe plaque psoriasis.

Safety from the initial treatment periods (Weeks 0–16) of three Phase III trials (BE SURE, BE VIVID, and BE READY[11]) was evaluated for patients who received ≥1 dose of BKZ, UST, ADA, or PBO. Longer-term safety was also evaluated for patients who received ≥1 dose of UST through 52 weeks in BE VIVID, and for patients who received ≥1 dose of BKZ in BE SURE, BE VIVID, BE READY, the BE BRIGHT[12] open-label extension Phase III trial (interim cut-off: 1st Nov 2019), and four Phase II trials (BE ABLE 1,[13] BE ABLE 2,[14] PS0016,[15] and PS0018[16]).

A total of 989 patients received ≥1 BKZ dose for 16 weeks, representing 306.0 patient-years (PY) of exposure, 163 patients received UST (50.1 PY), 159 received ADA (48.8 PY), and 169 received PBO (51.6 PY). Mean psoriasis duration in the study patients was >16 years. Around one-third of the patients had received prior biologic therapy (38.4% on BKZ 320 mg q4w, 33.3% on ADA, 38.7% on UST, and 41.4% on PBO).

During the initial 16 weeks of treatment, the authors reported that at least one TEAE was experienced by 593 (60.0%) patients on BKZ, 83 (50.9%) on UST, 96 (60.4%) on ADA, and 74 (43.8%) on PBO, with no significant trend noted. Serious TEAE were reported in 15 (1.5%) patients on BKZ, five (3.1%) on UST, three (1.9%) on ADA, and four (2.4%) on PBO. Treatment discontinuation as a result of TEAE occurred in 17 (1.7%) patients on BKZ, three (1.8%) on UST, four (2.5%) on ADA, and seven (4.1%) on PBO. One death occurred in each treatment group.

Focussing on TEAE of special interest during the initial treatment period (Weeks 0–16), serious infections occurred in three (0.3%) BKZ-treated patients, oral candidiasis in 75 (7.6%), and *de novo* ulcerative colitis in one (0.1%). The *candida* infections with BKZ were expected considering the mode of action of this drug (IL-17 inhibition).

The authors highlighted that exposure-adjusted incidence rate per 100 PY of selected TEAE and TEAE of special interest generally did not increase with BKZ exposure duration (Table 3).

Over the long term, TEAE in BKZ-treated patients occurred at a rate (95% confidence interval [CI]) of 238.0 (226.0–250.5)/100 PY, serious TEAE at 6.6 (5.5–7.9)/100 PY, and discontinuations because of TEAE at 4.9 (4.0-6.1)/100 PY. Five deaths occurred (0.3 [95% CI: 0.1–0.6]/100 PY), all of which were unrelated to treatment.

A total of 304 (17.0%) BKZ-treated patients had mucocutaneous *candida* infection TEAE (18.7 [95% CI: 16.7–21.0]/100 PY). Of the 304, 271 (15.1%) had oral candidiasis (16.4 [95% CI: 14.5–18.5]/100 PY). Most candidiasis cases (>99%) were mild-to-moderate and easily treated and did not lead to discontinuation. One (<0.1%) serious case (oesophageal candidiasis) and 6 (0.3%) discontinuations as a result of candidiasis were reported.

There were low rates of malignancy (0.8 [95% CI: 0.5–1.4]/100 PY) and adjudicated major adverse cardiac events (0.7 [95% CI: 0.3–1.1]/100 PY) in patients who received BKZ. There was one case of active suicidal ideation (0.1/100 PY) in a BKZ-treated patient with a prior history of suicide attempt. There were no cases of anaphylaxis and no additional cases of inflammatory bowel disease with increased exposure to BKZ.

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Table 3: Treatment-emergent adverse events of interest (short and longer term).

	Initial treatment period (Week 0–16)				Short term (Week 0–16)	Longer term
	n (%)				EAIR per 100 PY (95% CI)	
	BKZ 320 mg q4w* n=989	ADA† n=159	UST‡ n=163	PBO§ n=169	BKZ 320 mg q4w* n=989	All BKZ** n=1,789
Exposure (PY)	306.0	48.8	50.1	51.6	306.0	1,830.4
Serious infections	3.0 (0.3)	0.0	2.0 (1.2)	0.0	1.0 (0.2–2.9)	1.4 (0.9–2.0)
Inflammatory bowel disease	1.0 (0.1)	0.0	0.0	0.0	0.3 (0.0–1.8)	0.1 (0.0–0.3)
Candida infections	90.0 (9.1)	0.0	0.0	0.0	30.6 (24.6–37.6)	18.7 (16.7–21.0)
Oral candidiasis	75.0 (7.6)	0.0	0.0	0.0	25.3 (19.9–31.8)	16.4 (14.5–18.5)
Adjudicated MACE	1.0 (0.1)	0.0	0.0	0.0	0.3 (0.0–1.8)	0.7 (0.3–1.1)
Malignancies (including NMSC)	4.0 (0.4)	1.0 (0.6)	0.0	1.0 (0.6)	1.3 (0.4–3.4)	0.8 (0.5–1.4)
Adjudicated SIB††	0.0	0.0	0.0	0.0	0.0	0.1 (0.0–0.3)
Serious hypersensitivity reactions‡‡	0.0	0.0	0.0	0.0	0.0	0.2 (0.0–0.5)
Injection site reactions	27.0 (2.7)	3.0 (1.9)	2.0 (1.2)	2.0 (1.2)	9.0 (5.9–13.1)	3.1 (2.4–4.1)
Hepatic events	19.0 (1.9)	9.0 (5.7)	0.0	2.0 (1.2)	6.3 (3.8–9.8)	5.6 (4.6–6.8)

EAIR are patient incidence of new cases per 100 PY.

* BKZ initial treatment period data are included from three pivotal Phase III studies.

† ADA initial treatment period data are from BE SURE.

‡ UST initial treatment period data are from BE VIVID.

§ PBO initial treatment period data are from BE VIVID and BE READY.

** BKZ longer-term data are pooled from four Phase III trials and four Phase II trials.

†† Includes one event adjudicated by the external Neuropsychiatric Committee (active suicidal ideation with some intent to act) in a patient with pre-existing psychiatric conditions.

‡‡ Includes one fatal event of circulatory failure (adjudicated MACE), one event of atopic dermatitis-like disseminated eczema, and one case of anaphylactic shock due to insect sting, all considered unrelated to study treatment.

ADA: adalimumab; BKZ: bimekizumab: CI: confidence interval; EAIR: exposure-adjusted incidence rate; MACE: major adverse cardiovascular event; NMSC: nonmelanoma skin cancers; PBO: placebo; PY: patient-years; q4w: every 4 weeks; SIB: suicidal ideation and behaviour; UST: ustekinumab.

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The majority of TEAE were mild-to-moderate and discontinuation rates were low. There were *candida* infections, as expected for this class (IL-17 inhibitors). Overall, the exposure-adjusted incidence rate of TEAE and TEAE of interest did not increase with BKZ exposure. The authors concluded that BKZ was well tolerated across the psoriasis clinical programme, with no new safety signals compared to other targeted therapies.

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Abstract Reviews

Read on for summaries of abstracts presented at the 29th EADV 2020 Virtual Congress, covering topics such as PD-1 and mTOR inhibitors, inflammatory bowel disease, and metformin, in skin disease.

Skin Toxicity Caused by Sequential Treatment with PD-1 Inhibitor and mTOR Inhibitor

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Everolimus, immune checkpoint inhibitors, maculopapular eruption, mTOR inhibitors, nivolumab, skin toxicity.

Citation: EMJ Dermatol. 2020;8[1]:44-45. Abstract Review No. AR1.

BACKGROUND

Immune checkpoint inhibitors and mTOR inhibitors are known to be associated with skin toxicity. mTOR inhibitors most commonly cause aphthous stomatitis, papule-pustulous dermatitis, and impaired wound healing.[1] Programmed cell death protein receptor (PD-1) inhibitors confer increased risk of lichenoid reactions, pruritus, and maculopapular lesions.[2] There has been an increased interest in studying idiosyncratic drug reactions arising during sequential treatment with immune checkpoint inhibitors and targeted immunotherapy drugs.[3] Here, the authors describe the case of an acute maculopapular eruption in a patient treated with nivolumab and everolimus.

CASE DESCRIPTION

A 69-year-old female patient diagnosed with renal cancer was treated with nine cycles of the multitargeted receptor tyrosine kinase inhibitor sunitinib (50 mg per day orally). The patient was subsequently prescribed nivolumab (3 mg/kg per day intravenously). Remission had not been achieved, and she was sequentially treated with everolimus (10 mg per day intravenously). Under treatment with everolimus, patient examination demonstrated diffuse maculopapular eruption with excoriations (Figure 1). Her body surface area index was 67%. She also complained of severe generalised pruritus, with 10 points on the

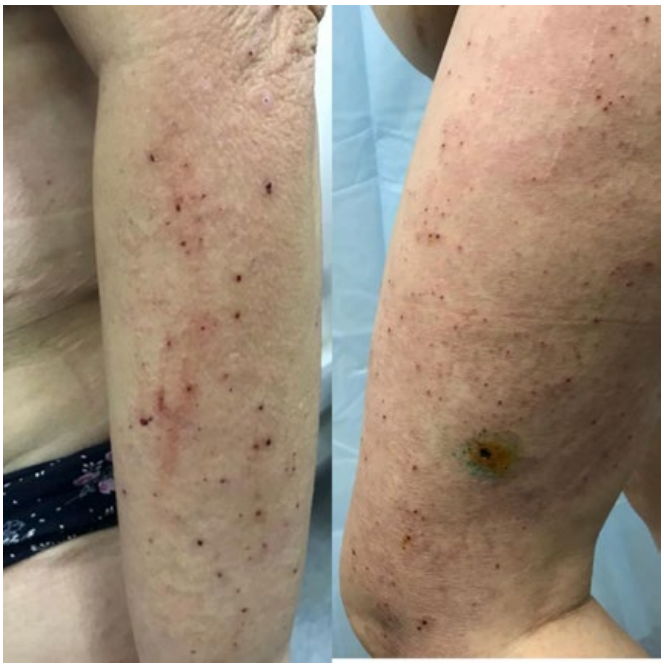

Figure 1: Acute maculopapular eruption with excoriations, induced by sequential treatment with nivolumab and everolimus.

pruritus severity scale. Treatment with systemic prednisone and combination topical therapy was effective.

DISCUSSION

This case represents the idiosyncratic drug reaction caused by sequential treatment with an immune checkpoint inhibitor and mTOR inhibitor. This type of drug toxicity stems from a double blockade of common immunogenic pathways. Paradoxical immune hyperactivity caused by this process is called 'paradoxical activation'.[4,5] This process underlying immunogenic skin toxicity requires further investigation, which may contribute to establishing patient management guidelines as well as developing proper preventive measures.

CONCLUSION

Combination cancer chemotherapy may induce idiosyncratic skin reactions. Patients sequentially treated with an immune checkpoint inhibitor and mTOR inhibitor may present with acute maculopapular eruptions and generalised pruritus. The described condition usually responds to systemic glucocorticoid therapy and topical combination therapy. Supportive treatment in patients with cancer includes early recognition and proper treatment of idiosyncratic drug reactions. Therefore, further investigations in this field would help provide optimal patient care without reducing and cancelling the anticancer therapy regimen.

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Mycobacterium bovis Infection Mimicking Pyoderma Gangrenosum and Inflammatory Bowel Disease in an Elderly Male

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The patient in this case has given written informed consent to publication of their images and case details.

Keywords: Atypical ulceration, inflammatory bowel disease (IBD), mycobacterial infection, pyoderma gangrenosum (PG).

Citation: EMJ Dermatol. 2020;8[1]:46-47. Abstract Review No. AR2.

BACKGROUND

Cutaneous ulceration presents many challenges to the dermatologist and multidisciplinary team due to a broad differential diagnosis, difficult management decisions, and delayed wound healing.[1] New ulceration should always prompt consideration of infection, with tissue samples rather than swabs often required, along with extended and cold cultures.[2,3] Reported here is a case of mycobacterial infection mimicking pyoderma gangrenosum (PG) and Crohn's disease (CD) in which tissue culture prevented potential disseminated infection with the use of immunosuppressant biologic agents.

CASE REPORT

A 78-year-old male presented to the emergency department with a 4-week history of an enlarging ulcer on the left upper thigh. On examination, a 10x5 cm area of ulceration was noted, with a violaceous undermined edge (Figure 1). Despite the appearance, the patient reported the ulcer to be nontender. The patient had been treated for suspected cellulitis at this site 3 weeks prior with 1 week of intravenous flucloxacillin followed by 1 week of oral treatment. In addition, he had been diagnosed with CD 4 months previously and received one dose of the gut-specific α4β7-integrin blocker vedolizumab. An improvement in stool frequency was noted, but he remained persistently anaemic with a haemoglobin of 95 g/L (130–170 g/L) dependent on regular red cell transfusion.

Routine bloods revealed a C-reactive protein of 26.4 mg/L (<5 mg/L) with a normal serum protein electrophoresis and negative autoantibody screen. The working diagnosis was pyoderma gangrenosum secondary to CD and possible exacerbation by vedolizumab.[4]

Incisional biopsy for histopathology demonstrated a dense neutrophilic infiltrate supportive of PG; however, multinucleated giant cells forming noncaseating granulomata were also noted (Figure 1). Ziehl–Neelsen and auramine–rhodamine staining for mycobacteria were negative. Prolonged culture for atypical organisms was requested.

Multidisciplinary input was sought and treatment initiated with oral prednisolone 0.5 mg/kg with screening bloods for biologics sent. A decision was made to commence infliximab to treat the CD and PG concurrently. *Pseudomonas aeruginosa* was subsequently isolated on swabs and due to increasing exudate, treatment with intravenous piperacillin/tazobactam and ciprofloxacin was commenced. While the exudate improved, the ulcer edge continued to appear violaceous and active.

Seven days before a planned admission for infliximab, *Mycobacterium bovis* was isolated from skin culture. The source of infection was not found. On review of gastrointestinal histology, no definitive features of CD had been identified and so primary colonic mycobacterial infection was suspected. The patient completed 9 months of antimycobacterial treatment consisting of rifampicin/isoniazid and ethambutol for 2 months followed by rifampicin/isoniazid alone for 7 months. He achieved complete healing of the ulcer site with resolution of all bowel symptoms and a return to activities of daily living unassisted.

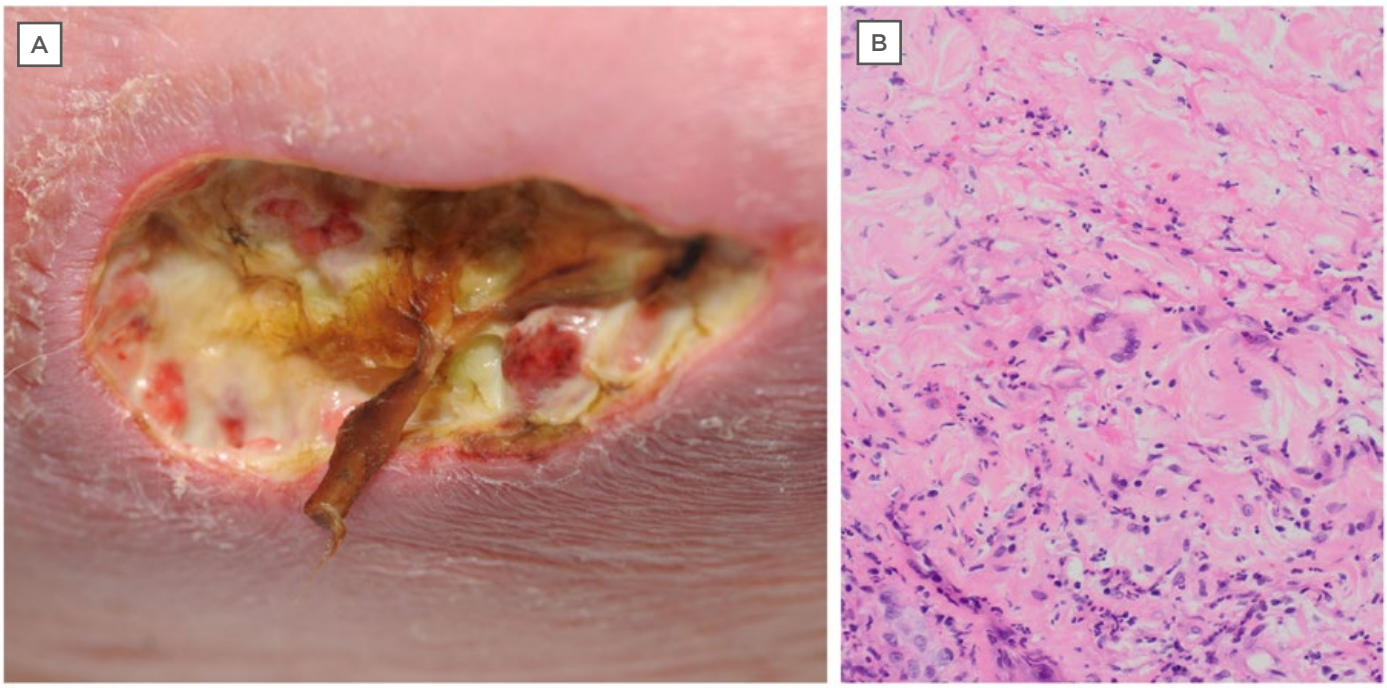

Figure 1: A) Clinical photograph of the left upper inner thigh. **B)** Histopathology photograph (haematoxylin and eosin staining 200x magnification) of inflammation with multinucleated giant cells.

CONCLUSION

PG is a diagnosis of exclusion with a differential diagnosis including malignancy, vasculitis, infection, and other rarer causes.[2] Fatal disseminated *M. bovis* infection following Bacillus Calmette–Guérin vaccination has previously been reported in an infant born to a mother taking infliximab.[5] Infliximab has been shown to be the anti-TNFα agent most commonly associated with mycobacterial infection.[6] This case underpins the value of routine tissue culture in both presumed PG and atypical ulceration, a step that can often be forgotten. It is easy to experience diagnostic bias when faced with clinical PG-like ulceration albeit in the absence of pain. In this present patient, without tissue culture, disseminated mycobacterial infection may have ensued.

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Coping Strategies as Predictors of Stress and Anxiety in Caregivers of Patients with Severe Drug Allergy

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Keywords: Anxiety, coping strategy, severe drug allergy, stress.

Citation: EMJ Dermatol. 2020;8[1]:48-49. Abstract Review No. AR3.

INTRODUCTION

The unpredictability and fear of potentially life-threatening allergic reactions influences the occurrence and manifestation of anxiety in patients with severe drug allergy, as well as their family members.[1] Allergic reactions can range from mild, with local symptoms, to severe, with the most extreme being anaphylactic shock.[2] Anxiety limits psychosocial functioning and has a strong impact on quality of life. Most mental health recommendations are focussed on patients,[3] however, it is frequently overlooked that their family members and caregivers are also affected.

MATERIALS AND METHODS

A total of 21 family members and caregivers of patients with severe drug allergy who had been diagnosed <6 months prior to the start of the study (Group A1), and 97 family members and caregivers of patients that were diagnosed >6 months prior to the study (Group A2), were included. Group B1 (control) included 22 family members of patients with severe food allergy (manifesting with adverse events) diagnosed <6 months prior to the study and 92 family members of patients diagnosed >6 months prior (Group B2). All participants underwent semi-structured interviews using the Ways of Coping Questionnaire (WCQ) and the Hamilton Anxiety Rating Scale (HAMA), specialised for the purpose of the study.

RESULTS

The least frequently used strategies for coping in Group A2 were distancing (14%), confrontation (11%), and avoidance (13%). However, in Group A1, confrontation was more pronounced (53%), especially during the initial phase of facing with the diagnosis. The most common strategies in Group A2 were planned problem solving, seeking social support, and positive evaluation of the state.

A high level of anxiety was diagnosed in Group A1, which, along with coping strategies, was found to have interfered with quality of life.

The most frequent coping strategy in Group B1 was confrontation (42%), followed by distancing and isolation. The most frequently used approachs in Group B2 were problem-solving coping strategies and a positive attitude and evaluation of the state. The general major concerns, as demonstrated in the results of the targeted seven-item questionnaire, were unpredictability of severe drug allergy and delayed access to urgent medical care. The general major concern of partners was the possibility of a lethal outcome; in contrast, the parents' major concern was having access to a treatment centre where their child could receive adequate treatment in a timely manner.

CONCLUSION

Participants with a functional, positive, and proactive coping style had a reduced level of stress and anxiety related to the disease and therapy. Adherence to healthcare professional's advice was higher and there was a positive effect on the patient's overall health and quality of life. Although patients with severe drug allergy are

independent, fully functional members of society, caregivers and family members must not be overlooked when considering comprehensive care. Understanding the complex impact severe drug allergy has on everyday life might also offer ideas for additional therapeutic approaches, both for patients with severe drug allergy and their caregivers.

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Comparison of Total Body Nevus Count in Patients with Multiple Primary Melanoma and Single Primary Melanoma: A Prospective Single Centre Study

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Keywords: Arm nevus count, head and neck nevus count, leg nevus count, multiple primary melanomas (MPM), single primary melanoma (SPM), sunburn with blistering, total body nevus count (TBNC), trunk nevus count.

Citation: EMJ Dermatol. 2020;8[1]:49-50. Abstract Review No. AR4.

BACKGROUND AND AIMS

A high number of benign melanocytic nevi has been implicated as a major risk factor for melanoma development;[1] however, there are sparse data on the total body nevus count (TBNC) and its relation to the propensity for multiple primary melanomas. The aim of this study was to evaluate TBNC in patients with melanoma.

METHODS AND RESULTS

A total of 263 patients, 30 (11.4%) with multiple primary melanomas (MPM) and 233 (88.6%) with a single primary melanoma (SPM), were included in the study. The 30 patients with MPM had two or more primary melanomas with an average of 2.66 melanomas per patient. The female:male ratio was 1. The mean age at the time of melanoma diagnosis was significantly lower in patients with MPM ($p<0.05$). There was no difference in skin type between the two groups ($p>0.05$). Mean TBNC was 96.87 (standard deviation [SD]±124.71) for SPM and was significantly different to 247.00 (SD±261.58) for patients with MPM ($p<0.0001$). Mean nevus count in specific body locations, including head and neck ($p<0.0001$), right arm ($p<0.000$), left arm ($p<0.000$), trunk ($p<0.000$), and lower extremities ($p<0.000$), were significantly high in patients with MPM. TBNC was strongly correlated with right arm (coefficient of determination [R^2]: 0.849), left arm (R^2: 0.884), and trunk (R^2: 0.919) nevus counts, and moderately correlated with lower extremity (R^2: 0.597) and head and neck (R^2: 0.346) nevus counts in both

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groups. The percentage of patients who gave a history of sunburn before 20 years of age was significantly higher in patients with MPM. The mean number of lifetime sunburns with blistering was significantly higher in patients with MPM (6.17 versus 2.33).

Previous studies have shown that TBNC is correlated with nevus count on specific sites[2] and that the arm nevus count appears to be the most predictive location for estimating TBNC.[2] The presence of 20 or more nevi on the arms was determined as an independent predictor of a high TBNC and risk of melanoma.[3] In this present study, right arm, left arm, and trunk nevi count were found to be strongly correlated with TBNC (r: 0.887, r: 0.913, r: 0.955, respectively). Among them, trunk nevus count was the most predictive location for estimating TBNC.

DISCUSSION AND CONCLUSION

Exposure to high levels of sunlight in childhood is a strong determinant for melanoma risk, but sun exposure in adulthood also plays a role in the melanoma development.[4] Previous studies have shown that having five or more blistering sunburns in childhood is associated with a 2-fold increased risk of melanoma development.[5,6] In this present study, having sunburn in earlier stages of life (<20 years of age) was more prevalent in patients with MPM, as well as total number of severe sunburn reactions. TBNC is one of the major phenotypic risk factors in melanoma development; therefore, it is not surprising that there is an association between TBNC and sun exposure in early stages of life based on the number of primary melanomas in high-risk individuals. This is possibly caused by the increased melanocyte burden posed by an increased number of melanocytic nevi and ultraviolet-induced carcinogenesis in individuals who are genetically susceptible. Further studies are needed to determine a treshold for TBNC and nevus count in specific body sites in order to assess the individuals under risk for developing MPM and ultraviolet protection is required to reduce the risk of melanoma development.

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Adverse Skin Reactions to Metformin: A Case Report and Mini Review

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Allergy, erythema annulare, hypersensitivity, rash, urticaria.

Citation: EMJ Dermatol. 2020;8[1]:50-53. Abstract Review No. AR5.

INTRODUCTION

Metformin, a widely used antidiabetic and antiobesity drug, exerts multiple effects on the skin, and could potentially induce a variety of dermatoses.[1]

Table 1: A list of the known drug-induced skin reactions to metformin.

ASDR	Mechanism	Reference
Alopecia	Transient and reversible inhibition of the hair cycle	Pierre Fabre Group[14] 2012
Angioedema	Urticaria-like	Pierre Fabre Group[15] 2013
Buccal lichen planus	Unknown	Pierre Fabre Group[16] 2018
DRESS syndrome	T-cell mediated Type IV hypersensitivity reaction	Voore et al.,[5] 2016
Eczematous dermatitis	T-cell mediated Type IV hypersensitivity	Pierre Fabre Group[6] 2012
Fixed pigmented erythema	Cytotoxic mechanism relying on CD8 lymphocytes	Pierre Fabre Group[12] 2010; Steber et al.,[17] 2016; Ramírez-Bellver et al.,[18] 2017
Flush	Often pharmacological	Pierre Fabre Group[19] 2012
Leukocytoclastic vasculitis	Immune-mediated reaction to a precipitating antigen	Salem et al.,[7] 2006
Lichenoid eruption	The drug acts as an antigen that attaches to epidermal cells and induces a cytotoxic response	Pierre Fabre Group[13] 2012
Maculopapular exanthema	Often immunological, mediated by lymphocytes	Pierre Fabre Group[8] 2019
Oedema	Multiple	Pierre Fabre Group[20] 2012
Pemphigus	Autoimmune, antigens specific to the epidermis	Pierre Fabre Group[9] 2012
Peripheral oedema	Multiple	Pierre Fabre Group[21] 2018
Photosensitivity	Variable	Pierre Fabre Group[22] 2012
Photosensitisation	Photosensitised oxidation by free radicals, photosensitisation by singlet oxygen, production of reactive oxygen species, cycloaddition, photoexcitation in a triplet state, etc.	Pierre Fabre Group[23] 2019; Harris et al.,[24] 1971
Pruritus	Several mechanisms: immunological, nonimmunological by release of proinflammatory factors, components of the complement, derivatives of the prostaglandin pathways, cytokines, and also pharmacological Toxic visceral liver and kidney involvement can also be responsible for the pruritus	Pierre Fabre Group[10] 2012
Pseudoporphyria	Phenomenon of phototoxicity	Pierre Fabre Group[25] 2012
Purpura	It can be caused by a thrombocytopenia or a parietal vascular alteration	Pierre Fabre Group[26] 2012
Rosacea	Anomalies in the external thermal regulation	Pierre Fabre Group[27] 2012
Rosacea-like facial rash	An allergic pathogenesis may be suggested	Mumoli et al.,[28] 2014
Urticaria	Several mechanisms are possible: immunological (IgE, immune complexes) or nonimmunological (complement activation, prostaglandin pathway, direct histamine secretion)	Pierre Fabre Group[11] 2012

CD: cluster of differentiation; DRESS: Drug rash with eosinophilia and systemic symptoms.

Among others, the most commonly described drug-induced skin reactions include rash, urticaria, and lichenoid eruption.[2,3]

CASE REPORT

The authors herein report a rare case of generalised erythema annulare in a 75-year-old female Caucasian patient with multiple comorbidities. The skin eruption was presented by polycyclic out-spreading erythematous lesions, with central clearing. Concomitant pathology included Type 2 diabetes mellitus, hypertension, coronary heart disease, coronary stent implantation, atrial fibrillation, mitral regurgitation, chronic obstructive pulmonary disease, chronic respiratory failure, Hashimoto's thyroiditis, hip arthroplasty, chronic gastritis, caecal and ascending colon polyps, and secondary iron deficiency anaemia. The concomitant therapy included metildigoxin, bisoprolol, valsartan, furosemide, acenocoumarol, spironolactone, pantoprazole, rosuvastatin, levothyroxine, metformin, allopurinol, fluticasone furoate/vilanterol, and tiotropium.

Histopathological examination of a skin biopsy showed a thinned epidermal layer and a tight lymphocytic infiltrate in the upper dermis containing eosinophils and surrounding the vessels in a 'coat-sleeve' distribution. Based on the characteristic clinical and histological appearance of the skin lesions, a diagnosis of erythema annulare centrifugum (EAC) was given. Therapy with topical clobetasol propionate 0.05% cream was started, as well as consecutive replacement of the concomitant medications. Only the exclusion of metformin led to the disappearance of the skin lesions in 2 weeks. No relapse of the EAC occurred thereafter.

DISCUSSION

First described by Darier in 1916,[4] EAC is a reactive condition that can be associated with drug intake. A list of the known drug-induced skin reactions to metformin are presented in Table 1.[5-28] The exact mechanisms on the development of skin reactions include Type IV hypersensitivity, circulating immune complex deposits, immunological or/and nonimmunological release of proinflammatory factors, components of the complement, derivatives of the prostaglandin pathways, cytokines, and cytotoxicity.[5-13]

CONCLUSION

The pathophysiology of drug-induced EAC probably includes a variety of mechanisms, and thus leads to versatile clinical manifestation. In this case of generalised EAC, only via the exclusion of metformin from the patient's therapy did their skin lesions resolve. Therefore, it seems most likely to have been responsible for the disease development.

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Congress Interviews

A conversation with European Academy of Dermatology and Venereology (EADV) President Prof Alexander Stratigos begins this collection of interviews and is followed by a roundtable interview with EADV Committee members. We spoke to the experts about the highlights and key innovations from EADV Virtual Congress.

Prof Alexander Stratigos

President, European Academy of Dermatology and Venereology (EADV); Professor of Dermatology-Venereology, University of Athens Medical School, Athens, Greece; Chair, First Department of Dermatology-Venereology, Andreas Sygros Hospital, Athens, Greece

Q1 With over 25 years' of experience in dermatology, what initially sparked your interest to pursue a career in this field and what motivates you to continue researching?

I became involved in dermatology for various reasons, but what really attracted me was the impressive range and diversity of the specialty. I remember as a medical student I was interested in different specialties, including surgery and paediatrics. When I rotated through dermatology, I became aware of the breadth of fascinating disciplines in which I could work. I could pursue clinical dermatology and at the same time practice dermatologic surgery. Or I could focus in paediatric dermatology or dermato-oncology. In other words, I could be involved in so many different fields under the roof of one specialty. I also started my career in dermatology at the time when research was unravelling the mechanisms of many skin diseases, a knowledge that has now been translated into a wide range of biologics and innovative therapies, which have significantly altered the way we treat our patients.

Q2 You undertook your education and training in both Greece and the USA, at the University of Athens and Harvard University. Are there differences in practice and training between the two regions, and how have your global experiences shaped your practice as a dermatologist and researcher?

I was privileged to receive my dermatology training in one of the most renowned academic centres in the USA. Working in clinic with the eminent Dr Thomas Fitzpatrick or interacting with masters such as Dr Sam Moschella and Dr Ernesto Gonzalez in clinical rounds, alongside many others, has been the highlight of my career. I not only learnt dermatology, but I was inspired to become a physician scientist, a mentor, and a trainer myself. Returning to Greece, I became faculty at the Department of Dermatology-Venereology at Andreas Sygros Hospital, the main referral institution for skin and venereal diseases with the largest residency programme in Greece. It was a unique opportunity for me to bring to this new environment all the didactic values and structured clinical care I had received through my training at Harvard. Overall, my experience from the USA and Europe has shown that, despite the different healthcare systems, patient care settings, and accessibility to medicines, there are more similarities than differences in the way we practice dermatology. And these similarities will become more pronounced in the future because of the increased connectivity and the diffusion of knowledge and expertise that occurs nowadays with continuous medical education activities.

"Research enables you to have an in-depth understanding of your clinical work and helps pose further questions that promote the field."

Q3 Beyond your clinical work, you have a PhD from the University of Athens and a research fellowship in cutaneous photobiology and lasers from Harvard University. How has your scientific experience affected your clinical practice as a dermatologist, and how important do you think it is for future dermatologists to have formal research training?

I believe it's very important to have a research background in any field one is involved with clinically, and this is what I encourage my younger colleagues to do. Research enables you to have an in-depth understanding of your clinical work and helps pose further questions that promote the field. The most important research questions often come from the clinical side. For me, research is part of my everyday activities and certainly one of the most inspiring parts of what I do. But regardless of whether one is actively involved in research or not, the practice of dermatology today requires a deep understanding of the underlying disease pathophysiology and pharmacology. For example, the proper clinical use of biologics in psoriasis or atopic dermatitis requires a broad knowledge of the immunology of these diseases and the mechanism of action of such agents.

Q4 You currently have over 280 international publications covering research in melanoma, psoriasis, and photobiology, among other dermatological conditions. What do you believe to be the current gaps in the literature?

There has been tremendous progress achieved in the fields that I have worked in over the years. For example, the way we manage psoriasis or melanoma today is so dramatically different to when I first started practicing dermatology and this has to do with the novel therapies and diagnostic technologies that we use, but also because patient care has become much more patient-centred, personalised, and multidisciplinary. However, I believe there are a lot of unanswered questions. Dermatology is full with many common and rare conditions, which cause a lot of suffering to our patients, and for which we do not know their aetiologies, pathophysiologies, or how to effectively treat these conditions. There is a need to expand research to a broader list of skin conditions for which our patients need better treatments.

Q5 Congratulations on your appointment as President of the European Academy of Dermatology and Venereology (EADV). What will be the focus of your term as EADV President, and what are you hoping to achieve in the role?

It is an honour to be president of the EADV, one of the most influential and prestigious

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academies in dermatology and venereology. My goal during my 2-year term is to strengthen the role of our Academy as the educational leader in dermatology-venereology and expand this role further in the digital era. Willingly or unwillingly, the coronavirus disease (COVID-19) pandemic will certainly be an important priority for next year, and the EADV will continue to support our members and colleagues so that they can deliver the best possible care to their patients in these unprecedented times. Based on the success of the first EADV Virtual Congress that took place a few weeks ago, we plan to develop and provide a comprehensive programme of webinars, online tools, and e-learning opportunities to help our members optimise patient care and improve their knowledge and expertise. We also want to increase our collaboration with other dermatology societies, as well as with nurse and patient organisations. Furthermore, as a leading professional society, it is essential that we have a very clear and long-term advocacy and public affairs strategy, and our plan is to become more systematically involved in the current European Union (EU) health initiatives.

Q&A The EADV Virtual Congress 2020 was held entirely online for the first time. What were your key learnings from the congress, and what research developments are you anticipating over the next year?

This year's virtual congress was an exceptional meeting, offering a unique learning experience in an all-virtual frame. I think the one important lesson was discovering our capability to organise a successful meeting on an entirely virtual level, from choosing the platform to marketing the concept in a way that would excite audiences. I'd like to praise the work done by the EADV committees, departments, and operational teams in organising such an extraordinary event during these immensely difficult times. It took determination and flexibility and all of us had to learn new skills.

For the delegates, the congress gave the opportunity to explore the latest, cutting-edge developments in science and patient care in dermatology and venereology. The scientific sessions discussed the important topic of COVID-19, highlighting its impact on dermatology and venereology and how the pandemic has affected practitioners and patients. Several scientific sessions focussed on the treatment advances in psoriasis, atopic dermatitis, skin cancer, infectious diseases, and hair disorders, with all the new transforming medicines that promise to fulfil our patients' unmet needs. Aside from the research developments in these

"cultivating skills such as compassion, empathy, and ability to communicate are equally important to acquiring the knowledge and expertise of treating the disease."

areas, I anticipate a remarkable progress in several fields of relevance to dermatology-venereology, for example artificial intelligence, satellite power technology, teledermatology, and skin microbiome research. I trust that these areas with be hot topics of the 30th EADV Annual Congress next year, which I hope will take place as a face-to-face meeting in Vienna, Austria. It will be a wonderful opportunity to reunite after the pandemic.

Q7 In your work with medical students and trainee dermatologists, what advice do you give to those developing their skills and careers? Where do you hope they will take the field of dermatology over the coming decades?

I'm constantly surrounded by young colleagues and trainees, who inspire me with their enthusiasm and willingness to learn and to make a difference. What I would advise them is to focus on what really interests them; what makes them passionate in their professional or academic pursuits. Sometimes it is obvious, but in many cases it needs work and exploration. It's important to channel this interest in constructive paths and also make sure to network with the right persons that will help guide your work and productivity.

I am very optimistic about the prospects of future dermatologists who will have a lot more tools and skills to deliver optimal care for their patients. Artificial intelligence, mobile technology, big data, and genomic medicine are all fields that will be gradually integrated to daily clinical medicine, offering higher standards of care and precision medicine. On the other hand, practicing in a highly digitalised world may create challenges for patient–physician relationships. It's important to remember that medicine is not limited to disease management but also involves the healing of the patient. Thus, cultivating skills such as compassion, empathy, and ability to communicate are equally important to acquiring the knowledge and expertise of treating the disease.

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Roundtable Interview with Asst Prof Asli Bilgic, Prof Dedee Murrell, Prof Marie-Aleth Richard and Assoc Prof Myrto Trakatelli

Asst Prof Asli Bilgic
Communications Committee; Akdeniz University, Antalya, Turkey

Prof Dedee Murrell
Communication Committee and International Board Member; The George Institute for Global Health, Sydney and St George Hospital, University of University of New South Wales, Sydney, Australia

Prof Marie-Aleth Richard
Chair of EADV Communication Committee; French Member of the Board, Timone Hospitals, Marseille, France

Assoc Prof Myrto Trakatelli
Chair of EADV School; Papageorgiou Hospital, Aristotle University Thessaloniki, Thessaloniki, Greece

Q1 What fascinates you the most about dermatology, and why did you decide to pursue a career in this field?

Prof Trakatelli: The skin is visible, accessible to touch, and enables us to discover conditions by examining it. There are so many illnesses one can detect through the skin: the specialty is vast, spanning different facets of medicine from skin cancers, tumours and conditions that can be treated through intervention to inflammatory, autoimmune and systemic diseases, paediatric dermatology, allergology disorders, and infectious and venereal ailments that can be treated medically. This certainly is not an exhaustive list! It comprises so many, and diverse, scenarios that it can appeal to all with a taste for problem-solving. Whether you are a blade or medication fan, whether you are an action taker or an enigma solver, you will definitely find the facet that will engage your interest, or dare I say, steal your heart?

When I was in Kindergarten I had quite a serious condition: I had a Steven–Johnson-like reaction to sulfonamides. I had to stay confined in the house for days with pain, oozing, and crusting in all my mucous membranes. My eyes were stuck shut each morning until the lids were prised open by using a form of glass stick. It was horrible. I can still 'feel' the pain I suffered! This disease marked me (luckily, not externally or functionally)

"Dermatologists can make a big difference to patients of all ages, who are grateful because they can see the difference you make."

and as a teenage I became quite obsessed with the wellbeing of my own skin, taking extreme care of it and slathering it with creams constantly. My friends used to chide me gently: *How come you wear all those sticky, disgusting creams? Are you going to be a dermatologist?* Classic teenager attitude!

I started medical school wanting to become a biochemist or molecular biologist and solve things with my trusty microscope; but, going through clinical training and later entering the lab for my biochemistry PhD made me realise that I loved working with patients and I that I missed seeing them. My passion for skin and its health had never abandoned me so it was a clear choice for me to become a dermatologist. And as I like working both with my hands and my brain, I became specialised in skin cancer and dermatologic surgery.

Prof Murrell: What drew me into dermatology was the puzzle of the picture: you have something visual on the outside of the body which is caused by, or related to, something that has 'gone wrong' inside the body (including the immune system, genetics, infection, or hormonal), or induced by something on the outside (including UV, allergens, infections). It is intellectually stimulating. Patients care a lot about how their skin is affected compared to internal diseases which don't cause physical pain. They have emotional pain. Dermatologists can make a big difference to patients of all ages, who are grateful because they can see the difference you make to them.

Prof Richard: The skin is the showcase of the body and internal organs and is often affected in cases of serious illness. It is a varied and rich specialty with over 3,000 different skin diseases that affect the youngest to the very old. It is a specialty based on the examination of lesions and patients which requires you to be a real doctor, have knowledge in semiology, and in histology. We can perform many technical procedures and laser surgery, and we also have access to the most innovative molecules. Dermatology offers so many perspectives to treat our patients that my passion is endless.

Dr Bilgic: I love dermatology because it is mostly a visual science section. There are more

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than 3,000 dermatological conditions, always forcing you to read and research. There are many dermatological signs of systemic diseases, systemic cancers and genetic problems for example, which we can help to diagnose early. Furthermore, there are many different sections of dermatology and venereology that you can choose to master in, including autoimmune bullous diseases, paediatric dermatology, cosmetic dermatology, and more. I am just fascinated by the opportunities of dermatology as a career.

Q2 Could you tell us about your most recently published paper, and the impact that you hope the conclusions to have on the dermatology community?

Prof Richard: One of my most recent publications is about 'out-of-pocket expenditures' for the management of adult patients with psoriasis in France. The article illustrates some of the uncovered needs for patient management and the economic burden associated with skin diseases.

Prof Murrell: A recent study[1] I did investigated why patients with psoriasis might be more susceptible to the coronavirus disease (COVID-19), triggered by noticing that a 14-year-old male in Portugal, who seemed very fit and was a soccer player, died suddenly of COVID-19. In the paper he looked slim and well, but the article said he had psoriasis. It was most likely not that severe as it was not visible. I started investigating whether angiotensin-converting enzyme 2 (ACE2) was increased in psoriasis as this is the receptor for COVID-19 and is connected with hypertension, something that patients with psoriasis develop quite often. There was nothing published about it. I contacted Prof Jim Krueger, whose lab I had worked in as a postdoc years ago, to suggest that we investigate if ACE2 was increased in lesional psoriasis or not. He had collected skin samples of patients with psoriasis before and after sekukinumab treatment. These samples were then tested for ACE2 and it was found to be increased in lesional and nonlesional skin of patients with psoriasis compared to normal skin. After treatment with sekukinumab, the levels returned to normal. We proposed that the biologic helped to make the patients less susceptible to a large dose of COVID-19 and the statistics so far show that these patients on biologics do not have an increased mortality from COVID-19 despite being relatively immunosuppressed.

Dr Bilgic: My most recently published paper[2] was about plasma-rich platelet (PRP) injections for the treatment of male androgenetic alopecia (AGA). PRP treatment for various dermatological diseases has been investigated as an emerging therapeutic option, yet there remains a dearth of data on the effectiveness of this approach. Thus, we investigated the efficacy and safety of physically activated PRP injections versus placebo in the treatment of male AGA. Our study provided data supporting the positive effects of PRP treatment on AGA in males.

Prof Trakatelli: When COVID-19 hit, we started thinking about how to deal with our patients with skin cancers that had to undergo surgery. I was in touch with my 'sisters of the blade', Dr Elena Rossi and Prof Christina Magnoni, in the eye of the storm and we thought it would help our colleagues in Europe if we could come up with a plan and draft a paper on how to deal with this group of patients. I hope the paper will help colleagues managing patients that present with skin cancers needing excision.[3]

Q3 What does your role on the EADV Committee entail, and what have you achieved so far in this position?

Dr Bilgic: Primarily, EADV is a community composed of dedicated researchers and clinicians to work on improving quality of patient care and research, education, and training in the field of dermatology and venereology. We share an ambition to improve and maintain high standards in the dermatology and venereology profession and dermatology public health services.

As a Communication Committee member, I echo EADV's voice through social media platforms and work as an ambassador to enhance awareness of EADV and its activities. Our main aims are to enhance internal and external communications at EADV, to play a consultative role drawing upon members' expertise/experience as medics, to bring a communications lens into early internal discussions on projects, and help shape external perception of EADV.

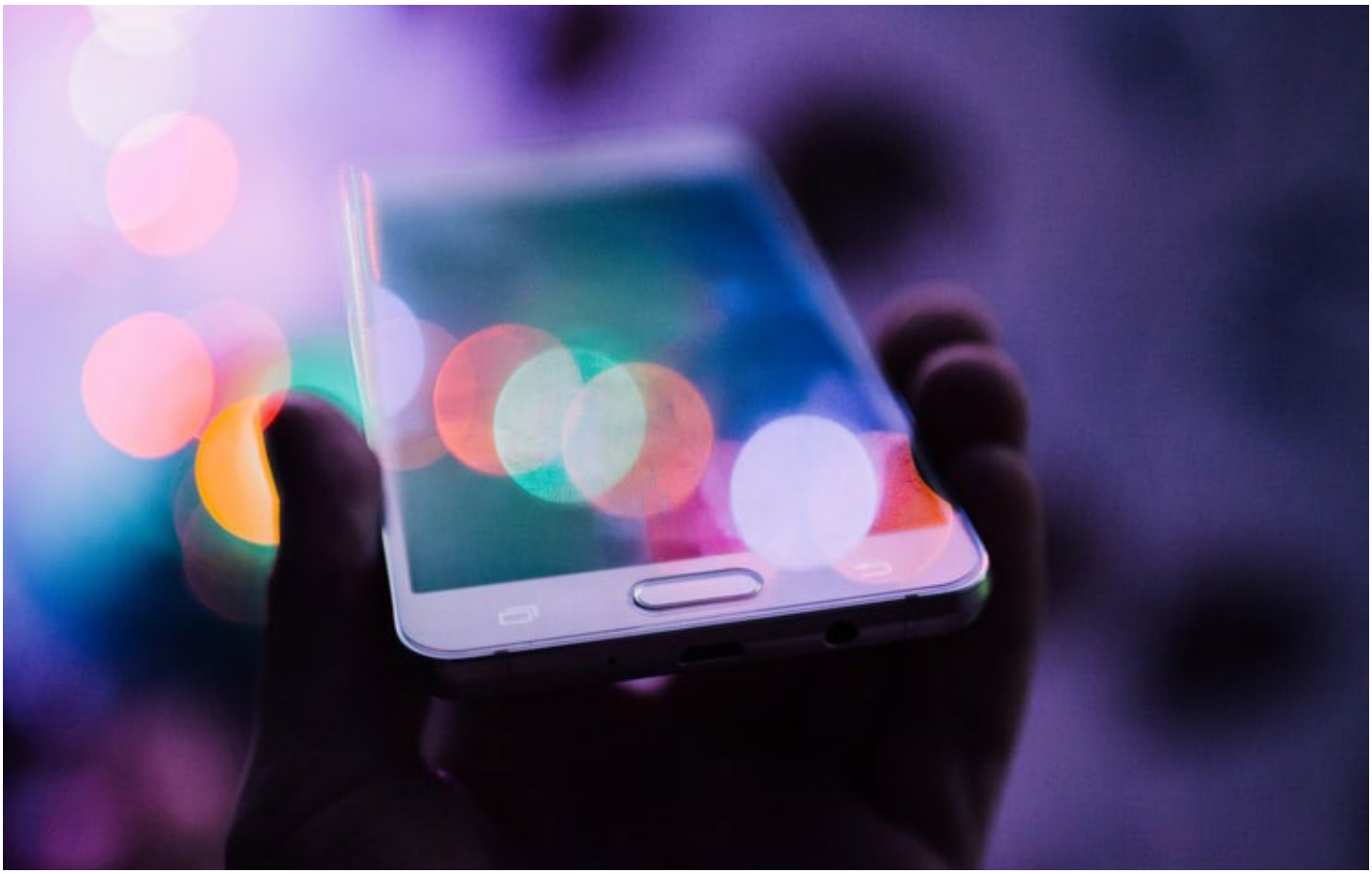
We were responsible for the creation and/or collection of material for publication on the EADV Virtual COVID-19 resource centre. We created an anonymous questionnaire investigating the impact of COVID-19 on European dermatologists. The survey included 30 questions in three main areas: participants' profile, impact of COVID-19 on professional activity, and on personal life. The survey results were presented at the EADV 29th Virtual Congress.

We reviewed and approved the shortlist of abstracts and presentations that are being recommended as the key drivers for the EADV media activity. We worked as EADV ambassadors and influencers during the EADV virtual congress to drive awareness among followers on social media through highlighting the benefits of attending and specific presentations that we were looking forward to attending. We also worked as official EADV spokespeople and attended media interviews.

"As a Communication Committee member, I echo EADV's voice through social media platforms and work as an ambassador to enhance awareness of EADV and its activities."

Prof Richard: I have two positions in the EADV. I am the French Representative Board Member of the EADV and the Chair of the Communication Committee. The Communication Committee requires a lot of investment and work to improve the promotion and recognition of dermatologists, patients, and skin diseases throughout the academy. Very important surveys are now ongoing to promote patients' needs and the role of dermatologists throughout Europe, and to advocate the position of dermatologists in health.

Prof Trakatelli: I am the Chair of the Education Committee for EADV (EADV School); I organise and oversee all educational activities of the academy outside of our congresses. For many years we held 'fostering courses' in classroom for residents and specialists but more recently, since I became the chair, we started developing virtual learning in the form of webinars and e-Learning courses.



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In 2020, having to manage the cancellation or postponement of all of our face-to-face courses, we had to rapidly refocus and produce a series of 'long-distance learning' activities and I am proud to say that the Education Committee (Drs Daiva Jasaitiene, Paola Pasquali, Rossi, Catherine (Bibi) Van Monfrans, Sarah Walsh, and junior resident member Stella Siskou) managed to deliver many educational activities to our members and dermatologists all over the world. We created a special COVID-19 series that informed and supported colleagues on different aspects of the coronavirus impacting our specialty. We transformed our Nails Masterclass to a webinar series, which was adeptly chaired by Prof Bertrand Richert, and was shared during the first wave of quarantine (now a Continuing Medical Education [CME]-accredited e-Learning course). We developed a new e-Learning course initiating knowledge in dermatopathology, artfully chaired and organised by Prof Maite Teresa Fernández Figueras (also CME-accredited). We also liaised with Goleman EI and its CEO Ms Michele Nevarez to produce three special webinars on emotional intelligence and healthcare to help strengthen the positive outlook and resilience of health providers all over the world; the father of Goleman EI, Daniel Goleman himself, featured on the first webinar. Finally, we continue to provide monthly webinars on interesting topics in dermatology featuring top experts in their field. Our endeavours are accessible on our e-Learning platform.

We are hoping to do more and develop an optimised learning ecosystem for the future to offer our members excellent scientific knowledge in an accessible and simple manner.

Prof Murrell: I have two positions within the EADV board. The first is as an International Board Member representing the one-third of members who are outside the European Union (EU). I am also on the Communication Committee. My roles include promoting the activities of the EADV on social media; we have many followers on LinkedIn, our open Twitter page, private Instagram, and Facebook including friends and colleagues. As a journal editor, member of editorial boards, and author, my work involves submitting articles, citing the literature of the EADV, and the EADV Task Forces, for which I am a member of Autoimmune Blistering Diseases. As a member of many other dermatology societies and a lecturer at many international congresses I work to promote the EADV and I have received media training over the past 15 years and so I am interviewed about dermatology or career topics.

Q4 The decision was made to move the EADV 2020 Congress to a virtual meeting this year. What do you believe to be the advantages of an online congress?

Prof Murrell: The online platform enables more people who cannot afford to travel because of cost, family, or work commitments to learn, usually in the evenings or on weekend, which is when the on-demand lectures are useful. Although costs are reduced there are many disadvantages. For example, people are likely to listen to far fewer lectures than when they have the dedicated time off to be at a congress and to be able to arrange collaborations with others.

Dr Bilgic: The EADV congress was of equal quality as the previous EADV congresses but even better as the virtual congress provided us an exceptional opportunity to involve more colleagues around the world from their homes. EADV Virtual offered, as always, a programme that consisted of outstanding educational and brainstorming sessions; however, this time it was easier to attend our favourite sessions via the online platform, and better still, we can watch the sessions we missed as they are offered on demand until 31st January 2021.

Prof Trakatelli: It is accessible to all who are interested, including those that wouldn't have the chance to travel to a regular face-to-face meeting, providing top scientific lectures from the comfort and security of your own home.

Prof Richard: The greatest benefit is to allow us dermatologists to continue to communicate and exchange with each other and to share the latest data and advances in dermatology.

Q5 'New Frontiers in Dermatology and Venereology' was the overarching theme of the EADV 2020 Virtual Congress. How have recent advancements in technology helped research and patient care?

Dr Bilgic: With COVID-19 challenging all our understanding of life and daily routines, EADV Virtual committed its focus to improve

our understanding of the unmet needs of dermatological care.

At the virtual congress, the first clinical evidence of an oral microbial therapy was shared for modulation of systemic inflammation in psoriasis. This would offer us a therapy without immunosuppressive properties which is an important issue during pandemics. Furthermore, huge therapeutic advances in the field of hand eczema and alopecia areata were shared at EADV Virtual which could end the therapeutic drought in these frequently seen dermatological diseases.

Moreover, the innovations in artificial intelligence shared during the congress will help us as powerful monitoring and triage enablers; ground-breaking new therapies in immunotherapy and targeted therapy in cutaneous oncology and autoimmune diseases offer patients and clinicians life-extending treatment options.

Prof Trakatelli: We have wonderful new drugs for psoriasis that achieve skin clearance for a lot of patients, advances in promising therapies for metastatic skin cancers, and novel insight to mechanisms of disease. Furthermore, the use of teledermatology has helped provide medical care in times of social distancing!

Prof Richard: Artificial intelligence, teledermatology and new ways of communication, were, and are still are in my opinion, crucial during the current health crisis to protect patient care and safeguard ongoing research.

Prof Murrell: The new biologic revolution in dermatology has, for the first time, made psoriasis invisible. It's still lurking under the surface like other diseases are if you stop treatment, but at last the patients don't have to be stigmatised.

Q6 The mission of the EADV is to improve the quality of patient treatment, and the EADV frequently run campaigns on skincare education. As we head into winter, could you give our readers some expert dermatological advice on how best to protect our skin? What are the main threats to our skin's health?

Prof Trakatelli: Winter dries skin out. People should hydrate the skin regularly applying nourishing emollients and avoid as much exposure to extreme temperature differences. For example, try to take short showers that are not too warm or too cold. Eat well, with seasonal fruits and vegetables and drink plenty of water daily!

"The new biologic revolution in dermatology has, for the first time, made psoriasis invisible. It's still lurking under the surface like other diseases are if you stop treatment, but at last the patients don't have to be stigmatised."

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Dr Bilgic: Hand hygiene is crucial in the prevention of viral transmission during the pandemic and beyond. The first and foremost important action is to wash our hands frequently. However, this comes with its risk regarding eczema exacerbation. To prevent eczema, I suggest using fragrance-free, perfume-free, and dye-free creams and ointments immediately after you wash your hands.

In the bath, use warm water and keep it to 5–10 minutes. Hot water could remove your skin's natural oils and long showers could dry out your skin. Cleanse you skin gently with mild, fragrance-free cleansers and avoid rubbing your skin. After your bath, use a soft towel gently pat your skin dry and apply moisturisers immediately to allow your skin to lock in moisture. Use a sunscreen with broad spectrum sun protection factor (SPF) 30+ to protect your skin, even in winter. If you apply makeup, use it after your moisturiser and sunscreen.

Eat a healthy well-balanced diet to provide necessary ingredients for your skin. Get a good night's sleep to build up your immune system. Dress in loose-fitting natural clothing like cotton or silk.

Prof Murrell: The skin is a major part of the body's immune defence system which is why vaccination works so well when delivered via the skin. In heated indoor winter conditions the skin barrier dehydrates, so it is important to hydrate the skin daily, soaking in the bath or shower, and applying a moisturiser which replaces the skin's ceramides and doesn't introduce potential allergens (such as plants, perfumes, and many preservatives).

Prof Richard: The main threats are excessive drying from the cold; heating or excessive washing of the skin with detergents and other products should be avoided.

Q7 The EADV produced Task Force Recommendations for clinicians, to help provide expert care for patients during the COVID-19 pandemic. Could you summarise the key recommendations?

Prof Richard: Patients should wear masks, use hydroalcoholic solutions as often as possible, and must respect social distancing. Most dermatological treatments can and must be maintained during the pandemic.

Prof Murrell: Protect your airways from inhaling the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by wearing a mask when outside your home, wash your hands frequently and apply moisturiser each time, limit any unnecessary travel and gatherings, do not cease your regular medication without consulting first with your doctor.

Dr Bilgic: General suggestions are to practise sensible social distancing, to wash hands frequently, to use skin care lotions and creams between hand hygiene procedures, to wear a mask as advised by national or local authorities. Always wear a mask if you are taking immunosuppressive drugs to treat, for example, autoimmune blistering diseases, psoriasis, hidradenitis suppurativa, atopic dermatitis, and melanoma, especially when outside and if you are unwell and coughing and sneezing. People must undertake or complete vaccination protection according to their national guidelines, at present with priority against influenza and pneumococcus if not already done and should avoid busy public transport and closed areas.

Immunosuppressive drugs are frequently used medications for many dermatological diseases and there are immunosuppressives that could increase the risk of more severe COVID-19. The Task Force on Autoimmune Blistering Diseases suggested patients should not stop or modify their treatment without discussing with their dermatologist as a relapse of autoimmune blistering disease could be more severe than an infection with COVID-19. In case of COVID-19 infection, modification of the treatment could be an option within close collaboration between the dermatologist managing the autoimmune blistering disease and the physician treating COVID-19.

The EADV Psoriasis Task Force, The EADV Vasculitis and Vasculopathy Task Force, and the EADV Acne, Rosacea, Hidradenitis Suppurativa (HS) Task Force, and the European Hidradenitis Suppurativa Foundation suggested that immunosuppressed patients are not at increased risk for severe manifestations and complications of COVID-19 compared to the general population based on available data on past and present outbreaks of coronavirus infections. Patients with cutaneous immune-mediated diseases, including psoriasis, hidradenitis suppurativa,

vasculitis, and atopic dermatitis, are suggested to continue their treatment during the COVID-19 outbreak unless suggested otherwise by their dermatologists. This would prevent disease flares that can contribute to increasing patient burden, disability, poor quality of life, and healthcare overuse.

Of course, immunosuppressive or biologic treatments in patients with active COVID-19 infection or with any other active infection is contraindicated. It is also advised to pause such treatments if patients develop symptoms consistent with COVID-19 infection. Furthermore, if patients live in areas with a high incidence of COVID-19 infection, or are close contacts of confirmed cases, individual consideration of immunosuppressive therapy temporary discontinuation is suggested, considering factors such as age or comorbidities. Caution is suggested for individuals generally at risk of developing a more serious course of COVID-19 disease. The EADV STI Task Force suggested that some individuals should have access to sexual healthcare services during the pandemic.

Prof Trakatelli: Wear a mask, keep a safe 1.5 m distance, wash hands regularly and protect them with hydrating creams, don't stop taking a prescription drug unless consulting with your doctor, and if you have something that is highly suspicious or that is worrying you on your skin try to consult a dermatologist; if possible, virtually by teleconsultation otherwise by face-to-face consultation. Skin cancers continue to appear, and some must be dealt with urgently even during a pandemic!

Q8 What have been your personal clinical experiences during the COVID-19 pandemic, and what lasting impacts do you anticipate the pandemic will have on dermatological care?

Dr Bilgic: COVID-19 has first and foremost created a fear in my heart for my loved ones. As working at the hospital created a huge risk, I tried to protect my family and so was all alone at home communicating via calls. Following this fear, I tried to shape my life and work according to our new routines. I had time both for research and dermatological projects, as well as having some extra time to watch films and television series because of working in shifts during the first peak of COVID-19.

In terms of lasting impacts of COVID-19, I believe we will see increasing tendencies to have virtual meetings and an increasing demand for virtual health services. It is important to be a part of this process to have the contribution and authority on new virtual healthcare policies.

Prof Richard: It is important to protect the management of all skin diseases to avoid missing opportunities to treat skin conditions early.

Prof Murrell: Patients were initially scared to come in for face-to-face consultations. Skin cancer checks are very difficult to conduct by telehealth; however, existing chronic skin problems which have been diagnosed can be managed via telehealth. Biologics do not appear to be increasing the incidence of COVID-19 as originally feared.

Prof Trakatelli: I discovered that I could find strength and be flexible in situations that challenged my comfort zone. I think that this adverse era will help bring in new ways of working such as the use of teledermatology, virtual patient management, and virtual learning, which will further advance dermatology!

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Managing Chronic Urticaria: *Quo Vadis*?

EDITOR'S PICK

This comprehensive and detailed review by Petkova and Staevska puts chronic urticaria under the spotlight. As the title suggests, the ongoing management of this commonly diagnosed skin disease must be carefully monitored to establish effective treatment plans for patients. The article expertly discusses our current position and guidelines for classification, diagnosis, and management of chronic urticaria including therapeutic options currently under investigation.

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Abstract

Chronic urticaria (CU) is one of the most commonly diagnosed skin conditions. CU is characterised by the presence of recurrent wheals and/or angioedema and intense pruritus persisting for at least 6 weeks. Subtypes of CU include chronic spontaneous urticaria and chronic inducible urticaria. Following diagnosis, adequate trigger identification and appropriate treatment can significantly reduce disease activity and improve the patient's quality of life and disease outcomes. Current guidelines recommend a stepwise approach in the management of CU, including non-sedating oral antihistamines, administered in up to four times the conventional dose, the monoclonal antibody omalizumab (anti-IgE), and eventually cyclosporine as an add-on therapy for patients with antihistamine-refractory CU. Potential disease-related biomarkers are needed to predict the therapeutic response that would lead to establishment of personalised regimens and treatment plans. This paper reviews the current perspectives and guidelines for classification, diagnosis, and management of CU.

INTRODUCTION

Urticaria is one of the most common skin diseases, and one of the most common reasons for a general practitioner, paediatrician, dermatologist, allergist consultation, or emergency room visit.[1] It is estimated that up to 25% of the American population experience at least one episode of urticaria during their lifetime.[2] In 50% of all patients, urticaria and angioedema occur simultaneously: 40% only have hives, and 10% present with isolated angioedema.[3] A study

by Baptist and Baldwin[4] showed that general practitioners were likely to refer patients with atopic dermatitis to dermatologists and those with chronic urticaria (CU) to allergists.[4]

DEFINITION

According to the 2018 International Consensus Guidelines for the Diagnosis and Treatment of Urticaria, urticaria is characterised by the sudden appearance of wheals, angioedema, or both.[5] Wheals or hives are characterised by central oedema of variable size, almost always surrounded by a reflex erythema, which disappears with vitropression. They have a transient nature and the skin returns to normal usually within 30 minutes to 24 hours. Patients usually report an itching or burning sensation. Itching is relieved by rubbing the skin rather than by scratching it. Excoriations are therefore not common in urticaria, which helps to differentiate it from atopic dermatitis, typically characterised by severe skin excoriations. Angioedema is characterised by sudden, marked, erythematous, or pale swelling of the underlying dermis and subcutaneous tissue or mucous membranes that can be painful rather than itchy. This can have a slower resolution of symptoms compared to papules, which would take up to 72 hours.[5]

CLASSIFICATION

Urticaria is generally classified as acute or chronic. Acute urticaria usually resolves within 6 weeks. An external cause can be identified in approximately 50% of all cases: viral infections are the most common causes and less common triggers include specific drugs or food. The cause may not be identified in the remaining 50% of patients.[6] CU and angioedema are defined as daily or almost daily symptoms for >6 weeks. The cases of intermittent urticaria, recurrent episodes of urticaria that last for a few minutes or several days, were also included in this definition.[7] In turn, CU can be classified as spontaneous and inducible. The term 'spontaneous' underlines the spontaneous nature of rashes and oedema as opposed to inducible urticaria, in which rashes are triggered by specific factors, for example, symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, and aquagenic urticaria. In spontaneous urticaria, rashes usually develop spontaneously; however, in some patients the condition can be aggravated by certain triggers, such as stress, viral infections, and nonsteroidal anti-inflammatory drugs (NSAID). It is important to distinguish recurrent chronic intermittent urticaria from the repeated episodes of acute urticaria. For example, if a patient suffers multiple episodes of antibiotic-induced acute urticaria, they are considered separate episodes of acute urticaria as a manifestation of a drug allergy; in the case of multiple episodes of NSAID-induced urticaria the episodes are more likely to be a presentation of chronic intermittent spontaneous urticaria, which is exacerbated by NSAID via a pseudoallergic mechanism. Often, the administration of NSAID overlaps with viral infections which makes it difficult to determine the risk factor for exacerbations. Intermittent CU triggered by viral infections is more common in children. Importantly, two or more urticaria subtypes, for example, chronic spontaneous urticaria (CSU) and symptomatic dermographism/delayed pressure urticaria, can coexist in the same patient.

Following the natural course of the disease, remission of CSU is achieved in 50% of patients within 6 months and 20% of them become asymptomatic at Year 3 and another 20% at Year 5 of disease onset. It is estimated that 2% of all patients will achieve remission after 25 years. However, at least one-half of patients will relapse at least once after remission.[8] Recent data shows somewhat similar results for remission rates: approximately 25% after 3 months; 50% after 1 year; approximately 80% after 3 years; and approximately 90% after 5 years.[9]

Despite similar terminology or presentation, rash and/or oedema, urticaria pigmentosa (cutaneous mastocytosis), urticarial vasculitis, familial cold urticaria, and bradykinin-mediated angioedema (for example, hereditary and acquired angioedema or angiotensin-converting enzyme inhibitor-related angioedema) are not urticaria subtypes; however, they should be considered in the differential diagnosis of urticaria. CU and other urticaria subtypes can be signs and symptoms of other conditions or syndromes.[5]

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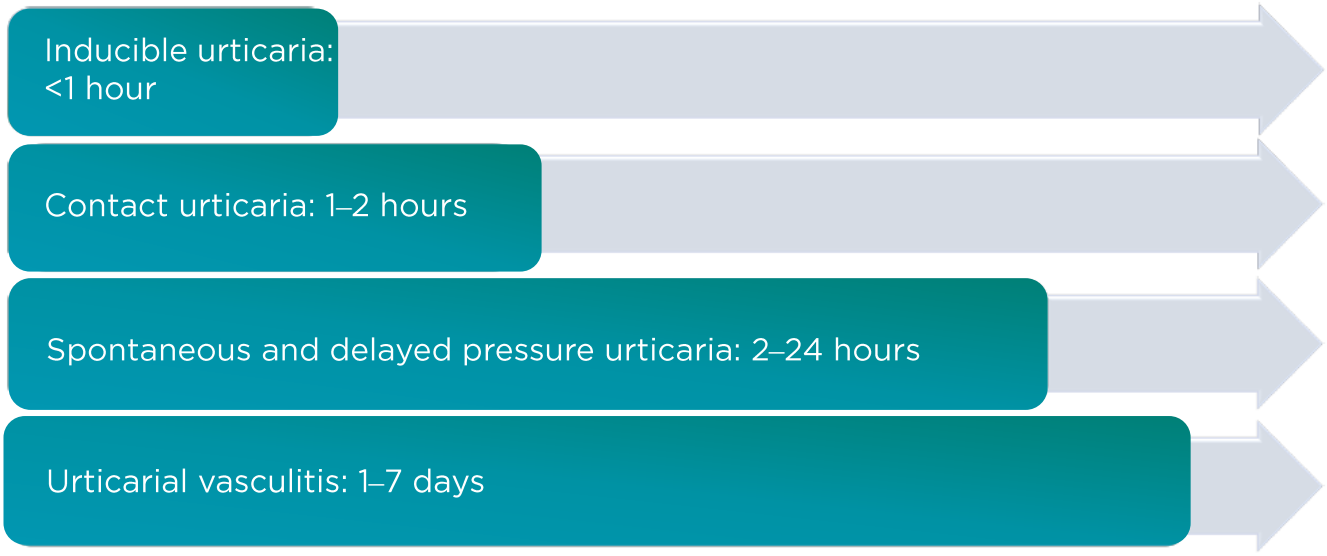

Figure 1: What is the average wheal duration?

The duration of wheals is an important factor in the initial diagnosis of urticaria.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The presence of extensive skin lesions is generally associated with a disease with a more severe course which is more difficult to treat. Skin lesion colour may provide useful information. The histamine-induced papules are light-coloured with surrounding pink erythema because of skin vessel dilation. In contrast, dark red or purple papules are signs of more intense vascular damage and impaired vessel integrity, which are typical features of urticarial vasculitis.[5] The size of the lesions and the affected area is associated with the disease severity, but not with the specific type of urticaria or angioedema. The duration of lesions is a useful guide for differentiating between the various conditions as they may have overlapping features (Figure 1).[10]

DIAGNOSIS

Acute urticaria is a self-limiting condition and therefore the International Consensus guidelines do not recommend extensive diagnostic procedures.[5] Diagnostic evaluation can be useful in the cases of food allergy and IgE-mediated NSAID hypersensitivity (pyrazolones, acetaminophen, ketorolac, nimesulide).[11] The three main goals of the diagnostic workup in CU are to rule out differential diagnoses (diagnostic algorithm and main differential diagnoses are shown in Figure 2);[12] to evaluate the disease activity and its impact on control and quality of life by using several validated tests for disease activity assessment including urticaria activity score (UAS), angioedema activity score (AAS), urticaria and angioedema quality of life questionnaires (CU-Q2oL, AE-QoL), and the urticaria control test (UCT); and to identify risk factors and exacerbation triggers, as well as aetiology, if possible. Type 1 hypersensitivity reactions are rarely recognised as causes of chronic persistent urticaria but can be considered in some cases. For example, in food-dependent, exercise-induced anaphylaxis, one should take into consideration both allergic and nonallergic food sensitivity, especially Type 1 allergic reaction to cereals and gliadin, as well as nonspecific reactions to alcohol (alcohol intolerance). CU may be triggered by an underlying persistent infection caused by *Helicobacter pylori, Streptococci, Staphylococci,* or *Yersinia*.[13] The incidence and impact of infectious diseases may vary considerably between different patient groups and regions. For example, viral hepatitis is a common cause of CU in Southern European countries but is rarely associated with the condition in Northern Europe.

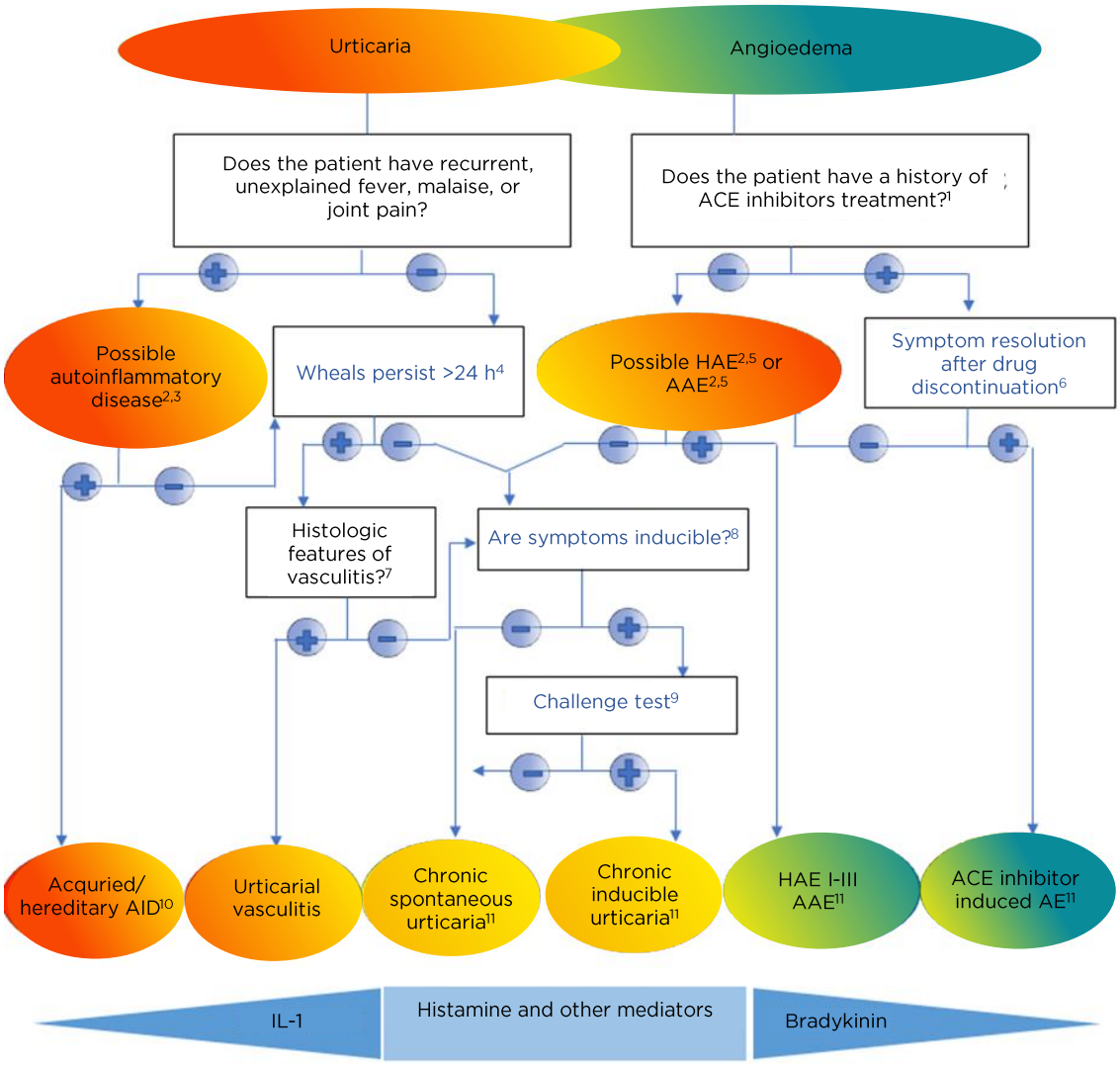

Figure 2: Diagnostic algorithm for urticaria, angioedema or both.

[1]Apart from ACE-inhibitors, other renin inhibitors and sartans can also cause angioedema but much less frequently. [2]Patients should be asked for a detailed family history and age of disease onset. [3]Tests for elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate), tests for paraproteinaemia in adults, look for signs of neutrophil infiltration in skin biopsy; gene mutation analysis for hereditary periodic fever syndromes (for example, cryopyrin-associated periodic syndrome), if strongly suspected. [4]Patients should be asked: "For how long does each wheal last?" [5]Test for complement C4, C1-INH levels, and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; gene mutation analysis, if tests are normal but history of hereditary angioedema. [6]If no remission is achieved after 6 months of ACE-inhibitor discontinuation, C1-inhibitor should be tested. [7]Does the skin biopsy show small vessels in the papillary and reticular dermis damage and/or fibrinoid deposits in perivascular and interstitial areas suggestive of urticarial vasculitis? [8]Patients should be asked: "Can you trigger your wheals? Can you bring out your wheals?" [9]In patients with a history of inducible urticaria standardised provocation testing according to International Consensus recommendations should be performed. [10]Acquired autoinflammatory syndromes include Schnitzler's syndrome, systemic juvenile idiopathic arthritis, and adult-onset Still's disease; hereditary autoinflammatory syndromes include cryopyrin-associated periodic syndromes such as familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease, and more rarely hyper-IgD syndrome, and TNFα-associated periodic syndrome. [11]In some rare cases, recurrent angioedema is neither mast cell-mediated nor bradykinin-mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as "idiopathic angioedema" by some authors.

AAE: acquired angioedema because of C1-inhibitor deficiency; ACEi: angiotensin-converting enzyme inhibitor; AE: adverse event; AID: autoinflammatory disease; HAE: hereditary angioedema.

Adapted from Zuberbier et al.[5]; Magerl et al.[12]

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Infestation with *Anisakis simplex*, a sea fish nematode, may be an important cause of anaphylaxis in regions with raw fish consumption.[14] The incidence of dental and ear, nose, and throat infections appears to vary between patient groups. In general, laboratory tests are rarely outside the normal range and very rarely influence diagnosis and management of the disease.[15]

Acetylsalicylic acid (aspirin) and other NSAID inhibit cyclooxygenase (COX)-1 and inducible COX-2, thus diverting arachidonic acid metabolism towards the 5-lipoxygenase metabolic pathway in certain cells, especially eosinophils.[16] This modulation is associated with overproduction of cysteinyl-leukotrienes LTC4, D4, and E4 which results in vasodilation and oedema. There is a known cross-sensitivity between different nonselective NSAID in affected individuals that depends on their pharmacological ability to inhibit COX rather than on their chemical structure.[17]

Aspirin and NSAID can cause both acute urticaria and exacerbation of pre-existing chronic spontaneous, but not physical, urticaria. The incidence of intolerance is 0.3% in the general population,[18] whereas aspirin-induced CSU exacerbations have been reported in 20–40% of all patients.[18,19] At least 22% of patients with CSU visit the emergency room or hospital for disease exacerbation because of aspirin intake, and not because of physical urticaria.[18] Furthermore, aspirin-induced acute urticaria is a risk factor for CSU development.[11]

Currently, the only widely available test for screening for autoantibodies against the IgE receptor is the autologous serum skin test. This is a nonspecific test that assesses the presence of serum histamine releasing factors of all types, not just autoantibodies. This test should be performed with caution to minimise potential risks of accidental infection in case the patient is injected with unknown serum by mistake. In some specialised centres, more specific laboratory tests for *in vitro* histamine release from basophils, using a basophil histamine release assay (BHRA) evaluation or the basophil activation test, are also available and could be used for autoantibody search.

MANAGEMENT

The recent international consensus EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria 2018[5] includes nonpharmacological approaches such as identification and elimination of underlying causes, triggering factor avoidance, and inducing tolerance, and pharmacological treatment.

Identification and Elimination of Underlying Causes

Spontaneous remission of CU can occur at any time in the disease course; therefore, it can be very difficult to assess the effect of elimination of a suspected cause or trigger. For example, concomitant infection may be a cause, aggravating factor, or unrelated. Remission and elimination of the suspected cause can also occur coincidentally. Underlying immunological mechanisms, autoimmunity and autoallergy associated with the persistent disease also may not be eliminated.

Triggering Factor Avoidance

NSAID can be a causative or aggravating factor in approximately 20–40% of patients with CU and in 17% of Bulgarian patients (Staevska, unpublished data). Elimination of these drugs and use of non-COX-1 agents, namely specific COX-2 inhibitors and paracetamol (acetaminophen), is recommended in these patients. Patients with inducible urticaria should avoid known eliciting factors such as lifting heavy objects, intense pressure in delayed pressure urticaria, or friction in dermographism. Eradication of infectious agents and treatment of inflammatory processes are recommended, although studies show conflicting results about their effect on the natural course of the disease. Reduction of physical and emotional stress is beneficial as there is some evidence that disease activity and severity are correlated with stress levels.[20] Plasmapheresis of functional autoantibodies may be recommended in some severely affected patients, but this treatment is neither established nor widely available.

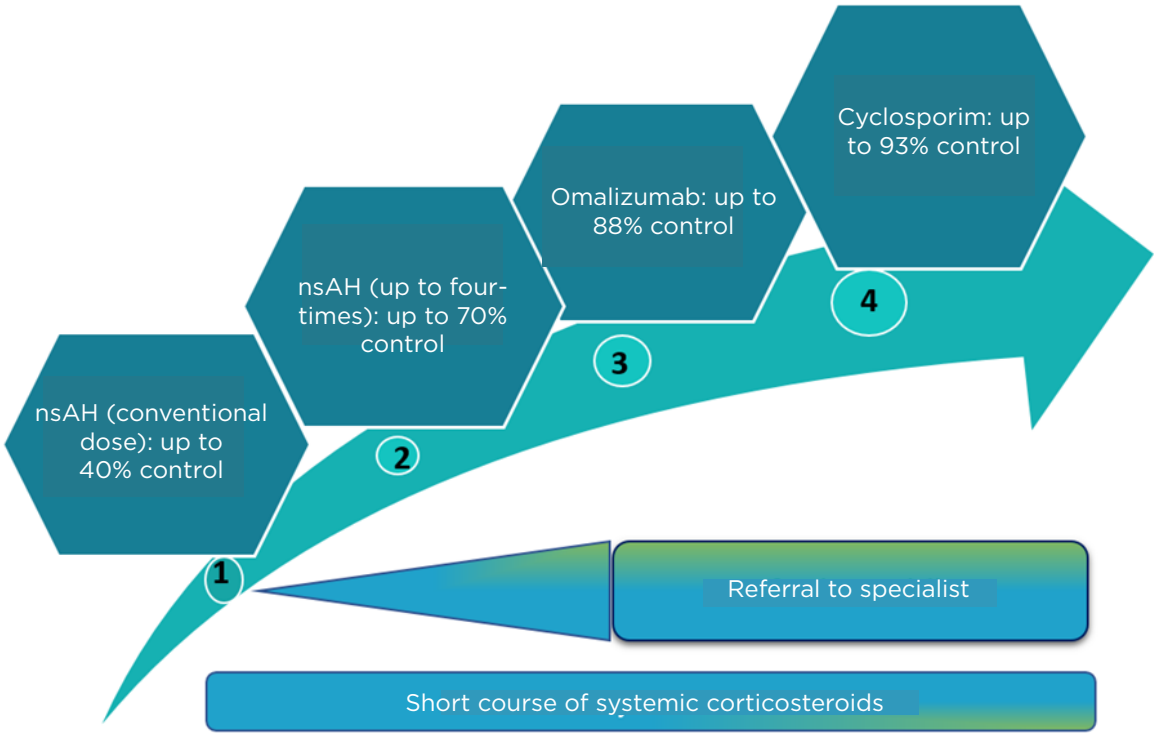

Figure 3: Rates of control, achieved with first-, second-, third-, and fourth-line treatment, according to the 2018 International Consensus guidelines.

nsAH: nonsedating antihistamines.

Adapted from Zuberbier et al.[5]; Kocatürk et al.[22]

Dietary restrictions are only recommended in the case of IgE-mediated food allergy. Avoidance of histamine-, pseudoallergen-rich foods, or foods containing salicylates has been proposed but is a controversial measure because there is a lack of 'good' evidence from randomised controlled trials to draw conclusive evidence about the diet's effectiveness.[21]

Inducing Tolerance

Inducing tolerance can be achieved in some subtypes of inducible urticaria, such as cold urticaria, cholinergic urticaria, and solar urticaria. However, tolerance only lasts for a few days and its maintenance is often not accepted by patients; for example, in cases of cold urticaria where daily cold showers are needed to achieve tolerance.

Pharmacological Treatment

Treatment recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Figure 3).[5] A structured consensus process was used by the International Consensus Working group to review evidence and discuss and agree upon recommendations. The main goal of the pharmacological treatment is to achieve complete symptom relief.

Another general principle in pharmacotherapy is to use as much as necessary as little as possible and thus the treatment may vary in the disease course. First-line treatment includes modern second-generation H1-antihistamines in licensed doses. The International Consensus guidelines recommend that modern second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile. The use of first-generation antihistamines is not recommended. Experts advise that antihistamines should be taken daily, or regularly, rather than only when symptoms occur, or as needed. It is estimated that approximately 40% of all patients achieve control with this treatment.[6]

Second-line treatment includes up-dosing to four-fold the conventional dose of modern second-generation H1-antihistamines. Up-dosing second-generation H1-antihistamines to four-fold is recommended in patients with CU with inadequate control or intolerable symptoms within 2–4 weeks of treatment or earlier. Many studies demonstrate the benefit and safety of a higher dosage of second-generation antihistamines.[23] Patients with urticaria who do not respond to up-dosing of H1-antihistamines to four-fold the licensed dose are not recommended to receive further up-dosing. Some experts advise against using different H1-antihistamines at the same time, although this is an expert opinion and scientific evidence is lacking. Although some authors expect achievement of disease control with antihistamines in <50% of all patients[24] others report achieving control in up to 70% of patient with CU.[23,24] Older guidelines recommend adding a first-generation antihistamine at night;[25] however, the International Consensus guidelines recommend against the use of these sedating antihistamines for the routine management of CU, which is also supported by the authors' own experiences.[26]

More recently, several biomarkers related to the disease prognosis and therapeutic response have been described in CSU.[27] Asero[28] demonstrated that higher levels of D-dimer are associated with insufficient clinical response to antihistamines. Kolkhir et al.[29] confirmed these results and showed that not only measurements of D-dimer, but also high levels of fibrinogen, C-reactive protein, and erythrocyte sedimentation rate should be considered predictors of poor response to antihistamines. Other biomarkers for antihistamine-resistant CSU could be increased complement C5a levels, higher disease activity, longer duration of wheals, and higher autologous serum skin test positivity.[30]

Third-line treatment includes adding on omalizumab to nonsedating second-generation H1-antihistamines. Many studies have demonstrated that omalizumab (anti-IgE) is very effective and safe in the treatment of CSU and inducible urticaria and is currently licensed for these indications. In CSU, omalizumab prevents angioedema development, significantly improves quality of life, and is suitable for long-term treatment. The recommended dose is 300 mg every 4 weeks. Dosing is independent of total serum IgE. Add-on treatment with omalizumab is effective in 65–70% of patients who are unresponsive to high doses of H1-antihistamines and 35–40% of patients are able to achieve complete symptom control.[31] Thus, based on the total patient population, it can be estimated that control can be achieved with antihistamines and omalizumab in 80–85% of patients with urticaria,[32] though one study has suggested this could be up to 88%.[22]

Several biomarkers related to treatment with omalizumab have been proposed. A recent study showed that lower baseline levels of IL-31 were associated with satisfactory clinical response.[33] A recent Spanish study demonstrated that lower baseline levels of basophil high-affinity IgE receptor (FcεRI) expression was associated with insufficient clinical response to omalizumab.[34] Ertas et al.[35] found that clinical response to omalizumab can be predicted by total serum IgE levels and their change during treatment, particularly by Week 4/baseline ratio of total IgE (lower baseline levels and a lesser increase after start of treatment predict insufficient clinical response to omalizumab).[35] More recently, Riccardo et al.[36] added that this biomarker could be more specific in nonatopic nonresponders with low levels of IgE than in atopic nonresponders and speculated that this finding could be considered as indirect evidence for pathogenetic role of autoreactive IgE.[36] Additionally, BHRA and autologous serum skin test positivity have been recently proposed as predictors for slow therapeutic response to omalizumab, whereas increased IgE levels seem to be associated with faster relapse.[37,38]

Fourth-line treatment includes adding cyclosporin A to nonsedating second-generation H1-antihistamines. Cyclosporine A has a moderate, direct effect on histamine release. Efficacy of cyclosporine A in combination with a second-generation H1-antihistamine has been demonstrated in two placebo-controlled trials including 129 CU patients (45 with placebo),[39] but it cannot be recommended as standard treatment because of the higher risk of adverse effects. Cyclosporine A is not licensed for the treatment of urticaria and its off-label use in urticaria is recommended for patients with severe refractory disease to combinations

of antihistamine and omalizumab only. The cyclosporine dose suggested for urticaria is 2–4 mg/kg/day.[39] It should be noted that cyclosporine A has a far better risk/benefit ratio compared with long-term use of corticosteroids. Cyclosporine A increases the success rate of CU treatment by up to 93%.[22,32]

Recent studies show that baseline levels of D-dimer and BHRA are linked to response to cyclosporine. Asero[40] found that lower D-dimer levels are associated with satisfactory clinical response to cyclosporine, which suggests that D-dimer levels could be a useful tool to predict and monitor clinical response to cyclosporine. Furthermore, two independent studies demonstrated that BHRA positivity is associated with satisfactory clinical response to cyclosporine.[41,42]

Leukotriene receptor antagonists and H2-antihistamines are no longer recommended by the International Consensus guidelines due to low levels of evidence for their efficacy in urticaria. For acute urticaria and acute exacerbations of CU, a short course of oral corticosteroids may be used to reduce disease duration and activity. Treatment with systemic corticosteroids should be limited to a maximum of up to 10 days in doses between 20 and 50 mg/day (Figure 3).[5] Tacrolimus, mycophenolate, sulfones (dapsone and sulfasalazine), and hydroxychloroquine were also tested for the treatment of CSU but evidence in support of their use is limited.

CONCLUSION

In recent years, the use of high dose nonsedating antihistamines, and especially omalizumab, has been considered a revolution in the treatment of CU but unfortunately the price (lack of reimbursement in some countries) limits the use of this highly effective biological treatment. Other biologics are currently under investigation for the treatment of refractory CSU. These include the high-affinity anti-IgE monoclonal antibody, ligelizumab; the anti-IL-5 monoclonal antibody, mepolizumab; the anti-IL-5 receptor α monoclonal antibody, benralizumab; the anti-IL-4 and IL-13 monoclonal antibody, dupilumab; antisialic acid-binding Ig-like lectin-8 drugs such as spleen tyrosine kinase inhibitors; oral treatments such as LOU064, a Bruton's tyrosine kinase selective inhibitor;[43] antagonists of prostaglandin D2 receptor 2; and IL-1 inhibitors.[44]

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Impaired Mitochondrial and Metabolic Function of Fibroblasts Derived from Patients with Recessive Dystrophic and Junctional Epidermolysis Bullosa

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Abstract

Background: Recessive dystrophic epidermolysis bullosa (RDEB) and junctional EB (JEB) are inherited disorders characterised by fragility and blistering of epithelial tissues leading to pain, pruritus, and adherent scarring. The severity and chronic nature of the resultant skin wounds significantly reduces quality and length of life. Current therapies primarily consist of protective bandaging and nutritional supplementation; there is no cure for these disorders. Although the skin fragility results from a lack of C7 protein (RDEB) and laminin-332 (JEB), other serious aspects of these disorders, such as inflammation that interferes with healing and aggressive squamous cell carcinoma, have not been completely elucidated. Recent research has suggested that mitochondrial function plays a significant role in skin healing.

Objective: To evaluate how mitochondrial function differs in patients with RDEB and JEB.

Method: The energy status of RDEB and JEB patient-derived fibroblasts was determined by Seahorse analysis and metabolite production. The energetics and overall morphology of RDEB and JEB patient-derived fibroblasts were assayed as a measure of metabolic stress.

Results: EB patient-derived fibroblasts showed impaired oxidative phosphorylation with concomitant compensation by glycolysis. Morphological parameters were altered in RDEB and JEB fibroblasts compared with controls.

Conclusion: This is the first study to describe changes in mitochondrial energy metabolism, metabolic profile, and mitochondrial morphology of EB patients.

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INTRODUCTION

Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous group of rare inherited disorders, characterised by fragility of epithelial tissues with blistering following minimal mechanical trauma.[1] Four major subtypes of EB have been described, each defined by a distinct plane of epidermal-dermal separation: EB simplex, junctional EB (JEB), dystrophic EB, and Kindler syndrome.[1] The most severe forms of EB are recessive dystrophic EB (RDEB) and JEB, which currently have no curative treatment. Blister cleavage presents immediately below the lamina densa in RDEB and at the lamina lucida in JEB.[1] The typical phenotype of these two forms involves mutilating mucocutaneous blistering, chronic cutaneous infection, and aggressive squamous cell carcinoma.[1,2]

The molecular pathology of RDEB results from biallelic loss-of-function mutations in the Type VII collagen gene (*COL7A1*), resulting in a lack of an extracellular matrix molecule critical for skin integrity. Absent or deficient production of functional Type VII collagen (C7) protein leads to the loss of C7 homotrimer anchoring fibrils that interact with dermal and epidermal proteins to connect the skin basement membrane to the papillary dermis. One of the most severe forms of JEB is caused by loss-of-function mutations in any of the three genes (*LAMA3*, *LAMB3*, or *LAMC2*) composing the heterotrimeric protein laminin-332. This protein interacts with C7 at the basement membrane to attach the epidermis to the underlying layers through the integrin receptors α3β1 and α6β4.

Although genetic mutations have been identified as the origin of these diseases, the complex EB phenotype cannot be completely explained based on the adhesive functions of C7 and laminin-332. For example, the mechanisms responsible for the clinical features of EB, such as photosensitivity and cancer risks, are still poorly understood.[3]

Several pathognomonic features not directly related to skin fragility, such as ageing, inflammation, and squamous cell carcinoma, have been strongly associated with mitochondrial dysfunction and oxidative stress.[4-7] In addition, there is emerging evidence that mitochondria play an important role in skin physiology and pathophysiology.[8] Recent research has suggested mitochondrial function promotes keratinocyte and melanocyte differentiation and pigmentation, as well as epidermal progenitor stem cell function.[9-11]

Mitochondria are double-membrane enclosed organelles that generate the majority of cellular energy through the citric acid cycle and oxidative phosphorylation (OXPHOS).[12] In addition to energy production in the form of ATP, mitochondria are involved in several metabolic pathways including fatty acid β-oxidation,[13] the formation of iron/sulphate clusters, and haem biosynthesis.[14] They participate in the metabolic processes of lipogenesis, gluconeogenesis, ketogenesis, steroid hormone synthesis, and ammonium detoxification.[15-17] Mitochondria regulate calcium homeostasis by buffering calcium flux for the plasma membrane, endoplasmic reticulum, and apoptotic pathways.[18-20]

Mitochondria are highly complex and dynamic organelles that can change in number and morphology within a cell during development, cell cycle, or when challenged by various endogenous or exogenous conditions. Defective mitochondrial architecture-function relationships are linked to many human diseases, including metabolic disorders, neurodegenerative disease, ageing, and cancer.[21]

For these reasons, the work presented here focusses on defining the morphologic, bioenergetic, and metabolic characteristics of RDEB and JEB fibroblasts when compared to unaffected fibroblasts. This study showed altered mitochondrial morphology in both forms of EB, and its functional correlation in impaired OXPHOS and subsequent insufficient glycolytic compensation in RDEB and JEB patient-derived fibroblasts.

MATERIALS AND METHODS

Cell Line Derivation

Samples were obtained after receiving written informed consent, as approved by the University of Minnesota Institutional Review Board and in adherence with the Declaration of Helsinki. RDEB and JEB patients were screened for disease-causing mutations as part of the University of Minnesota Epidermolysis Bullosa Center standard

of care. Primary fibroblasts were obtained from a skin punch biopsy of patients with RDEB (six patients, ranging in age from 1 to 14 years), JEB (five patients, ranging in age from 1 month to 11 years), or unaffected matched donors (two donors aged 9 and 13 years), and derived by mincing the skin tissue that had been immobilised under a sterile coverslip. Biopsies were taken from skin near blistered regions. Cells were grown in Dulbecco's modified Eagle medium (Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA), supplemented with 15% fetal bovine serum (Thermo Fisher Scientific Inc.), and 0.1 µg/mL each with penicillin and streptomycin (Thermo Fisher Scientific Inc.) at 37 °C in a humidified 5% CO_2 incubator. The culture medium was changed every third day; all experiments were conducted between passage three and passage 10.

Oxygen Consumption Rate Measurement

Oxygen consumption rate (OCR) was measured in primary fibroblasts with the XF24e Extracellular Flux Analyzer (Seahorse Bioscience, North Billerica, Massachusetts, USA). Cells were seeded at a density of 35×10^3 cells per well in 24-well plates and cultured overnight at 37 °C in a humidified, 5% CO_2 incubator. For the bioenergetics profile, the fibroblasts were consecutively treated with oligomycin A (1.0 µM), carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP) (0.7 µM), and rotenone plus antimycin A (1.5 µM). Data were normalised by cell number using the CyQuant® NF Cell Proliferation Assay kit (Thermo Fisher Scientific Inc.). Fluorescence was measured on the SpectraMax® M2 (Molecular Devices, San Jose, California, USA) with an excitation wavelength of 485 nm and an emission detection wavelength of 530 nm.

ATP/ADP Assay

Cells were seeded at a density of 1×10^3 cells per well in 96-well plates. Following 24-hour incubation, the EnzyLight™ ATP/ADP ratio assay was performed (BioAssay Systems, Hayward, California, USA) according to the manufacturer's protocol. The assay was normalised to the total number of cells using the CyQuant NF Cell Proliferation Assay.

Confocal Microscopy

For all experiments, cells were plated at 2.5×10^5 cells per 6 cm dish (Thermo Fisher Scientific Inc.) and images were obtained after 48 hours on a Nikon FN1 upright microscope equipped with an A1R scan head and Plan Apo LWD 25× water-immersion objective lens NA 1.1. Images of different fluorophores were acquired sequentially using the two settings: NADH 405 nm excitation, 425–475 nm emission; and flavin adenine dinucleotide (FAD) 488 nm excitation, 500–550 nm emission. The 12-bit 2048×2048-pixel images were acquired, and final magnification was adjusted by zooming with the laser to attain appropriate pixel size.

Electron Microscopy

Normal, RDEB, and JEB fibroblasts were collected using Trypsin-EDTA (Thermo Fisher Scientific Inc.) and pelleted. Cell pellets were sent to the University of Minnesota University Imaging Core for processing and imaging. The work was performed using a Philips CM12 Transmission Electron Microscope. Images were taken with the SIA L3C Digital Camera.

Live Cell Imaging

All images were obtained after 48 hours on a Nikon FN1 upright microscope equipped with an A1R scan head and Plan Apo LWD 25× water-immersion objective lens with NA 1.1 in the chamber at a stable temperature of 37 ˚C. The cells were stained with MitoTracker® Deep Red FM (Thermo Fisher Scientific Inc.), 640 nm excitation and emission 650–720 nm. Z stacking was performed. 12-bit, 2048×2048-pixel images were acquired, and the final magnification was adjusted by zooming with the laser to attain appropriate pixel size.

Image Analysis

For all experiments testing the optical redox ratio, cells were plated at 2×10^5 per 60 mm glass-bottomed dish (MatTek Corporation, Ashland, Massachusetts, USA). Cell images were obtained approximately 48 hours later using a Nikon FN1 upright microscope (UMN Imaging Center). Images of different fluorophores were acquired sequentially using two settings: NADH 405 nm excitation, 425–475 nm emission; and FAD 488 nm excitation, 500–550 nm emission. The

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pinhole, gain, and offset remained the same for every experiment. For each imaging session, there were two plates of each cell line and two fields of view for both NADH and FAD. Image acquisition took approximately 16 seconds (Z stack). Following data collection, the NADH/FAD ratio (a measure of the reduction-oxidation ratio) was calculated for every cell in each image. For each acquired NADH and FAD image, ImageJ software (Research Service Brand, National Institute of Mental Health, Bethesda, Maryland, USA) was used to obtain the integrated intensity of NADH and FAD for each cell in the image after the background fluorescence was subtracted. Box fractal dimension was calculated from two-dimensional mitochondria images, converted to binary images, then run in built-in box fractal dimension in ImageJ. Box sizes of 2, 3, 4, 6, 8, 12, 16, 32, and 64 pixels were used. For analysis of mitochondrial volume/cell volume ratio, pictures were first deconvoluted using AutoQuant X3 (Media Cybernetics, Rockville, Maryland, USA), then analysed by Imaris 7.7.0 software (Bitplane, Concord, Massachusetts, USA).[22]

L-lactate Assay

Cells were seeded at a density of 1×10^3 cells per well in 96-well plates. After 48 hours incubation, the L-lactate assay (ScienCell Research Laboratories, Carlsbad, California, USA) was performed according to the manufacturer's protocol. The assay was normalised to cell number using the CyQuant NF Cell Proliferation Assay.

Statistical Analysis

Results are expressed as mean ± standard error of the mean (SEM). The significance of the difference between control and experimental conditions was analysed by unpaired Student's t-test; $p<0.05$ was considered statistically significant.

RESULTS

Morphologic Changes of Mitochondria in Epidermolysis Bullosa Fibroblasts

Mitochondrial structure and function are intertwined, and the alteration of one often impacts the other. Transmission electron microscopy was used to image mitochondria in normal, RDEB, and JEB fibroblasts between five and eight matched passages after isolation (Figure 1A-C). Box fractal dimension was used to identify structural changes of the mitochondria in RDEB and JEB fibroblasts compared with control cells.[22-24] Box fractal dimension is a measure of the texture of an object from two-dimensional images derived from a Z stack; it reflects a character of the outer mitochondrial membrane structure whereby a grainier structure correlates to higher fractal dimension. Box fractal dimension increased significantly: 25% in RDEB and 9% in JEB fibroblasts compared with non-EB cells (Figure 1D). These observations are consistent with the moderately swollen and more sparsely packed cristae in mitochondria from both EB groups compared with mitochondria of control fibroblasts (mean ± SEM). Live cell imaging using MitoTracker suggests a more fragmented mitochondrial network with less overall mitochondrial volume in RDEB and JEB fibroblasts compared to controls (Figure 2).

Oxidative Phosphorylation Is Impaired in Epidermolysis Bullosa Fibroblasts

To examine and quantify different components of mitochondrial function in RDEB and JEB fibroblasts during Seahorse experiments, the cells were analysed in three passages (passages six to nine). After passage 10, an overall decline in respiratory function of all cell types was observed. This may be attributed to telomere-dependent senescence.[25] OCR was measured first in a basal state, then after addition of the ATP synthase (complex V) inhibitor oligomycin, the proton ionophore FCCP, and the respiratory complex I and III inhibitors rotenone and antimycin. Basal respiration was significantly decreased both in RDEB and JEB fibroblasts compared to unaffected fibroblasts derived from healthy individuals (Figure 1E). Respiration measured after treatment with oligomycin reflects decreased OCR to the extent cells are using mitochondria to generate ATP. The remaining OCR is attributed to residual electron transport and oxygen consumption independent of oxidative phosphorylation. Maximal oxygen consumption, measured after addition of FCCP (which collapses the mitochondrial membrane potential), was decreased in JEB fibroblasts (Figure 1F).

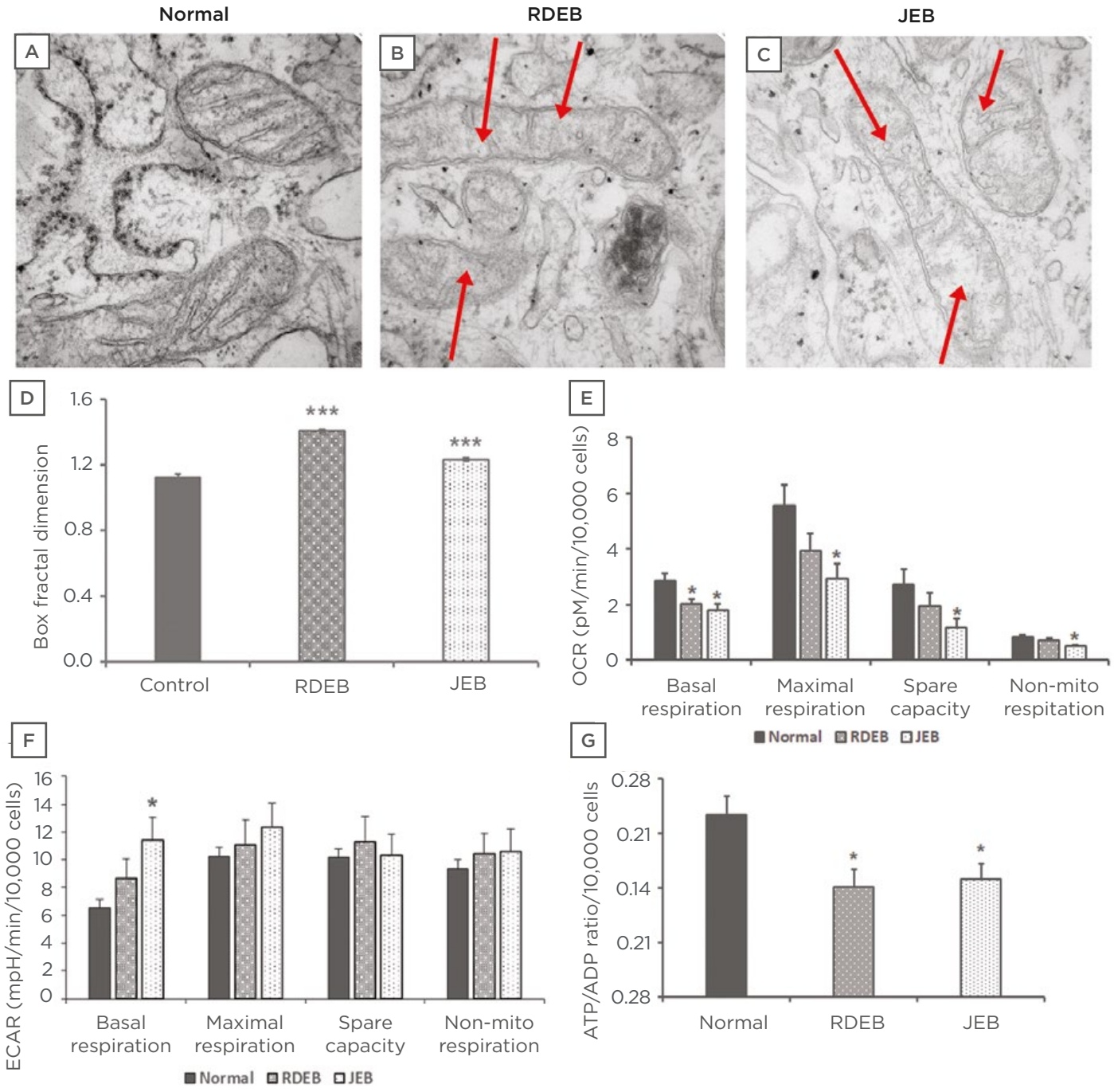

Figure 1: Mitochondria morphology and bioenergetic profile of recessive dystrophic epidermolysis bullosa and junctional epidermolysis bullosa skin fibroblasts.

TEM of mitochondria in **A)** normal; **B)** RDEB; and **C)** JEB fibroblasts. **D)** Mitochondrial morphologic changes in RDEB and JEB fibroblasts quantified using box fraction dimension. A total of 30 mitochondria were assayed for each of two normal control, six RDEB, and five JEB patient fibroblast lines (SEM error bars). **E)** Seahorse X24 measurement of OCR of RDEB and JEB fibroblast lines upon sequential addition of oligomycin (1.0 µM), FCCP (0.7 µM), and rotenone and antimycin (1.0 µM each). **F)** Seahorse X24 measurement of ECAR of normal, RDEB, and JEB fibroblast lines upon sequential addition of oligomycin (1.0 µM), FCCP (0.7 µM), and rotenone and antimycin (1.0 µM each). **G)** ADP/ATP ratio measured following 24-hour incubation.

Values represent the means over three passages of fibroblasts from each of two normal control, three RDEB, and three JEB fibroblast lines ±SEM.

The age ranges for the cell lines: normal (9–13 years), RDEB (1–6 years), and JEB (2–10 months).

Statistical significance was calculated with the Student's t-test: *p<0.05; *** p<0.001.

ECAR: extracellular acidification rate; FCCP: carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone; JEB: junctional epidermolysis bullosa; OCR: oxygen consumption rate; RDEB: recessive dystrophic epidermolysis bullosa; TEM: transmission electron microscopy.

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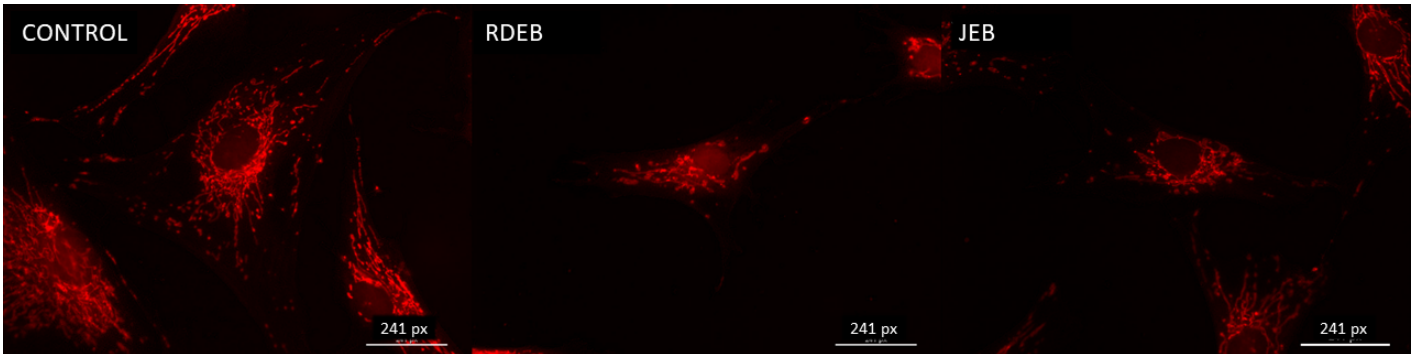

Figure 2: MitoTracker imaging profile of recessive dystrophic epidermolysis bullosa and junctional epidermolysis bullosa skin fibroblasts.

Representative images of control, RDEB, and JEB fibroblasts using the live cell MitoTracker mitochondria stain (bar: 241 pixels).

JEB: junctional epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa.

Lastly, rotenone and antimycin were injected to inhibit electron flux through complexes I and III of the electron transport chain, causing dramatic suppression of the OCR. The remaining OCR, attributable to O_2 consumption in non-mitochondrial organelles, was also significantly decreased in JEB fibroblasts. Moreover, the cellular energy ratio (cytosolic ATP/ADP) of RDEB and JEB fibroblasts was decreased (Figure 1G). These lower cytosolic ATP/ADP ratios determined the cell metabolism to be predominantly glycolytic.

Epidermolysis Bullosa Fibroblasts Compensate Impaired Oxidative Phosphorylation by Glycolysis

The normalised optical redox ratio was used to further estimate the metabolic profile of EB fibroblasts.[26,27] NADH and FAD are the primary electron donor and acceptor of electron transport chain complexes I and II, respectively.[28-31] Interestingly, mRNA expression profiling of RDEB fibroblasts has found significant differences in the expression of genes involved with nicotinamide metabolism compared to control fibroblasts.[32] The oxidation-reduction ratio is the most common optical method for measuring cell redox state, as determined by the fluorescence intensity of FAD and NADH (FAD/[FAD+NADH]).[31,33] The redox ratio is strongly associated with NAD^+/NADH concentration[34,35] and has been used *in vitro* and *in vivo* to track metabolic changes during cell differentiation and malignant transformation.[27,36-39]

In the case of impaired OXPHOS in RDEB and JEB fibroblasts, the authors hypothesised these cells would have a significant difference in redox state compared to unaffected fibroblasts. To test this, confocal microscopy was used to examine a panel of six RDEB, five JEB, and two non-EB fibroblast lines between five and eight matched passages after isolation (Figure 3A). The optical redox ratio of RDEB and JEB fibroblasts was found to be significantly lower than the optical redox ratio of unaffected control cells (Figure 3B), consistent with abnormal respiration in these cells. To determine if glycolytic metabolism is augmented in EB cells with impaired respiration, extracellular acidification rates (ECAR) of RDEB, JEB, and control fibroblasts were measured, and it was observed that ECAR of JEB fibroblasts was significantly higher during basal respiration, but not in RDEB fibroblasts (Figure 1F). ECAR was unchanged in RDEB and JEB fibroblasts relative to normal fibroblasts during maximal and non-mitochondrial respiration. These results could indicate RDEB and JEB fibroblasts are not able to compensate for impaired OXPHOS by increasing glycolysis, although modestly elevated concentrations of L-lactate in the culture media in RDEB and JEB fibroblasts, compared to control fibroblasts, may indicate increased reliance on glycolysis for ATP production under normal oxygen conditions in these cells (Figure 3C).

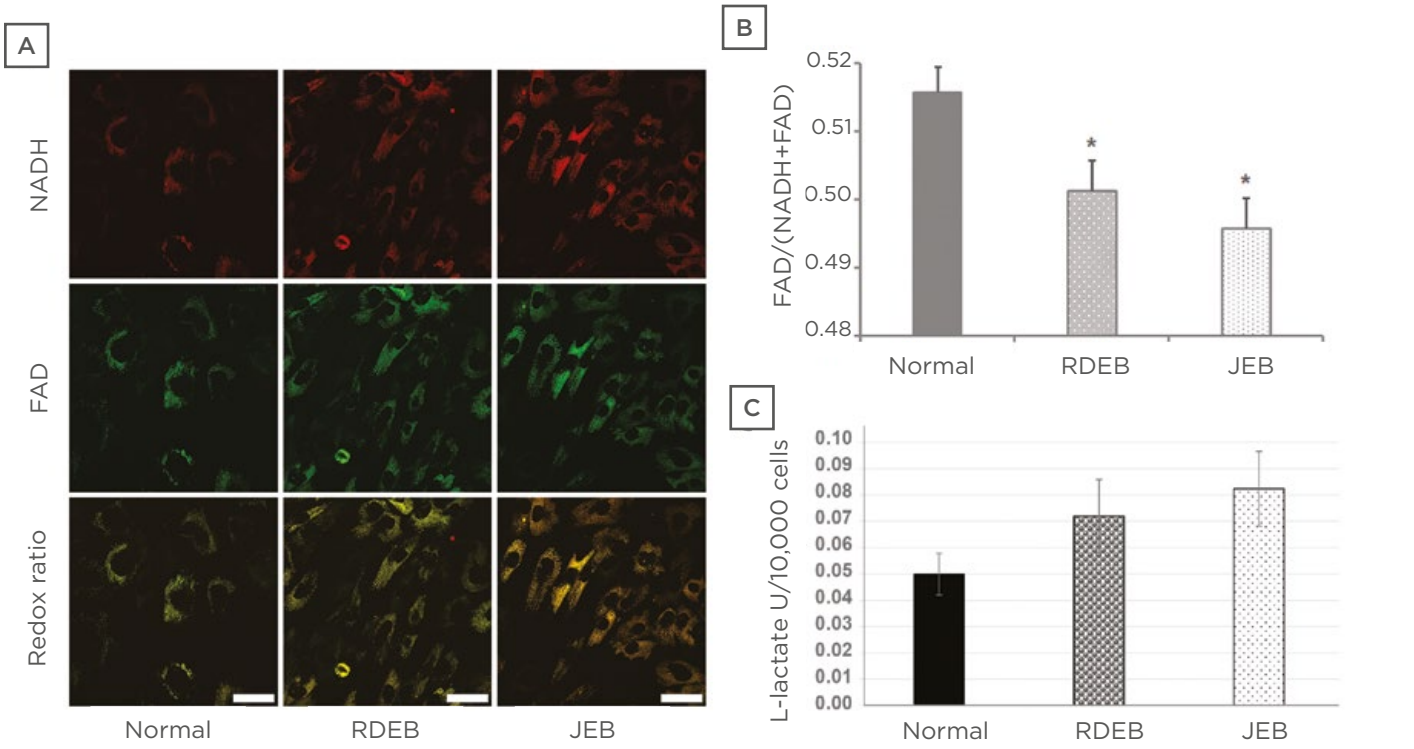

Figure 3: Metabolic profile of recessive dystrophic epidermolysis bullosa and junctional epidermolysis bullosa skin fibroblasts.

A) Representative images of NADH and FAD from RDEB and JEB fibroblasts. Redox ratio images (FAD/[NADH+FAD]) corresponding to representative NADH and FAD images (bars: 10 µM). **B)** Normalised optical redox ratio (FAD/[NADH+FAD]). Values represent the means over three passages of fibroblasts from each of two controls, six RDEB, and five JEB patients ±SEM. **C)** L-lactate production of RDEB and JEB fibroblasts.

Values represent the average over three passages from each of two normal control, six RDEB, and five JEB patient cell lines ±SEM.

The age ranges for the cell lines: normal (9–13 years), RDEB (1–14 years), and JEB (2 months to 11 years).

Statistical significance was calculated with the Student's t-test: *p<0.05; ***p<0.001.

FAD: flavin adenine dinucleotide; JEB: junctional epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa.

DISCUSSION

New data are emerging that mitochondria have critical functions in skin physiology.[8] RDEB and JEB both involve massive trauma to the skin caused by the loss of structural integrity of the basement membrane. However, the effects on bioenergetic and metabolic status of these conditions have not been studied at the cellular level. Using measurements for OCR, ATP/ADP energy ratio, and mitochondrial morphology, this study has identified a number of important variables in fibroblasts derived from RDEB or JEB patients. Critically, OXPHOS is reduced in RDEB and JEB fibroblasts. The lower basal respiration of EB fibroblasts readily indicates a lower energy output from the electron transport chain. This can reduce the amount of energy available to cells and can be detrimental for cells that carry a large metabolic load, such as fibroblasts involved in the perpetual wound healing found in patients with EB. Paired with this decreased metabolic capability appears to be an increase in the complexity of the mitochondria in EB fibroblasts, which is symptomatic of mitochondrial stress. These overall results are indicative of cell autonomous effects in RDEB and JEB fibroblasts independent of the patient wound status or extracellular environment. Future study is necessary to determine the extent

to which these cell autonomous effects are impacted by the environmental cues present in EB skin, such as oxidative imbalance and reduced antioxidant enzymes.[40]

CONCLUSION

EB cells responded to reduced mitochondrial OXPHOS energy production by modestly increasing anaerobic energy production through glycolysis. This was observed through increased production of L-lactate and a reduced redox ratio, while ECAR was only significantly higher in JEB fibroblasts under basal respiratory conditions. This is significant as the cells rely upon glycolysis for energy needs, but still exhibit an energy deficit at the level of ATP availability. The reliance of EB fibroblasts upon glycolysis in a reduced energy state may contribute to the observed range of EB phenotypes. Cells that are better able to adapt or overcome changes in bioenergetic and metabolic states may lead to uneven clinical presentation among patients, or even in different areas of the same patient. One of the treatments for EB patients is bone marrow transplantation.[41] Transplant outcomes have been shown to be affected by patient and donor mitochondrial haplotype.[42] Haplotype differences in mitochondrial function and stress response may prove significant as this work has demonstrated the first evidence of altered function and structure of mitochondria in fibroblasts derived from RDEB and JEB patients. EB at its core is more than an extracellular matrix or wounding disorder. This work suggests that systemic response to injury may decide the outcome of cellular and subcellular defects, in turn affecting the severity and treatment response in EB patients. Skin-directed mitochondrial research opens a novel avenue toward the development of EB treatments.

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Management of Plaque Psoriasis: A Review and Comparison of IL-23 Inhibitors

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Abstract

With the recent advancements of biologic therapies that block IL-23, there is increasing need for analysis of which biologics are most efficacious in treatment of plaque psoriasis. Guselkumab and risankizumab have each individually been compared to adalimumab in head-to-head trials, but no prior clinical trials have directly compared them to each other. The authors performed a literature review of guselkumab and risankizumab to determine which treatment is more efficacious in the management of plaque psoriasis. Using PubMed, a literature review was conducted using the terms "adalimumab psoriasis", "risankizumab psoriasis", and "guselkumab psoriasis". Fifteen studies resulted, and all were nonduplicate clinical trials written in English that were conducted within the past 5 years and included plaque psoriasis in the title. The data supports that risankizumab is more effective in improving Dermatology Life Quality Index (DLQI), static Physician's Global Assessment (sPGA), and Psoriasis Area and Severity Index (PASI) 90 scores. However, risankizumab may be associated with more adverse events than guselkumab. Major limitations of this review include that only one prior head-to-head trial comparing risankizumab to adalimumab has been conducted and there are no Phase II studies comparing the two biologics. Furthermore, risankizumab is a recently approved treatment and data regarding long-term efficacy and side effects are limited. Risankizumab and guselkumab are both highly effective, very safe, and very convenient psoriasis treatments that can be considered first-line treatment options for patients with moderate-to-severe plaque psoriasis.

INTRODUCTION

Psoriasis is an immune-mediated disease that causes excessive keratinocyte proliferation resulting in erythematous, irritating lesions.[1,2] Critical cytokines involved in the pathogenesis of psoriasis include TNF-α, IL-23, and IL-17.[1] IL-23 plays a large role in supporting maintenance and survival of T helper 17 cells, which produce proinflammatory cytokines IL-22 and IL-17, contributing to the development of psoriasis.[1-3]

Plaque psoriasis is the most common variant of psoriasis and accounts for 75–80% of patients.[4,5] Approximately 100 million individuals worldwide are affected by psoriasis and many patients experience reduced quality of life and negative psychological impacts attributable to the pain, scaling, and pruritus from the disease.[1,2,6,7]

Psoriasis therapies range from topical treatments in mild limited disease, to systemic treatments in severe disease.[8] Topical therapy is indicated for psoriasis affecting <5% of total body surface area (TBSA) without involvement of the feet, hands, genitals, or face.[9] Systemic therapy or ultraviolet-based therapy is indicated for psoriasis affecting ≥5% of TBSA.[9] Approved nonsystemic therapies include phototherapy and topical agents such as corticosteroids and vitamin D3.[10] Systemic therapies include biologics as well as nonbiologic agents such as cyclosporine, methotrexate, acitretin, tofacitinib, and apremilast.[10,11]

Biologics are the most recent advancement in the management of psoriasis and they exert their effect via inhibition of TNF-α, IL-23, or IL-17.[12] Adalimumab, a TNF-α inhibitor approved in 2008 to treat plaque psoriasis, is one of the most commonly used biologics.[1] Ixekizumab and secukinumab are two biologics that block IL-17. While these drugs are very effective, drugs that block IL-23 are among the most promising psoriasis treatments.[1,3,7] Many genes associated with psoriasis correspond to the genes for the two subunits of IL-23 (p40 and p19) and the genes for the IL-23 receptor.[1] Drugs that block IL-23 require few injections (as little as every 3 months), are very effective, and have proven very safe in both clinical trials and large registries.[1,3,7,11]

The first approved IL-23 blocker was ustekinumab, an antibody directed against the p40 subunit of IL-23 (the drug also blocks IL-12 as p40 is a subunit of both cytokines).[3,11] Ustekinumab is dosed every 3 months, achieves a 75% improvement in Psoriasis Area and Severity Index (PASI) at 3 months in about 70% of patients, and has a strong safety track record.[3,7,11] Nevertheless, IL-23 blockers based on p19 binding may replace ustekinumab in the treatment of psoriasis.[3,7]

Three p19-based IL-23 inhibitors are currently approved for psoriasis: guselkumab (first approved), tildrakizumab, and risankizumab (most recently approved). This study assessed the relative benefits and risks of these drugs using adalimumab as a common comparator. Tildrakizumab was excluded from this review as there is currently no direct comparison to adalimumab. Guselkumab and risankizumab both selectively bind to the p19 subunit of IL-23 and inhibit downstream intracellular signalling of IL-23 which helps prevent the role of inflammatory cytokines in psoriasis.[1,6] While guselkumab and risankizumab have each been directly compared to adalimumab in the management of plaque psoriasis, no prior head-to-head comparison of guselkumab and risankizumab has been conducted to determine which biologic is more efficacious in the management of plaque psoriasis. This article evaluates the efficacy of guselkumab and risankizumab using a literature review of prior clinical trials analysing each biologic's efficacy in comparison to adalimumab.

METHODS

A PubMed review of the literature was performed using the key terms "risankizumab psoriasis" or "guselkumab psoriasis" or "adalimumab psoriasis" (Figure 1). Results were further filtered and clinical trials were restricted to those written in English within the past 5 years (2015–2019). In total, this resulted in 78 articles. Articles that included plaque psoriasis in the title were further evaluated for a total of 15 articles. Additional results were obtained using the terms "guselkumab," "adalimumab," "risankizumab," "ustekinumab," and "tildrakizumab" to perform a more focussed search.

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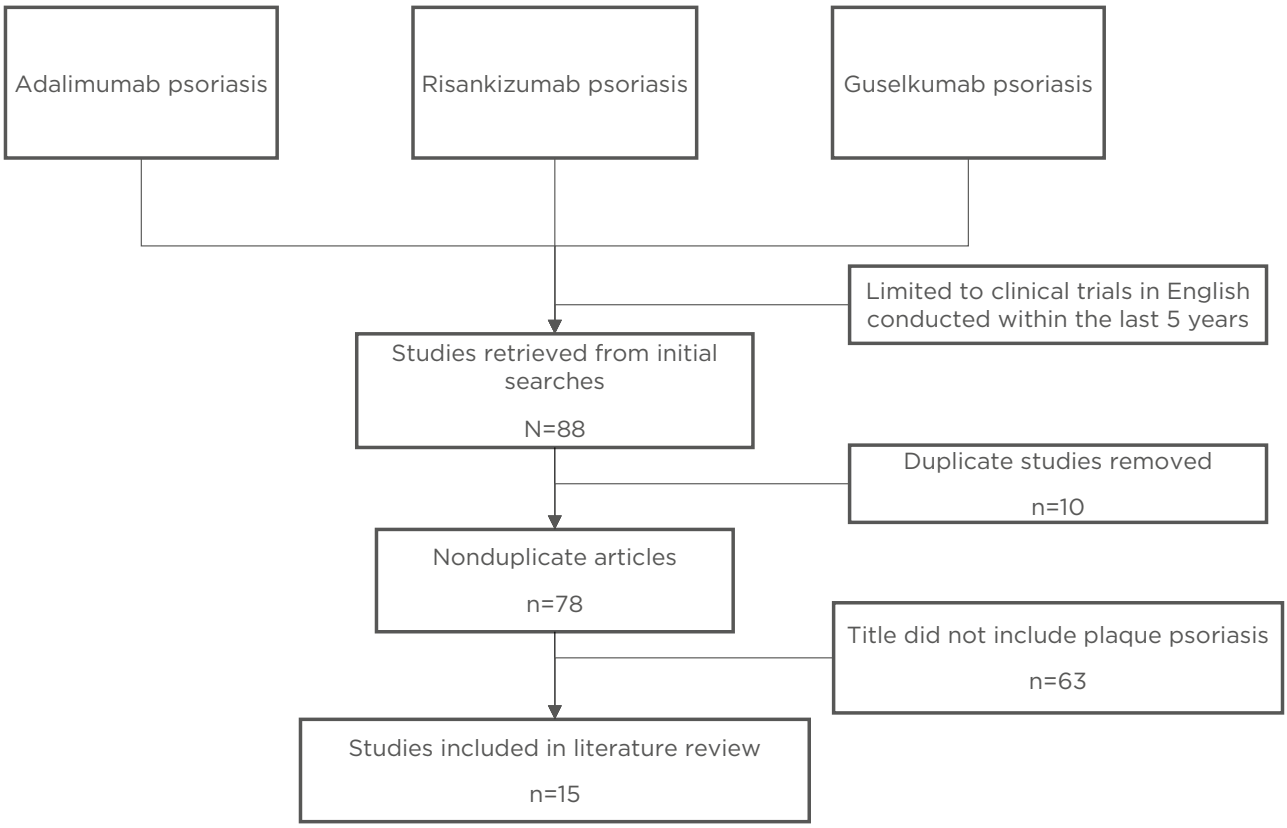

Figure 1: Literature review in PubMed.

RESULTS

Guselkumab Compared with Risankizumab

In a Phase III trial comparing guselkumab to adalimumab, 58.9% of guselkumab patients achieved a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 24.[6] DLQI assesses a patient's perception of the effect of psoriasis on their daily life with scores ranging from 0 (no impact) to 30 (maximum impact).[6] In a Phase III trial comparing risankizumab to adalimumab, more risankizumab patients (66%) achieved DLQI scores of 0 or 1 at Week 16.[1] Additionally, 66% of the patients who were adalimumab intermediate responders (IR) and were rerandomised to risankizumab achieved DLQI scores of 0 or 1 at Week 44.[1] It appears that risankizumab has a greater impact on quality of life scores and may lead to quicker improvement in scores than guselkumab (Table 1).[1,2,6,13,14]

In a Phase II trial of guselkumab, 71% of patients in the 50 mg group, 77% in the 100 mg group, and 81% in the 200 mg group achieved a Physician's Global Assessment (PGA) of 0 or 1 at Week 40.[2] PGA score determines the degree of psoriasis involvement with scores ranging from 0 to 5.[2] A score of 0 indicates cleared psoriasis, 1 minimal, 2 mild, 3 moderate, 4 marked, and 5 severe psoriasis.[2] In a Phase III trial of risankizumab, 84% of patients achieved a static PGA (sPGA) score of 0 or 1 at Week 16.[1] However, guselkumab had a greater difference from adalimumab on this variable (Table 2).[1,2,6,13,14] Risankizumab, when dosed at 150 mg, is more effective in improving PGA scores than 50, 100, and 200 mg doses of guselkumab (Table 3).[1,2]

In a Phase II trial of guselkumab, 34% of patients in the 5 mg treatment group, 34% in the 15 mg group, 45% in the 50 mg group, 62% in the 100 mg, and 57% in the 200 mg group achieved PASI 90 at Week 16.[2] PASI is used to determine psoriasis severity. Scores range from 0 to 72, with higher scores indicating greater severity.[2]

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Table 1: Comparison of risankizumab, guselkumab, and adalimumab outcomes across three clinical trials.

Outcomes	Reich K et al.,[1] 2019			Gordon KB et al.,[2] 2015			Armstrong AW et al.,[6] 2019*		
	Risankizumab[a]	Adalimumab[a]	Variance	Guselkumab	Adalimumab	Variance	Guselkumab[e]	Adalimumab[e]	Variance
DLQI score of 0 or 1	66.0	49.0	17.0	70.0[a] (200 mg)	49.0[a]	21.0[a]	58.9	40.2	18.7
PGA score of 0 or 1	x	x	x	81.0[c] (200 mg)	49.0[c]	32.0[c]	x	x	x
sPGA score of 0 or 1	84.0	60.0	24.0	x	x	x	x	x	x
PASI 90	72.0	47.0	25.0	62.0[a] (100 mg)	44.0[a]	18.0[a]	x	x	x
Adverse events	56.0	57.0	-1.0	49.0[d]	61.0[d]	-12.0[d]	x	x	x

All results are based on percent of people achieving each outcome. Variance refers to the difference in results between risankizumab or guselkumab and adalimumab.

[a]indicates outcome achieved at Week 16.

[b]indicates outcome achieved at Week 44.

[c]indicates outcome achieved at Week 40.

[d]indicates outcome achieved at Week 52.

[e]indicates outcome achieved at Week 24.

*indicates the referenced study results came from the original studies of Blauvelt A et al.,[13] 2017 and Reich K et al.,[14] 2017.

DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; sPGA: static Physician's Global Assessment.

Table 2: Comparison of risankizumab and guselkumab variances from adalimumab across three clinical trials.

Outcomes	Risankizumab - adalimumab	Guselkumab - adalimumab
DLQI score of 0 or 1	17.0[a,e]	21.0[a,f,h]; 18.7[d,g]
PGA/sPGA score of 0 or 1	24.0[a,e]	32.0[b,f,h]
PASI 90	25.0[a,e]	18.0[a,f,i]
Adverse events	-1.0[a,e]	-12.0[c,f]

All results are percentages and reflect the variance between risankizumab or guselkumab and adalimumab. The variance was calculated from the percent of people achieving each outcome.

[a]outcome achieved at Week 16.

[b]outcome achieved at Week 40.

[c]outcome achieved at Week 52.

[d]outcome achieved at Week 24.

[e]results from Reich K et al.,[1] 2019.

[f]results from Gordon KB et al.,[2] 2015.

[g]results from Armstrong AW et al.,[6] 2019 which used data from the original studies of Blauvelt A et al.,[13] 2017 and Reich K et al.,[14] 2017.

[h]a dosage of 200 mg.

[i]a dosage of 200 mg.

DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; sPGA: static Physician's Global Assessment.

In a Phase II study, 72% of risankizumab patients achieved PASI 90 at Week 16.[1]

Of the adalimumab IR rerandomised to risankizumab at Week 16, 66% achieved PASI 90 at Week 44.[1] Risankizumab had a greater number of patients achieve PASI 90 at Week 16 than guselkumab (Table 3).

Differences exist when comparing guselkumab and risankizumab to IL-17 inhibitors in head-to-head trials. PASI 100 was achieved at Week 12 for 25% of patients randomised to guselkumab and 41% of patients randomised to ixekizumab with all major endpoints for ixekizumab having statistically significant greater improvement compared to guselkumab at Week 12.[15] An additional study showed that 87% of risankizumab patients achieved PASI 90 at Week 52 compared to only 57% of secukinumab patients ($p<0.001$), with risankizumab having superiority compared to secukinumab for all secondary endpoints at Week 52 ($p<0.001$).[16] Risankizumab may be a more effective treatment for achieving PASI 90 than IL-17 inhibitors with IL-17 inhibitors being more effective than guselkumab at achieving PASI 100.[15,16]

As with any medication, it is important to understand the risk of adverse events (AE). The most commonly reported AE in guselkumab patients were infections, but no serious infections were noted compared to a serious case of pneumonia in the adalimumab group.[2] Serious AE (SAE) in the guselkumab group included one case of high-grade cervical cancer and one death from a myocardial infarction.[2] In a Phase II

trial, 49% of the patients receiving guselkumab reported AE at the end of 52 weeks.[2] A Phase III study of risankizumab reported that 56% of the patients experienced AE at Week 16 and 76% of adalimumab IR patients, rerandomised at Week 16 to risankizumab, reported AE at Week 44.[1] Furthermore, when comparing guselkumab and risankizumab to IL-17 inhibitors, 3% of both the guselkumab and ixekizumab groups at Week 12 experienced SAE with 5.5% of risankizumab patients and 3.7% of patients in the secukinumab group reporting SAE at Week 52.[15,16] Guselkumab is less likely than risankizumab to cause AE when treating plaque psoriasis (Table 3) and risankizumab may be more likely to cause SAE than IL-17 inhibitors.[15]

A known difference between risankizumab and guselkumab is the convenience of dosing. Guselkumab requires starter doses at Weeks 0 and 4 with one injection every 8 weeks after starter injections are complete.[11] In contrast, risankizumab requires starter doses at Weeks 0 and 4 with two-injection maintenance dosing every 12 weeks starting at Week 16. Although risankizumab requires two injections, the four yearly maintenance doses may be more appealing for patients compared to the six yearly maintenance doses of guselkumab.

Guselkumab Compared with Adalimumab

In a 52-week Phase II placebo-controlled, double-blind, randomised trial, guselkumab was compared to adalimumab in patients with moderate-to-severe plaque psoriasis.[2] In total, 293 patients were randomised to receive either placebo, one of five guselkumab treatment regimens, or adalimumab (Table 3).[1,2,6,12-14] To be included in the study, patients had to be ≥18 years and have experienced moderate-to-severe plaque psoriasis for at least 6 months. Moderate-to-severe was defined as a PGA score of ≥3, involvement of >10% TBSA, and a PASI score of ≥12. Patients previously treated with guselkumab or adalimumab were excluded from the study. The primary outcome was the achievement of a PGA score of 0 or 1 in patients at Week 16 (Table 1).[2]

Compared to adalimumab, the proportion of patients with a PGA score of 0 or 1 at Week 16 was higher for all guselkumab groups except for the 5 mg regimen group (Table 1). By Week 16, the 5, 15, 50, 100, and 200 mg guselkumab groups achieved PASI 90 in 34%, 34%, 45%, 62%, and 57% of the patients, respectively.[2] By Week 16, 44% of the adalimumab group achieved PASI 90. By Week 40, the guselkumab groups had achieved a PGA score of 0 or 1 in 71%, 77%, and 81% of patients in the 50, 100, and 200 mg groups, respectively. In comparison, only 49% of the adalimumab group achieved a PGA score of 0 or 1 ($p<0.05$). During the first 16 weeks of the trial, infection rates for guselkumab and adalimumab were 20% and 12%, respectively.[2] Fewer injection-site reactions occurred with guselkumab (1%) than adalimumab (6%). Fewer patients (49%) treated with guselkumab experienced AE from Week 16–52 of the study compared to adalimumab recipients (61%). No association was noted between the dose of guselkumab and increased rate of AE.[2]

In two 24-week Phase III placebo-controlled, double-blind, randomised trials, guselkumab was compared to adalimumab in patients with plaque-type psoriasis.[13,14] Patients were randomised to receive either guselkumab, adalimumab, or placebo (Table 1). Inclusion criteria included age >18 years, diagnosis of plaque-type psoriasis for at least 6 months with 10% or more TBSA involvement, PASI score of 12 or higher, Investigator's Global Assessment (IGA) score of at least 3, and eligibility for systemic or phototherapy treatments.[13] Patients with a history of active tuberculosis, a progressive, uncontrolled, or severe medical condition, or a history of malignancy (except nonmelanoma skin cancer) within the previous 5 years were excluded from the study.[13] Similarly, patients who received guselkumab, adalimumab, or another anti-TNF-α therapy in the past 3 months; IL-12/23, IL-17, or IL-23 inhibitors in the past 6 months; phototherapy in the past 1 month; or systemic immunosuppressant therapy in the past 1 month were excluded.[13] Pooled data from the two 24-week trials were used to compose two studies which examined different endpoints and effects of the treatments.[6,12]

The primary endpoints of the first pooled study included the patient proportion with a DLQI score of 0 or 1 (no impact on quality of life) that had a baseline score greater than 1 and the proportion of patients with a DLQI score that changed from baseline to Weeks 8, 16, and 24 (Table 1).[6]

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Table 3: Comparison of risankizumab and guselkumab to adalimumab in Phase II and III clinical trials.

Author	Study design	Total patients	Primary endpoint	Primary outcome	Treatment arm	Week 8 results, n (%)	Week 16 results, n (%)	Week 24 results, n (%)	Week 44 results, n (%)
Gordon et al., 2015[2]	Phase II	293	Week 16	PGA 0 or 1	Guselkumab 5 mg at Weeks 0, 4, and every 12 weeks after (n=41)	x	14.00 (34.0)	x	x
					Guselkumab 15 mg every 8 weeks (n=41)	x	25.00 (61.0)	x	x
					Guselkumab 50 mg at Weeks 0, 4, and every 12 weeks after (n=42)	x	33.00 (79.0)	x	x
					Guselkumab 100 mg every 8 weeks (n=42)	x	36.00 (86.0)	x	x
					Guselkumab 200 mg at Weeks 0, 4, and every 12 weeks after (n=42)	x	35.00 (83.0)	x	x
					Adalimumab 80 mg at Week 0, 40 mg at Week 1 and every other week up to Week 39 (n=43)	x	25.00 (58.0)	x	x
					Placebo for 15 weeks then guselkumab 100 mg every 8 weeks starting at Week 16 (n=42)	x	3.00 (7.0)	x	x
Armstrong et al., 2018[6,*]	Phase III	1829	Weeks 8, 16, 24	DLQI 0/1 with a DLQI baseline score >1	Guselkumab 100 mg at Weeks 0, 4, 12, and 20 (n=825)	266.82 (32.9)	433.89 (53.5)	477.68 (58.9)	x
					Adalimumab 80 mg at Week 0, 40 mg at Week 1 and every other week through Week 25 (n=582)	138.99 (24.6)	219.22 (38.8)	227.13 (40.2)	x
					Placebo at Weeks 0, 4, 12 then guselkumab 100 mg at Week 16 and 20, (n=422)	7.87 (1.9)	14.90 (3.6)	x	x
				Change in DLQI score from baseline	Guselkumab 100 mg at Weeks 0, 4, 12, and 20 (n=825)	-9.00(c)	-11.00c	-12c	x
					Adalimumab 80 mg at Week 0, 40 mg at Week 1 and every other week through Week 25 (n=582)	-8.00(c)	-9.00c	-9c	x
					Placebo at Weeks 0, 4, 12 then guselkumab 100 mg at Week 16 and 20 (n=422)	-2.00(c)	-1.00c	x	x

Table 3 continued.

Author	Study design	Total patients	Primary endpoint	Primary outcome	Treatment arm	Week 8 results, n (%)	Week 16 results, n (%)	Week 24 results, n (%)	Week 44 results, n (%)
Gordon et al., 2018[12,*]	Phase III	1829	Week 16	IGA 0/1	Guselkumab 100 mg at Weeks 0, 4, 12, and 20 (n=825)	x	697.13 (84.5)	x	x
					Adalimumab 80 mg at Week 0, 40 mg at Week 1 and every other week through Week 25 (n=582)	x	390.20 (66.7)	x	x
					Placebo at Weeks 0, 4, 12 then guselkumab 100 mg at Week 16 and 20 (n=422)	x	32.92 (7.8)	x	x
Reich et al., 2019[1]	Phase III	605	Week 16a	PASI 90	Risankizumab 150 mg at Weeks 0 and 4 (n=301)	x	218.00 (72.0)	x	x
				sPGA 0 or 1		x	252.00 (84.0)	x	x
				PASI 90	Adalimumab 80 mg at Week 0, 40 mg at Week 1 and every other week through Week 15 (n=304)	x	144.00 (47.0)	x	x
				sPGA 0 or 1		x	183.00 (60.0)	x	x
			Week 44b	PASI 90	Risankizumab 150 mg at Weeks 16, 20, and 32 (n=53)	x	x	x	35.00 (66.0)
					Adalimumab 40 mg every other week from Week 17 through Week 41 (n=56)	x	x	x	12.00 (21.0)

[a]part A of study.

[b]part B of study which analysed adalimumab intermediate responders.

[c]median change.

*the referenced study came from the original studies of Blauvelt A et al.,[13] 2017 and Reich K et al.,[14] 2017.

n the number of people achieving results in each category.

DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; sPGA: static Physician's Global Assessment.

An additional endpoint was the proportion of patients with a DLQI individual domain score of 0 and the percent improvement in individual domains among patients with scores of 3 reflecting the most severe impact. At Week 24, a greater proportion of guselkumab patients (58.9%) achieved a DLQI score of 0 or 1 when compared to patients receiving adalimumab (40.2%; p<0.001).[6] Guselkumab patients experienced greater improvement in individual DLQI domains at Week 24 compared to adalimumab patients (p<0.001). A greater proportion of patients (35.6%) treated with guselkumab at Week 24 achieved a Psoriasis Symptoms and Signs Diary (PSSD) symptoms score of 0 (free of symptoms) than those receiving adalimumab (22.0%; p<0.001).[6] The proportion of patients who achieved a PSSD score of 0 was also higher for patients treated with guselkumab (28.4%) compared to adalimumab (15.6%).[6]

The primary endpoint of the second pooled study was an IGA score of 0 or 1 (cleared or minimal psoriasis) at Week 16 when compared to placebo (Table 1).[12] Two of the major secondary endpoints included an IGA score of 0 (cleared) or IGA of 0 or 1 (cleared or minimal psoriasis) at Week 24 when compared to adalimumab.[12] At Week 24, a statistically significant proportion of patients treated with guselkumab achieved IGA 0 or IGA 0 or 1 for all comparisons except for the African American or black subgroup which was small and included 12 guselkumab and 13 adalimumab patients, respectively.[12] Additionally, clinical responses for baseline weight strata were higher for the guselkumab group compared to adalimumab at Week 24. Both guselkumab and adalimumab had lower response rates in patients who weighed more, but the response rates were more consistent for guselkumab. In individuals of any weight, the clinical response is more consistent with the 100 mg guselkumab dose than adalimumab which is less efficacious in patients of greater weight.[12] Regardless of prior treatment, patients treated with guselkumab achieved statistically significant improvements in IGA 0 (52.1%) and IGA 0 or 1 scores (83.8%) compared to adalimumab patients (IGA 0 [30.2%] and IGA 0 or 1 [63.1%]) at Week 24.[12]

Risankizumab Compared with Adalimumab

No Phase II studies have been conducted comparing efficacy of risankizumab to adalimumab. One Phase III double-blind, randomised, active-comparator-controlled trial was conducted in patients with moderate-to-severe plaque psoriasis to evaluate the efficacy of risankizumab.[1] This Phase III trial was the first head-to-head trial comparing risankizumab to adalimumab. The trial lasted 44 weeks and was composed of Part A (Weeks 0–16) and Part B (Weeks 16–44). During Part A, patients were randomised to receive either risankizumab or adalimumab (Table 1). In Part B, patients who were randomised to adalimumab in Part A and achieved PASI 90 remained on adalimumab treatment while those who achieved a PASI 50 or less were switched to risankizumab (Table 1). Patients receiving adalimumab in Part A who achieved greater than PASI 50 but less than PASI 90 (adalimumab IR) were rerandomised to continue adalimumab or were switched to risankizumab in Part B. Additionally, patients who were originally randomised to the risankizumab regimen in Part A remained on this regimen in Part B. Participant inclusion criteria included age over 18 years, 10% or more TBSA with moderate-to-severe plaque psoriasis that was stable for at least 6 months, PASI score of at least 12, sPGA of at least 3, and eligibility for phototherapy or systemic psoriasis treatment as well as adalimumab.[1] Patients were excluded if they had non-plaque or drug-induced psoriasis, ongoing inflammatory active disease, prior exposure to adalimumab, use of restricted medications, chronic or active infections, or had a history of malignancy in the preceding 5 years (except nonmelanoma skin cancer or uterine cervix *in situ* carcinoma).[1] Primary endpoints for Part A of the study were achievement of PASI 90 and achievement of sPGA score of 0 or 1 (clear or almost clear at Week 16 (Table 1).[1] The primary endpoint for Part B of the study was achievement of PASI 90 among adalimumab IR at Week 44 (Table 1).

By the end of Week 16 (Part A), more patients randomised to risankizumab achieved PASI 90 (72%), sPGA score of 0 or 1 (84%), PASI 75 (91%), and PASI 100 (40%) compared to adalimumab (PASI 90, sPGA score of 0 or 1, PASI 75, PASI 100 of 47%, 60%, 72%, and 23%, respectively).[1] Additionally, adalimumab IR at the end of Part A who were rerandomised to risankizumab had a larger proportion of PASI 90 (66%) and PASI 100 (40%) compared to patients rerandomised to continue adalimumab (PASI 90, PASI 100 of 21% and 7%, respectively) at Week 44. A greater proportion of patients receiving risankizumab achieved a sPGA score of 0 in both parts of the study than adalimumab patients ($p<0.0001$ for Part A and B). Starting at Week 8, the proportion of patients achieving PASI 90 was higher for patients receiving risankizumab compared to adalimumab ($p=0.0012$). Differences between risankizumab and adalimumab regarding proportion of patients achieving sPGA scores of 0 and PASI 100 became apparent at Week 8. In Week 44, patients rerandomised to risankizumab during Part B had a higher mean improvement (93%) compared to patients rerandomised to adalimumab (72%) during Part B.[1]

Quality of life improvement was greater for patients receiving risankizumab than those receiving adalimumab with a greater proportion of risankizumab patients having DLQI scores of 0 or 1 (66%) compared to adalimumab (49%) at

Week 16.[1] Additionally, adalimumab IR who were rerandomised to risankizumab at the end of Part A had a greater proportion of DLQI scores of 0 or 1 at Week 44 (66%) than patients rerandomised to continue adalimumab (29%). Adalimumab patients who achieved PASI 50 or less at the end of Part A and were switched to risankizumab experienced clinical benefit with 61% achieving PASI 90 and 63% achieving sPGA scores of 0 or 1 at Week 44. Patients who were treated with risankizumab continuously throughout the 44-week study and achieved sPGA score of 0 or 1 and PASI 90 at Week 16 were maintained until the end of the study. In Part A, 56% of risankizumab patients and 57% of adalimumab patients reported nonserious AE, most commonly headache and upper respiratory tract infection. In Part A, 3% of patients in both risankizumab and adalimumab treatment groups experienced serious AE. In Part B, 76% of patients rerandomised to risankizumab and 66% of patients rerandomised to continue adalimumab experienced AE, most commonly headache, back pain, arthralgia, and upper respiratory tract infection. SAE occurred in 6% of patients rerandomised to risankizumab and 4% of patients rerandomised to continue adalimumab. No serious infections occurred in patients rerandomised to adalimumab during Part B of the study, but one patient did report a serious AE of depression.

No cases of serious hypersensitivity or active tuberculosis were reported in the study and no events of opportunistic infections, death, malignancy, or major cardiovascular events occurred in Part B. In Part A, there was one major adverse cardiovascular event, one case of depression in the risankizumab group, and one case of oral candidiasis in the adalimumab group. Five patients receiving risankizumab reported hepatic events with one patient discontinuing the medication and three patients receiving adalimumab reported hepatic events. Three reported deaths occurred during the study, however, none of them were related to the study drugs. During Part B, a patient rerandomised to risankizumab developed latent tuberculosis and a patient who was continuously on risankizumab throughout the study experienced depression. Hepatic events were reported in one patient rerandomised to risankizumab and four patients rerandomised to adalimumab.[1]

Risankizumab and Guselkumab Head-to-Head Studies Compared to IL-17 Inhibitors

Two recent head-to-head trials of guselkumab to ixekizumab and risankizumab to secukinumab provide additional information on which IL-23 inhibitor is more effective when compared to IL-17 inhibitors.[15,16] To further provide additional information on which IL-23 inhibitor is more effective when compared to IL-17 inhibitors these studies were analysed. The head-to-head comparison of guselkumab to ixekizumab concluded that the primary endpoint of PASI 100 was achieved by 25% of patients randomised to guselkumab and 41% of patients randomised to ixekizumab at Week 12.[16] Furthermore, all primary and secondary major endpoints for ixekizumab had statistically significant greater improvement compared to guselkumab at Week 12.[16] The frequency of SAE was 3% for both the guselkumab and ixekizumab groups at Week 12.[16] New head-to-head Phase III data comparing risankizumab to secukinumab analysed the primary endpoint of PASI 90 at Week 52.[16] Of the risankizumab patients, 87% achieved PASI 90 at Week 52 compared to 57% of secukinumab patients ($p<0.001$).[16] The other primary endpoint was noninferiority of risankizumab to secukinumab at Week 16 using PASI 90. At Week 16, 74% of risankizumab patients achieved PASI 90 compared to 66% of secukinumab patients.[16] Additionally, risankizumab exhibited superiority compared to secukinumab for all secondaryendpoints at Week 52 ($p<0.001$).[16] SAE were reported for 5.5% of patients in the risankizumab group and 3.7% of patients in the secukinumab group.[16]

Tildrakizumab

Tildrakizumab was excluded from this review as there is currently no direct comparison of this IL-23 inhibitor to adalimumab. However, the reSURFACE 2 study concluded that a greater proportion of patients receiving tildrakizumab (61% in 100 mg group and 66% in 200 mg group) achieved PASI 75 compared to patients receiving etanercept (48%) at Week 12 ($P<0.05$).[17] Improvements in PGA scores to 0 or 1 occurred more frequently in both tildrakizumab groups (66% in 100 mg group and 71% in 200 mg group) than the etanercept group (48%) at Week 28 ($p<0.001$).[17] SAE were similar across

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the tildrakizumab groups (2% in 200 mg group, 3% in 100 mg group) and etanercept (5%) at the end of the study.[17] Since the primary endpoints are different in the VOYAGE trials of guselkumab and the reSURFACE trials of tildrakizumab direct comparisons cannot be made.[17,18] However, results of the VOYAGE and reSURFACE trials suggest that guselkumab may be more effective than tildrakizumab because a higher percentage of patients at Week 12 achieved a PGA score of 0 or 1, PASI 75, PASI 90, or PASI 100 for guselkumab groups when compared to tildrakizumab groups.[18] Tildrakizumab is more effective than the TNF-α inhibitor etanercept at achieving PASI 75.[18] Previous randomised controlled trials support that tildrakizumab is well tolerated for up to 64 weeks in large groups of patients with moderate-to-severe psoriasis.[17,19,20] Future research is needed regarding tildrakizumab and how it compares in head-to-head trials to adalimumab and risankizumab.

CONCLUSION

With continued emergence of new psoriasis medications, there is an increasing need for analysis of which biologics are most efficacious in the treatment of plaque psoriasis. This clinical review compares guselkumab and risankizumab to provide some sense of which IL-23 inhibitor biologic is more effective in treating plaque psoriasis. Guselkumab and risankizumab have each individually been compared to adalimumab in head-to-head trials, but no prior clinical trials have directly compared them to each other.

A major limitation of this review is that only one prior head-to-head trial comparing risankizumab to adalimumab has been conducted and there are no Phase II studies comparing the two biologics. Furthermore, risankizumab is a recently approved treatment and data regarding long-term efficacy and side effects are limited. However, a Phase III trial comparing the efficacy of risankizumab to secukinumab (IL-17 inhibitor) is underway,[21] and the resulting data will be helpful for comparing risankizumab to guselkumab using secukinumab as the common comparator.[1] The indirect comparisons have the advantage of coming from studies in which there were also placebo-controls (head-to-head trials without placebo controls often find higher response rates than those with placebo controls). Additional limitations include lack of current research comparing tildrakizumab, the third IL-23 inhibitor, to adalimumab; therefore, this review was unable to directly compare risankizumab and guselkumab to tildrakizumab. While previous trials suggest that guselkumab may be more effective than tildrakizumab, further research is needed to compare tildrakizumab to adalimumab, guselkumab, and risankizumab to comprehensively evaluate the efficacy of IL-23 inhibitors.[18]

According to previous clinical trials, risankizumab is more effective in improving DLQI scores and PGA scores, and results in more patients achieving PASI 90.[1,2,6] However, risankizumab may be associated with more AE than guselkumab.[1,2] Additionally, although risankizumab requires two injections, the four yearly maintenance doses may be more appealing for patients compared to guselkumab's six yearly maintenance doses.[11] Psoriasis treatment targets of PASI 100/DLQI 0 or 1, and of PGA 0 have been promulgated.[11,22] Both risankizumab and guselkumab can achieve these outcomes, though the difference in their ability to do so may not be clinically relevant. Risankizumab may be a more effective treatment for achieving PASI 90 than IL-17 inhibitors with IL-17 inhibitors being more effective than guselkumab at achieving PASI 100.[15,16] Risankizumab and guselkumab are both highly effective, very safe, and convenient psoriasis treatments that can be considered first-line treatment options for patients with moderate-to-severe plaque psoriasis.

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Case Report: Suspected Case of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis Overlap Due to Ursodeoxycholic Acid

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Abstract

Stevens–Johnson syndrome and toxic epidermal necrolysis are well-known severe cutaneous adverse reactions, with >100 medications previously implicated, most frequently sulfonamide antibiotics. Ursodeoxycholic acid (UDCA), normally present in human bile at a low concentration, is used for the treatment of various cholestatic disorders. Reports of UDCA causing cutaneous complications are, however, rare. The present report describes a suspected case of UDCA-induced Stevens–Johnson syndrome–toxic epidermal necrolysis overlap in a 24-year-old female, admitted with a whole-body maculopapular rash with oromucocutaneous ulceration and skin desquamation. The patient was managed with supportive care, including fluid and electrolyte replacement, corticosteroids, antibiotics, antihistamines, and intravenous Ig. Early identification, prompt intervention with effective care, and support are the key action points in these severe cutaneous adverse reactions.

BACKGROUND

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are well-known severe cutaneous adverse reactions (SCAR). First reported in 1922, these reactions were initially thought to be infectious in nature, however, the concept has changed over the years. Although their aetiology is not fully understood, most cases of SJS and TEN are now attributed to an immunologically mediated response to drug exposure, belonging to Type IV hypersensitivity.[1] SJS–TEN refers to SCAR associated with widespread epidermal detachment and mucocutaneous involvement. Incidence of SJS and TEN is estimated to be 1.0–6.0 per million and 0.4–1.2 per million, respectively.[2] Over 100 medications have been implicated in SJS and TEN, most frequently sulfonamide antibiotics,

followed by nonsteroidal anti-inflammatory drugs and antigout drugs, particularly allopurinol.[3,4] Risk of developing these SCAR after drug exposure appears to be greatest during the first few weeks of treatment initiation. These SCAR are characterised by fever, rash, and mucosal blisters. Diagnosis depends on the total body surface area involvement of detached/detachable skin lesions: <10%, 10–30%, and >30% represent SJS, SJS–TEN overlap, and TEN, respectively. Both SJS and TEN can occur at any age, but appear to be more prevalent in adults, especially in older adults over 65 years.[5] SJS–TEN overlap is slightly predominant in females compared with males (3:2).[6]

The dihydroxy bile acid ursodeoxycholic acid (UDCA) is used for the treatment of chronic cholestatic liver disorders. It is normally present in human bile at a low concentration of almost 3% of total bile acids.[7] Regarded as a well-tolerated drug, few safety concerns have been reported since its initial clinical use. Cutaneous complications are rare, though there have been reports of generalised rash, fixed drug eruptions, and lichen planus secondary to this drug.[8,9] However, no prior reports of SCAR were available through an extensive literature search. The present report describes a suspected case of UDCA-induced SJS–TEN overlap.

CASE REPORT

A 24-year-old female, who was normotensive and euglycaemic, was admitted with whole-body maculopapular rash with oromucocutaneous erosions and skin desquamation. The patient had a history of viral hepatitis 1 year previous, and was symptom-free before the development of the rashes. No other viral infections were reported during this 1-year time frame. Ten days prior to the presenting features, she was commenced on UDCA 300 mg twice daily (bid), along with a fixed-dose combination of omeprazole and domperidone once daily (qd), by a local physician owing to deranged liver function tests. On the seventh day of consumption of these medications, she presented with a rash, appearing first on the face and then slowly progressing all over the body. The rash was pruritic in nature and was followed by blister formation. The blisters were confined to the facial region, particularly involving the oromucocutaneous region. The blisters were followed by denudation of the skin (Figure 1). The patient was afebrile with no urinary abnormalities, and there were no genital lesions. She also described watery discharge from her eyes and had difficulty in opening her eyes and mouth.

The patient was admitted, with prompt cessation of all ongoing medications. She had a history of previous treatment with omeprazole and domperidone on multiple occasions, without any adverse event. However, skin biopsy and histopathology of the involved area was not performed, due to its unavailability in the rural setting of this case. Considering the clinical presentation and involved total body surface area, the patient was diagnosed with a suspected case of UDCA-induced SJS–TEN overlap. The temporality ruled out the probability of the reaction being related to any viral condition. Prognosis was assessed using SCORe of Toxic Epidermal Necrosis (SCORTEN) criteria, which conferred a score of 2 for the index case. The patient was managed with a short course of steroid therapy with qd dosing of dexamethasone for 3 days, intravenous fluid (normal saline) 8 hourly, cyclosporine 100 mg bid, chlorhexidine mouthwash, calaminol lotion, hydroxyzine 25 mg qd, moxifloxacin eye drops, and methylcellulose eye drops. The patient responded to this regimen and was discharged within 3 weeks. Her laboratory investigations were within normal limits.

Causality assessment of the reaction conferred it to be “probable”, with a score of 5 using the Naranjo causality assessment algorithm, while the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality assessment scale also graded it as “probable”; severity assessment using the Hartwig and Siegel Scale assessed it to be severe (Level 5). The event was reported under the Pharmacovigilance Programme of India (PvPI).

DISCUSSION

Approximately 45% of adverse drug reactions are manifested in the skin, with the majority being mild. However, drug-induced SCAR are not rare and are potentially life threatening.

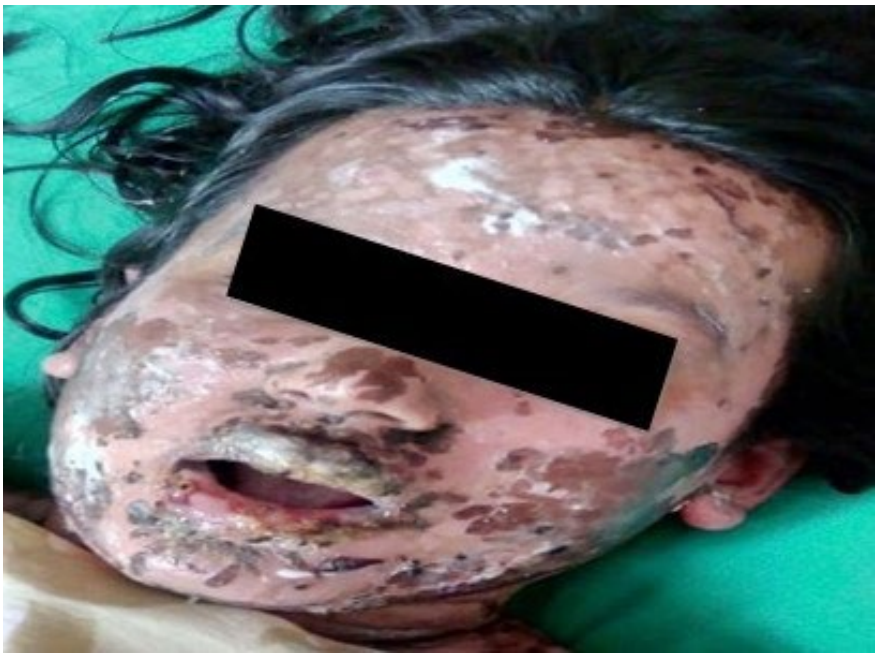

Figure 1: Oromucocutaneous ulceration and skin desquamation, consistent with Stevens–Johnson syndrome and toxic epidermal necrolysis overlap severe cutaneous adverse reaction.

These hypersensitivity reactions, including SJS and TEN, are primarily recognised as a dysregulation of cellular immunity caused by a release of various cytotoxic signals, including granulysin, perforin/granzyme B, and Fas/Fas ligands, which are activated by cytotoxic T lymphocytes and natural killer cells. These SCAR differ from classical allergies as there is no classic sensitisation. As evidenced in the literature, mortality rates of SJS, SJS–TEN overlap, and TEN are 5–10%, 30%, and 50%, respectively.[10] Patients usually give a history of constitutional symptoms, including fever, malaise, arthralgia, and sore throat. To start with, the lesions are erythematous to violaceous and purpuric macules, which coalesce to form patches. Targetoid lesions may be present. Mostly, the lesions initially involve the trunk and upper torso, which spread distally to involve the limbs, followed by skin exfoliation. Presentation of flaccid bullae is also common. SJS is characterised by involvement of <10% body surface area, SJS–TEN overlap signifies 10%–30% involvement and the most severe form of the spectrum, and TEN is characterised by involvement of >30% body surface area. Mucosal inflammation (oral, ocular, and genitourinary) is nearly universal. Pseudo-Nikolsky and Asboe-Hansen signs can be elicited in most cases. The hallmark findings include full-thickness epidermal necrosis, subepidermal bullae, and scanty inflammatory infiltrates in the papillary dermis.[11] However, owing to logistic concerns, the present report could not describe the pathological findings of the affected area, which remains a limitation of this study. The clinical differentials of these SCAR include morbilliform drug rash, erythema multiforme, drug-induced linear IgA disease, acute generalised exanthematous pustulosis, acute graft-versus-host disease, drug reaction with eosinophilia and systemic symptoms syndrome, or staphylococcal scalded skin syndrome. UDCA, the suspect drug in this report, is virtually considered safe. However, rare reports of mild- to moderate-grade skin reactions have surfaced. Cutaneous manifestations such as lichenoid skin eruptions, itching, and prurigo have been cited.[12,13] The present report is a rare case of UDCA-induced SCAR. To the authors' knowledge, it is the first of its kind reported from this country. Though regarded to have negligible safety concerns, the responsible mechanism behind such a reaction may be due to the cytotoxic profile of this drug.[8]

An effective modality may be drug provocation testing by preparing a list of suspected drugs

to which the patient has previously experienced drug reactions; however, such tests should be performed under strict medical supervision, preferably in a day care setting.[14] Several serum markers have also been explored, which can serve to detect an early TEN case and prognosticate its due progression. Of these many markers, few are soluble, including Fas ligand, granzyme B, soluble CD40 ligand, granulysin, serum high mobility group protein B1, serum lactate dehydrogenase, a-defensins 1–3 in the blisters, Bcl-2 expression in the dermal infiltrates, thymus and activation-regulated chemokine, and glutathione-S transferase-pi expression. IL-15 has been found to be useful in predicting severity and monitoring prognosis.[11]

Patients with SJS or TEN are managed with supportive care, such as fluid and electrolyte replacement, corticosteroids, immunosuppressants, antibiotics, antihistamines, and intravenous Ig. Owing to multi-organ system involvement, complications can be varied depending on the reaction extent and point of therapeutic intervention, thus mandating early consultation with concerned specialties for ensuring safer patient outcomes.[11,15] Early identification and prompt intervention with effective care and support are the key action points in these SCAR. However, knowledge and health-seeking behaviour for drug-induced allergies are multifactorial and are thought to differ between various communities. Continuous and repetitive community education may raise the public awareness of allergy and increase prompt health-seeking patterns in affected individuals.

CONCLUSION

Keeping in mind the significant morbidity and mortality associated with these SCAR, it would have been extremely beneficial if the culprit drug could be prevented. Proper elucidation of drug allergy history is imperative. If a patient is found to be allergic to a particular drug group, pharmacogenetic screening can be considered.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. The patient has given their consent for their images and other clinical information to be reported in the eJournal. The patient understands that their names and initials will not be published, and due efforts will be made to conceal their identity.

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Differential Diagnosis of Nail Psoriasis and Onychomycoses: A Report Based on 40 Years of Specialised Nail Consultations

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Abstract

Ungual psoriasis and onychomycosis are common nail diseases. Despite their different aetiology and course, surprisingly they have much in common both clinically and histopathologically, rendering their distinction often very challenging. Because their treatments are fundamentally different, anti-inflammatory–immunosuppressive for psoriasis and anti-infective for onychomycoses, an exact diagnosis is crucial for their management. Psoriasis is the dermatosis with the most frequent nail involvement. Pits, ivory-coloured spots, salmon or oil spots, subungual hyperkeratosis, onycholysis, and splinter haemorrhages are the most common nail signs. Onychomycoses are thought to be the most frequent nail diseases. This statement is disputed for toenails, for which orthopaedic abnormalities are said to be even more frequent and mimic fungal nail infections.

INTRODUCTION

Nail disorders account for approximately 10–15% of the workload of dermatologists. Patients request, and deserve, an accurate diagnosis and treatment.[1,2] This can be difficult when the most frequent onychopathies such as nail psoriasis, onychomycoses,[3,4] and nail alterations of the asymmetric gait nail unit syndrome are clinically very similar.[5] They all have a severe impact on a patient's quality of life.[6]

UNGUAL PSORIASIS

Psoriasis is the dermatosis that most frequently affects the nails.[2] Approximately half of psoriasis patients have nail alterations at any time, but 80–90% will experience nail changes at least once during their lifetime.[2,7] Nail psoriasis is frequently associated with arthritis, particularly of the distal interphalangeal joints. The nails are even more often involved in psoriatic arthritis.[8] Fingernails are more frequently affected than toenails.[2,7] In contrast to cutaneous psoriasis, there is no association of nail psoriasis and psoriatic arthritis with HLA-C0602.[7] Nail psoriasis is also frequently associated with enthesitis, an inflammation of tendon and ligament insertions. This is interpreted as being a Köbner phenomenon rather than an autoimmune disease.[9]

Psoriasis causes both specific and less characteristic nail alterations (Figure 1A).[10,11]

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Pits are the most frequent alterations of matrix psoriasis.[2] They develop from minute psoriatic foci in the apical matrix resulting in circumscribed parakeratotic mounds that break out and leave a small depression in the nail plate surface.[12] However, some parakeratotic foci often remain and are seen as small whitish to ivory-coloured spots. The pits and spots are of relatively regular depth and size with random distribution; however, they are sometimes arranged in horizontal or longitudinal lines. More than 10 pits per nail or a total of more than 60 pits and spots are generally seen as confirming the diagnosis of nail psoriasis (Figure 1A).[2] Psoriatic lesions in the distal matrix may be seen as red spots in the lunula and those in the mid-matrix may cause psoriatic leuconychia. The most common signs of nailbed involvement are subungual hyperkeratosis and oil or salmon spots. When the latter grow to the hyponychium they result in onycholysis, which is typically bordered proximally by a reddish-brown band reflecting an active psoriatic lesion.[2,12] Small, thin, longitudinally arranged dark lines are splinter haemorrhages and correspond to microthromboses of the longitudinally arranged nailbed capillaries;[2] thus, they are comparable to Auspitz's phenomenon.

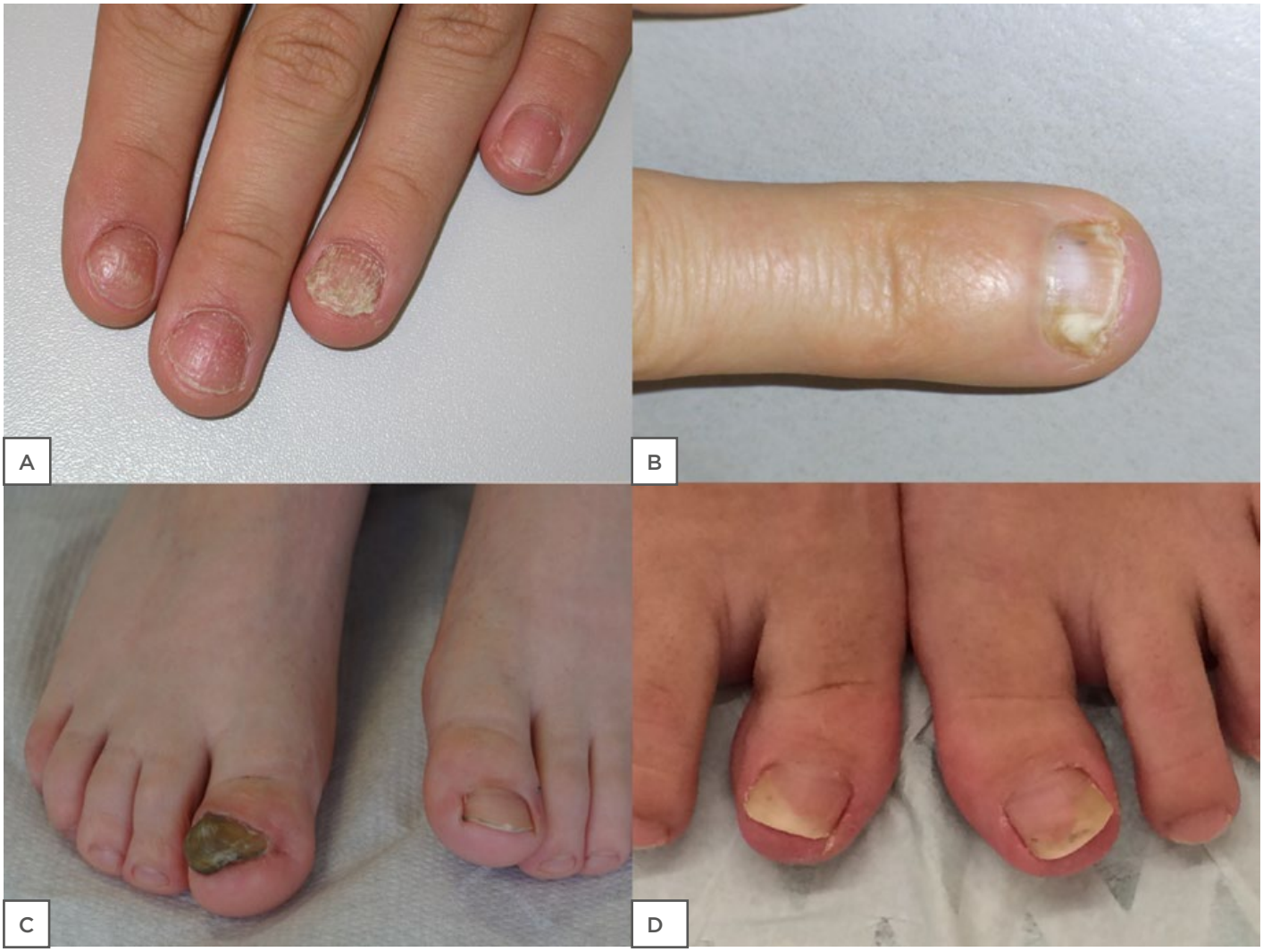

Figure 1:

A) Nail psoriasis; **B)** deep type of superficial white onychomycosis; **C)** massive nail thickening, discolouration, onycholysis, distal bulge formation, and lateral deviation in right-sided congenital malalignment of the big toenail; **D)** AGNUS of both big toenails: inward rotation of the toes, slight hallux erectus, and onycholysis of the distal lateral nail portion.

Involvement of the proximal nailfold leads to psoriatic paronychia with spontaneous loss of the cuticle. Affection of the entire nail apparatus causes complete nail destruction. Depending on the extent and severity of the involvement of the different parts of the nail, extremely variable intra- and interindividual clinical patterns can be seen. Finger and toenail involvement often present different clinical aspects. The distal phalanx is swollen in psoriatic arthritis and the joint may be stiffened in a slightly bent position. Psoriatic pachydermoperiostosis is almost exclusively observed on big toes with minor or no nail changes.[13]

All three forms of pustular psoriasis affect the nails.[2] Small yellowish spots are seen under the nail in generalised pustular psoriasis of von Zumbusch, whereas larger lakes of pus can be observed under the nail together with larger surface defects called elkonyxis in palmar plantar pustular psoriasis.[2,7] Acrodermatitis continua suppurativa of Hallopeau is an excessively recalcitrant disease, mostly isolated on the tip of a digit. This may turn red, inflamed, develop small to medium-sized pustules that destroy the nail, and finally result in a rounded naked digit tip without a nail.[13] Concomitant psoriasis lesions elsewhere on the skin may develop but this is rather rare. As seen in generalised pustular psoriasis, an IL-36 receptor antagonist defect was found in acrodermatitis continua suppurativa.[14] Because of its frequent monodigital involvement, acrodermatitis continua suppurativa often remains undiagnosed for years. An important differential diagnosis is nail involvement in reactive arthritis.[13] Additionally, nail psoriasis is also observed in children. The diagnosis is often missed because paediatricians commonly do not think of psoriasis in this age group.[15]

Approximately 5% of cases are isolated nail psoriasis without skin lesions.[2,4] A diagnostic adjunct to the clinical diagnosis and to avoid an invasive biopsy is the histopathological examination of nail clippings with as much of the subungual hyperkeratosis as possible.[11,12,16-18] As nail psoriasis has a serious negative impact on the quality of life, an early and exact diagnosis is warranted. Chronic trauma and professional stress to the digit aggravate nail psoriasis. The common course is chronic or chronic recurrent. This waxing and waning of nail lesions often helps to distinguish it from onychomycosis.[7,13] For scientific reasons and therapeutic studies, nail psoriasis grading systems were established to reproducibly determine the extent and severity of ungual psoriasis. The Nail Psoriasis Severity Index (NAPSI) is used most frequently although several other grading systems were created that also cover other aspects.

ONYCHOMYCOSES

Fungal infections of the nail unit are commonly designated as onychomycoses. They are said to be the most frequent nail diseases constituting 40–50% of all nail disorders. They are distinguished by their responsible pathogens and the route of infection determining the nail structures primarily involved.[19,20] This classification is particularly important for onychomycosis treatment and prognosis.

The most common pathogens of onychomycoses are dermatophytes, which contain specific enzymes capable of degrading keratin. *Trichophyton rubrum*, followed by *T. interdigitale* (*mentagrophytes*) are the leading pathogens; *T. soudanense*, *T. violaceum*, *T. tonsurans*, and *Microsporum spp.* rarely cause nail infections.[21] Some *Candida* species contain acid peptidases that can digest nail keratin, although they are more commonly found in chronic paronychia of fingers. *C. albicans* and *C. parapsilosis* are the leading yeasts, but *C. glabrata*, *C. tropicalis*, and *C. krusei* are uncommon. Nondermatophyte moulds are now also accepted as being primary nail pathogens, particularly *Scopulariopsis brevicaulis*[22] and *Fusarium spp.,* with the latter presenting as new emerging nail pathogens.[23] There are differences in the spectrum of nail pathogens depending on geography, climate, and common habits;[24,25] however, clinical distinction of the different pathogens is usually not possible.[19] Yeasts and nondermatophyte moulds are comparatively more frequent in psoriatic nails.[26,27]

Estimates of the prevalence of onychomycoses differ.[24] Between 3% and 8% of the population are said to have fungal nail infections; however, in some professional groups, the prevalence was 8–40%. Of patients with tinea pedum, 20–30% have onychomycoses. Men appear to be affected more frequently than women and the frequency increases steadily with age.[28] The susceptibility

to develop an onychomycosis is an autosomal dominant trait evidenced by the frequent vertical spread within affected families.[29] Those with psoriasis will experience fungal nail infections more frequently, making the differential diagnosis difficult or impossible.[2,4,12] Toenails growing only one-third of the rate of fingernails are 7–10 times more frequently infected. Mixed infections make up for 5% of all onychomycoses,[19,20,30] and immunosuppressed individuals are prone to rare fungal species that are usually difficult to treat.[19]

The differentiation of onychomycoses according to the route of invasion is important in clinical practice because it also explains the severity and chances of a successful therapy.[31] By far the most common type is distal lateral subungual onychomycosis (DLSO).[1] From the infected skin of the tip of the digit and lateral nail folds, the fungus grows into the hyponychium and then invades the nailbed. This reacts with a mild distal hyperkeratosis that extends proximally and thickens eventually raising the nail. The overlying nail plate covers the infection and only later gets invaded, which is seen by the loss of transparency and fragility of the plate (Figure 1B).[19,31] Histopathology of nail clippings with subungual hyperkeratosis demonstrates fungi in the keratin and undersurface of the nail. It shows that the nail is not the primary target but rather a barrier for the fungus.[12] The further course of the infection is characterised by slow invasion into the direction of the matrix; however, this may remain stable for months or years in many cases. Dermatoscopy often shows a fringed proximal border compared to an aurora borealis.[32] Another feature not infrequently seen in toenails is the development of a yellow spike pointing proximally, extremely rich in thick-walled fungi including both short filaments and spores, and therefore also called dermatophytoma. It is very recalcitrant and usually requires mechanical debridement for treatment. After years or decades, this DLSO can involve the entire nail and destroy it. White superficial onychomycosis (WSO) is divided into 3 subtypes. The classical form of WSO exhibits chalk-white spots with a lustreless surface on toenails and arises due to a particular growth pattern of *T. mentagrophytes*. Another form is seen in immunocompromised patients, primarily observed on fingernails, arises due to *T. rubrum,* and has a shiny surface. The third form is the 'deep' WSO, which develops when the classical form of WSO extends under the proximal nailfold and, because of this occlusion, can invade into the nail plate (Figure 1B). Proximal subungual white onychomycosis develops when a pathogenic fungus breaks the barrier of the cuticle and grows along the eponychium in a proximal direction until it reaches the matrix from where it is both included into the growing nail plate and actively invades distally towards the nailbed. A rare form caused almost exclusively either by *T. soudanense* or *T. violaceum* is endonyx onychomycosis, which histopathologically shows fungal organisms in the middle layer of the nail plate but without nailbed involvement.

C. albicans has enzymes capable of splitting up keratin. Particularly in hot climates, an infection similar to DLSO is observed whereas in temperate climates, paronychia may develop. Proximal subungual white onychomycosis caused by *Candida spp.* is occasionally observed in neonates. Nondermatophytes are increasingly found in onychomycoses;[5] however, their aetiopathogenetic role is not always clear. All forms of onychomycosis can ultimately develop into total dystrophic onychomycoses, in which the nail is destroyed and substituted by keratotic debris. A primary total dystrophic onychomycosis is characteristic for chronic mucocutaneous candidiasis.[33]

DIAGNOSIS OF FUNGAL NAIL INFECTIONS

Although onychomycoses are often diagnosed on clinical grounds alone, this should not be the standard because treatment is always long, tedious, and potentially associated with serious side effects.[34] The most common examinations are direct microscopy of subungual keratotic material after clearing with potassium hydroxide plus mycological cultures. Direct microscopy is rapid, easy, and inexpensive, but often nonspecific. Although capable of identifying the fungus, cultures take 4–6 weeks, give false-negative results in 30–50% of cases, and cannot distinguish between a true invasive onychomycosis and colonisation. Histopathology of nail clippings only takes 1–3 days, is twice as sensitive as cultures, insensitive to contamination, allows the differentiation between infection and contamination to be made, and gives permanent preparations. It does not, however,

permit species identification.[35,36] For superficial white onychomycosis, a thin slice from the nail surface may be taken with a No. 15 scalpel blade and for proximal subungual white onychomycosis, a disc of nail plate may be punched out and then divided into halves for culture and histopathology. Nail clipping histopathology also allows psoriasis and onychomycoses to be differentiated by their different neutrophil and parakeratosis distribution.[37,38] Immunohistochemistry should theoretically allow species identification *in situ*, but there were, until now, no reliable antibodies on the market. Similar problems exist for *in situ* hybridisation. New diagnostic techniques include PCR and matrix assisted laser desorption ionisation – time of flight (MALDI-TOF) mass spectroscopy.[39] Both are expensive, require specialised laboratories, and cannot differentiate between true infection and contamination.

DIFFERENTIAL DIAGNOSES

The most important differential diagnosis of nail psoriasis is onychomycosis and vice versa.[40] They have many clinical and histopathological features in common, though to a variable degree (Figure 1A and 1B) (Table 1). Onychoscopy may help in the differential diagnosis.[41] Compared to onychomycosis, a thinner nail plate, structural bone changes, and a higher power Doppler signal was found in nail psoriasis by ultrasonography.[42] Confocal laser scanning microscopy and optical coherence microscopy may identify intraungual fungi.[43,44] Recently, a genetic susceptibility to acquire onychomycosis in psoriasis was found with *HLA-DR*08* and *HLA-DR*01*, likely increasing the susceptibility to fungal nail infection.[45] The prevalence of onychomycosis in psoriasis patients is estimated to be between less than a quarter to one-third,[46-52] but was found in 50% of patients in a recent study from Italy; however, yeasts were statistically significantly more frequent in the non-psoriatic control group.[53] In a case-control study from Pakistan, nearly one-third of nail psoriasis patients had onychomycosis.[54] It was assumed that the pathogenic fungus benefits from the damaged nail of psoriasis.[55]

Other very frequent differential diagnoses of toenail changes are caused by mechanical irritation such as friction from footwear, overlapping toes, or sports activities. The asymmetric gait nail unit syndrome is a characteristic condition seen in individuals with orthopaedic abnormalities that may begin in the vertebral column, continue over the hip to the knees, but is usually most obvious in the feet.[5,56,57] This is associated with distal lateral or distal medial onycholysis in the innermost toes with a smooth border and without a reddish-brown margin (Figure 1D). It is commonly mistaken for a fungal nail infection. Histopathology and cultures are usually negative for pathogenic fungi. However, dystrophic nails are more often infected by fungi.[58] Congenital malalignment of the big toenails is characterised by early onset lateral deviation of the nails, discolouration, oyster shell-like surface, and severe onycholysis (Figure 1C).[59] Trachyonychia, or rough nails, could affect single nails or almost all nails, particularly in 20-nail dystrophy of childhood. It describes nail changes that may be idiopathic or due to atopic eczema, lichen planus, psoriasis, or, although rarely, some other dermatoses. Clinically, they typically cannot be distinguished, and their exact diagnosis requires the histopathological examination of a nail biopsy. Nail lichen planus is characterised by longitudinal ridging and splitting, as well as permanent scarring and pterygium formation. Nail eczema exhibits irregular pitting and transverse bulges and ridging, the proximal nail fold is often thickened, and the cuticle is lost. Rough nails may also be due to fungal infection, characteristically chronic mucocutaneous candidiasis. Chronic toenail conditions, particularly in the elderly and weaker individuals, may lead to onychogryphosis, which is defined by ram's horn-like nails. These may show fungi in histopathology slides, but they are not the real cause of onychogryphosis. *Pseudomonas aeruginosa* often colonises predamaged nails causing a greenish discolouration. Onychotillomania and other habits occur both on finger and toenails and are often mistaken for a mycotic infection. Nail alterations in reactive arthritis may be almost indistinguishable from those of pustular psoriasis but are often more marked and the pustules have a brownish tinge due to frequent erythrocyte admixture. Palmar plantar lesions are seen as so-called keratoderma blenorrhagicum, and oral mucosal involvement is characteristic. Scabies may infest the nail unit, particularly in its crusted variant.[60,61]

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Table 1: Differential diagnostic features of nail psoriasis and onychomycoses.

	Psoriasis	Onychomycosis
Frequency	Most frequent dermatosis with nail involvement; 80% of patients with psoriasis will develop nail psoriasis during lifetime.	Most frequent nail disease. Up to 30–40% of all nail disorders.
Course	Chronic to chronic-recurrent, often with intermittent improvement.	Chronic progressive, but also often stable over years.
Symptoms	Embarrassment, often painful, and restricting daily activities.	Embarrassment, potentially painful.
Signs	Matrix: pits, leukonychia, nail crumbling. Nail bed: salmon spots, subungual hyperkeratosis, onycholysis, splinter haemorrhages.	Subungual hyperkeratosis, yellowish discoloration, onycholysis.
Pits and ivory-coloured spots	Pits and ivory-coloured spots.	Rare, irregular size.
Nail bed hyperkeratosis	Frequent.	Frequent.
Onycholysis	Frequent. Proximal border like a salmon spot.	Frequent. Proximal border irregular: ruin sign or 'aurora borealis'.
Discolouration	None or yellowish.	Yellow to brown.
Spores and hyphae	Rare, mostly spores.	Very frequent: spores and hyphae.
Transverse ridges	Rare.	Very rare.
Trauma	May act as Köbner phenomenon.	Important predisposing factor.
Heredity	Strong genetic component.	Susceptibility to develop onychomycosis is inherited as an autosomal dominant trait.
Lesions elsewhere	Psoriatic plaques often present in typical localisation.	Often concomitant tinea pedum.
Histopathology	Hyperkeratosis with parakeratosis and included neutrophils and serum globules.	Marked hyperkeratosis with neutrophils and serum inclusions, contains most of the pathogenic fungi.
	Leukocytes in subungual parakeratosis and rarely also in the nail plate (Munro's microabscesses).	Leukocytes in subungual hyperkeratosis surrounded by parakeratosis (Munro's microabscesses).
	Focal hypergranulosis.	Focal hypergranulosis.
	Papillomatous nail bed hyperplasia.	Papillomatous nail bed hyperplasia.
	Spongiosis, mononuclear, and neutrophil exocytosis.	Spongiosis, mononuclear, and rarely neutrophil exocytosis.
	Small depressions and parakeratotic mounds on the nail surface (psoriatic pits).	Hyphae and spores in the subungual hyperkeratosis and underside of the nail plate.

Many nail diseases can be colonised or superinfected with fungi; it is then usually not possible to determine what was first. Psoriasis and onychomycosis may occur together.

As psoriasis treatment is usually immunodepressive, onychomycoses should be treated first.[1]

TAKE HOME MESSAGES

- Onychomycoses are the most frequent nail diseases.
- Psoriasis is the dermatosis with the most frequent nail involvement.
- Up to 80–90% of all individuals with psoriasis will develop nail lesions in their lifetime.
- Onychomycoses are the most frequent and resistant fungal skin infections.
- Onychomycosis treatment requires proof of the fungal aetiology, although this is not always possible.
- Nail psoriasis and onychomycoses have many signs and symptoms in common and may co-occur, sometimes rendering their differential diagnosis very difficult.

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Photoprotection: Key Concepts, Current Status, and Special Patient Groups

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Abstract

This article aims to help non-dermatologist medical professionals regarding the current status of photoprotection so that they may be better positioned to advise and respond to their patients. While the effects of solar radiation have long been known to include sunburn and skin cancers derived from ultraviolet B radiation, advances in knowledge now recognise the relevance of ultraviolet A, visible, and infrared light as significant contributors to skin damage. Effects on the skin range from aesthetic signs of photoageing, which accumulate with daily exposure, to skin cancers. Despite some trends towards increased awareness of the dangers of solar radiation and the need for photoprotection, behaviours still put people at risk and sun protection is suboptimal. In addition to the general population, certain population groups require special consideration depending on their work environment, lifestyle, and health status. The efficacy and cosmetic properties of sunscreens have improved greatly and should help to improve compliance with recommended use, but a multifaceted approach focussed on education and enabling uptake of recommendations is essential.

INTRODUCTION

Cumulative or excessive solar exposure is detrimental to skin health.[1] Furthermore, certain population groups require extra care. This article is aimed at general medical practitioners who may be called upon to advise their patients on photoprotection. It provides a rationale for photoprotection based on the effects of solar radiation on the skin and the current status of associated skin pathology, highlights aspects of behaviour that may limit adherence to recommendations, looks at some of the key regulations surrounding sunscreens and how they work, and draws attention to special patient groups, including considerations for their management.

EFFECTS OF SOLAR RADIATION ON SKIN

Sunlight is essential for vitamin D synthesis in the human body, which plays a role in bone density and immune function;[2] however, uncontrolled

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exposure, especially over years or decades, leads to photoageing, immunosuppression, skin cancer, and exacerbation of photodermatoses. To understand the precepts of sun protection, it is helpful to understand the components of the solar spectrum and how they affect skin. Solar radiation is generally divided into ultraviolet radiation (UVR), consisting of UVA (at wavelengths of 320–400 nm) and UVB (290–320 nm), as well as UVC (200–290 nm), visible light (400–700 nm), and infrared (IR) (700–1,000 nm). The solar spectrum at the Earth's surface is limited to wavelengths between 290 and 3,000 nm because UVC is completely absorbed by stratospheric ozone.[3] The intensity of UVR reaching the skin depends on factors such as latitude, altitude, season, cloud cover, and time of day.[4] UVB exposure is associated with some potent changes in the human body; it is mainly responsible for sunburn (its erythemogenic effect is 1,000-fold greater than short wave UVA),[5] and can induce skin cancers (by causing direct DNA damage and covalent bonding between pyrimidine bases), immunosuppression, skin darkening, and ageing.[6] Consequently, early sunscreens were designed almost exclusively to protect from UVB. However, it was later demonstrated that both UVA and UVB are causative agents in skin cancers, with UVA acting indirectly mainly by triggering production of reactive oxygen species.[7,8] This same mechanism also provides an explanation of UVA as the main contributor to skin photoageing. More recently, the effects of visible light, including erythema, pigmentation, and radical production, have garnered much attention.[4,9] Given the multiple detrimental effects of solar radiation, it is easy to understand why photoprotection is an important preventative health strategy and why the approaches to this increasingly include protection beyond the UV range.

CURRENT STATUS: SKIN CANCER AND SUN BEHAVIOUR

Skin Cancer in Europe

Global incidence rates of melanoma and nonmelanoma skin cancer (NMSC) continue to increase. Worldwide, the highest rates are reported in Australia and New Zealand; within Europe, northern European countries see the highest incidence at 23.9 per 100,000 in Sweden (2012) versus 13.0 per 100,000 for Europe.[10] NMSC, which may be excluded from or incompletely recorded in registries, is more challenging to quantify, but incidence rates for basal cell carcinoma (BCC) of 90–129 per 100,000 person years, European standard, are described.[10] The majority (99%) of NMSC is BCC and squamous cell carcinoma (SCC), BCC being approximately 3–4 times more common than SCC.[10]

While history of episodic sunburn is associated with increased risk of melanoma, it is thought that cumulative solar exposure is key in the pathogenesis of NMSC.[10] NMSC occurs in up to one-third of outdoor workers compared with only 5% of office workers.[11] NMSC has a low metastatic potential and mortality rate, but still has a high burden of morbidity and cost.[10,12] Because increased age is a risk factor for NMSC, it seems likely that increased rates of the disease will accompany the ageing population. Up to 90% of skin cancers are related to UVR; consequently, UV exposure remains the most important modifiable risk factor in preventing skin cancer.[6,10,13]

Sun Protection Awareness and Behaviour

Despite overall increasing skin cancer rates (in 2018, approximately 300,000 new cases of melanoma and over 1 million cases of NMSC were diagnosed worldwide),[14,15] some countries lead the way in preventative health education, demonstrating that such education can indeed prove effective. Going against the trend, Australia has successfully managed a recent decrease in melanoma incidence, and a similar downtrend is anticipated for New Zealand.[10,16] This follows multiple initiatives from their cancer councils over the past 35 years, including early childhood programmes to increase public awareness and improve sun safety (use of protective clothing and hats, adequate sunscreen use, and avoidance of excessive exposure).[17,18]

General recommendations from the World Health Organization (WHO)[1] regarding sun protection are to limit midday sun exposure (from 10 am to 4 pm), to seek shade (particularly during midday hours), to consider the UV index when planning activities, to use protective clothing, to wear a wide-brimmed hat and sunglasses (with 99–100% UVA and UVB protection), and to use broad-spectrum minimum sun protection factor

(SPF) 15+ sunscreen liberally applied at 2-hour intervals, or after swimming or exercising. Artificial sun lamp and sun bed use should be absolutely discouraged and patients should be informed of the risk: these are categorised as Group 1 carcinogens.[1,19] Interestingly, sunbed use, while highest in northern European countries with low levels of sun, is also paradoxically high in Spain and Italy; practitioners in these countries should not therefore assume that such advice does not apply to their population.[20] The European Skin Cancer Foundation's (ESCF)[21] recommendations do not differ greatly from those of the WHO: the ECSF suggests an SPF of at least 25, plus high UVA protection, applied 20–30 minutes before exposure.

Thus, multiple behavioural modifications are recommended, and modifying long-term behaviour is a complex task. Sunscreens form just one component of sun protection; they should not be considered sufficient protection on their own but used as one of multiple methods to protect the skin. However, they are often the main, or only, form of protection used. Modern sunscreens can provide high protection levels and are available in many formats, but despite these advances, data on the actual use of sunscreens also paints a rather unsatisfactory picture. While some studies show improvements over time, most of them demonstrate persistent misunderstandings and inadequate behaviours. A report by Cancer Research UK®[22] found several significant positive trends in sun protection behaviours between 2003/2008 and 2013. The most notable improvements were in covering up (an estimated 30% of the population reported this behaviour) and using factor 15+ sunscreen (an estimated 50% of the population reported this behaviour). A study comparing university students in 2000 versus 1990 in 13 European countries found that the proportion using sun protection increased over the decade studied, with men showing a greater increase (but starting from a lower level), while women remained more likely than men to use sunscreen.[23] In a Welsh study by Jackson et al.,[24] despite increased knowledge, subjects with a past history or family history of melanoma did not have safer sun behaviour. Even in a private dermatology clinic in the USA a significant proportion of patients, including patients with skin cancer, did not understand the risk associated with sunlight and stated they had not received counselling on the subject.[25]

A Spanish study of beachgoers found that, despite reported use of high-factor sunscreens, 70% of individuals interviewed reported a history of sunburn.[26] Importantly, they reported false beliefs about sunscreen safety leading to longer sun exposure behaviours. It should also be borne in mind that when sunscreens are used, the rules of applying 2 mg/cm^2, the quantity needed to achieve a homogeneous film at the surface of the skin, and reapplying every 2 hours, are often forgotten by users. This was found in a Danish study in which only around one-quarter of the recommended amount of sunscreen was applied to the whole body.[27]

Motivations for sun-seeking or unsafe behaviour range from aesthetic reasons such as 'looking better with a tan,'[26] to inconvenience,[28] which can relate to the cosmetic properties of sunscreens: they are often sticky, greasy, or leave residues, particularly at high SPF. Such persistent misconceptions and insufficient protective behaviour indicate that public educational strategies and physician education of patients are essential. Photoprotection must be multifaceted; it should be emphasised to patients that sunscreen use does not justify otherwise unsafe behaviour and that avoidance of midday sun or prolonged exposure and wearing protective clothing, including wide-brimmed hats and glasses, should be viewed as highly important actions.

SUNSCREEN PRODUCTS: COMPOSITION AND PROPERTIES

Traditionally, sunscreens aimed simply to prevent sunburn at isolated exposures. Nowadays, in light of knowledge regarding the effects of chronic sun exposure, including UVA and its role in skin ageing, much more comprehensive protection is recommended. Consistent, everyday use is prudent, and sun filters, their vehicles, and additional ingredients are constantly being innovated to go beyond 'just' preventing sunburn, with the inclusion of antioxidants, DNA repair enzymes,[29] or skin hydrating agents. In Europe, most sunscreens are classified as cosmetics under regulation (EC) No 1223/2009.[30] For cases in which clinical conditions are targeted, they may

be classified as medical devices and undergo clinical trials as such.[29]

Sunscreens contain sun filters: molecules that absorb, reflect, or scatter solar radiation, limiting the quantity of radiation that reaches the skin. As a result of no single agent providing full solar protection, products are usually composed of a mixture of sun filters to cover the largest part of the UV spectrum. Filters can be broadly divided into organic/chemical and inorganic/physical filters (Table 1).

Table 1: Details of sun filters approved for use in Europe.

INCI name	Maximum concentration	UVA	UVB	Sun filter type
Camphor benzalkonium methosulfate	6%	×	✓	Chemical
Homosalate	10%	×	✓	Chemical
Benzophenone-3	10%	✓	✓	Chemical
Phenylbenzimidazole sulfonic acid	8%	×	✓	Chemical
Terephthalylidene dicamphor sulfonic acid	10%	✓	×	Chemical
Butyl methoxydibenzoylmethane	5%	✓	×	Chemical
Benzylidene camphor sulfonic acid	6%	×	✓	Chemical
Octocrylene	10%	×	✓	Chemical
Polyacrylamidomethyl benzylidene camphor	6%	×	✓	Chemical
Ethylhexyl methoxycinnamate	10%	×	✓	Chemical
PEG-25 PABA	10%	×	✓	Chemical
Isoamyl p-methoxycinnamate	10%	×	✓	Chemical
Ethylhexyl triazone	5%	×	✓	Chemical
Drometrizole trisiloxane	15%	✓	✓	Chemical
Diethylhexyl butamido triazone	10%	×	✓	Chemical
4-methylbenzylidene camphor	4%	×	✓	Chemical
Ethylhexyl salicylate	5%	×	✓	Chemical
Ethylhexyl dimethyl PABA	8%	×	✓	Chemical
Diethylamino hydroxybenzoyl hexyl benzoate	10%	✓	×	Chemical
Methylene bis-benzotriazolyl tetramethylbutylphenol	10%	✓	✓	Chemical
Disodium phenyl dibenzimidazole tetrasulfonate	10%	✓	×	Chemical
Bis-ethylhexyloxyphenol methoxyphenyl triazine	10%	✓	✓	Chemical
Polysilicone-15	10%	×	✓	Chemical
Benzophenone-4/5	5%	✓	✓	Chemical
Tris-biphenyl triazine (nano and non-nano)	10%	✓	✓	Chemical
Titanium dioxide (nano and non-nano)	25%	✓	✓	Physical
Zinc oxide (nano and non-nano)	25%	✓	✓	Physical

INCI: international nomenclature of cosmetic ingredients; PABA: para-aminobenzoic acid; PEG: polyethylene glycol; UV: ultraviolet.

Historically, organic filters were thought to absorb UVR, and inorganic to reflect and scatter it. However, recently it was confirmed that titanium dioxide and zinc oxide protect primarily via absorption of UVR and not through significant reflection or scattering. For these two inorganic sunscreens, the scattering and reflection increases in the visible part of the spectrum, which is why sunscreens formulated with these ingredients may leave a white appearance on the skin.[31] Another difference between the two classes is that inorganic filters, even in nanoparticles, have not been shown to permeate the skin, whereas organic filters can cross the skin barrier and have been found at low levels in the systemic circulation.[32] It should however be stressed that, after decades of use, sunscreens have not been demonstrated to adversely impact human health.[6,33]

Sunscreen efficacy is assessed in validated standardised tests and is usually described as the SPF value. The concept of SPF is used worldwide as an *in vivo* measure of the ability of a sunscreen to prevent sunburn (erythema, mainly caused by UVB): the SPF is defined as the ratio of [least amount of UVR required to produce minimal erythema on sunscreen-protected skin] to [amount of UVR required to produce the same minimal erythema on unprotected skin] (International Organization Standardization [ISO] 24444: 2019).[34] Other non-erythema-based sun protection factors have been proposed,[35-7] and some may form new ISO-approved testing methods in the near future.[38,39] *In vitro* methods of SPF testing may also come into use,[40] which would avoid the inherent disadvantages of human volunteers, including the ethical aspects of inducing sunburn and practical aspects such as time required. Currently, SPF value and the corresponding sun protection level (very high: SPF 50+; high: SPF 30–50; medium: SPF 15–25; or low: <SPF 15) remains the best index to communicate the protection level of a sunscreen to consumers, even if the conditions under which it is measured cannot fully reflect actual use. In Europe, the UVA protection factor can be measured *in vivo* by ISO 24442[41] or *in vitro* by ISO 24443.[42] This protection factor should be at least one-third of the SPF value; if this threshold is met, 'UVA' is written inside a circle on the packaging.[43,44]

While discussing ways to increase the uptake of sun protective behaviours, it is pertinent to mention the concerns of some users regarding the impact of sunscreen use on their vitamin D status. Since endogenous vitamin D synthesis requires skin being exposed to UVB, the logical question raised is whether vitamin D levels are affected by sunscreen use. However, latest research published indicates that there is no evidence of this in practice. An expert review of the literature concluded that "sunscreen use for daily and recreational photoprotection does not compromise vitamin D synthesis, even when applied under optimal conditions."[1]

SPECIAL SITUATIONS AND POPULATION GROUPS TO CONSIDER

In addition to the general recommendations, it is important to tailor these to the individual, in terms of both behavioural modifications and appropriate sunscreen products. Depending on their specific situation and health status, certain factors should be taken into consideration because health beliefs and behaviours are complex and may relate to perceived risks and benefits.[26] These are, in turn, influenced by factors such as the individual's medical history, family history, exposure to educational materials, or educational level.[24,28] For the purposes of this review, special population groups can broadly be categorised into five groups: 1) those undertaking recreational, acute, and intermittent high-to-extreme UV exposure (e.g., at the beach or skiing) where the user principally wants to be protected from sunburn; 2) daily photoprotection in a skincare routine in which chronic damage and photoageing prevention is the main driver; 3) skin diseases aggravated by sunlight where the patient wants to prevent flares; 4) immunocompromised patients; and 5) occupational exposure in outdoor workers with the objective of preventing skin cancers.

Prevention of Sunburn

Limitation of exposure is key, which may include adapting planned activities according to time of day and UV index. When advising or deciding on a sunscreen, taking into consideration that UVB is the main causative agent for solar erythema, SPF is the most relevant indicator because it is directly indicative of sunburn protection. The importance

of high SPF has been observed in recent studies in outdoor extreme conditions, which found that SPF 100 sunscreens provided more protection than SPF 50 products under these extreme conditions.[45,46] Importantly, for individuals with fair skin, even very high SPF (50+) may offer insufficient protection in conditions of very-high-to-extreme UVR, confirming that sunscreens should not be the only photoprotection strategy used.[47]

Prevention of Skin Ageing

Photoageing results from repeated UVR with subsequent reactive oxygen species production and activation of matrix metalloproteinases. Signs include skin roughness and dryness, wrinkles, and uneven pigmentation and telangiectasia, usually on the face, neck, chest, and dorsal hands. For such daily use, an SPF of 30 may be considered sufficient. Good UVA protection is needed to prevent photoageing, and finding a formulation that is pleasant to use may take priority over high SPF values if it is likely to result in regular use. The combination of sun filters and antioxidants such as vitamins (C and E, niacinamide), polyphenols, or flavonoids, have additive effects in reducing the concentration of free radicals in the skin.[48,49] Such details relate to sunscreen use, and daily habits should also be addressed.

Photoprotection in Photodermatoses

Photodermatoses represent a heterogeneous group of diseases with an abnormal cutaneous reaction to sunlight. Photoprotection is a key element of their management and selection of the most appropriate sunscreen usually depends on the identification of the wavelengths responsible for inducing the disease. Polymorphic light eruption, the most common photodermatosis with a prevalence of 10–20% in the general population,[50,51] and lupus erythematosus, the most common photoaggravated dermatosis,[51,52] are triggered by UVA and UVB; thus, in addition to protection with clothing, exposed areas require a broad-spectrum sunscreen with high SPF and high UVA protection.

In subjects with pigmentary disorders such as melasma, the deleterious role of visible light and particularly its blue component has been confirmed:[53] daily use of a broad-spectrum sunscreen including visible light protection is essential. Iron-oxide-containing sunscreens (tinted sunscreens) have been shown to absorb high energy visible (HEV), the short wavelengths of the visible light spectrum, and help prevent the pigmentary effect of this part of visible light.[38,54]

Immunocompromised Patients

Organ transplant recipients represent a high-risk group for skin cancers as a result of their post-transplant immunosuppressive therapy.[55] Other diseases requiring immunosuppressive therapies, such as inflammatory bowel disease, have also been identified as having increased risk of skin cancer.[56,57] The risk of SCC may be increased several hundred-fold in transplant recipients,[58] and tumours may behave more aggressively.[58] Type and level of immunosuppression play a role in the incidence of skin cancer.[58] Strict sun avoidance and use of very high SPF products is essential; consequently, vitamin D supplementation may be required.

Children represent a population group with a physiologically immature immune system, and also generally spend a greater amount of time outdoors, therefore requiring a careful approach to photoprotection and reliance on adults to enforce it.[59,60] A pleasant-to-use, water-resistant, and rub-proof sunscreen formulation may provide a practical improvement to photoprotection in real-life use.

Outdoor Workers

Despite the fact that a high number of outdoor workers worldwide are exposed to UVR for the majority of their working life, as well as the existing literature on NMSC risk factors, solar exposure risk remains undervalued as an occupational risk factor[61] and skin cancers are scarcely reported as occupational disease.[11,62] Peters et al.[63] estimated that in 2011 in Canada, 6.3% of NMSC cases were attributable to occupational exposure to UVR. Yet, awareness of prevention strategies recommended by health authorities remains low among these high-risk groups.[3,64]

Education on protective clothing, whether something does or does not constitute protection, and addressing common misconceptions (for example, a so-called 'protective' tan) are fundamental.

The SPF recommendation should be as high as possible: at least SPF 50+. Perceived barriers to occupational sunscreen use include taking too long to apply, causing discomfort or irritation, and financial expense.[28] Addressing barriers such as cost, messy application, unpleasant after-feel, and stinging of the eyes may therefore improve compliance.[65] Another key difficulty is achieving 2-hourly reapplication, as this is not always feasible.

In the near future, preventative interventions should include collective measures such as specific legislation, workers' education, and training; individual measures such as personal protective equipment including sunscreens; and health surveillance of outdoor workers.[66] The benefits of such formal and informal workplace initiatives are likely to outweigh the costs and should be borne in mind for workplace policy decision-makers.

CONCLUSIONS AND FUTURE AREAS OF STUDY

Effective photoprotection is best achieved by exposure avoidance: seeking shade, use of protective clothes and glasses, avoiding midday sun, and appropriate use of sunscreens. Photoprotection is a key preventative health strategy as most skin cancers are a result of UVR exposure. Yet, uptake of photoprotective measures remains insufficient and inconsistent. Current limitations do not stem from a lack of efficacy of existing methods or products, but rather from adherence to use and misconceptions or inconveniences leading to unsafe behaviours.[67]

Everyday sun protection is advisable to the general public, but some groups are at increased risk. Tailoring advice to individual situations and addressing barriers to compliance are likely to contribute to better usage. Widespread cultural changes appear to still be somewhat in their beginnings, with some apparent improvements in knowledge that are not yet accompanied by the corresponding behaviours. Initiatives to normalise sun-safe behaviour are required to protect against skin ageing, chronic dermatoses, and, most importantly, skin cancers. Clear examples of successful educational and nationwide campaigns are available, and medical practitioners have a significant role to play in protecting vulnerable groups and empowering and educating their patient population.

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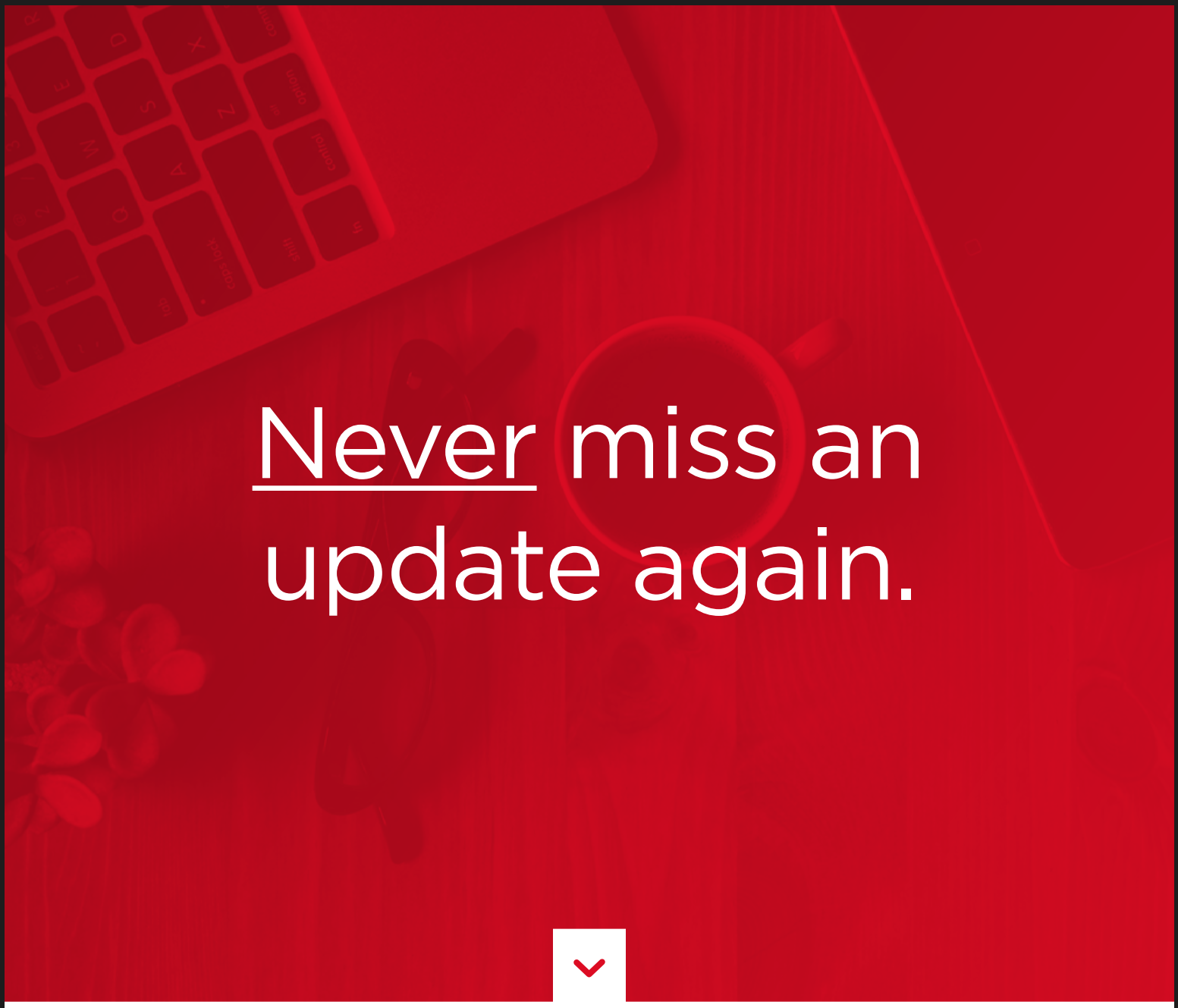

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