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PEER-REVIEWED CONFERENCE REPORT

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Editor Prof. Peter van de Kerkhof, Radboudumc, the Netherlands

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Letter from the Editor

Prof. Peter van de Kerkhof

Dear colleagues,

AAD VMX 2021 was a well-organised virtual AAD. It also provided continuous medical education on dermatology in its broadest sense. Innovations were reported in various areas of dermatology. In particular, the development of new treatments for inflammatory diseases: psoriasis, atopic dermatitis, acne.

For the treatment of psoriasis, the anti-IL-17A and F inhibitor bimekizumab has showed superior efficacy compared with secukinumab. The TYK2 inhibitor deucravacitinib proved an effective oral treatment in psoriasis. Also presented were innovative topical treatments such as the PDE4 inhibitor roflumilast. In generalised pustular psoriasis, the IL-36 inhibitor imsidolimab is in a phase of investigation. Psoriasis is more than skin deep. Two separate studies demonstrated that therapy with a biologic led to a decrease in the inflammatory process that stabilises atherosclerotic plaques in patients with psoriasis.

In contrast to what has been suggested in the past, COVID-19 is not so seldom in children and cutaneous manifestations are more frequent in children than in adults. For children and adults: What to do if patients are on immunomodulatory treatments? Patients with psoriatic disease should stay on their treatment during the pandemic unless they become acutely infected. Psoriasis patients should further take any mRNA-based vaccine as soon as offered.

In atopic dermatitis, new small molecules, particularly JAK inhibitors, are innovating the treatment.

Important innovations were presented on acne. Clascoterone is an exciting new topical anti-androgen. Trifarotene is an innovative topical retinoid. Sarecycline is a small spectrum tetracycline. Efficacy has been shown for these new principles.

Attention at the AAD was also given to areas which may not be regarded as dermatological therapy. Sofpironium gel proved effective and well tolerated in primary axillary hyperhidrosis. Also sunscreens were highlighted: safety aspects, screening visible light, tanning, and the advice to take vitamin D supplements in case patient are shielding rigorously from the sun.

AAD 2021 provided us with insights into innovative treatments and skin care and remains a resource for continual education at the highest level.

Best Regards,
Prof. Peter CM van de Kerkhof

Biography

Peter C.M. van de Kerkhof is emeritus Professor of Dermatology and immediate past chairman of the Department of Dermatology of Radboud University Nijmegen. He is currently the coordinating Medical Officer of the International Psoriasis Council and chair of the scientific advisory board of the Dutch burn association. He has been working for many years on the pathogenesis and treatment of psoriasis. He has published more than 700 publications in peer-reviewed journals and has given many presentations on invitation at international conferences. He has served as president of the ESDR, EDF, and the International Psoriasis Council, and was board member of various international societies. Current interests are pathogenesis and development of biomarkers for psoriasis; real clinical practice research; and personalised medicine.

Conflict of Interest Statement:
Consultancy services for: Celgene, Almirall, Amgen, Pfizer, Philips, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Biotech, Janssen-Cilag, LEO Pharma, Sandoz, Mitsubishi Tanabe, Sandoz, Bristol Meyer Squibb, UCB, Dermavant.
Speaker services for: Celgene, Almirall, Eli Lilly, Novartis, Jansen-Cilag, LEO Pharma, Sandoz, Bristol Meyer Squibb.

Late-Breaking Abstracts

Small molecule effective in moderate-to-severe psoriasis

In the phase 3 trials POETYK PSO-1 and POETYK PSO-2, the tyrosine kinase 2 inhibitor deucravacitinib was compared with apremilast and placebo. Deucravacitinib appeared an effective oral option for the treatment of psoriasis.

Prof. April Armstrong (Keck School of Medicine at UCLA, CA, USA) pointed out that deucravacitinib is a novel oral selective tyrosine kinase 2 (TYK2) inhibitor with a unique mechanism of action distinct from Janus Kinase inhibitors [1]. Deucravacitinib binds selectively to the TYK2 regulatory domain, thus inhibiting TYK2-mediated signalling of cytokines involved in psoriasis pathogenesis, such as IL-23, IL-12, and type-1 interferon.

The efficacy and safety of deucravacitinib were assessed in 2 global phase 3 studies, the POETYK PSO-1 (NCT03624127) and the POETYK PSO-2 (NCT03611751). Both studies included patients with moderate-to-severe psoriasis. In POETYK PSO-1, in contrast to POETYK PSO-2, patients from Asian countries including China were enrolled.

Patients were treated with deucravacitinib, the currently available treatment apremilast, or placebo. In both trials, the co-primary endpoints were the percentage of patients achieving Psoriasis Area and Severity Index (PASI) 75 and the percentage of patients achieving static Physician's Global Assessment (sPGA) score of 0 or 1 (i.e. clear or almost clear skin) at week 16 versus placebo. After this time, placebo patients, as well as patients who failed apremilast, were switched to deucravacitinib and all patients were treated to week 52 (secondary endpoint).

At week 16, significantly greater proportions of patients in the deucravacitinib compared with placebo and apremilast arms achieved PASI 75. Similarly, a greater proportion of patients in the deucravacitinib compared with placebo and apremilast arms gained sPGA 0/1 at week 16 in both trials. The selective TYK2 inhibitor was also superior to apremilast at week 24 in both trials. Of deucravacitinib-treated patients who achieved PASI 75 at week 24, 82.5% in POETYK PSO-1 and 81.4% in POETYK PSO-2 continued treatment and maintained their PASI 75 response at week 52.

"Deucravacitinib was also better in multiple secondary endpoints," Prof. Armstrong said. Significantly more patients in the deucravacitinib arms achieved a quality of life no longer impeded by the disease (corresponding to a score of 0/1 in the Dermatology Life Quality Index). The TYK2 inhibitor also improved symptoms of psoriasis such as burning, itch, and pain. After 16 weeks, 70.8% of patients in the POETYK PSO-1 trial achieved complete or almost complete clearance of their scalp lesions, compared with 39.1% in the apremilast arm and 17.4% in the placebo arm.

The most common adverse events were nasal pharyngitis and headache. "As in previous studies, there was a mild signal for folliculitis," Prof. Armstrong added. However, cases were mild to moderate, and only 1 patient with folliculitis discontinued deucravacitinib treatment.

1. Armstrong A, et al. Efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: Results from the phase 3 POETYK PSO-1 study. Session S033, AAD VMX 2021, 23-25 April.

Bruton's tyrosine kinase inhibition promising for pemphigus vulgaris

An open-label, phase 2 study with the oral and reversible Bruton's tyrosine kinase inhibitor rilzabrutinib for pemphigus vulgaris patients resulted in substantial rates of disease control and less usage of corticosteroids.

"Bruton's tyrosine kinase (BTK) has a broad role in the rapid innate as well as the delayed adaptive immune response in pemphigus. Rilzabrutinib is not simply a BTK inhibitor, but it is a potent oral and reversible BTK inhibitor," said Prof. Dedee F. Murrell (St George Hospital, University of New South Wales, Australia), explaining the rationale for the presented phase 2, proof-of-concept BELIEVE study (NCT02704429) [1-3]. The trial investigated rilzabrutinib for the treatment of newly diagnosed or relapsing pemphigus vulgaris [1].

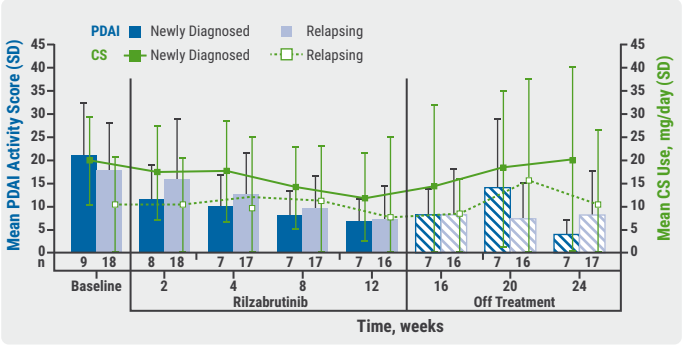
The open-label study included 27 patients with a median age of 51. Among them, 33% were newly diagnosed and 67% relapsing.

Concerning disease severity, 41% suffered from moderate pemphigus and 59% from moderate-to-severe pemphigus. The mean time from diagnosis was 8.9 years. Oral rilzabrutinib was administered at a dose of 400–600¬ mg twice daily while concomitant low-dose corticosteroids were allowed.

The primary endpoint was control of disease activity (CDA) after 4 weeks; secondary endpoints consisted of complete response rate, pemphigus disease area index (PDAI), decrease in steroid use, and quality of life. After 4 weeks, 52% of participants reached the primary CDA endpoint and this percentage increased to 70% after 12 weeks. After week 12, CDA was 67% in newly diagnosed and 72% in relapsing pemphigus patients. In moderate and moderate-to-severe grades at the same time point, CDA was 64% and 75%, respectively. "The CDA rates consistently improved over time, irrespective of pemphigus duration or the severity of pemphigus at onset," Prof. Murrell elaborated.

Treatment with rilzabrutinib also improved PDAI scores significantly and reduced the extent of steroid use (see Figure). Overall, a clinically meaningful improvement in quality of life was found at week 12 compared with baseline, which stabilised during the post-treatment follow-up to week 24; the greatest effect was observed in the group of newly diagnosed patients.

Figure: Results for PDAI activity scores and use of corticosteroid in part A of the BELIEVE trial [1]



CS, corticosteroids; PDAI, pemphigus disease area index; SD, standard deviation.

"In terms of safety, we saw only transient and mild-to-moderate adverse events, giving an overall favourable risk-benefit profile," said Prof. Murrell. Further results for rilzabrutinib will be seen in part B of BELIEVE and the ongoing phase 3 PEGASUS pivotal study (NCT03762265).

1. Murrell D. Treatment with rilzabrutinib results in rapid and significant decrease in steroid use and improved quality of life in patients with chronic Relapsing Pemphigus: BELIEVE Phase II Study. Session S033, AAD VMX 2021, 23-25 April.
2. Didona D, et al. Front Immunol. 2019;10:1418.
3. Bradshaw JM, et al. Nat Chem Biol. 2015;11(7):525-31.

Bimekizumab superior to secukinumab in psoriasis

The phase 3b trial BE RADIANT documented superior efficacy of dual IL-17A and IL-17F blockade with bimekizumab compared with an IL-17A-only blockade by secukinumab for the treatment of psoriasis.

BE RADIANT (NCT03536884) is the first phase 3 study in which an IL-17A/F blocker –bimekizumab– is compared with an IL-17A-only blocker – secukinumab [1]. "This trial will allow us to learn something about the role of IL-17F in the skin," explained Prof. Kristian Reich (University Medical Center Hamburg-Eppendorf, Germany).

Both IL-17A and IL-17F are overexpressed in psoriasis and have a role in psoriasis pathogenesis. BE RADIANT was a head-to-head comparison between bimekizumab and secukinumab. Primary endpoint was complete healing of psoriasis skin lesions (PASI 100 response at week 16). In addition, efficacy and safety results after 48 weeks were assessed.

From week 16 onward, bimekizumab was applied either every 4 or every 8 weeks. At week 16, >60% of bimekizumab-treated patients achieved a PASI 100 response compared with 48.9% of patients treated with secukinumab (P<0.001). "After 48 weeks, the gap was even wider: 20% more patients treated with bimekizumab gained complete skin clearance compared with secukinumab," Prof. Reich said. No difference in PASI 100 response was observed between the 2 dose intervals with bimekizumab. A similar pattern was seen for PASI 90 response, which was assessed as a secondary endpoint. Bimekizumab had a faster onset of treatment response than secukinumab: both the PASI 75 and PASI 90 response at week 4 were significantly higher with bimekizumab.

No new safety signals were observed. However, oral candidiasis was seen more frequently in patients treated with the dual IL-17 blocker: 19.3% versus 3.0% with secukinumab. Fortunately, 97.2% of oral candidiasis cases were mild to moderate, and none led to discontinuation of study treatment. "Hence, these study results suggest that for the optimal inhibition of the IL-17 pathway in psoriasis, both IL-17A and IL-17F need to be blocked. This approach is faster as well. This points to a relevant role of IL-17F in the pathogenesis of psoriasis," Prof. Reich concluded.

1. Reich K, et al. Bimekizumab efficacy and safety versus secukinumab in patients with moderate to severe plaque psoriasis: Results from a multicenter, randomized, double-blinded, active comparator-controlled phase 3b trial (BE RADIANT). Session S033, AAD VMX 2021, 23-25 April.

Etrasimod – a new mode of action for treatment of atopic dermatitis

The sphingosine 1-phosphate modulator etrasimod demonstrated reassuring therapeutic potential in different outcomes (both investigator- and patient-reported) of adult patients with atopic dermatitis.

Currently, sphingosine 1-phosphate (S1P) modulation is being assessed for different indications in immune-mediated inflammatory diseases [1,2]. The phase 2 placebo-controlled ADVISE trial (NCT04162769) is the first to test the oral $S1P_{1,4,5}$ modulator etrasimod for safety and efficacy in treatment of atopic dermatitis (AD) [1]. "Etrasimod disrupts immune cell trafficking to skin including multiple types of lymphocytes such as B cells, T cells, and eosinophils, thus reducing inflammation in the skin," explained Prof. Emma Guttman-Yassky (Icahn School of Medicine at Mount Sinai, USA).

ADVISE included 140 patients with moderate-to-severe AD that were treated in 3 different groups over 12 weeks with placebo, etrasimod 1 mg, or etrasimod 2 mg and followed up for 4 weeks more. After that, an open-label extension with all patients on 2 mg of etrasimod started that is still in progress. "In terms of demographics, the groups were highly balanced, but I want to point out that severity in the vast majority of patients was moderate," Prof. Guttman-Yassky pointed out. The mean age was 42.5 and 61.4% were women.

The primary endpoint was defined as the rate of change in Eczema Area and Severity Index (EASI), whereas the key secondary endpoint was the percentage of patients achieving a validated Investigator Global Assessment (vIGA) of 0 or 1 (i.e. clear or almost clear) and a ≥2-point change from baseline at week 12. Additional patient-reported outcomes included weekly Peak Pruritus Numeric Rating Scale, Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM).

Overall, the results showed a better performance of the 2 mg dose of etrasimod with improvements in physician-reported as well as patient-reported outcomes compared with placebo. At week 12, 29.8% on 2 mg of the study drug reached vIGA 0/1 ($P<0.05$ vs placebo). Furthermore, the peak pruritus gradually decreased under etrasimod 2 mg with 42.1% improving ≥4 points. DLQI amelioration was significant with DLQI decrease ≥4 points in 85.7% (2 mg dose) of patients. As for POEM, significance was achieved in both the 1 mg and the 2 mg group.

Etrasimod was well tolerated, no serious adverse events occurred, and no new safety issues emerged. Among the adverse events that occurred in ≥5% of patients, nausea, constipation, back pain, and dizziness were reported more often in the etrasimod 2 mg than in the placebo group. A grade 1–3 decrease in lymphocytes in 8 etrasimod cases was interpreted as an on-target effect that probably presented a beneficial therapeutic impact of etrasimod. "These results support the rationale of $S1P_1$ modulation as a potential new mechanism of action and oral treatment for our patients with AD," concluded Prof. Guttman-Yassky.

1. Guttman-Yassky E, et al. Etrasimod, a novel, oral, selective sphingosine 1-phosphate receptor modulator, improves patient and clinician reported outcomes in adults with moderate-to-severe atopic dermatitis in a randomized, double-blind, placebo-controlled phase 2 study (ADVISE). Session S033, AAD VMX 2021, 23-25 April.
2. Sandborn WJ, et al. Gastroenterology. 2020;158(3):550-561.

Women at higher risk for dermatologic side effects during immunotherapy

A retrospective cohort study has shown an association between female sex and the risk for dermatologic adverse events due to checkpoint inhibition. This risk was approximately twice as high as the risk for males.

Targeted therapy with immune checkpoint inhibitors (ICI) has become an important treatment in many forms of advanced cancer [1–3]. It is known that, despite ICI therapy not only being effective but also safe, immune-related adverse events (irAE) appear regularly. "Dermatologic adverse events (dAE) are the most common set of irAE and occur in 30–50% of patients on ICI monotherapy," said Mr Jordan T. Said (Harvard School of Medicine, MA, USA). These dAE may present as psoriasiform dermatitis, lichenoid reactions, vitiligo, and bullous pemphigoid. In severe cases, steroid use or even discontinuation of ICI therapy may be necessary.

Until now, evidence was limited on potential risk factors for the development of irAE or dAE. However, as previous study results identified a greater risk for irAE in pre- compared with post-menopausal women on ICI, the current retrospective single-centre cohort study strove to further evaluate the impact of sex on the development of dAE in patients with metastatic melanoma that received ICI treatment between 2011 and 2016. The study included 142 men with a mean age of 65 years and 93 women with a mean age of 60 years. Among the females, 27 had a pre- and 66 a post-menopausal status. In 62.4% of the women and 48.6% of the men, ICI-associated dAE were confirmed.

A multivariate logistic regression identified that women had a >2-fold likelihood to suffer from dAE compared with men (OR 2.11; 95% CI 1.17–3.82; P=0.01). When differentiating by hormonal status, results were only significant in the post-menopausal group. However, the secondary analysis detected that the OR for the pre- versus post-menopausal groups was numerically similar (OR 1.97; 95% CI 0.56–6.67; P=0.4 vs OR 2.17; 95% CI 1.00–4.69; P=0.05). This led the authors to assume that factors beyond sex hormones might have an influence. Mr Said concluded that the findings of the study may guide clinicians when counselling women about the risk of dAE entailed by ICI.

1. Bui AN, et al. Female sex is associated with higher rates of dermatologic adverse events among patients with melanoma receiving immune checkpoint inhibitor therapy: a retrospective cohort study. Session S033, AAD VMX 2021, 23-25 April.
2. Wang E, et al. Ann Allergy Asthma Immunol. 2021:S1081-1206(21)00127-7.
3. Tattersall IW, et al. Yale J Biol Med. 2020;93(1):123-132.

Novel easy-to-use foam formulation clears scalp psoriasis in one-third of patients

Roflumilast foam is an attractive novel topical treatment for scalp and body psoriasis with a fast onset of action and remarkable efficacy in a phase 2 study.

"Almost 80% of our patients have scalp psoriasis; itching and flaking are some of the most burdensome symptoms of psoriasis," said Prof. Leon Kircik (Icahn School of Medicine at Mount Sinai Medical Center, USA) [1]. These symptoms can cause social embarrassment and have a high impact on quality of life.

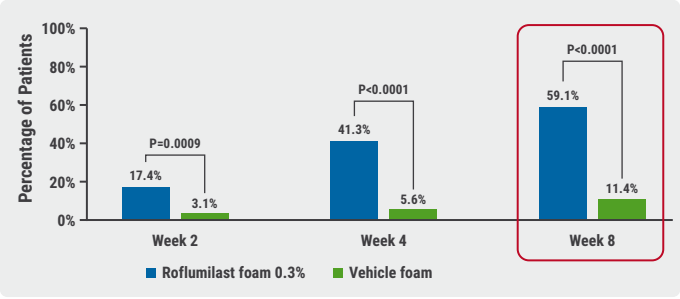
Treatment of the scalp is difficult because the hair may limit the efficacy of creams and ointments [2]. Roflumilast is a potent, non-steroidal phosphodiesterase-4 inhibitor being investigated as a topical treatment for various dermatologic conditions. It is formulated in a moisturising foam that can be easily applied on the scalp and the body.

In the current double-blind, randomised, placebo-controlled phase 2 study (NCT04128007), patients (n=304) were randomised in a 2:1 ratio to treatment with roflumilast foam (0.3%) once daily or a vehicle. Included patients were ≥12 years old and had at least mild severity psoriasis on both scalp and body. "Therefore, to document improvement, these patients had to be clear," Prof. Kircik explained. Patients received treatment for 8 weeks with visits at week 2, 4, and 8, plus 1 week post treatment. Primary endpoint was scalp success according to an Investigator Global Assessment (IGA), indicated by clear or almost clear skin with a ≥2-grade improvement from baseline.

Nearly 90% of patients completed the study. Most participants had moderate, 14.5% mild, and 9.0% severe scalp psoriasis. At baseline, body (B-)IGA was mild in 59.5% of patients. "Of our patients, 87% had a severity of >4 in an itch numerical rating scale (NRS)," Prof. Kircik emphasised.

At week 8, 59.1% of patients achieved scalp (S-)IGA success with roflumilast foam versus 11.4% with the vehicle (P<0.0001; see Figure). Significant efficacy could be already demonstrated at week 2. "Of note, 34% of patients achieved a totally clear scalp. There is a huge delta compared with the vehicle, which is unusual for topical treatment," Prof. Kircik said.

Figure: Roflumilast foam significantly increased the percentage of patients with S-IGA success at week 8 (primary endpoint) [1]



In addition, 26% of patients receiving roflumilast foam achieved the secondary endpoint of clear B-IGA. The foam was also effective in alleviating pruritus, with 71% of patients achieving a 4-point response in the worst-itch NRS. Regarding safety, there was little difference between the vehicle and roflumilast: ≥99% of roflumilast and ≥98% of vehicle-treated patients had no evidence of irritation. "Scalp treatment with creams gets messy and most patients stop treatment. The foam application will be a welcome addition to our treatments," concluded Prof. Kircik.

1 Kircik LH, et al. Once-daily roflumilast foam 0.3% for scalp and body psoriasis: A randomized, double-blind, vehicle-controlled phase 2b study. AAD VMX 2021, 23-25 April.
2 Blakely K, Gooderham M. Psoriasis (Auckl) 2016;6:33-40.

Anti-cholinergic gel demonstrates superior long-term tolerability and efficacy in axillary hyperhidrosis

Sofpironium gel proved effective and well tolerated in primary axillary hyperhidrosis in children and adults for a treatment period over a year.

The vast majority of patients suffering from hyperhidrosis report a profound negative impact on their social life, well-being, and emotional and mental health [1]. "Long-term

treatment of primary axillary hyperhidrosis is often necessary given the chronic nature of the condition; therefore, chronic use has to be studied," explained Dr Brandon M. Kirsch (Kirsch Dermatology, USA) [2]. Sofpironium is an analogue of the anti-cholinergic agent glycopyrrolate. Sofpironium is a retro-metabolic molecule that is rapidly metabolised into less active moieties following absorption after topical application. "Glycopyrrolate has more systemic side effects, in contrast to sofpironium," Dr Kirsch explained.

The long-term safety, tolerability, and efficacy of sofpironium gel was evaluated in an open-label phase 3 trial (NCT03627468) including adult and paediatric subjects (n=300) with primary axillary hyperhidrosis. All participants were randomised to receive either sofpironium bromide gel 5% or 15%. Patients enrolled were naïve to the treatment; 190 patients completed the 52 weeks' study duration.

The safety results of the gel were consistent with a prior phase 2b dose-finding study. Most adverse events were mild or moderate and transient. Side effects were typical anti-cholinergic adverse events, most often dry mouth (in 7.8% of patients using the 5% gel and 16.8% using the 15% gel), and blurred vision (in 4.9% of patients using the 5% gel and 18.8% using the 15% gel).

The incidence of treatment-related adverse events decreased over time: after 12 weeks, there were no new side effects. "This finding suggests that patients have to get used to the medication, and they did in the trial," Dr Kirsch explained. In line with these results, the incidence of discontinuations due to treatment-related adverse events decreased over time as remaining subjects acclimated to treatment. There were no treatment-related serious adverse events.

In terms of efficacy (assessed in the Hyperhidrosis Disease Severity Measure-Axillary) the gel demonstrated clinically meaningful reduction in sweat severity from week 2 until the end of the study.

1. Doolittle J, et al. Arch Dermatol Res 2016;308(10):743-9.
2. Schmid S, et al. A Multicenter, Randomized, Open-Label, Phase 3 long-term safety study of topically applied sofpironium bromide gel, 5% and 15%, in subjects with axillary hyperhidrosis. S033, AAD VMX 2021, 23-25 April.

Psoriasis – The Beat Goes On

Psoriasis: The treatment armamentarium continues to grow

Various new substances to treat psoriasis are on their track to approval, while already available drugs widen their indication spectrum.

"Amazing new medications are being developed that are going to change the way you approach psoriasis over the next decade," Prof. Bruce Strober (Yale University, CT, USA) started his presentation [1]. One new study tested apremilast in patients with mild and moderate psoriasis, defined by an affected body surface area (BSA) of 2–15%, a Psoriasis Area Severity Index (PASI) of 2–15, and inadequate control by topical agents [2]. "These patients had a Dermatology Life Quality Index of around 10 and that means they suffered a lot, even though BSA and PASI are low," explained Prof Strober [1]. The primary endpoint, static Physicians Global Assessment (sPGA) 0 or 1 (i.e. clear or almost clear skin) at week 16, was achieved by 21.6% with apremilast versus 4.1% with placebo. A label update is foreseen for the use of apremilast in this population.

A different drug in the form of a once-daily allosteric tyrosine kinase (TYK)2 inhibitor is deucravacitinib, which will likely be approved in about 1 year. As it does not bind to the kinase domain, it is selective but to a regulatory domain of TYK2, thus specifically blocking TYK2. In the 2 phase 3 trials POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751), deucravacitinib demonstrated impressive results versus placebo and apremilast [3]. "Deucravacitinib has all the makings of an important medication," Prof. Strober emphasised.

Another rising star is bimekizumab. The IL-17A/F inhibitor led to PASI 90 responses of 90.8% at week 16 in patients with moderate-to-severe psoriasis in the BE READY trial (NCT03410992) [4]. This level of efficacy was stable in

maintenance up to 52 weeks [1]. Notable safety issues included oral Candida infections, which occurred in 10–20% of patients in different studies.

The IL-36 inhibitor imsidolimab exhibited good results for generalised pustular psoriasis (GPP) in a phase 2 study (NCT03619902) in which 6 out of 8 patients, affected with a baseline BSA of 24%, reached the primary endpoint with about 94% reduction in erythema with pustules [5]. Spesolimab, a drug with the same mode of action, also holds promise for GPP as 5 out of 7 enrolled patients achieved a GPP Physician Global Assessment score of 0 or 1 by week 1, and all 7 patients at 4 weeks after a single dose of spesolimab [6]. "We will soon see the pivotal study with more patients, and this shows hopefully that the drug carries out its rapid efficacy for people with GPP," Prof. Strober commented.

1. Strober BE. Psoriasis: New data. Session S009, AAD VMX 2021, 23-25 April.
2. Stein-Gold L, et al. Session psoriasis 2021, Maui Derm 2021, 25-29 January.
3. Armstrong A, et al. Session S033, AAD VMX 2021, 23-25 April.
4. Gordon K, et al. Late-breaking abstract, AAD VMX 2020, 12-14 June.
5. Strober BE. Symposium for Inflammatory Skin Disease 2021, 10 April.
6. Bachelez, et al. D3T01.1E, EADV 2018, 12-16 September.

Psoriasis management in times of COVID-19: the knowledge is growing steadily

A task force of psoriasis experts is offering guidance to dermatologists caring for psoriatic patients during the COVID-19 pandemic. Patients with psoriatic disease should stay on their treatment during the pandemic unless they become acutely infected. Psoriasis patients should further take any mRNA-based vaccine as soon as offered. Lastly, adhering to evidence-based treatments only is encouraged.

The COVID-19 task force of the National Psoriasis Foundation has already issued nearly 30 recommendations concerning COVID-19 and psoriasis that are constantly updated [1–3]. The aim of this group of experts is to aid decision-making for psoriasis patients during the pandemic [4]. Discussed was whether psoriatic patients have an augmented risk for severe disease when infected with SARS-CoV-2. Results indicated the underlying psoriasis itself does not put patients at a higher risk but the higher prevalence of co-morbidities such as hypertension, obesity, and chronic kidney disease does, as those have been identified to contribute to poor outcomes of COVID-19.

A particular concern was the potential effect of biologic therapy for psoriasis on infection risk and the course of COVID-19. "The registry data is largely reassuring; it does not seem that any strong signal exists for psoriatic disease treatment being associated with higher risk of COVID-19 or worse outcomes in any meaningful way," said Prof. Joel Gelfand (University of Pennsylvania Perelman School of Medicine, PA, USA). Results from clinic-based cohorts have provided mostly reassuring insights concerning biological treatment: rates of infections, hospitalisation, and mortality were similar to those in the general population. Furthermore, results from automated databases such as TriNetX –containing electronic medical records of 53 million people– indicated that patients on TNF inhibition or methotrexate did not have a heightened risk of hospitalisation [5]. All in all, the existing literature gives mostly encouraging results, but larger and long-term studies are still needed [4]. "The committee suggests that we should be balancing known benefits of our therapies with theoretical risks and, in general, our consensus is that patients with psoriatic disease should stay on their treatment during the pandemic, unless they become acutely infected," summarised Prof. Gelfand.

In terms of mRNA-based vaccination, Prof. Gelfand indicated that dermatologists should be aware of the occurrence of about 0.8% delayed injection-site reactions 2, 3, or up to 8 days after vaccination. These reactions do not pose a contraindication for receiving a second dose. Due to the latest pause of the adenovirus-vectored vaccine, the current recommendation is that patients with psoriasis should take any mRNA-based vaccine as soon as offered and in general continue their systemic treatment.

Finally, concerning treatment of a SARS-CoV-2 infection, Prof. Gelfand encouraged to adhere only to evidence-based treatments. For outpatients, cocktails of bamlanivimab plus etesevimab and casirivimab plus imdevimab have demonstrated benefit in preventing progression to severe COVID-19. Among the recommendations for inpatients are dexamethasone and remdesivir, also in combination with baricitinib depending on the individual patient's specific criteria. Lastly, Prof. Gelfand encouraged staying in touch with the continuously updated COVID-19 resource centre for psoriasis patients.

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Lower burden of high-risk atherosclerotic plaques in psoriasis patients treated with biologics

Two separate studies demonstrated that therapy with a biologic led to a decrease in the inflammatory process that stabilises atherosclerotic plaques in patients with psoriasis.

"Over the last decade or so, psoriasis has shown to increase the effect of not only having a heart attack or stroke but also dying from it," stated Prof. Nehal N. Mehta (National Heart, Lung, and Blood Institute, MD, USA) [1]. In patients with psoriasis, high-risk plaques that underlie acute myocardial infarction are significantly more prevalent and occur >10 years earlier than in subjects without psoriasis. Prof. Mehta and his team performed a study that investigated biologic treatment versus non-biological treatment on characteristics of coronary disease over 1 year [2]. The control group consisted of psoriasis patients who had refused biologic treatment when offered. They found a significant reduction in C-reactive protein, indicating inflammation, but not in the other cardiovascular risk factors blood pressure and lipids [1,2]. Of note, the plaques changed structure: necrotic plaques were decreased in size and even showed signs of calcification suggestive of healing. There was also a reduction in fibro-fatty burden of the plaques that the researchers interpreted as loss of lipid from the plaques. So, after 1 year of biologics, total plaque burden and non-calcified plaque burden (NCB) decreased by 5% and 7%, respectively, while during the same period these parameters increased by 2% and 5% in patients not under biologics [2]. "Most striking was that in those who did go on biologic therapy, high-risk plaque features, which are known to cause rupture, actually decreased by 55% and 57%. Hence, fibro-fatty burden and necrotic core burden were both reduced," underlined Prof. Mehta [1].

Another study including 260 psoriatic patients evaluated whether those with metabolic syndrome have a heightened plaque burden (assessed with coronary computed tomography angiography) [3]. The study also evaluated whether certain components of metabolic syndrome are associated with NCB. Patients with metabolic syndrome were older, male, had higher body weight, worse cardiovascular risk profile, and higher values for inflammatory markers. This study indeed confirmed the link between metabolic syndrome and coronary disease as well as a rise of NCB in the presence of increased metabolic syndrome. Blood pressure (P=0.03) and obesity/waist circumference criteria (P<0.001) were the strongest determinants of NCB compared with HDL-cholesterol (P=0.31), while glucose and triglycerides were not statistically significant (P=0.06).

"So, in summary, I have shown you that inflammation drives a lipid streak to a non-calcified plaque that gives way to a high-risk plaque with a lipid-rich necrotic core and that biologic therapy reduced these events in psoriasis," Prof. Mehta concluded his talk.

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COVID-19: What Dermatologists Need to Know

Psoriasis and hidradenitis suppurativa during COVID-19: keep calm and carry on

In the management of patients with chronic dermatologic diseases during the pandemic, many questions have arisen. Guidance is provided by various experts.

"Our discussion about biologics needs to be contextualised with regard to which phase of COVID-19 the patient might be in," explained Prof. April W. Armstrong (University of Southern California, LA, USA) [1,2]. She started by looking at various clinical trial results in a meta-analysis for respiratory tract infection (RTI). Concerning TNF inhibition for psoriasis and hidradenitis suppurativa (HS), RTI rates were comparable between the various study drugs and placebo [2,3]. Moreover, RTI data in psoriasis trials with IL-17 inhibitors was not different between IL-17 inhibitor treatment and placebo in

most cases. Furthermore, no increased risk of RTI was found for IL-23 inhibitors in phase 3 trials [1]. Even the likelihood of viral infections was not elevated either with IL-23 or IL-12/23 inhibition, the latter in the absence of concomitant immunosuppressants.

Also available are real-world findings. A US investigation of real-world data concluded that treatment with biologics and JAK inhibitors was not associated with higher odds of a hospitalisation for COVID-19 [4]. Similar conclusions were drawn from an Italian study including 980 psoriasis patients on biologics [5]. Research from Detroit, however, found an increased hospitalisation rate in case of multidrug treatment for psoriasis and psoriatic arthritis (PsA) [6]. Nonetheless, monotherapy with biologics and especially TNF inhibition reduced this rate.

In light of the available research findings, the COVID-19 Taskforce of the National Psoriasis Foundation stated that therapy for psoriasis and PsA generally involves no meaningful alteration in the risk of acquiring COVID-19, nor of having a worse outcome. Thus, patients should continue their biologic or oral therapies [7,8]. Although corticosteroids can be beneficial for COVID-19 patients in need of oxygen therapy, chronic systemic steroids for PsA should be avoided, if possible, as they may contribute to worse outcomes in case of acute infection. The timing of the restart of treatment after infection should be a matter of individual case evaluation. "The general guidance is that most patients can restart their psoriasis and/or PsA treatments after complete resolution of COVID-19 symptoms," said Prof. Armstrong. She also indicated that vaccinations for psoriasis patients are encouraged under ongoing biologic or oral therapies.

The impact of systemic treatment on COVID-19 and HS was evaluated and expert opinions of the HS Foundation have been issued [9]. "I certainly reference these when I manage my patients with HS," stated Prof. Armstrong. "Patients who are well controlled on a stable treatment regimen should probably continue that regimen including immune-modulating agents whether it is a biologic or an oral agent," she said. Prof. Armstrong also pointed to the importance for HS patients who develop COVID-19 symptoms of getting in touch with their physician to discuss whether there is an indication for delaying a dose of their treatment.

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COVID-19 in children – cutaneous involvement is common

COVID-19 cases in children are rising and the same appears for the potentially lethal complication of multi-system inflammatory syndrome. Skin lesions such as chilblains may often be present in paediatric cases of COVID-19.

By the end of April 2021, the number of children tested positive for COVID-19 had risen to over 3.78 million – over 13% of all reported cases [1]. "Infections can occur as young as the neonatal period," said Prof. Elena B. Hawryluk (Massachusetts General Hospital, MA, USA). She also pointed out that children rarely suffer from severe disease and encounter fewer bad outcomes [2]. Children have several distinguishing features compared with adults, leading to generally milder courses of COVID-19: a strong antiviral innate immunity, healthy endothelium, sporadic presence of factors contributing to the risk of severe disease, and fewer receptors for angiotensin-converting enzyme in nose and lung, which may hinder host-cell invasion.

As children often lack the common signs of COVID-19, skin signs can play an important role. "Over 8% of hospitalised children have a cutaneous eruption," stated Prof. Hawryluk. A rare but grave complication of COVID-19 that may appear in children at a median of 25 days after viral symptoms is called multisystem inflammatory syndrome (MIS-C). By the end of March 2021, the Centers for Disease Control and Prevention (CDC) reported 3,185 cases of MIS-C with 36 fatalities [3]. Criteria for having MIS-C are suspected or confirmed COVID-19, fever of ≥38°C for ≥1 day, the need for hospitalisation, involvement of ≥2 organ systems, and laboratory results confirming inflammation [2,3]. "Skin involvement is common in MIS-C: >50% of cases show mucocutaneous changes which can present with polymorphous rash, distal extremity changes, oral mucous membrane changes, and conjunctivitis," Prof. Hawryluk summed up [2]. MIS-C can present in 3 different phenotypes: (i) overlapping with either severe acute COVID-19, (ii) Kawasaki disease (KD), and (iii) without overlap of one of these 2 diseases. Black and Hispanic children have the

highest risk for MIS-C [4]. For distinguishing children with MIS-C from those with KD, it is important to know that <50% meet the formal criteria of KD. They also tend to be older and gastrointestinal symptoms are more common than in KD. "Fortunately, most MIS-C patients recover," Prof. Hawryluk highlighted. Nevertheless, MIS-C entails ICU admission rates of 80% and a mortality of about 2% [5].

Of the pernio-like lesions (PLLs) that dermatologists see, around 29% are in children and adolescent COVID-19 patients [2,6]. PLLs present as acral lesions with purpuric of erythematous surfaces on the base of immune mechanisms that could involve interferon [5]. PLLs may be recurrent, normally only last for 1-3 weeks, and are self-limiting [2]. Also, other acral and non-acral skin lesions have been reported in children with COVID-19, but confirmation of the virus in tissue biopsies was not always given. Positive biopsies were found in erythema multiforme-like lesions [7].

"Dermatologists have an important role in containing the pandemic by appropriately counselling patients and testing for acute infection if indicated," Prof. Hawryluk emphasised in her summary. She encouraged her colleagues to report paediatric presentations to the AAD COVID-19 Dermatology Registry.

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Cutaneous reactions after COVID-19 vaccination: an update

Cutaneous reactions after vaccination for COVID-19 do not only occur immediately but can be seen up to 11 days after the first shot. They are most common in patients vaccinated with Moderna.

"First reports of unusual COVID-19 vaccine skin reactions came through social media rather than classic media," explained Prof. Esther Freeman (Harvard Medical School, MA, USA) [1]. The first publication included 12 case reports in the *New England Journal of Medicine* this year [2]. Of note, all reactions appeared near the injection site after complete resolution of the initial local and systemic symptoms associated with vaccination. These delayed large reactions were evident at day 7 or 8 after the first shot with various morphologies. Biopsies revealed a basic lymphocytic infiltrate. These large local reactions were mainly seen after vaccination with Moderna. A possible cause might be a reaction to polyethylene glycol. "We have seen few reactions with the other mRNA vaccine; the reasons are still not clear. However, it is reassuring that the reaction was either less severe or did not recur after the second dose of the vaccine," Prof. Freeman stated. The reactions were seen sooner after the second vaccination – around day 2 or 3. As there is no infection, there is no indication for antibiotics.

Fortunately, anaphylaxis to mRNA vaccines is rare. Allergic reactions to mRNA vaccines were assessed in a prospective cohort of 64,900 healthcare employees in the USA [3]. For 3 days after vaccination, employees completed symptom surveys and were asked for symptoms of acute allergic reactions including itch, rash, hives, swelling, and/or respiratory symptoms. In this cohort, 40% received the Pfizer-BioNTech vaccine and 60% the Moderna vaccine. Most participants (98%) reported not having any symptoms of an allergic reaction after receiving an mRNA COVID-19 vaccine. Some allergic symptoms were reported by 2%, but severe reactions consistent with anaphylaxis were rare: they occurred at a rate of 2.47 per 10,000 vaccinations. Moreover, all individuals with anaphylaxis recovered without shock or endotracheal intubation. "This study shows us that anaphylaxis is extremely rare with mRNA vaccines," Prof. Freeman said.

The latest phase 3 trial published on the Pfizer-BioNTech vaccine showed no serious cutaneous reactions, only injection-site reactions [4]. In the phase 3 trials with Moderna, no serious cutaneous reactions were reported, but there were delayed injection-site reactions with an onset on or after day 8. These reactions were observed in 0.8% of patients after the first dose and 0.2% of patients after the second dose [4]. "They were really rare, but I suspect this was underreported in the trial," Prof. Freeman said. There were also cutaneous reactions reported in the Johnson & Johnson vaccine trials (phase 1/2a). Reported cutaneous reactions in the overall vaccinated cohort were erythema (in 7%), swelling (in 5%), and pain (in 49%).

"The trial data did not give us much – I think we need to look at the real-world data," Prof. Freeman said. This year, a registry-base study was published covering cases of cutaneous reactions after Moderna and Pfizer-BioNTech vaccination [5]. In this study, cases of cutaneous manifestations after

COVID-19 vaccinations were collected from December 2020 to February 2021. Patients (n=414) reported one or more cutaneous reactions to Moderna (83%) or Pfizer-BioNTech (17%). The most common reactions were delayed large local reactions, local injection-site reactions, urticaria, and morbilliform eruptions. These reactions followed a typical timeline after the vaccination: local site reactions happened directly after the vaccination. Urticaria was seen around day 3, and 89% of cases were women. Morbilliform eruptions were seen 3–7 days after the first vaccination, most frequently on arms. Delayed large local reactions appeared 7–11 days after the first vaccination. "They were observed in >200 cases, 94% of those were vaccinated with Moderna," Prof. Freeman said. These large local reactions were also seen after the second vaccination but on day 3. Other less common reactions included pernio and cosmetic filler reactions. The latter are not specific for COVID-19 and also occur in patients after influenza shots.

"Patients who have massive reactions after the first vaccine often do not want their second shot, but overall, we can be reassuring." Prof. Freeman concluded that only 43% of patients with first-dose reactions experienced a recurrence after the second vaccination, and there was not a single case of anaphylaxis [5].

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Novel Developments in Sun Protection

Sunless tanning and other developments in sun protection

Sunscreen use is an important means to prevent photodamage, yet data gaps still exist with regard to UV filters. Novel areas are sunless tanning and the prevention of damage by visible light.

As Dr Henry Lim (Henry Ford Health System, MI, USA) pointed out in his presentation, the FDA recognises only 2 UV filters –zinc oxide and titanium dioxide– as generally safe [1]. For most of the other filters, insufficient safety data is available.

In an absorption study assessing 6 active ingredients, including oxybenzone and octinoxate, levels of >0.5 ng/ml in the blood and skin after single use were detected for all agents. Levels remained elevated longest with oxybenzone, until day 21. "But the results do not indicate that individuals should refrain from the use of sunscreens with UV filters; their use is still safe," Dr Lim said. A review published last year analysed 29 studies on the impact of UV filters on human health. The study found that oxybenzone seems to have no adverse effect on male and female fertility, but associations were found of oxybenzone with thyroid hormone levels, testosterone level, kidney function, and pubertal timing that should be investigated further [2]. The authors concluded that current evidence is not sufficient to support the causal relationship between elevated systemic levels of oxybenzone or octinoxate and adverse health outcomes.

In a recently published article on the environmental impact of organic UV filter exposure, a risk was identified of oxybenzone and octinoxate above a certain concentration that might adversely impact corals. However major data gaps still need to be addressed [3]. Both agents were banned in Key West and Hawaii due to their toxic effects on marine ecosystems in January 2021.

Small molecules for sunless tanning appear to be an attractive novel concept for consumers. One example is afamelanotide, a potent alpha-melanocyte-stimulating hormone (αMSH) analogue, which stimulates the production of eumelanin in the skin. Subcutaneous implantation of afamelanotide is currently approved by the FDA for the treatment of erythropoietic protoporphyria; use as a self-tanning medication is off-label. Cyclic adenosine monophosphate inducers such as topical forskolin or salt-inducible kinase inhibitors are other interesting agents. However, all of them are still in the early stages of development [4].

A novel area in sun protection is the protection against visible light. Broad-spectrum sunscreens protect against ultraviolet radiation but do not adequately protect against visible light. Exposure to visible light can lead to melasma in people with dark skin and to erythema in those with light skin. "To protect against visible light, a sunscreen has to be tinted," Prof. Lim explained. Tinted sunscreens use different formulations and concentrations of iron oxides and pigmentary titanium dioxide to provide protection against visible light. Many shades of tinted sunscreens are available by combining different amounts of iron oxides and pigmentary titanium dioxide to cater to all skin phototypes [5].

On how to advise our patients, Prof. Lim emphasised: "The practice of photoprotection is an entire package." Patients should be advised to seek shade if possible and wear photoprotective clothing, a wide-brimmed hat, and sunglasses. In otherwise exposed areas people should apply SPF >30 broad-spectrum (to cover UVA), tinted (to cover visible light) sunscreen. Patients with concerns about the environmental effect of chemicals can use mineral sunscreens. Last but not least, patients who practise rigorous photoprotection should be recommended taking an oral supplement of vitamin D (600–800 IE daily).

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What Is Hot in Atopic Dermatitis

Comorbidity is common in adult and paediatric atopic dermatitis patients

Most atopic dermatitis patients have a higher comorbidity compared with the general public; this is even true for paediatric patients.

Comorbidity of atopic dermatitis (AD) has been studied extensively. There is a plethora of concomitant diseases not only from the allergic disease spectrum (e.g. food allergy, hay fever, or asthma) but also other diseases including sleep disturbances, psychiatric comorbidities such as anxiety and depression, and an elevated cardiovascular risk. Having a comorbid health disorder does not always equate to patients having poor health outcomes. "Therefore, it is important to determine who the 'sick' patients are," explained Prof. Jonathan Silverberg (George Washington University, Washington DC, USA) [1].

Generally, multimorbidity is most common in the elderly, but some diseases such as rheumatoid arthritis, systemic sclerosis, or cancer can also increase the risk of multimorbidity in younger populations. A common tool to assess comorbidity is the Charlson Comorbidity Index (CCI). In a Danish case-control study including 10,738 adults with an AD diagnosis and 42,952 controls, patients had significantly higher CCI scores than controls (0.13 vs 0.09; P<0.001) [2]. Specific patient subsets with increased CCI included severe AD patients and smokers with AD. Another study demonstrated that multimorbidity according to CCI scores and estimated 10-year survival were similar between AD and psoriasis [3]. "We also assessed the multimorbidity in children with AD and found that young children aged <11 years with mild-to-moderate AD or severe AD and adolescents with mild-to-moderate AD had significantly higher CCI scores compared with no-AD populations," Prof. Silverberg stated [4]. AD patients with atopic comorbidities had a particularly increased multimorbidity score.

But why are some AD patients "sicker" with multimorbidity, yet most do not have multimorbidity? According to Prof. Silverberg, there are probably a couple of reasons, including genetics (filaggrin mutations are a possible culprit), immunology, and environmental causes such as smoking. "AD patients with multimorbidity would likely benefit from interdisciplinary coordination of care," he said. CCI is only a research tool and in daily practice comorbidity should be assessed by a thorough medical history and assessment of health-related quality of life using more global scales such as the PROMIS global health. "These tools more holistically assess the impact of AD and comorbidities," Prof. Silverberg concluded.

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Significant improvements in the system armamentarium for AD treatment

New systemic therapies offer fascinating changes for AD treatment. In particular, JAK inhibitors are an attractive and long-awaited oral treatment possibility for patients with moderate-to-severe disease.

Prof. Eric Simpson (Oregon Health & Science University, Portland, USA) covered systemic therapy in atopic dermatitis (AD) patients, an ever-evolving field [1]. But who needs it? In Prof. Simpson's opinion, quality of life should be the determining factor. If it is still impaired when using topicals, AD patients should proceed to systemic treatment. "The choice of an agent should always depend on a shared decision-making with the patient," Prof. Simpson recommended. Methotrexate remains a valuable choice for patients with moderate AD. "The IL-4/13 blocker dupilumab works well for the majority of our patients and is safe in the elderly," he stated. Further options will be available in the near future, such as the selective IL-13 blocker tralokinumab, which has a more modest efficacy than dupilumab but good long-term efficacy.

"Maybe we should not block 1 or 2 cytokines but multiple cytokines for the best effects," Prof. Simpson said. This is the approach taken by JAK inhibitors. According to Prof. Simpson, these agents act more as immune modulators instead of having a single target like the biologics. "If a patient has a preference for oral dosing and a really quick response is warranted, that might be a good reason to use them," he suggested. However, there are also various reasons to choose different agents (see Table).

Table: Systemic JAK inhibitors for AD [1]

When to use	When NOT to use
• No reason they cannot be first-line systemic • Preference for oral and flexible dosing • When a quick response is desired (within the first week) • Inadequate or loss of response to dupilumab	• History of malignancy • History of severe infection • History of thrombosis • Severe renal or liver disease • Pregnant or breastfeeding • Elderly – use lower dose • Patient with low tolerance for rare risk

The JAK inhibitors baricitinib and upadacitinib have a black box warning for serious infections, malignancies, and thrombosis. Methotrexate has such a warning for liver disease. Thus, Prof. Simpson suggested using these agents cautiously. All JAK inhibitors improve itch rapidly, often within a day and faster than biologics, and all are appropriate as first-line therapy. Safety and tolerability issues to pay attention to are headache, acne, and herpes zoster. "My biggest concern with JAK inhibitors is venous thrombosis, this is what I look at most closely," Prof. Simpson urged. The JAK-1/2 inhibitor baricitinib has the lowest efficacy of all JAK inhibitors but is well tolerated. "The efficacy of abrocitinib 100 mg is comparable with dupilumab; the higher dose is probably even better," Prof. Simpson said.

Upadacitinib seems to have the highest efficacy of all JAK inhibitors. However, it has the least amount of published safety data. Acne is a unique side effect for upadacitinib observed in up to 17% of patients at a high dose. The risk of venous thrombosis is unknown. In a head-to-head study, 61% of patients treated with upadacitinib achieved an EASI 90 response at week 16 versus 39% with dupilumab. In addition, there was a 67% change from baseline in worst itch compared with 49% with dupilumab. "We have never seen this – but I need to see long-term safety data before I can state that this is the oral treatment of choice. Finally, there are great new options for your AD patients in 2021. Will they fill all the gaps? I sure hope so," Prof. Simpson concluded.

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No increased risk of infection with long-term dupilumab for atopic dermatitis

Data from the ongoing, open-label, extension study LIBERTY AD OLE indicated no elevation in number of cases of overall and serious infections emerging from dupilumab therapy for atopic dermatitis over 3 years.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that includes alterations of the skin barrier and carries an increased risk for cutaneous infections of both bacterial and viral origin that may lead to systemic infections [1]. Dupilumab –an IL-4/IL-13 blocker not categorised as immunosuppressant– previously demonstrated in clinical trials to be linked to a reduced risk for severe infections and no elevation on overall rates for infection [2]. To learn more about the occurrence of infections in long-term treatment with dupilumab in patients with moderate-to-severe AD, the new evaluation presented by Prof. Andrew Blauvelt (Oregon Medical Research Center, USA) described incidence rates over 3 years by number of patients (nP) per 100 patient-years (PY) within the ongoing, open-label, extension study LIBERTY AD OLE (NCT01949311) [3].

All study subjects in this trial took part in phase 3 trials with dupilumab. They were treated with 300 mg of dupilumab once per week. As there is no control arm in OLE, the current analysis compared the infection rates from OLE to data from CHRONOS (NCT02260986), the largest study to date to investigate placebo versus 300 mg dupilumab weekly with concomitant topical corticosteroids (TCS) in both arms over 52 weeks. The current analysis included 2,677 patients receiving 300 mg dupilumab in the OLE. The 2 study arms of CHRONOS had 315 patients each, receiving either dupilumab with TCS or placebo plus TCS.

In general, infection rates were lower in OLE than in CHRONOS. Treatment-emergent overall infections were present in 74.07 nP/100 PY in OLE versus dupilumab plus TCS with 93.66 nP/100 PY and placebo plus TCS with 106.98 nP/100 PY in CHRONOS, respectively. Infections leading to a termination of treatment were found in 0.35 nP/100PY in OLE, 0.92 nP/100 PY (placebo + TCS), and 0.00 nP/100 PY (dupilumab + TCS). As for treatment-emergent severe or serious infections, the corresponding rates were 1.43 nP/100 PY in OLE compared with 2.12 nP/100 PY in the placebo arm and 0.34 in the dupilumab group of CHRONOS (see Figure). The most frequent infections were nasopharyngitis, upper respiratory tract infections, and conjunctivitis. The authors concluded that dupilumab is a suitable long-term treatment for moderate-to-severe AD, as no augmented risk of skin or systemic infections was found.

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Topical pan-JAK inhibitor cream safe and efficacious in atopic dermatitis

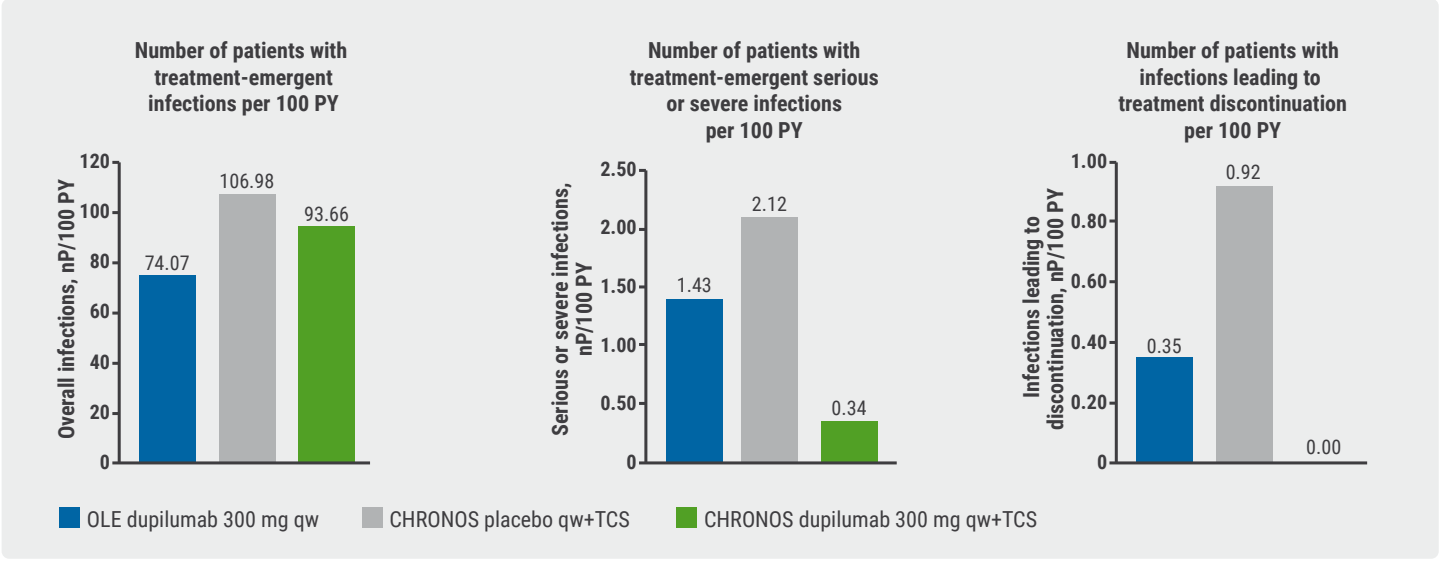
Delgocitinib cream was surprisingly effective in a randomised, multi-dose, vehicle-controlled trial that included adult patients with atopic dermatitis: two-thirds of patients treated with the highest dose had a >75% improvement in the Eczema Area and Severity Index (EASI 75).

The agent delgocitinib is a broad-spectrum JAK inhibitor blocking signal pathways including JAK-1/2/3 and tyrosine kinase 2. In a previous study, delgocitinib was successful in patients with chronic hand eczema.

The study presented during the AAD VMX 2021 meeting was a randomised, vehicle-controlled, dose-ranging phase 2b trial involving adults with atopic dermatitis (AD) of at least 1-year duration (NCT03725722) [1]. Eligible patients had a mean body surface area (BSA) affected by AD of 10 and disease severity according to the investigators global assessment (IGA) ranging from mild to severe. Patients were treated with a vehicle cream or delgocitinib cream in 4 different doses (i.e. 1, 3, 8, and 20 mg/g), which was applied twice daily. The primary endpoint of the study was the change in EASI score from baseline to week 8.

Included in the analysis were 251 patients. In the highest dose group (20 mg), EASI score dropped by 7.6 from baseline to week 8 compared with 1.9 in the placebo group (P<0.05). With regard to change from baseline in EASI score, all delgocitinib doses separated distinctly from the vehicle arm by week 1, which continued up to week 8. “Clearly, the highest

Figure: Infection rates in LIBERTY AD OLE (dupilumab monotherapy) and CHRONOS (dupilumab + topical steroids and placebo + topical steroids) [3]



dose had the greatest efficacy," Prof. Jonathan Silverberg (George Washington University, Washington DC, USA) emphasised during his presentation. The EASI 75 response rate at week 8 showed a similar pattern. In the highest dose group, this difference became significant as early as week 1 compared with the control group. Treatment with delgocitinib was accompanied by a significant improvement in the quality of life, assessed in the Dermatology Life Quality Index (DLQI).

"Itch is the most common and most burdensome symptom in AD," Prof. Silverberg said. In this study, itch relief was assessed as secondary endpoint: patients had a baseline itch score of 6.1, which decreased by 4.6 points in the highest dose group by week 8 and by 2.8–3.0 point in the other delgocitinib arms, compared with 1.0 in the placebo group (P<0.05). Daily itch score declined significantly versus the control group by day 2 in all but the lowest dose of delgocitinib. The safety profile of the JAK inhibitor was comparable to that of the control group.

1 Silverberg J, et al. The topical pan-JAK inhibitor delgocitinib in a cream formulation is efficacious with a favorable safety profile: results from an 8-week phase 2b dose-ranging trial in atopic dermatitis. AAD VMX 2021, 23-25 April.

Atopic dermatitis in children has a severe impact on their families

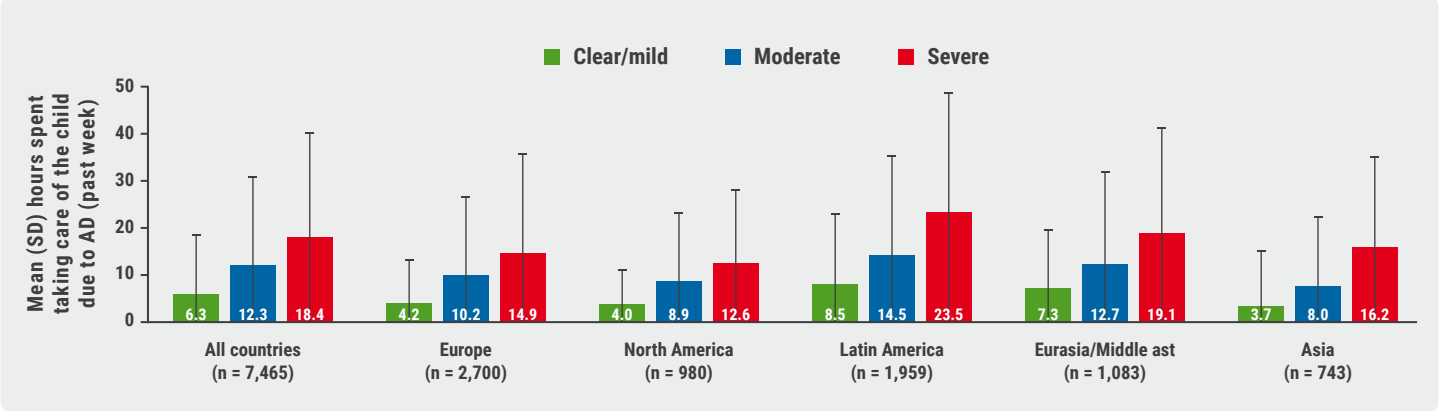
A worldwide survey conducted in 18 countries found that atopic dermatitis can considerably decrease quality of life in families of affected children in various domains.

Although atopic dermatitis (AD) is common in childhood, information on the impact of the disease on the family is lacking. To fill this gap, a cross-sectional, web-based survey of children aged 6 months to <18 years was conducted in 18 countries in 5 regions [1]. Parents were invited to participate without knowledge of the survey topic. To be considered as having AD, the patients should meet the following 3 criteria: (i) ever had an itchy rash that was coming and going for at least 6 months; (ii) had this rash at any time in the past 12 months; and (iii) the rash was noted on the fold of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes. In addition, there had to be a physician diagnosis of eczema with or without skin allergies. Children were stratified as having clear/mild, moderate, or severe AD based on patient's global assessment in the past week. Parents reported on the impact of living with a child with AD on their family quality of life (QoL) in the past week using the Dermatitis Family Impact (DFI) questionnaire (0–5, normal; 6–10, low impact; 11–20, moderate impact; >20, high impact), time spent taking care of their child due to AD in the past week, and time missed from work for AD-related issues in the past 4 weeks.

Data was analysed of 7,465 children with diagnosed AD (clear/mild 59.0%; moderate 35.9%; severe 4.9%). There were increasing scores of DFI assessed on a scale of 0 (no impact) to 30 (highest impact) with increasing AD severity in all countries. In addition, time spent on care and the need to take time off work increased in parallel with AD severity in all countries (see Figure). All domains of family life were considerably disrupted including everyday-life activities, social activities, sleep, and emotional and financial domains. The survey highlights that childhood AD negatively impacts quality of life of the patient's family and their caregivers, with the burden generally increasing with AD severity.

1. Barbarot S, et al. Worldwide survey shows that atopic dermatitis in children is associated with a negative impact on their families. Poster 27473, AAD VMX 2021, 23-25 April.

Figure: Time spent on care in dependence of AD severity in participating countries [1]



Meaningful amelioration of quality of life in paediatric AD patients on dupilumab

In the phase 3 LIBERTY AD PEDS trial, health-related quality of life in 6 to <12-year-old patients with atopic dermatitis demonstrated significant improvements in the majority of patients treated with dupilumab.

Decreased health-related quality of life (HRQoL) plays an important role for children with atopic dermatitis (AD) and can result in a substantial burden – not only on the patients themselves but also on their parents [1,2].

The phase 3 LIBERTY AD PEDS trial (NCT03345914) investigated the influence of treatment with dupilumab on the HRQoL of children suffering from severe AD [1]. They had all previously failed adequate response to topical treatments. The trial measured HRQoL using the Children's Dermatology Life Quality Index (CDLQI). This validated questionnaire includes 10 items that can be grouped by domains into sleep, leisure, school/holidays, personal relationships, symptoms and feelings, and treatment as reported by patients and caregivers [3]. LIBERTY AD PEDS enrolled 367 patients between 6 years and <12 years of age [1]. The HRQoL analysis stratified into 4 subgroups: dupilumab 300 mg every 4 weeks plus topical corticosteroids (TCS) in subjects with a body weight <30 kg (group 1), dupilumab 200 mg every 2 weeks plus TCS ≥30 kg (group 2), and 2 groups receiving placebo plus TCS with the same weight distinctions (group 3: <30kg; group 4: ≥30 kg).

At baseline, 80.7–90.2% of patients were at least moderately affected by AD. Statistically significant differences were observed in least square mean change of total CDLQI with a reduction of -6.4 and -6.3 in the placebo groups versus -10.7 (P<0.0001) and -10.4 (P<0.0001) in the dupilumab groups. Similarly, in dupilumab-treated patients, 81.8% and 80.8% achieved an improvement in CDLQI of ≥6 points. At week 16, the great majority of dupilumab treated patients reported no or only a small effect of AD on their HRQoL with 79% in those <30 kg and 82% in group 2. The corresponding values for groups 3 and 4 were 48% and 55%, respectively. The improvements in HRQoL were found in all domains of the questionnaire. Of note, clinically meaningful treatment responses were seen as early as week 2.

1. Irvine AD, et al. Dupilumab improves health-related quality of life in children aged ≥6 to <12 years with severe atopic dermatitis. Poster 27431, AAD VMX 2021, 23-25 April.
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Hairy Matters – What Is New in Alopecia

Allergies: an underrated factor in alopecia pathogenesis

Several interesting novel treatment options will soon be available for different forms of hair loss. Also, scalp allergic contact dermatitis may be an underestimated cause of hair loss.

In the past years, novel treatment choices for alopecia areata (AA) have emerged, including the Janus Kinase (JAK) inhibitors. "Unfortunately, trials slowed down due to the pandemic, and all 3 approved JAK inhibitors –ruxolitinib, tofacitinib, and baricitinib– have no indication for AA," said Prof. Natasha Mesinkovska (UC Irvine School of Medicine, CA, USA) [1]. Based on currently available data, one can expect response rates of 46–75%. The agents are well tolerated but expensive. "Long-term use is needed; when the medication is discontinued, hair falls out again," said Prof. Mesinkovska. In addition, AA is a chronic condition, and sometimes after an initial response, hair still falls out despite continued JAK inhibitor treatment. Although the agents have been associated with a risk of herpes zoster, the risk is small.

JAK inhibitors have also demonstrated to be effective in children and adolescents with hair loss and in alopecia universalis. Even in patients who did not have any hair for years, regrowth has been observed. Unfortunately, about one-third of patients do not respond to treatment. Whether higher doses or longer treatment periods might be justified in these patients remains unclear. Other options currently under investigation are dupilumab, apremilast, and ustekinumab. The selective sphingosine-1-phosphate (S1P) receptor modulator etrasimod may be an interesting novel different pathway in AA.

Allergies contribute to AA

Allergies seem to play a role in AA. In a histopathology study, an eosinophilic infiltrate around the hair bulbs of AA patients was detected in 30.8% of cases in the acute stage but only in 7.7% in the chronic stage [2]. A higher risk of allergic disease such as rhinitis, asthma, and atopic dermatitis (AD) has been reported in AA. One study found that AA patients had higher IgE concentrations, and dust mite allergy against was associated with early-onset AA and severe AA [3]. Mast cells were also found in histologic samples of AA patients. Patients with AA have a 2.6 time increased risk for AD. "We all notice a seasonal pattern in AA with more flares in spring and late autumn," Prof. Mesinkovska said. These flares coincide with flare frequencies of patients with AD. "This is the rationale to try antihistamines in AA," Prof. Mesinkovska suggested. Antihistamines such as fexofenadine might be able to enhance hair regrowth. According to Prof. Mesinkovska, their use should be considered in the high-risk seasons: autumn and spring.

A potential novel treatment option for AA patients may be the IL-4/13 antagonist dupilumab. However, the role of this biologic is controversial: some patients with new-onset alopecia had hair regrowth after they were treated with dupilumab for their AD but other patients developed AA after having been treated with dupilumab for their AD.

Scalp allergic contact dermatitis: another cause of alopecia

Many hair products can potentially cause scalp allergic contact dermatitis (ACD). Typical symptoms are erythema (25%), pruritus or itching (22%), and scale (10%). Of note, only 9.3% of patients suffer from scalp dermatitis solely. In most cases, signs can be found elsewhere on the body, including neck, face, and forehead. A review demonstrated that hair dye (most frequently phenylenediamine) is responsible for most ACD cases (48%), another 27% are caused by shampoo, and 8% by topical minoxidil. Alopecia develops in about 10% of ACD cases. To detect the culprit, a full history of allergies, a body exam, and a diagnostic biopsy are warranted. In addition, a patch test should be performed.

Frontal fibrosing alopecia (FFA) is a chronic cicatricial alopecia with unknown aetiology and a rising incidence worldwide. In previous years, a controversy arose about a possible correlation between facial sunscreen use and development of frontal fibrosing alopecia. A study found a high use of sunscreens in women with FFA [4]. A Brazilian case-control study in a multiracial population found a positive association between FFA and the use of moisturisers, facial soap, and hair straightening with formalin, and a negative association with the use of anti-residue/clarifying shampoo. The authors concluded that their study reinforces the possibility of an exogenous particle triggering FFA [5].

1. Mesinkovska N. HOT Topics: Alopecia. Session S027, AAD VMX 2021, 23-25 April.
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Botulinum toxin A: a contradictory role in hair loss

Botulinum toxin A can increase blood flow to the follicle, thus stimulating hair growth. However, in patients repeatedly treated for forehead wrinkles, it can induce hair loss.

Prof. Natasha Mesinkovska (UC Irvine School of Medicine, CA, USA) illustrated that therapy with botulinum toxin for hair loss was assessed in 6 studies since 2006: 4 showed improvement, 2 inconclusive results [1]. Most patients had androgenetic alopecia (AGA). In a pilot study including 50 patients with AGA, botulinum toxin therapy led to a significant increase in hair density [2]. The primary outcome was change in hair count in a fixed 2 cm area. After 3 sessions, hair count increased by 18% between the start of the trial and week 48 in the 40 male subjects that completed the trial. Hair loss was also significantly reduced, by a mean of 39%. The treatment response rate was 75%.

Yet, why is botulinum toxin effective in androgenetic hair loss? It is plausible that botulinum toxin interferes with the molecular mechanisms seen in AGA: the predisposed scalp exhibits high levels of dihydrotestosterone (DHT) and an increased expression of the androgen receptor. Conversion of testosterone to DHT within the dermal papilla plays a central role in AGA. The elevated DHT concentrations can at least in part be explained by a microvascular insufficiency in AGA: pO_2 is lower in bald patients compared with patients with hair. In a low-oxygen environment, conversion of testosterone to dihydrotestosterone is enhanced, whereas more testosterone is converted to oestradiol in a high-oxygen environment. As Prof. Mesinkovska pointed out in her talk, botulinum toxin increases both blood supply and transcutaneous pO_2. It relaxes the muscles of the scalp, eases the muscle tension in the scalp, thereby reducing pressure on the vessel. Therefore, blood flow to the follicle is increased and DHT is removed.

In 2020, a second study with botulinum toxin in Chinese AGA patients was published [3]. In this study 63 patients with AGA were treated every 3 months for a total of 4 times in 30 sites (100 U botulinum toxin in each site). Hair growth and density were significantly augmented, and the area of hair loss was attenuated after each treatment through head photographs.

Yet, data on a detrimental effect of botulinum toxin on hair growth is available as well. In particular, botulinum toxin seems to induce frontal alopecia accompanied by gradual regression of the frontal hairline in patients that are treated periodically with botulinum toxin injections for forehead wrinkles. In patients with botulin-induced frontal alopecia (BIFA), skin is normal and there is no atrophy, scarring or progressive hair miniaturisation at trichoscopy, or inflammatory responses [4]. One of the explanations for botulinum-induced hair loss is a decreased neurological stimulation of the hair follicle due to blockade of the function of autonomic fibres. "This is something to watch out for in our patients," Prof. Mesinkovska said. Taken together, many questions are left to answer regarding alopecia and the role of botulinum toxin.

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Platelet-rich plasma in androgenetic alopecia – hype or hope?

Platelet-rich plasma (PRP) might present a promising treatment option in androgenetic alopecia, but hair restoration using PRP is still at its infancy: more scientific data is urgently needed.

PRP is defined as a portion of the plasma fraction of autologous blood with a platelet concentration above baseline. However, as Prof. Ronda S. Farah (University of Minnesota, MN, USA) emphasised, its use in androgenetic alopecia is questioned: the first problem is that no standardised protocol for preparing PRP exists [1,2]. PRP probably acts by growth factors that stimulate and inhibit hair growth (see Figure). Platelets can be activated before application of PRP, but whether this is necessary is a matter of debate. In addition, there is no clear PRP regimen; most users recommend monthly injections with a possible booster about 6 months later.

The side effects of PRP include pain at the injection site. "Massage the area or distract the patient to alleviate pain," Prof. Farah recommended. She applies PRP specifically to the thinning regions.

In a real-world study, PRP combined with 5% minoxidil led to a positive response in 71% of patients at 2 months: the PRP combination demonstrated a significant increase in hair density. In a randomised controlled split-scalp study including 35 patients with androgenetic alopecia, one side of the scalp was treated with PRP and the other with a saline solution as placebo. Hair density increased on both sides, but this difference failed to reach statistical significance [3]. In a systematic review, 84% of studies demonstrated a positive effect, but only 50% had objective measurements [4]. The authors concluded that PRP is efficient and well tolerated. Simultaneous use of PRP and minoxidil demonstrated the highest rate of improvement and satisfaction [4]. PRP proved also effective in women with androgenetic alopecia [5].

Prof. Farah stressed that additional research with standardised PRP protocols is needed. There are several questions concerning the ideal volume or platelet concentration to inject. "One should disclose to patients that it is an off-label treatment," Prof. Farah recommended.

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3. Shapiro J, et al. J Am Acad Dermatol 2020;83(5):1298-1303.
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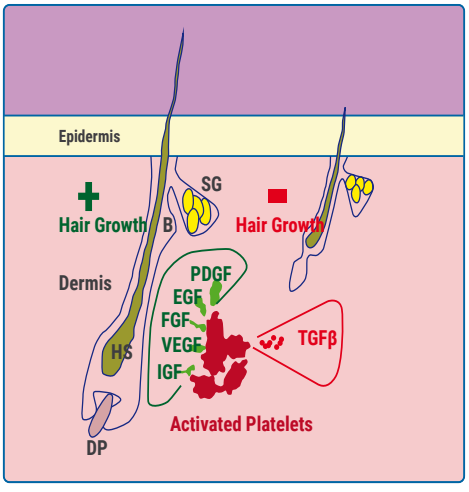
5. Dubin DP, et al. J Am Acad Dermatol 2020;83:1294-7.

Figure: Activated platelets release several growth factors that may be responsible for the treatment effect of platelet-enriched plasma [1]



SG, sebaceous gland; B, bulge region; HS, hair shaft; DP, dermal papilla; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; IGF, insulin-like growth factor; TGFβ; transforming growth factor β.

Acne – New Developments

New therapeutic options add value to current acne treatment

Novel topical and systemic therapies from different drug classes broaden the current acne armamentarium.

"Clascoterone is an exciting new topical anti-androgen for both men and women with acne," said Dr John Barbieri (Perelman School of Medicine, University of Pennsylvania, USA) [1]. The agent competes with androgens for binding to the androgen receptor, leading to blockade of the vicious circle of sebum production and pro-inflammatory cytokine release. Contrary to other anti-androgens, it is rapidly metabolised to cortexolone and has almost no systemic effect. Phase 3 trials support safety and efficacy of clascoterone: therapy with clascoterone cream led to a 20% success according to Global Investigator's Assessment (IGA) versus ~8% with the vehicle [2]. Inflammatory papules and pustules decreased by 45%. "There were only minimal side effects, so this is a great medication for patients with sensitive skin," Dr Barbieri concluded. "In addition, this is one of the first anti-androgens we can use in our male patients," Barbieri elaborated.

New topical retinoids and formulations may have better efficacy and tolerability, but additional comparative effectiveness data is needed. Another progress in acne therapy is the FDA approval of the fourth-generation retinoid trifarotene, which is a highly selective agonist for the retinoid acid receptor gamma. In 2 randomised phase 3 trials, trifarotene cream (50 µg/g) showed a similar efficacy profile to other retinoids, with an IGA success rate in the face of 29.3%; it was also effective in trunk acne [3]. Moderate erythema was present in 25% of patients and severe in 5%; the same percentages were observed for scaling. Dry skin was present in 30% of patients. "Future studies should assess how trifarotene compares with standard-of-care topical retinoids, but it is unique in its selectivity, and we can use it in children aged ≥9 years," said Dr Barbieri.

"Another interesting idea is to improve the tolerability by changing the vehicle," Dr Barbieri continued. In a phase 2 trial, tazarotene lotion caused side effects in only 14.7% versus 26.8% in patients treated with tazarotene cream; the efficacy was similar [4].

Minocycline foam (4%) is another interesting new topical antibiotic for acne. It was effective and well tolerated in 2 double-blind phase 3 trials compared with vehicle foam [5]. Again, Dr Barbieri emphasised that future studies are needed to assess how the foam compares with standard-of-care topical antibiotics.

Sarecycline is a narrow-spectrum tetracycline designed for acne which may have and improved side-effect profile and reduced risks of microbiome alterations and resistance than other tetracyclines. It is very active against *Cutibacterium acnes* but shows less activity against other bacteria, in particular gram-negative bacteria. Therefore, it causes less changes in microbiome, which might result in a lower risk of gastrointestinal side effects. In a phase 3 trial, it led to IGA success in about 20% of patients with good tolerability. The most common adverse event was nausea, occurring in about 2.5% of patients [6].

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Nicotinamide and probiotics can support acne therapy

An increasing number of acne patients asks for natural treatment options. Prof. Juliana Choi (Penn Dermatology Perlman, PA, USA) gave recommendations for adjunctive treatments in acne.

Niacinamide is a form of vitamin B3 that has demonstrated anti-inflammatory, anti-ageing, anti-carcinogenic, and moisturising properties, the latter by increasing the synthesis of ceramides [1-3]. Unfortunately, there are few randomised controlled studies evaluating topical treatment. In one study, 4% niacinamide had comparable efficacy with 1% clindamycin. Side effects were mild burning, pruritus, and erythema. No studies tested oral niacinamide as a single agent. However, 2 studies with combination products containing nicotinamide, zinc, copper, and folic acid led to a significant improvement of acne with no side effects: doses of the combinations were between 600 and 2,400 mg. Prof. Choi recommended topical niacinamide, particularly for patients with sensitive skin, as efficacy is similar to topical clindamycin without the concern for antibiotic resistance and side effects are minimal. "I recommend 4–5% nicotinamide or higher," she said. Prof. Choi advocates oral niacinamide supplements for patients who prefer 'natural' options or who may benefit from the anti-carcinogenic effect.

For these cases, 500 mg 1–3 times daily is appropriate. "In contrast, I do not recommend zinc to my acne and rosacea patients," she said. Reasons for this are the mixed efficacy for acne, and the distinct gastrointestinal side effects.'

Another adjunctive treatment for acne Prof. Choi favours are probiotics. Probiotics are live microorganisms that benefit the host by improving its microbial balance. Unfortunately, few studies have assessed oral probiotics for acne patients, but a trend has been observed towards improvement. In an open-label study including 45 female acne patients, probiotics and minocycline had similarly efficacy. Of those treated with minocycline, 13% developed vaginal candidiasis but not a single patient in the probiotic group did [4]. Evidence exists for the capability of probiotics to reduce antibiotic-associate diarrhoea: a meta-analysis of 19 studies found a 52% reduction with probiotic use [5]. "Therefore, I recommend oral probiotics as adjunctive treatment in otherwise healthy patients being prescribed oral antibiotics with antibiotic-associated diarrhoea or vaginal candidiasis," concluded Prof. Choi.

1. Choi J. Diet, "Natural" Treatments, and Maskne. Session F002, AAD VMX 2021, 23-25 April.
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'Maskne' – How can it be managed?

One of the dermatologic sequelae of the pandemic is rosacea or acne caused by mask wearing. Both proper skin care and a well-fitting mask are key to successful treatment.

"Diagnostic criteria for mask acne, often called 'maskne', were published recently," explained Prof. Juliana Choi (Penn Dermatology Perlman, PA, USA) [1,2]. Mask acne is defined as the onset or exacerbation of acne over the area covered by a mask within 6 weeks of regularly wearing a face mask [2]. Differentials such as perioral dermatitis, seborrheic dermatitis, or rosacea must be excluded.

Limited data has been available on maskne, but a recent study including 30 acne and 36 rosacea patients demonstrated that COVID-19-related masks increased severity of both acne and rosacea. All participants wore masks on average 8 hours/day for 6 weeks [3]. "Masks flare both acne (in masked areas) and rosacea, but the causes are still not entirely clear," Prof. Choi said. Based on observation, it appears a combination of acne mechanica due to the occlusion and friction of the face mask and tropical acne by heat and moisture. "The prolonged local pressure can cause poral occlusion. In addition, there is a rise of IL-1α due to the mechanical friction," Prof. Choi explained. Each 1-degree rise in temperature results in a 10% increase in sebum production. A change in sebum composition can cause changes in the skin microbiome. Humidity leads to additional occlusion, irritation, and swelling of keratinocytes.

Two papers with recommendations for the management of maskne were published recently, both stating that maskne patients should clean their skin with a gentle antibacterial cleanser daily [4,5]. "Maintaining the skin barrier is important," Prof. Choi said. Before and after wearing the mask, the skin should be moisturised – preferably several times a day. Moisturisers with ceramide or hyaluronic acid are particularly helpful. Those with oily or acne-prone skin should try a gel moisturiser. To prevent irritation, make-up under masks should be avoided – if this is not possible, non-comedogenic products are the best possible choice. Likewise, chemical sunscreens should not be applied under the mask. Whenever possible, 15 minutes mask breaks should be done every 4 hours. In these breaks, the skin can be moisturised. A new disposable mask should be used daily, cloth masks should be washed (without bleach) with a fragrance-free hypo-allergic laundry detergent. "Try to avoid irritating topicals such as retinoids. I have increased my use of non-antibiotic, anti-inflammatory agents, such as niacinamide, probiotics, and fish oil," Prof. Choi suggested. Ivermectin cream is helpful for mask rosacea.

To avoid maskne, it is important that masks fit: they should be snug, but still comfortable. At present, there is no consensus about the best fabric, but natural materials and synthetic, bio-functional textiles are probably most convenient (see Table).

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4 Teo WL. Int J Dermatol 2021;12 Feb; early view.
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Table: Face mask material and skin interactions. Data from [4]

Fabric			Surgical mask
Natural (cotton, silk)	**Synthetic (nylon, polyester, rayon)**	**Synthetic bio-functional textiles**	**Polypropylene**
• Soft, breathable • Wicks moisture away from skin; increases fluid saturation, weight, and sticky discomfort	• Less breathable • Less able to wick moisture	• Can be treated to improve cooling coefficient • High evaporation coefficient so fabric does not get weighed down	

Pearls of the Posters

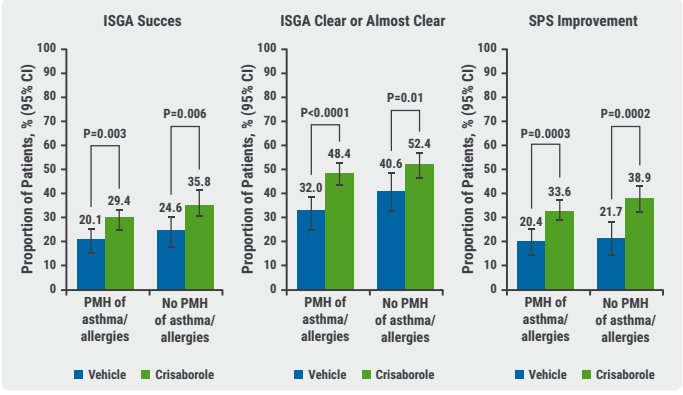
Comorbidity does not influence crisaborole efficacy in atopic dermatitis

A post-hoc analysis has demonstrated that topic treatment of atopic dermatitis with crisaborole is successful irrespective of a previous medical history with asthma or allergies.

As patients with atopic dermatitis (AD) are prone to comorbidities such as asthma, food allergies, and allergic rhinitis, the question was raised whether safety and efficacy of crisaborole ointment differs according to the presence of those comorbidities [1,2]. Hence, a post-hoc analysis of 2 randomised, double blind, vehicle-controlled trials with identical design was performed to clarify whether the phosphodiesterase-4-inhibitor ointment treatment led to different results in patients with or without allergic asthma or allergies (A/A) [2].

The phase 3 studies CrisADe CORE 1 (NCT02118766) and CrisADe CORE 2 (NCT02118792) included >1,500 patients aged ≥2 years with mild-to-moderate AD. Mean age within the crisaborole and vehicle groups ranged from 12.1 to 12.4 years. Of patients with a history of A/A, moderate disease according to Investigator's Static Global Assessment (ISGA) was present in 66.1% (vehicle) versus 63.6% (crisaborole) and in 55.5% versus 58.2%, respectively. In the group with A/A, the rate of patients with a moderate as opposed to severe status according to the Severity of Pruritus Scale (SPS) was 33.2% and 32.3% (moderate) versus 28.3 and 31.3 (severe), respectively.

Figure: Significant improvement in AD severity and pruritus with crisaborole independent of atopic comorbidity [2]



CI, confidence interval; ISGA, Investigator's Static Global Assessment; PMH, past medical history.

Results were obtained in the crisaborole and vehicle groups for ISGA clear or almost clear, SPS improvement, and ISGA success, defined as clear or almost clear (0/1) at day 29 with a ≥2-grade improvement from baseline. For the new analysis, these parameters were stratified according to the presence of a history of A/A. All comparisons demonstrated statistical significance in favour of the crisaborole treatment, independent of the atopic comorbidity status. ISGA success was achieved by 29.4% of patients with A/A (P=0.003 vs vehicle) and 35.8% in those without A/A (P=0.006 vs vehicle). ISGA of 0/1 was attained by 52.4% (P=0.01 vs vehicle) in the non-A/A group and by 48.4% (P<0.0001 vs vehicle) in the A/A group. Furthermore, improvement of pruritus was highly significant irrespective of A/A presence (see Figure).

The most common treatment-emergent adverse event was pain at the application site, occurring in 5.1% in the A/A cohort and in 3.5% of the non-A/A cohort in patients on crisaborole versus 1.7% and 0.5% in the corresponding vehicle groups. Of note, 6 patients of the A/A group suffered from serious adverse events that were deemed unrelated to treatment and 9 patients in the same group had an exacerbation of their asthma.

The authors concluded that crisaborole is safe and efficacious in AD management, regardless of comorbidity with A/A.

1 Dharmage SC, et al. Allergy. 2014;69(1):17-27.
2 Lio PA, et al. Efficacy and safety of crisaborole in patients with mild-to-moderate atopic dermatitis with and without comorbid allergies or asthma. Poster 26304, AAD VMX 2021, 23-25 April.

Convincingly low levels of infections with long-term tildrakizumab

A post-hoc analysis of data from the reSURFACE 1 and 2 trials confirmed safety with low rates of drug-related infections of tildrakizumab treatment in patients with moderate-to-severe plaque psoriasis over 5 years.

Tildrakizumab is an IL-23 inhibitor that has previously demonstrated efficacy combined with favourable safety data for 3 years in patients with moderate-to-severe plaque psoriasis in phase 3 trials [1,2]. In these randomised, controlled studies, adults were treated with tildrakizumab 100 mg or 200 mg or

placebo at weeks 0 and 4, and subsequently every 12 weeks. The reSURFACE 2 (NCT01729754) trial also included an arm with the active comparator etanercept [2]. After the base studies, patients eligible to enter the extension part of the trials were continued on tildrakizumab according to their response or previous study arm within the base trial. Hence, the extension included 506 patients of reSURFACE 1 (NCT01722331) and 730 of reSURFACE 2 [3].

As long-term safety is of major interest in chronic inflammatory diseases such as psoriasis, the new post-hoc analysis of the pivotal large reSURFACE 1 and 2 trials assessed rates of serious and drug-related infections over 5 years of drug exposure. To evaluate safety, all patients who received ≥1 dose in the extension phase of the same medication as in the base study were investigated for infections categorised as serious adverse events (SAE), as well as all infections. The analysed exposure to tildrakizumab equalled over 2,800 patient-years (PY) of 100 mg and over 2,900 PY of 200 mg. Mean age of the participants ranged from 44.2 to 47.1 in the different study arms, mean baseline Psoriasis Area Severity Index (PASI) score varied between 19.3 and 21.3.

The exposure-adjusted incidence rate for SAE infections in reSURFACE on both dosages of tildrakizumab was ≤1/100 PY, whereas exposure-adjusted incidence rate for serious drug-related infections was ≤0.3/100 PY. Most reported serious infections were diverticulitis, appendicitis, and gastroenteritis. Most frequently drug-related infections were nasopharyngitis, upper respiratory tract infections, and bronchitis; in reSURFACE 2 also rhinitis. In conclusion, no indications of new safety issues emerged and the exposure-adjusted incidence rate for drug-related infections over 5 years can be considered overall low and comparable between the 100 mg and 200 mg doses.

1. Reich, K, et al. Br J Dermatol. 2020;182(3):605–17.
2. Reich K, et al. Lancet. 2017;390:276–88.
3. Gebauer K, et al. Serious infections and infections related to study drug and leading to discontinuation through 5 years of tildrakizumab exposure in 2 phase 3 clinical trials. Poster 25363, AAD VMX 2021, 23-25 April.

IL-17 inhibitor effective in axial manifestations of psoriatic arthritis

The IL-17 inhibitor secukinumab is the first biologic that demonstrated distinct activity in axial manifestations of psoriatic arthritis. This was the result of the phase 3b MAXIMISE study.

Psoriatic arthritis (PsA) affects approximately 20–30% of patients with psoriasis and 25–70% may have axial disease [1–3]. Despite the frequency of this phenomenon, validated criteria to classify this subtype of PsA are still lacking. In addition, not much data is available on whether biologics used to treat psoriasis are effective in axial manifestations. In the case of the IL-17 inhibitor secukinumab, this question has now been answered positively in the MAXIMISE phase 3b study (NCT02721966) [2].

MAXIMISE included 498 patients with PsA according to the CASPAR criteria and axial manifestations (with a spinal pain visual analogue score ≥40/100 and Bath Ankylosing Spondylitis Activity [BASDAI] score ≥4). All patients had severe axial pain despite therapy with ≥2 non-steroidal anti-inflammatory drugs. Included patients were treated with either 150 or 300 mg secukinumab or placebo for 4 weeks and every 4 weeks thereafter. At week 12, placebo patients were re-randomised to secukinumab (300 or 150 mg) and treated until week 52. Modified nail psoriasis severity index (mNAPSI) score was an exploratory endpoint at weeks 12 and 52 measured by the least squares mean.

After a treatment period of 12 weeks, significantly more PsA patients achieved a 20% and 40% improvement, respectively, in axial manifestations, determined as Assessment of SpondyloArthritis International Society (ASAS) 20 and 40 response, a well-established tool in rheumatology for assessing axial skeletal manifestations. The primary and key secondary endpoints were met: ASAS 20 responder rates at week 12 were 62.9% (secukinumab 300 mg; P<0.0001) and 66.3% (secukinumab 150 mg; P<0.0001) versus 31.2% (placebo). At week 12, the mNAPSI score improved with secukinumab: it was reduced by -4.8 in the group receiving 300 mg secukinumab and by -3.5 in the group receiving 150 mg secukinumab versus -1.4 in the placebo group. The responder rates further improved in treatment period 2 (12–52 weeks): at week 52, ASAS 20 responder rates for secukinumab 300 mg were 81.3% and 80.1% for the lower secukinumab dose group. In addition, the mNAPSI improvement observed at week 12 increased through week 52: at this time 84% and 81% of patients achieved clearance of nail psoriasis with 300 and 150 mg secukinumab, respectively. The clinical improvement was accompanied by a significant improvement in inflammatory lesions on MRI over the 52 weeks. This included lesions in both the spine and sacroiliac joints.

1. Baraliakos X, et al. Efficacy of secukinumab in managing axial manifestations and nail psoriasis in patients with psoriatic arthritis: results from the MAXIMISE trial. Poster 25851, AAD VMX 2021, 23-25 April.
2. Reich K, et al. Br J Dermatol 2009; 160 (5):1040-7.
3. Mease PJ, et al. J Am Acad Dermatol 2013; 69 (5):729-35.