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PEER-REVIEWED CONFERENCE REPORT

DELTA 1: delgocitinib for chronic hand eczema

DELTA 1 findings showed that delgocitinib significantly improved chronic hand eczema, with more patients achieving clear or almost clear skin at week 16, as compared with a vehicle cream.

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Baricitinib as a future treatment for LP?

In a first-in-human trial, baricitinib had a response rate of >90% without raising safety, showing promise as an upcoming treatment for lichen planus (LP).

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BE HEARD I-II: bimekizumab for HS

Bimekizumab induced meaningful ameliorations, attaining a 50% hidradenitis suppurativa (HS) clinical response by half of the patients, in BE HEARD I and II.

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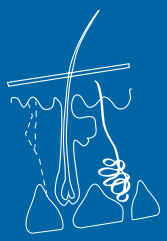

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Letter from the Editor

Dear Reader,

What started in psoriasis research has spread out to several inflammatory dermatoses: biologics and small molecules as targeted treatments. This innovation is empowering the dermatological practice with respect to the treatment of a myriad of inflammatory dermatoses.

In psoriasis and atopic dermatitis, a series of different biologics and small molecules are available. The lectures were focused on the adequate use in clinical practice of these treatments. We need to know better for which patients to prescribe which molecules and for how long.

The audience of AAD was happy to see the new options for a host of other inflammatory dermatoses besides psoriasis and atopic dermatitis. Lichen planus has not had an innovation for years, and now baricitinib was reported to be effective. Izokibep en bimekizumab proved to be effective in hidradenitis chronica suppurativa. Alopecia areata can be treated effectively with JAK inhibitors and the efficacy of deuruxolitinib was illustrated.

Delgocitinib was reported to be effective in chronic hand dermatitis. Vitiligo proved to improve on ruxolitinib and nemolizumab was effective in prurigo nodularis.

The treatment of inflammatory dermatoses is innovative. The question remains whether budget is available to implement these innovations in dermatological practice. It remains important that patients suffering from severe manifestations of these diseases all have important unmet needs. In cost-effectiveness, the realisation of substantial improvements, and substantial gains in quality of life and health will justify increments in costs. The future of inflammatory dermatoses is bright.

Best regards,
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:
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New Developments in Dermatology

Delgocitinib shows promise as topical therapy for chronic hand eczema

The DELTA 1 trial on topical treatment with the pan-JAK inhibitor delgocitinib demonstrated significant improvement in chronic hand eczema at week 16. More patients with chronic hand eczema achieved clear or almost clear skin in the Investigator's Global Assessment (IGA) with delgocitinib compared with a vehicle cream.

Chronic hand eczema (CHE) is a highly prevalent, chronic, inflammatory dermatosis that causes a high burden of disease and is often challenging to treat. Currently, approved topical treatments specific for CHE are lacking [1]. After encouraging results on topical delgocitinib for CHE in a phase 2b dose-ranging study, the development further advanced to the phase 3 DELTA 1 trial (NCT04871711) [2]. Included were adults with moderate-to-severe CHE represented by an IGA score of 3 or 4. IGA-CHE scores includes 0 (clear), 1 (almost clear, with little or no disease left), 2 (mild), 3 (moderate), and 4 (severe). As per inclusion criteria, their disease had lasted more than 3 months, and the patients had contraindications for topical steroids.

The study randomised 487 patients 2:1 to delgocitinib cream (20 mg/g; twice daily) or vehicle. The primary endpoint, which was considered a "very high bar" according to Dr Robert Bissonnette (Innovaderm Research, Canada), consisted of a 2-grade improvement with a final IGA 0/1 at week 16.

The mean age of the DELTA 1 cohort was 44 years, with a median age of 32 years at the onset of CHE. One-third of the participants had severe CHE and the median Dermatology Life Quality Index (DLQI) was 12.0, which stands for a very high impact of the disease on the quality of life.

At week 16, 19.7% of the 325 participants in the active-treatment arm reached the IGA-CHE score of clear or almost clear skin, which was significantly more than in the vehicle arm (9.9%; P=0.006). A 75% improvement in the hand eczema severity index (HECSI) was achieved by 49.2% versus 23.5% and a 90% improvement in HECSI by 29.5% versus 12.3%, for delgocitinib and vehicle cream respectively (P<0.001 for both comparisons in favour of delgocitinib). A ≥4-point improvement in DLQI was observed in 74.4% in the delgocitinib arm versus 50.0% in the vehicle arm (P<0.001).

The safety assessment revealed higher rates of adverse events in the vehicle arm (50.6% vs 45.2%) with similar proportions of serious adverse events (1.9% vs 1.8%). COVID-19 infections and nasopharyngitis were the most common adverse events with comparable rates between the treatment arms. Adverse events of special interest, such as thromboembolic events, did not occur.

In his conclusion, Dr Bissonnette emphasised that delgocitinib cream significantly improved patient-reported and clinician-reported efficacy outcomes compared with vehicle treatment in this difficult-to-treat patient population.

1. Bauer A, et al. Contact Dermatitis. 2023 Apr 10. DOI: 10.1111/cod.14303.
2. Elsner P, Agner T. J Eur Acad Dermatol Venereol. 2020; 34:13–21.
3. Bissonnette R. Efficacy and safety of delgocitinib cream in adults with moderate-to-severe chronic hand eczema: results of the phase 3 DELTA 1 trial. S025, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Vitiligo patients maintain re-pigmentation after ruxolitinib cream withdrawal

New long-term extension data from the TRuE-V studies show that the effect of treatment was sustained for more than 1 year in one-third of patients with vitiligo who withdrew from active treatment subsequent to achieving a nearly complete re-pigmentation. Moreover, re-acquiring response after about 15 weeks was possible for 68.8% of those that restarted on ruxolitinib after a relapse.

The FDA approval of ruxolitinib cream for vitiligo treatment was based on the results of the phase 3 TRuE-V1 (NCT04052425) and the TRuE-V2 (NCT04057573) trials [1]. According to Prof. John Harris (UMass Chan Medical School, MA, USA), this can be seen as a milestone in vitiligo therapy, but it is also interesting to see the long-term results [2].

In 1 cohort of the long-term extension study (NCT04530344) of TRuE-V1 and the TRuE-V2 trials, 116 patients who had achieved a re-pigmentation of at least 90% in the face area were re-randomised to either continue twice-daily ruxolitinib

cream 1.5% or withdraw from active treatment by switching to a vehicle. Prof. Harris' maintenance analysis aimed to investigate the time span to relapse of vitiligo and the duration of maintenance.

At baseline (i.e. week 52 of TRuE-V1 and TRuE-V2), participants with a facial vitiligo area scoring index (F-VASI) ≥90 had a median age of 42.0 years, more than half were women, and 31.9%, 30.2%, and 25.0% had the Fitzpatrick skin types 2, 3, and 4, respectively. Stable disease was present in 70.7%, while the rest had progressive vitiligo.

One year after withdrawal, 39.3% of the participants still had an F-VASI ≥75 response, while 28.6% experienced a relapse defined as F-VASI ≤75. The relapses happened within the first 4 months in half of the cases. Interestingly, 21.4% of the participants in the withdrawal arm and 61.8% who continued on ruxolitinib cream had a sustained F-VASI ≥90 response over 1 year, with a median duration of F-VASI ≥90 response of 195.0 days on vehicle only. Re-starting active treatment in case of relapse in the withdrawal group, resulted in 75% of participants achieving a F-VASI ≥75 scoreover a median period of 12 weeks. An F-VASI ≥90 response was regained in 68.8% of the participants after a median of 15 weeks.

In general, ruxolitinib cream was well tolerated with only mild and moderate treatment-related adverse events. No incidence of application-site acne or pruritus was reported.

"There is a population that really maintains response. If patients lose pigment, put them back on [ruxolitinib] and they will regain it in most cases," Prof. Harris concluded.

1. Rosmarin D, et al. N Engl J Med 2022;387(16):1445–1455.
2. Harris JE. Relapse and maintenance of clinical response in the randomised withdrawal arm of the TRuE-V long-term extension phase 3 study of ruxolitinib cream in vitiligo. S025, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Nemolizumab decreases lesions and itch in prurigo nodularis

The phase 3 OLYMPIA 2 trial observed an improvement in skin lesions, itch, and other symptoms of prurigo nodularis (PN) on active treatment with nemolizumab. In addition, therapy with the IL-31 inhibitor led to a significant decrease in sleep disturbances.

Patients diagnosed with the neuroimmune disease PN, suffer from intense pruritus and pruritic papulonodules that negatively influences sleep and quality of life [1]. IL-31 is believed to play a major role in the pathogenesis of PN and is seen as a driver of the associated itch-scratch cycle [2].

The OLYMPIA 2 trial (NCT04501679) was designed to assess the IL-31 Receptor α antagonist nemolizumab for its potential in treating PN [3]. After a 2:1 randomisation, the 274 adult participants with PN were treated with either subcutaneous nemolizumab at a dosage of 30 mg (bodyweight <90 kg) or 60 mg (bodyweight ≥90 kg) every 4 weeks or placebo. The co-primary endpoints were defined as an at least 4-point improvement in the Peak Pruritus Numerical Rating Scale (PP-NRS) at week 16 and the percentage of participants with Investigator's Global Assessment (IGA) success in terms of a score of 0/1 plus a ≥2-grade reduction at the same time point.

The participants had a mean age of 52.7 years, just over 60% were women, and 43% experienced severe itch on the average weekly PP-NRS. Prof. Shawn Kwatra (Johns Hopkins University School of Medicine, MD, USA) emphasised that 37.2% had a nodule count of >100.

Compared with baseline, 56.3% of participants on nemolizumab and 20.9% on placebo reached a ≥4-point PP-NRS amelioration (P<0.0001). Of note, significant differences were present as early as week 4. Furthermore, a greater proportion of IGA success was noted in the nemolizumab arm than in the placebo arm: 37.7% versus 11.0% (P<0.0001). The agent also led to a significant decrease in sleep disturbance of ≥4-point on the PP-NRS: 51.9% for nemolizumab versus 20.9% for placebo (P<0.0001).

Any kind of treatment-emergent events happened in 61.2% on nemolizumab and 52.7% on placebo, with a proportion of any serious events in 2.2% and 5.5%, respectively. Among the most common events (≥5%), headache and atopic dermatitis occurred more often in the nemolizumab group (6.6% vs 4.4% and 5.5% vs 0%). Worsening of prurigo (neurodermatits) however, happened more often in the placebo group (3.8% vs 11.0%).

All in all, the monotherapy with nemolizumab involved significant benefits in itch, lesions, and sleep impairments, while showing a consistent safety profile.

1. Williams KA, et al. Expert Rev Clin Pharmacol. 2021;14:67–77.
2. Tsoi LC, et al. J Allergy Clin Immunol. 2022;149:1329–39.
3. Kwatra S. Nemolizumab monotherapy improves itch, skin lesions, and sleep disturbance in patients with prurigo nodularis: Results from a phase 3 trial (OLYMPIA 2). S025, AAD 2023 Annual Meeting, 17-21 March, New Orleans, USA.

Lichen planus: a future indication for baricitinib?

In phase 2, baricitinib demonstrated a response rate of over 90% without raising safety concerns in a first-in-human trial. Although too early to tell, the JAK inhibitor shows promise as an upcoming treatment for lichen planus (LP).

"Interferon is critical in LP," Ms Angelina Hwang (Mayo Clinic College of Medicine, AZ, USA) explained in her introduction of the first-in-human phase 2 study (NCT05188521) of baricitinib in LP [1]. This knowledge of LP pathophysiology led to the rationale for the study to examine the JAK1/2 inhibitor that suppresses the production of IFN-γ. Currently, there is still a great unmet need for disease-specific medication in LP, as treatment options only include drugs like corticosteroids, topical calcineurin inhibitors, and phototherapy.

Ms Hwang presented the interim analysis of the open-label study, which included data on 12 patients with LP, 41.7% of whom had hypertrophic disease. The mean age of the participants was 63.6 years, most were women (91.7%), and all participants but 1 had failed previous treatments. Participants received 2 mg of baricitinib.

The primary endpoint of a Physician Global Assessment (PGA) response at week 16 was defined as reaching a PGA score of 0-3, with 0 standing for clear skin/ no evidence of disease, while a score of 4 or 5 was deemed nonresponsive. The primary endpoint was met by 90.9% of the participants. At this point, 45.5% presented a PGA of 0 (i.e. clear skin). Responses were observed as of week 1 in 37.5% of participants. At weeks 12 and 20, the response rate was 100%. Moreover, significant ameliorations were also found in all secondary endpoints that included pruritus, body surface area, and Skindex-16, the latter measuring the effects of skin disease on the quality of life. Out of 12 adverse events, only 1 case of neutropenia was deemed treatment-related, but not serious in severity. All other adverse events were not adjudicated to the baricitinib treatment.

These promising, initial results on baricitinib at a dose of 2 mg for LP could justify further evaluation of the agent in randomised-controlled trials.

1. Hwang A. Baricitinib in the treatment of cutaneous lichen planus – interim analysis. S025, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Atopic Dermatitis: State of the Art

As-needed ruxolitinib shows successful long-term symptom control in AD

The topical JAK inhibitor ruxolitinib demonstrated good control of atopic dermatitis (AD) including skin lesions, itchiness, and sleep disturbance when used as needed over a 44-week long-term extension period in adults and adolescents. In addition, the cream containing either 0.75% or 1.5% ruxolitinib was well tolerated with no new safety signals.

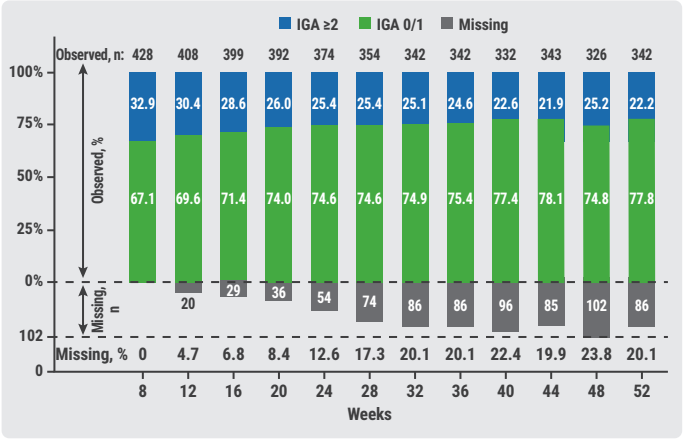
The quality of life of patients with AD can be significantly reduced by itch and sleep disturbances [1]. The parallel phase 3, randomised TRuE-AD1 (NCT03745638) and TRuE-AD2 (NCT03745651) trials assessed the long-term maintenance of disease and symptom control using ruxolitinib as needed in adolescent and adult patients with AD [2]. The studies included patients of ≥12 years with AD for at least 2 years who had an Investigator's Global Assessment (IGA) score of 2 or 3 (0, clear; 1 almost clear; 2, mild; 3, moderate; 4, severe) and 3–20% affected body surface area, excluding the scalp.

After the double-blind study phase, participants who were initially randomised to ruxolitinib (either 0.75% or 1.5% cream, twice daily) subsequently remained on their regimen for the 44-week long-term safety period (i.e. as-needed treatment). "In the long-term safety period, treatment was confined to active lesions, stopped 3 days after clearance, and resumed upon recurrence," Dr Andrew Blauvelt (Oregon Medical Research Center, OR, USA) explained. Participants were instructed to treat skin area with active AD only, but with the same regimen, twice daily. The participants did not receive concomitant or rescue treatment, and the current analysis included only those who applied ruxolitinib since day 1 (n=837).

Of the participants who applied the lower concentration ruxolitinib cream, 61.8% achieved an IGA of 0 or 1 at week 8

and 76.8% at week 52. The corresponding percentages in the participants that used the higher concentration cream were 67.1% at week 8 and 77.8% at week 52 (see Figure). Moreover, most participants (80–90%) maintained or improved their response between subsequent visits at 4-week intervals.

Figure: Change in IGA scores with as-needed treatment with 1.5% ruxolitinib cream during the long-term safety period [2]



IGA, Investigator's Global Assessment. All patients were 2/3 at baseline.

Most participants showed improvement in control of itch and sleep disturbance between consecutive assessments. Ruxolitinib was also well tolerated by the participants with no new safety signals.

The authors concluded that as-needed use of ruxolitinib cream is safe and effective to control AD in adults and adolescents.

1. Silverberg JI, et al. J Invest Dermatol. 2015;135:56–66.
2. Blauvelt A, et al. Ruxolitinib cream demonstrates maintenance of disease and symptom control with as-needed use in adults and adolescents with atopic dermatitis: pooled analysis from the long-term safety periods of two phase 3 studies. P44103, AAD 2023 Annual Meeting, 17-21 March, New Orleans, USA.

Dupilumab: a viable option for atopic hand and foot eczema

Dupilumab showed superiority over placebo as a treatment of atopic dermatitis (AD) affecting hands and feet. In the phase 3 LIBERTY-AD-HAFT trial, 40.3% of the patients achieved an Investigator's Global Assessment (IGA) of clear or almost clear (0/1) skin.

Atopic dermatitis on hands and feet can have a substantial impact on the quality of life of patients and as AD at these sites is often difficult to manage, potential therapeutic options are of particular interest [1,2]. The LIBERTY-AD-HAFT (NCT04417894) trial, presented by Prof. Eric Simpson (Oregon Health & Science University, OR, USA), included 133 patients with hand and/or foot AD, randomised to 16 weeks of treatment with dupilumab or placebo and 12 more weeks of safety follow-up [2]. All participants were at least 12 years old and presented with moderate-to-severe eczema on hands and feet (i.e. an IGA of 3 or 4).

The mean age in the dupilumab and the placebo study arms were 35.8 and 33.4 years, with 20.9% and 19.7% of the participants being under 18 years of age. Of the participants, 32.8% and 57.6% were women in the dupilumab and placebo groups, respectively. The mean duration of hand and foot AD was around 15.5 years, a baseline hand and foot IGA of 3 was present in just over 70%, and at least 70% of the participants also suffered from moderate-to-severe AD in other body locations.

At week 16, the study results were statistically significant, with a higher proportion of participants in the dupilumab arm (40.3%) meeting the primary endpoint of a hand and foot IGA 0/1, compared with 16.7% on placebo (P<0.01). The key secondary endpoint of achieving a ≥4-point improvement in the Peak Pruritus Numerical Rating Scale was also met at week 16: 52.2% versus 13.6% in favour of dupilumab (P<0.0001). Furthermore, the Hand Eczema Severity Index (HECSI) and the modified total lesion-symptom score for hand and foot and quality of life were significantly ameliorated in the dupilumab group over placebo.

Concerning safety, results were in line with dupilumab's previously observed profile. In the group of treatment-emergent adverse events that were reported from at least 5% of patients in comparison of the dupilumab to the placebo arm, nasopharyngitis (16.4% vs 10.6%) was the most common.

"Hopefully, we will get access to a drug like this soon, this will greatly improve the quality of life of our patients," Prof. Simpson concluded.

1. Thyssen JP, et al. Contact Dermatitis. 2022;86:357–78.
2. Simpson EL. Dupilumab treatment in patients with hand and foot atopic dermatitis: results from a phase 3, randomised, double-blind, placebo-controlled trial. S025, AAD Annual Meeting 2023, 17-21 March, New Orleans, USA.

Topical roflumilast beneficial in atopic dermatitis

Early itch reduction in patients with atopic dermatitis (AD) was observed as soon as 1 day after the application

of roflumilast cream. The primary endpoint of a validated Investigator's Global Assessment (vIGA) of 0/1 was achieved by around 30%.

In 2022, the FDA approved the phosphodiesterase 4 inhibitor roflumilast as a 0.3% water-based cream for the treatment of plaque psoriasis. The drug is also studied in other indications, such as seborrheic and atopic dermatitis, the latter most recently in the 2 presented phase 3 trials INTEGUMENT-I (NCT04773587) and INTEGUMENT-II (NCT04773600) [1–3].

A total of 1,337 patients were randomised to a vehicle or once-daily roflumilast 0.15% cream use over 4 weeks [1]. Participants had to be at least 6 years old and present with mild or moderate AD. Prof. Lawrence Eichenfield (University of California San Diego, CA, USA) underlined that almost 50% of the participants were paediatric patients between 5–17 years of age. Around one-third of the participants in both trials presented a vIGA of 3 at baseline, mean Eczema Area and Severity Index (EASI) scores ranged from 9.8 to 10.3, and mean Worst Itch Numeric Rating Scale (WI-NRS) values ranged from 5.9 to 6.2.

At week 4, the proportions of participants achieving the primary endpoint of vIGA of clear or almost clear skin plus a 2-grade amelioration were significantly higher in the roflumilast arms than in the vehicle arms: 32.0% versus 15.5% (P<0.0001) and 28.9% versus 12.0% (P<0.0001) in INTEGEMUNT-I and INTEGEMUNT-II, respectively. Also, the EASI75 results were in favour of roflumilast cream (43.2% vs 22.0% for INTEGUMENT-I and 42.0% vs 19.7% for INTEGUMENT-II), with a significance level of P<0.0001 for both trials.

Since itch is an important symptom of AD, reaching a ≥4-point WI-NRS reduction was also evaluated as a secondary endpoint: in INTEGEMUNT-I, the ratios were 33.6% versus 20.7% at week 4 (P=0.0089) and in INTEGEMUNT-II were 30.2% versus 12.4% (P=0.0014) for roflumilast and vehicle, respectively. Prof. Eichenfield stressed that an itch improvement could be noted within 24 hours after the first application of roflumilast.

The most common treatment-emergent adverse effects were headache, nausea, application site pain, and nasopharyngitis, but none of these events occurred at a rate above 3.5% in the roflumilast groups. Thus, the investigators adjudicated an overall favourable safety and tolerability profile to the active treatment.

1. Eichenfield L. Efficacy and safety of roflumilast cream 0.15% in adults and children aged ≥6 with mild to moderate atopic dermatitis in two phase 3 trials (INTEGUMENT-1 and INTEGUMENT-2). S025, AAD Annual Meeting 2023, 17–21 March, New Orleans, USA.
2. Thurston Jr AW, et al. Am J Clin Dermatol. 2023;24:315–24.
3. Jackson JM, et al. J Am Acad Dermatol. 2022;S0190-9622:03307–2.

IL-22 receptor blocker reduces itch and skin lesions in AD

IL-22 might be a novel therapeutic target in the therapy of moderate-to-severe atopic dermatitis (AD) as it has a profound effect on multiple inflammatory pathways in AD. In a first phase 2a study in patients with moderate-to-severe AD, the investigative IL-22 receptor blocker LEO138559 showed high efficacy and was well tolerated.

Blockade of IL-22 has shown to be associated with a significant downregulation of multiple immune pathways, such as Th1/CXCL9 [1]. The expression of this proinflammatory cytokine is increased and thought to contribute to epidermal hyperplasia and barrier defects in patients with AD. Prof. Diamant Thaçi (University of Lübeck, Germany) presented the results of a phase 2a, randomised, double-blind, placebo-controlled, proof-of-concept trial (NCT04922021) to assess the efficacy and safety of LEO138559, a monoclonal antibody that specifically targets the IL-22 receptor, blocking signalling of IL-22 and potentially also IL-20 and IL-24 [2]. Included were 58 patients, randomised 1:1 to receive the agent or placebo every 2 weeks for 16 weeks, followed by a 16-week safety follow-up.

At week 16, the Eczema Area and Severity Index (EASI) change from baseline, the primary study endpoint, was -15.3 in the participants treated with LEO138559, a 65.4% improvement compared with -3.5 in the placebo group (P=0.003). "The agent really works fast," Prof. Thaçi said. In addition, the antibody was superior regarding all secondary endpoints, namely EASI75, EASI90, and EASI100 responses and in the Investigator's Global Assessment scale. LEO138559 also had a pronounced antipruritic effect: 20% of the participants that got the active ingredient achieved a reduction in a numerical rating scale of ≥4 compared with 7 in the placebo group (P=0.14).

The new antibody showed good tolerability with no serious adverse events and only 1 case of conjunctivitis.

1. Brunner PM, et al. J Allergy Clin Immunol 2019;143:142–54.
2. Thaçi, D. Efficacy and safety of IL-22R inhibition in patients with moderate-to-severe atopic dermatitis: results from a Phase 2a monotherapy trial. S042, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Psoriasis: New Developments

Switching to risankizumab successful in IL-17 inhibitor non-responders

In daily practice, many patients are switched from one biologic to another with no washout period. The aIMM study demonstrated that switching patients to risankizumab for difficult-to-treat psoriasis is both safe and effective.

With more and more biologics entering the therapeutic arena, it is important to know the consequences of switching between biologics. As Prof. Richard Warren (University of Manchester, UK) pointed out, data from the phase 3 aIMM study (NCT04102007) "gives us a very clear definition of suboptimal response and the very clear benefit of switching to risankizumab, offering further scientific proof when considering treatment options for patients".

In the open, single-arm study, all included patients (n=252) had to be on an IL-17 blocker (i.e. secukinumab or ixekizumab) for at least 6 months and show a suboptimal response (defined as static Physicians' Global Assessment [sPGA] 2/3 and body surface area affected 3% to <10%) on treatment. They were then treated with 150 mg risankizumab at weeks 0, 4, and every 12 weeks through week 40 without a washout period. "That reflects reasonably what we do in clinical practice," Prof. Warren commented on the study design.

The primary study endpoint was the percentage of participants achieving a PGA 0/1 (i.e. clear or almost clear skin) at week 16 after switching. In addition, the percentage of participants achieving PGA 0, a Dermatology Life Quality Index of 0 (i.e quality of life no longer impaired by the disease), and Psoriasis Symptom Scale (PSS) scores were assessed at week 16 and 52 as secondary endpoints. "The mean disease duration was 20.8 years; this is a tough-to-treat population," Prof. Warren said.

At week 16, 52% of the participants treated with risankizumab achieved the primary endpoint (sPGA 0/1). Moreover, participants demonstrated a numerical improvement in all endpoints between week 16 and week 52. "Between weeks 16 and 52, there is an accrual of each outcome," Prof. Warren said. An sPGA of 0/1 was achieved by 63% of the participants and 46% achieved an Dermatology Life Quality Index (DLQI) scores of 0/1 (i.e. no effect on patient's life). A PSS of 0 was achieved by 27.4% of participants at this time; a "hard-to-meet endpoint," as Prof. Warren put it. No new safety signals were observed in this analysis.

1. Warren R. Efficacy and safety after 52 weeks in psoriasis patients switching to risankizumab after suboptimal response to secukinumab or ixekizumab. S025, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Novel, selective TYK2 inhibitor shows promise for psoriasis

A novel, highly-selective, allosteric tyrosine kinase 2 (TYK2) inhibitor showed remarkable efficacy in patients with psoriasis for an oral agent. On the highest dose of NDI-034858, almost one-third of patients achieved complete skin clearance. The safety profile of this 'new kid on the block' is consistent with experiences from previous trials with TYK2 inhibitors.

Prof. April Armstrong (Keck School of Medicine of University of California, LA, USA) pointed out that TYK2, an essential component in the JAK/STAT signalling pathway, is an important target in psoriasis as it is central to mediating some of the key pathogenic signals that may be increased in patients with psoriasis [1]. The agent NDI-034858 is a highly selective, oral, allosteric inhibitor of TYK2. By selectively inhibiting TYK2, receptor-mediated activation and downstream signal transduction of immune-related cytokines, like IL-6, IL-10, IL-12 and type I interferon, can be prevented.

At this year's AAD meeting, the results of the phase 2b, randomised, double-blind, placebo-controlled study (NCT04999839) were presented. The 259 participants with moderate-to-severe psoriasis were randomly assigned to receive 1 of 4 doses of this agent or placebo. The primary endpoint was the percentage of patients who achieved a 75% improvement in the Psoriasis Area and Severity Index (PASI) score at week 12.

At this time, a significantly greater proportion of patients achieved PASI75 at doses ≥5 mg (44%, 68%, and 67% with

5 mg, 15 mg, and 30 mg, respectively) versus placebo (6%; P<0.001 for each comparison). "What we learn from this is that 15 mg and 30 mg were superior to 5 mg, and almost 7 out of 10 achieved PASI75 by week 12," Prof. Armstrong said. Moreover, 46% of patients achieved PASI90 with the higher doses, which was assessed as a secondary endpoint. Almost one-third of patients achieved PASI100 with the highest dose; "an impressive result for an oral agent," as Prof. Armstrong pointed out.

Adverse event frequency was 53–62% with no clear dose dependence in the active arms and 44% in the placebo arm. COVID-19 infection was the most frequent adverse event as the study was performed during the pandemic. One patient experienced 2 serious adverse events considered unrelated to treatment. Additionally, participants presented with acne and folliculitis of the truncal area and diarrhoea. Mean lab values and changes from baseline did not reveal adverse trends in cell counts; however, creatine kinase showed some variability in the high doses. These promising results support further studies of the TYK2 inhibitor in psoriasis.

1. Armstrong A. Efficacy and safety results from the randomized, double-blind, placebo-controlled phase 2b trial of TYK2 inhibitor NDI-034858 in moderate-to-severe psoriasis. S025, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Hidradenitis Suppurativa: What You Need to Know

Izokibep shows remarkably high grades of clinical response in HS

Hidradenitis suppurativa (HS) treatment with the antibody mimetic izokibep induced exceptionally high HS clinical response (HiSCR) at week 12. More than 70% of participants reached a 50% reduction in HiSCR (HiSCR50) and 33% achieved a 100% reduction in HiSCR (HiSCR100).

As Dr Kim Papp (Probity Medical Research, Canada) emphasised, drug exposure in HS is lower compared with other inflammatory conditions, such as psoriasis [1]. Therefore, the novel, selective inhibitor of IL-17A izokibep has been designed to achieve enhanced tissue penetration with the potential to achieve higher drug concentrations. Dr Papp presented the single-arm part A of a phase 2b/3 trial (NCT05355805) that included 30 patients with moderate-to-severe HS with Hurley Stage II and III. Treatment consisted of 160 mg of izokibep dosed subcutaneously every weekly in patients with HS lesions in ≥2 separate anatomic areas and ≥3 abscesses or nodules. The randomised clinical part B of the study with 150 patients is still ongoing.

The participants had a mean age of 38 years, and 70% were women. They had an HS diagnosis for a mean of 12.8 years and one-third of patients had Hurley stage 3. At week 12, HiSCR50 (i.e. a ≥50% reduction from baseline) was present in 71% of the participants. HiSCR75 and HiSCR90 were observed in 57% and 38% of the participants, respectively.

The safety results did not see cases of candidiasis up to week 12, and the most common adverse events were injection site reactions. The profile of izokibep corresponded to what has already been recognised for IL-17A inhibitors.

"One-third achieved HiSCR100. That is something we have never seen before," Prof. Papp underlined. An efficacy this high supports further development. Hence, a second phase 3 study has been fast-tracked.

1. Papp K. Izokibep, a novel IL-17A inhibitor, demonstrates HiSCR100 responses in moderate-to-severe hidradenitis suppurativa: open-label part A results of a phase 2b/3 study. S025, AAD 2023 Annual Meeting, 17-21 March, New Orleans, USA.

Bimekizumab could be the new up-and-comer for HS treatment

Therapy of hidradenitis suppurativa (HS) with bimekizumab entailed meaningful ameliorations for patients in the BE HEARD I and II trials. The treatment goal of a 50% hidradenitis suppurativa clinical response (HiSCR50) was attained by about half of the participants.

As IL-17A and IL-17F play an important role in various immune-mediated inflammatory diseases including HS, the principle of dual inhibition of both cytokines appeared promising to increase response rates in HS [1,2]. The pivotal, phase 3 BE HEARD I trial (NCT04242446) and BE HEARD II trial (NCT04242498) included a total of 1,014 patients with moderate-to-severe HS with at least 5 lesions and ≤20 draining tunnels [3]. Concomitant antibiotics were allowed and patients receiving antibiotics were classified as non-responders. The study treatment varied among the 4 study arms of the 2 studies, with an initial period up to week 16, and subsequent maintenance part up to week 48.

Group 1 received 320 mg of bimekizumab every 2 weeks over both study periods (Q2W/Q2W). Group 2 started with bimekizumab at 320 mg bi-weekly and switched to every 4 weeks after week 16 (Q2W/Q4W). Group 3 was kept on an every 4 weeks dose of bimekizumab 320 mg (Q4W/Q4W) from start to week 48. Group 4 began with a placebo until week 16 and continued on 320 mg of bimekizumab every second week (PCO/Q2W). The primary endpoint was the HiSCR50 response at week 16.

Baseline measures in BE HEARD I and BE HEARD II included mean age of 36.7 and 36.6 years, 63.0% and 50.7% were women, mean duration of HS of 9 and 7 years, Hurley stage 3 in 49.7% and 38.9%, and previous biologic medication in 25% and 13.2% of participants.

At the primary endpoint, in BE HEARD I a HiSCR50 was reached in 45.3% of participants in Q4W (P=0.03 vs placebo), 47.8% in Q2W (P=0.006 vs placebo), and 28.7% in the placebo group (see Table). The corresponding results from BE HEARD II were 53.8% (P<0.01), 52.0% (P<0.01), and 32.2%, respectively. As can be expected, the rates for achieving HiSCR75 at week 16 were overall lower. In BE HEARD II, the rates were 33.7% and 35.7% in the 2 bimekizumab arms versus 15.6% in the placebo arm (P<0.01 for both comparisons). During the maintenance period, the responses were overall sustained with a HiSCR75 in 59.8% (PCO/Q2W), 53.9% (Q4W/Q4W), 48.8% (Q2W/Q4W), and 47.3% (Q2W/Q2W) in BE HEARD 2 at week 48. The participants in the placebo group also demonstrated clinical response within the range of the other treatment arms.

Table: Results from BE HEARD I and BE HEARD II

	BE HEARD I		BE HEARD II			
	HiSCR50	P versus placebo	HiSCR50	P versus placebo	HiSCR75	P versus placebo
Q4W	45.3%	0.030	53.8%	<0.01	33.7%	<0.01
Q2W	47.8%	0.006	52.0%	<0.01	35.7%	<0.01
Placebo	28.7%		32.2%		15.6%	

"In particular, the HiSCR results we achieved in the BE HEARD II trial are a huge milestone for our patients," Prof. Alexa Kimball (Harvard Medical School, MA, USA) underlined in her conclusion.

1. Glatt S, et al. JAMA Dermatol. 2021;157:1279–88.
2. Fletcher JM, et al. Clin & Exp Immunol 2020;201:121–34.
3. Kimball A. Bimekizumab in patients with moderate-to-severe hidradenitis suppurativa: 48-week efficacy and safety from BE HEARD I & II, two phase 3, randomized, double-blind, placebo controlled, multicentre studies. S042, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Pearls of the Posters

Biologics in psoriasis: can they prevent joint involvement?

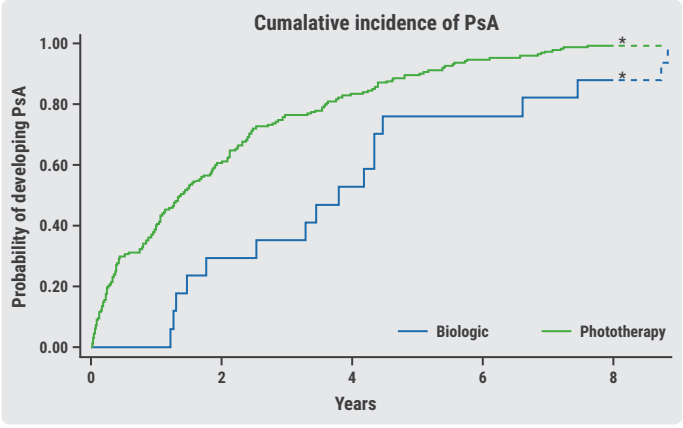
Psoriatic arthritis (PsA) occurs at lower rates in patients with psoriasis receiving biologics than in patients receiving phototherapy. This was demonstrated with PsA incidence rates of 24.6 versus 50.0 per 1,000 person-years in a retrospective cohort study.

As the diagnosis of psoriasis often precedes the incidence of PsA, the potential of psoriasis treatments in delaying or preventing PsA was at the centre of the research by Ms Kathleen Miao (Keck School of Medicine of USC, CA, USA) and her colleagues [1,2]. Their retrospective cohort study strove to explore whether treatment with biologics would influence the incidence of PsA in patients with moderate-to-severe psoriasis compared with those receiving phototherapy [1]. The researchers analysed data from 4,695 patients with psoriasis from Optum's de-identified Clinformatics® Data Mart Database between 2007 and 2021. All patients included in the study cohort received phototherapy as an index

treatment for psoriasis; 461 later switched to biologics. The incidence of PsA after 10 years was defined as an outcome measure.

At diagnosis, the patients changing to biologics were younger (44.9 years) compared with the phototherapy patients (53.8 years). Over half of the cohort were women. PsA occurred at an incidence of 46.2 per 1,000 person-years in the entire group. Distinguished by treatment, this incidence changed to 50.0 per 1,000 person-years in the phototherapy arm and 24.6 per 1,000 person-years in the biologics arm (see Figure). With a difference of -25.48 cases of PsA per 1,000 person-years, this corresponded to a significantly lower incidence in the biologics group (P=0.0011). The hazard ratio of biologic versus phototherapy, identified by means of a Cox regression that adjusted for age, sex, and time on oral systemics, was 0.476 (P=0.005).

Figure: Intensive early therapy can reduce the cumulative incidence of psoriatic arthritis [1]



In their conclusion, the researchers suggest that biologics may reduce the incidence of PsA among psoriasis patients. To evaluate the protective extent of biologic treatment further, prospective and randomised-controlled trials are indicated.

1. Miao KL, et al. Do Biologics for Psoriasis Prevent the Development of Psoriatic Arthritis? A population-based study. P42744, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.
2. Mease PJ, Armstrong AW. Drugs. 2014;74:423–41.

JAK inhibitor deuruxolitinib shows encouraging hair re-growth in alopecia areata

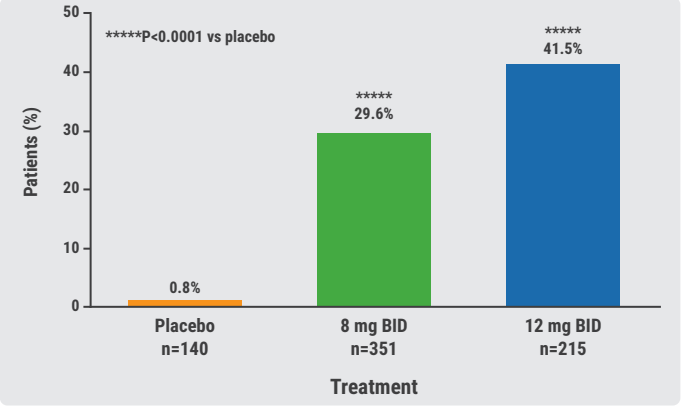
Comparing oral deuruxolitinib with placebo resulted in significantly greater rates of improvement of alopecia areata in the THRIVE-AA1 trial. The distinction in the Severity of Alopecia Tool (SALT) score reductions was observed as early as week 8.

Alopecia areata is known to exert a substantial psychosocial burden and its negative effect on the quality of life may include depression or anxiety [1,2]. Currently, an unmet need still exists for highly efficacious therapies. After favourable results in phase 2, the JAK1/2 inhibitor deuruxolitinib has now been assessed in phase 3. The results from the THRIVE-AA1 trial (NCT04518995) were presented by Dr Maryanne Senna (Lahey Hospital and Medical Center, MA, USA) [2].

The trial included 706 adult patients with a SALT score ≥50 (SALT score 0 indicates no scalp hair loss and SALD score 100 indicates complete scalp hair loss). The mean duration of the current episode at baseline was 3.7 years, the mean SALT score was 85.9, and complete or near-complete hair loss (i.e. SALT ≥95) was present in 55.8% of the participants. The participants were randomised 2:3:5 to receive a placebo, deuruxolitinib 12 mg twice daily, or deuruxolitinib 8 mg twice daily.

The primary endpoint of a SALT score of 20 or less at week 24 was met by both dosing regimens: 29.6% on 8 mg and 41.5% on 12 mg (P<0.0001 vs placebo for both comparisons; see Figure). Interestingly, the SALT score differences between the active agent (low and high group) versus placebo were significant as of week 8. The proportions of participants with a SALT score ≤10 at week 24, a secondary endpoint, were 0%, 20.8%, and 34.5% for placebo, deuruxolitinib 8 mg, and 12 mg, respectively. A 90% reduction in SALT at week 24 was achieved by 19.2% and 32.0% in the 2 active treatment arms (both P<0.0001 vs placebo).

Figure: Primary efficacy endpoint of proportion of patients achieving SALT score ≤20 at week 24 [1]



The safety evaluations of THRIVE-AA1 considered deuruxolitinib as mostly well tolerated since over 95% of treatment-emergent adverse events were mild-to-moderate [3]. For long-term safety, open-label extensions are underway.

All in all, the study authors rated the efficacy of deuruxolitinib in the treatment of moderate-to-severe AA as encouraging.

1. Lintzeri DA, et al. Dtsch Dermatol Ges. 2022;20:59–90.
2. Senna MM, et al. Efficacy of the oral JAK1/JAK2 inhibitor CTP-543 (Deuruxolitinib) in adult patients with moderate to severe alopecia areata: results from the multinational double-blind, placebo-controlled THRIVE-AA1 phase 3 trial. P41701, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.
3. King B, et al. Safety assessments in the multinational phase 3 THRIVE-AA1 trial with CTP-543 (Deuruxolitinib) in adult patients with moderate to severe alopecia areata. P42736, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.

Biomarkers predicting response of different CSU treatments in children

Assessment of mean platelet volume, tryptase, and age may help to pick the right treatment for paediatric patients with chronic spontaneous urticaria (CSU). The authors of this single-centre retrospective study emphasised that this result should be confirmed in a larger trial. Despite this limitation, the study won the second poster prize at the AAD 2023 meeting.

Until present, there are very few studies on biomarkers for CSU in children. Therefore, Mr Alex Nguyen (McGill University, Canada) aimed to better understand the role of different biomarkers in treatment response and disease resolution in children with CSU [1].

Data was obtained from 109 children from the Montreal Children's Hospital Allergy and Immunology Clinic who reported hives for at least 6 weeks from 2013 to 2022. The mean age of the children was 9 years and 55% of the study population were girls. The researchers obtained levels of thyroid stimulating hormone (TSH), anti-thyroxine peroxidase (anti-TPO), total immunoglobulin E (IgE), CD63, tryptase, eosinophils, mean platelet volume (MPV), and platelets. Diseases activity was recorded at study entry using the weekly urticaria activity score (UAS7).

Univariate and multivariate logistic regressions were compared to determine factors associated with different treatment levels, namely antihistamines at the standard dose, at 4 times the standard dose, omalizumab, and resolution of treatment.

According to the results of the univariate analysis, elevated levels of MPV were associated with use of 4 times the standard dose of antihistamines treatment level, whereas younger age was associated with disease resolution. In the multivariate logistic analysis adjusted for age, sex TSH, anti-TPO, total IgE, CD63, eosinophils, MPV, and platelets, elevated tryptase levels were associated with antihistamines use at the standard dose (OR 1.15; 95% CI 1.02–1.30) and lower tryptase levels with disease resolution (OR 0.86; 95% CI 0.78–0.96).

Although these results should be confirmed in a larger study, the authors conclude that the underlying mechanisms of tryptase may help identify paediatric patients with CSU who will respond to different treatment options.

1. Nguyen A, et al. Association of Biomarkers with Treatment and Disease Resolution of Chronic Spontaneous Urticaria in Children. P43608, AAD 2023 Annual Meeting, 17–21 March, New Orleans, USA.