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PEER-REVIEWED CONFERENCE REPORT

Ritlecitinib shows remarkable efficacy in AA

Almost 60% of patients with total hair loss achieved an 80% hair regrowth at month 24 in a subset analysis of the ALLEGRO trial.

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Chronic hand eczema: finally a specific treatment

In the DELTA 3 trial, a cream containing the pan-JAK inhibitor delgocitinib showed remarkable efficacy.

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HS: New mode-of-action with BTK inhibition

Phase 2 results show promise in efficacy and safety for a novel approach to HS treatment with remibrutinib.

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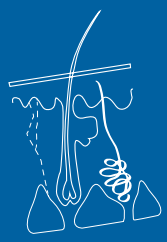

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Letter from the Editor

Dear colleagues,

The AAD 2024 in San Diego was a meeting with broad information on innovations in Dermatology. In this introduction, I highlight two major leads in dermatology innovations at AAD 2024.

JAK inhibitors have a major impact on inflammatory skin diseases. A phase 2 trial showed that upadacitinib (a JAK1 inhibitor) led to a fast improvement in repigmentation in vitiligo. Povorcitinib was superior to placebo in prurigo nodularis. ESK-001 is a new TYK2 inhibitor, which was shown to be effective in psoriasis in a phase 2 trial: more than half of the participants achieved ≥4-point improvement in itch and PASI75 was reached in 90.9% of the patients at week 28. JAK3/TEC kinase inhibitor ritlecitinib: almost 60% of patients with total hair loss achieved at least 80% regrowth of hair after 24 months. Moreover, chronic hand eczema treatment with delgocitinib (a pan JAK inhibitor) cream was effective in a phase 3 trial, and delgocitinib is a first-in-class topical pan-JAK inhibitor that targets the key mediators of chronic hand eczema. In hydradenitis suppurativa, ruxolitinib (a JAK1/2 inhibitor) cream led to significant improvement.

Another major development is the insights into pathomechanistic principles, providing new opportunities for targeted drugs. A lower hazard for all skin conditions besides psoriasis was shown in patients starting with SGLT2 inhibitors. Future clinical trials are worthwhile on SGLT2 inhibitors in patients with type 2 diabetes and concomitant inflammatory skin disease. OX40 Ligand-OX40 axis is a secondary co-stimulatory pathway important for the proliferation and survival of antigen-specific T cells. By inhibiting these, the antigen-specific memory T cells are depleted. Amlitelimab is an anti-OX40 antibody that showed a remarkable maintenance of response after treatment discontinuation in patients with atopic dermatitis: after 28 weeks of discontinuation, more than 60 % of patients maintained response. In the KNOCKOUT trial, high induction doses of the IL-23 blocker risankizumab caused a depletion of resident memory T cells for up to 36 weeks.

In a hidradenitis suppurativa phase 2 study, the BTK inhibitor remibrutinib was found to be effective. And, targeting IL-1 pathway in anti-TNF resistant hidradenitis suppurativa might be a new opportunity, as shown in a clinical trial with the IL-1α/1β antagonist lutikizumab.

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

New Developments in Dermatology

Upadacitinib: A novel treatment option for vitiligo

In a phase 2 trial, the JAK1 inhibitor upadacitinib led to a fast improvement in repigmentation in patients with non-segmental vitiligo. After 52 weeks, participants showed continuous further pigmentation in both facial and body areas.

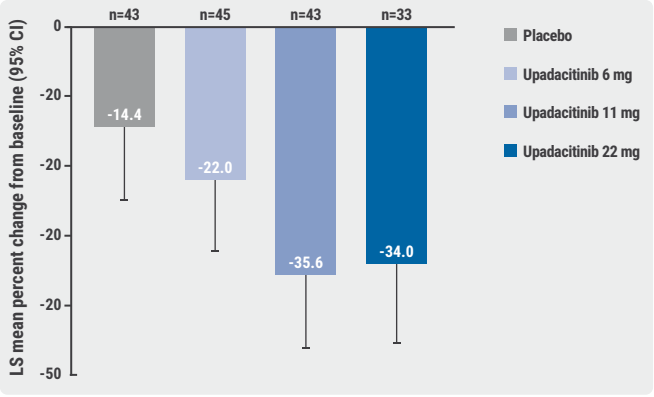
Previous research has shown that disruption of IFN-γ signalling by inhibiting the JAK/STAT pathway is an attractive therapeutic target for vitiligo [1,2]. Thus, the objective of the current phase 2 dose-ranging study (NCT04927975) was to evaluate the efficacy and safety of the JAK1 inhibitor upadacitinib for the treatment of adults with non-segmental vitiligo, a disease with only limited treatment options [3]. Prof. Thierry Passeron (Nice University Hospital, France) presented the results.

The 184 participants were randomised to placebo or upadacitinib at either 6 mg, 11 mg, or 22 mg once daily for 24 weeks. The primary endpoint was the percentage change from baseline in the Facial Vitiligo Area Scoring Index (F-VASI) at week 24. After the double-blind period at week 24, participants on placebo were switched to either 11 mg or 22 mg upadacitinib and continuously treated until week 52.

The study met its primary endpoint with a significantly greater percentage change with the 2 highest upadacitinib doses (i.e. 11 mg and 22 mg). F-VASI was reduced by -34% in the 22 mg group (P<0.05 vs placebo) and -35.6% in the 11 mg group (P<0.01 vs placebo), compared with -14.4% in the placebo group (see Figure). Significant reductions were also noted for the change in total VASI (T-VASI).

Moreover, participants treated with upadacitinib experienced continued improvement in F-VASI through week 52. At this time, participants achieved an approximately 60% to 65% reduction in F-VASI with 11 mg and 22 mg upadacitinib, respectively. Similar improvements in F-VASI were observed in participants who switched at week 24 from placebo to upadacitinib 11 mg or 22 mg. T-VASI values also improved up to week 52.

Figure: Primary endpoint of percentage change from baseline in F-VASI at week 24 (MMRM) [3]



BL, baseline; CI, confidence interval; F-VASI, Facial Vitiligo Area Scoring Index; LS, least squares; MMRM, mixed-effects model for repeated measures; PBO, placebo; UPA, upadacitinib.

The safety assessment disclosed similar rates of treatment-emergent adverse events between upadacitinib and placebo groups with the most frequently reported treatment-emergent adverse events being a COVID-19 infection, acne, headache, and nasopharyngitis.

1. Qi F, et al. Front Immunol 2021;12:790125.
2. Boniface K, et al. Front Immunol 2021;12:613056.
3. Passeron T. Efficacy and safety after 52 weeks of once-daily upadacitinib in adults with extensive non-segmental vitiligo (NSV): final results from a phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

JAK1 inhibitor meets primary endpoint in prurigo nodularis

Povorcitinib outperformed placebo in treating prurigo nodularis (PN). More than half of the participants in this phase 2 trial achieved a ≥4-point improvement in itch on the numeric rating scale (NRS4) on the highest study dose of povorcitinib.

PN is a debilitating inflammatory skin disease with severely itching lesions, pain, stinging and burning sensations, and the JAK/STAT pathway has been associated with its pathogenesis [1–3]. Thus, Prof. Martin Metz (Charité University Hospital, Germany) and colleagues set out to explore this pathway as a novel management option for PN in a phase 2 trial (NCT05061693), comparing the JAK1 inhibitor povorcitinib with placebo [1]. The 146 participants

were randomised to placebo or 1 of 3 povorcitinib regimens (i.e. 15 mg, 45 mg, and 75 mg daily).

"We see a typical population with a lot of comorbidities," Prof. Metz commented on the baseline findings. He highlighted a mean body mass index (BMI) of 31.5 kg/m2, a mean itch score of 8 on the NRS, and a much-impaired quality-of-life.

The primary endpoint was the rate of participants with itch NRS4 at week 16, which showed significant and dose-dependent superiority in the 15 mg, 45 mg, and 75 mg arms of povorcitinib compared with placebo: 36.1% (P<0.01), 44.4% (P<0.001), and 54.1% (P<0.0001), versus 8.1%. The highest dose demonstrated the fastest efficacy with a median time of 17 days to itch NRS4. Treatment success in the Investigator's Global Assessment (IGA-TS) in terms of an IGA 0/1 (i.e. clear or almost clear skin) with a ≥2-grade improvement from baseline was achieved by 13.9%, 30.6%, and 48.6% of participants on povorcitinib compared with 5.4% on placebo. Proportions of participants reaching the combination of NRS4 and IGA-TS were also higher in the povorcitinib arms with 8.3% (15 mg), 22.2% (45 mg), and 35.1% (75 mg) versus 2.7% with placebo.

Overall, the JAK inhibitor was well-tolerated. Headache was the most common treatment-emergent adverse event in 11.1% of those treated with povorcitinib. One death occurred that was deemed not treatment-related.

In his conclusion, Prof. Metz pointed to the early and meaningful impact of povorcitinib on itch, making the agent a promising potential treatment for PN.

1. Metz M. Efficacy and safety of oral povorcitinib in patients with prurigo nodularis: results from a randomized, double-blind, placebo-controlled phase 2 study. LB2, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Aggarwal P, et al. Clin Exp Dermatol. 2021;46(7):1277-1284.
3. Agrawal D, et al J Cosmet Dermatol. 2022;21(9):4009-4015.

Botanical drug solution leads to sustained hair regrowth in paediatric alopecia

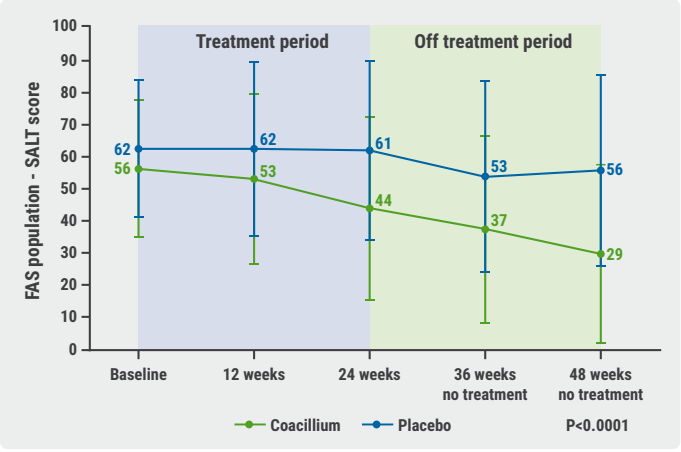
Coacillium, a solution containing plant extracts, led to sustained hair regrowth up to 24 weeks off-treatment and improved the quality-of-life of children and adolescents with alopecia areata (AA) in the phase 2/3 RAAINBOW trial.

A remaining unmet need in AA is an approved drug with a favourable benefit/risk profile for children and adolescents [1]. Recently, the randomised, double-blind, multicentre, phase 2/3 RAAINBOW trial (NCT03240627) assessed the efficacy and safety of the botanical drug solution coacillium (22.3%). RAAINBOW enrolled 62 participants aged 2–18 years with a Severity of Alopecia Tool (SALT) score of 25–50 (i.e. moderate AA) and 50–95 (i.e. severe AA). The SALT score is a weighted sum of the percentage of hair loss in the 4 quadrants of the scalp, ranging from 0 (i.e. no hair loss) to 100 (i.e. complete hair loss).

The solution met the primary endpoint with a mean change in SALT score of +22.9%, versus -8.0% in the placebo group (P<0.0001), and 26% even achieved at least a 40% relative reduction in SALT score [1]. Prof. Bianca Piraccini (University of Bologna, Italy) presented further results of the RAAINBOW study [2].

After coacillium discontinuation, SALT continued to improve from up to week 48, 24 weeks after the last application of the solution (see Figure). Of the participants treated with the botanical solution, 82% experienced hair growth after treatment discontinuation. Efficacy was positively correlated with an improvement in quality-of-life, assessed in 2 different quality-of-life questionnaires.

Figure: Continued improvement in SALT scores after coacillium discontinuation [2]



FAS, full analysis set; SALT, Severity of Alopecia Tool.

At week 48, almost half (46.7%) of the participants in the intervention arm achieved SALT scores ≤20 (compared with 9.1% in the placebo group; P=0.0031), a third of participants even gained a SALT score ≤10 (compared with 0% in the placebo group; P=0.0065). The average relative SALT change for responders to coacillium treatment was 41%.

The solution was generally well tolerated. As Prof. Piraccini emphasised in her conclusion, coacillium is the first drug to

show sustained remission off-treatment in AA. The solution is rapidly absorbed by the hair follicle and is easy to apply.

1. Blume-Peytavi U, et al. D1T01.1L, EADV Congress 2023, 11–14 October, Berlin, Germany.
2. Piraccini BM. Efficacy and safety of coacillium in children and adolescents with moderate to severe alopecia areata: a randomised, double-blind, placebo-controlled, international, phase 2-3 trial. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

SGLT2 inhibition: A possible mode-of-action for inflammatory skin diseases?

Comparing incidence rates of various inflammatory skin diseases among patients starting their type 2 diabetes treatment either on sodium-glucose cotransporter-2 (SGLT2) inhibitors or dipeptidyl peptidase-4 (DPP4) inhibitors, a population-based cohort study found a lower hazard for all skin conditions besides psoriasis in patients on SGLT2 inhibitors.

Besides their glucose-lowering and weight-lowering properties, SGLT2 inhibitors are suggested to include anti-inflammatory and immunological features that are associated with protective cardiorenal effects [1]. For MD candidate Allison Holt (UMass Chan Medical School, MA, USA) and colleagues, these properties of SGLT2 inhibitors together with existing data on links between inflammatory skin diseases and diabetes, induced an interest in a possible effect of SGLT2 inhibition on the occurrence of these conditions in diabetic patients.

Their population-based cohort study analysed 550,195 patients with type 2 diabetes who initiated treatment with SGLT2 inhibitors in the US between 2014 and 2024. Based on a propensity score, these were matched to the same number of patients starting DPP4 inhibitors. Besides matching for demographics and socioeconomics, the covariates included comorbidities such as cardiovascular and renal disease, laboratory data such as mean HbA1c, and knowledge about medication, smoking, and healthcare utilisation. The participants were followed up for new onsets of inflammatory skin diseases like psoriasis, seborrheic dermatitis, lichen planus, acne vulgaris, alopecia areata, and vitiligo.

The results revealed differences in the incidence of the diseases between the SGLT2 inhibitors and the DPP4 inhibitors users. Incidence rates of alopecia areata, vitiligo, acne vulgaris, and seborrheic dermatitis were decreased in the cohort on SGLT2 inhibitors with incidence rates per 1,000 person-years of 0.09, 0.09, 0.56, and 1.24 compared with 0.17, 0.15, 0.83, and 1.8 in the DPP4 inhibitors cohort.

Using a Cox proportional hazard model, the corresponding hazard ratios for the likelihood of a new onset of these conditions were calculated: alopecia areata 0.7 (95% CI 0.60–0.82), vitiligo 0.79 (95% CI 0.68–0.92), acne vulgaris 0.87 (95% CI 0.81–0.93), and seborrheic dermatitis 0.89 (95% CI 0.86–0.94). In contrast, a hazard ratio of 1.08 (95%CI 1.03–1.13) stood for a somewhat increased risk of psoriasis on SGLT2 inhibitors. “This is consistent with an earlier study,” explained Ms Holt, referring to a population-based Taiwanese investigation [1,2].

Bearing in mind that these findings stemmed from medical record data, the researchers believe that future clinical trials are warranted to evaluate the safety and efficacy of SGLT2 inhibitors in patients with type 2 diabetes and concomitant inflammatory skin disease [1].

1. Holt A. Inflammatory skin disease following the use of SGLT2 inhibitors for diabetes mellitus. LB2, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Ma SH, et al. Clin Exp Dermatol. 2022;47(12):2242-2250.

Promising first results of novel topical treatment for congenital ichthyosis

A novel 0.05% isotretinoin ointment specifically developed for congenital ichthyosis showed encouraging preliminary efficacy results with a clinically relevant reduction in scaling and fissures. Importantly, there is almost no systemic absorption compared with oral isotretinoin.

A high medical need exists for treatment options for congenital ichthyosis, as there are currently no approved therapies [1]. Patients with moderate-to-severe recessive X-linked (RXLI) or autosomal recessive congenital ichthyosis subtypes often suffer from considerable hyperkeratosis, skin scaling, dryness, and erythroderma. At present, management of the disease is typically limited to the use of emollients and keratolytics. For severe congenital ichthyosis, systemic retinoids are recommended. However, chronic use of systemic retinoids is associated with considerable toxicity such as skeletal changes and teratogenicity.

TMB-001 is a novel topical 0.05% isotretinoin formulation believed to reduce hyperkeratinisation, comedogenesis, and inflammation. It was developed specifically to treat congenital ichthyosis and uses a patented polyethylene glycol technology to provide hydration, lubrification, and scaling reduction at affected areas while exhibiting a more

favourable safety profile compared with systemic retinoids. The agent showed efficacy in previous phase 2 trials [2,3].

The ongoing ASCEND trial (NCT05295732) is the first phase 3 study of TMB-001 for patients with congenital ichthyosis ≥6 years of age. All 110 participants had an affected body surface area of 75–90% and an Investigator's Global Assessment (IGA) score of ≥3. The primary endpoint of the ASCEND trial is an improvement in a combined IGA score (i.e. scaling and fissures) of ≥2 points from baseline.

Dr Christopher Bunick (Yale School of Medicine, CT, USA) presented the treatment results of the first 17 participants (adolescents and adults). "In our patients, large body areas were affected, and we wanted to see whether we could apply the agent safely," Dr Bunick explained.

According to this preliminary data, TMB-001 led to statistically and clinically significant improvements in IGA scaling, fissuring, and combined scores at week 12. At this time, mean total IGA scaling/fissuring decreased from 3.2 to 1.6 (P=0.0001). A ≥1-point IGA change from baseline was achieved by 14 out of 17 participants (82%), 10 out of 17 participants (59%) achieved a ≥2-point improvement, and 10 out of 17 participants (59%) achieved clear or almost clear skin (IGA 0/1).

Eleven participants experienced at least 1 of a total of 35 adverse events. However, 24 of 35 events were local skin reactions, with a mild-to-moderate intensity, that resolved over 12 weeks. No serious adverse events or other treatment-related events were reported. The pharmacokinetic assessment revealed only minimal systemic absorption.

These preliminary results from subjects with RXLI or autosomal recessive congenital ichthyosis treated with the novel isotretinoin ointment demonstrate promising efficacy, with more than half of the participants achieving clear or almost clear skin. "Almost 60% reach clear or almost clear skin. This can be life-changing for these patients who up to now had little hope," Prof. Bunick concluded.

1. Bunick Ch. Efficacy, Safety and Pharmacokinetics of First 17 Adult and Adolescent Subjects in Maximal Use Portion of Vehicle Controlled ASCEND Trial of Polyethylene Glycol (iPEG™)-Based Topical Isotretinoin 0.05%. LB2, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Paller AS, et al. J Am Acad Dermatol 2022;87:1189-91.
3. Teng JMC et al. J Am Acad Dermatol 2022;87:1455-8.

Ritlecitinib also effective in patients with total hair loss

Almost 60% of patients with total hair loss achieved at least 80% regrowth of hair after 24 months of ritlecitinib treatment. Notably, sustained responses in this subgroup of patients were comparable with those in the overall ALLEGRO trial.

Treatment success for alopecia areata (AA) is higher in patients treated early (i.e. as long as hair is still present) [1]. This makes alopecia totalis (AT) and alopecia universalis (AU) difficult-to-treat subtypes of AA. In a subset analysis, Dr Melissa Piliang (Cleveland Clinic, OH, USA) and colleagues assessed the efficacy of ritlecitinib treatment up to 24 months in patients with AT/AU who took part in the ALLEGRO phase 2b study (NCT03732807) and the ongoing, long-term phase 3 ALLEGRO-LT study (NCT04006457) [2].

In the recent ALLEGRO trial, the JAK3/TEC kinase inhibitor ritlecitinib demonstrated efficacy and acceptable safety in patients with AA aged ≥12 years [3]. At week 24, 31% of participants treated with the highest ritlecitinib dose achieved a Severity of Alopecia Tool (SALT) score of 20 or less. In the new analysis, SALT scores were evaluated on an observed or last-observation-carried-forward (LOCF) basis [2]. AT/AU was defined as patients with a SALT score of 100 at baseline.

At month 24, 59.6% of the participants with AT/AU at baseline achieved a SALT score ≤20 in the as-observed analysis (36.1% in the LOCF analysis). Thus, sustained responses in the subgroup of participants with AT/AU were similar to those in the overall trial. Both in the AT/AU and the non-AT/AU population, responses increased over time and were maintained for as long as participants remained on therapy. A SALT score ≤10 was reached by 53.2% of the AT/AU population in the as-observed analysis (31.4% in the LOCF analysis).

Dr Piliang emphasised that a SALT score <10 means that patients have 90% hair regrowth. "A substantial proportion of patients with AT/AU are achieving 90% or more of hair regrowth, so really an excellent response," she concluded.

1. King B. S022, 2024 AAD Annual Meeting, 8-12 March, San Diego, USA.
2. Piliang M. Efficacy of ritlecitinib up to months 24 in patients with alopecia totalis (AT) and alopecia universalis (AU) from the ALLEGRO phase 2b/3 and long-term phase 3 clinical studies. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
3. King B, et al. Lancet 2023;401: 1518-29.

Dr Andrew Blauvelt
MD, MBA

Meet the Trialist:
Revolutionising psoriasis treatment with high-dose therapy

Medicom interviewed Dr Andrew Blauvelt about the phase 2 KNOCKOUT trial (NCT05283135), which he presented as a late-breaking abstract at the American Academy of Dermatology (AAD) 2024 Annual Meeting in San Diego, CA, USA [1]. The 52-week results showed that a high induction dose of risankizumab is associated with significantly improved skin area severity among patients with moderate-to-severe plaque psoriasis. The primary outcome was long-term reduction in tissue-resident memory T 17 ($T_{RM}17$) cells among patients with plaque psoriasis.

Could you introduce yourself and share your work and research focus?

"My pleasure. I'm Dr Andrew Blauvelt, a dermatologist based in Portland, Oregon. My career has traversed three phases: starting as a physician-scientist at the NIH for 12 years, then as a professor of dermatology and immunology at Oregon Health and Science University, and for the past 13 years, I've been heavily involved in clinical trials at the Oregon Medical Research Center, focusing primarily on clinical trial work."

You've recently discussed the KNOCKOUT study in psoriasis. Can you elaborate on its primary objectives and the findings?

"The KNOCKOUT study was initially an investigator-initiated grant, born from my idea and protocol, and later funded by AbbVie and the National Psoriasis Foundation. It turned into a collaborative study focusing on high induction doses of risankizumab for moderate-to-severe plaque psoriasis. Our main interest was in observing the effects of high doses (600 mg, as opposed to the standard 150 mg dose), inspired by a phase 1 study where significant and prolonged skin clearance was noted. This study aimed to explore the potential of high induction dosing to 'knockout' psoriasis, specifically targeting the IL-23 pathway and its effect on resident memory $T_{RM}17$ cells believed to be responsible for psoriasis recurrences."

Were there any innovative endpoints in this trial?

"Yes, our primary endpoint was quite novel. We looked at the loss of resident memory T cells at week 52, aiming to correlate long-term remissions with the reduction of these cells. We hypothesised that higher doses would result in a greater loss of these cells and thus longer remission periods."

What were the major findings?

"The study revealed 3 key outcomes: firstly, the high efficacy of the 600 mg induction dose in significantly reducing resident memory T cells at week 52. Secondly, we observed remarkable short-term clearance rates, with 83% of patients achieving complete clearance at week 28. Lastly, we noted long-term remission in a significant portion of patients, with 43% remaining clear at week 52, showcasing the potential of this dosing strategy for prolonged disease management."

Did the study address safety concerns with such high doses?

"Indeed, safety was a crucial aspect of our study. IL-23 inhibitors, including risankizumab, are known for their favourable safety profiles. Our study's safety data mirrored this, with no significant side effects observed beyond what's expected in the general population, affirming the safety of high induction dosing."

What are the implications for psoriasis treatment?

"The implications are substantial. This approach, by significantly increasing the clearance rate with a pre-existing drug through altered dosing and scheduling, hints at a shift towards less frequent, more effective treatments. This method has garnered significant interest from patients and could disrupt the current treatment paradigm, offering a novel, highly effective treatment strategy for psoriasis."

How do you see this treatment model moving forward?

"It's a bit in flux. The likelihood may be greater for a new entrant in the pharmaceutical industry to adopt high induction dosing for an IL-23 inhibitor from the outset, rather than established players revising the dosing strategies of their current drugs. There's a buzz about advancing this approach, so it's an exciting time for psoriasis treatment."

1. Blauvelt A, et al. High Induction Dosing of Risankizumab in Patients with Moderate-to-Severe Plaque Psoriasis: 52 Week Results From the Phase 2 KNOCKOUT Study. LB1, AAD 2024 Annual Meeting, 8–12 March, San Diego, USA.

Atopic Dermatitis and Eczema in 2024

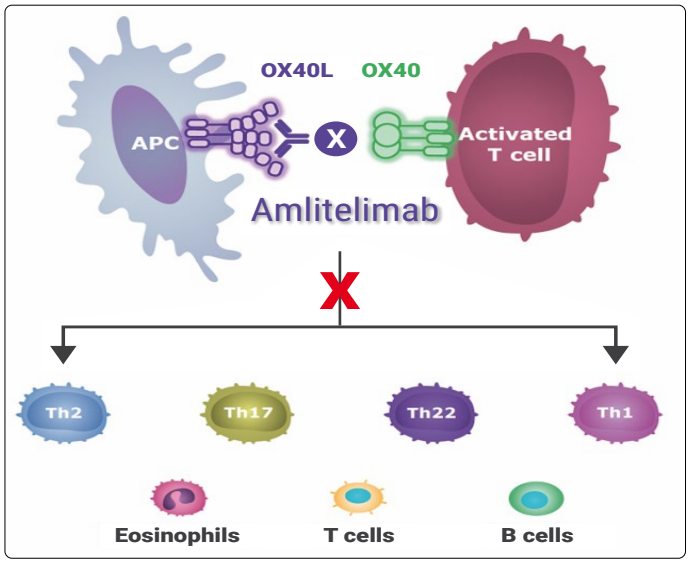
Amlitelimab leads to a high response 28 weeks after treatment discontinuation

The investigative anti-OX40 antibody amlitelimab showed remarkable maintenance of response after treatment discontinuation in patients with atopic dermatitis (AD) enrolled in the STREAM-AD study. Even 28 weeks after amlitelimab discontinuation, more than 60% of STREAM-AD participants maintained clinical response. This observation might implicate an extension of the treatment interval.

"The OX40 ligand signalling pathway is important for the proliferation and survival of antigen-specific T cells. If I inhibit these, I also block the antigen-specific memory T cells, which repeatedly fuel the immune response, especially in inflamed tissue, i.e. the skin. This approach could promise to achieve long-lasting effects in AD therapy," explained Prof. Stephan Weidinger (Christian-Albrechts-University Kiel, Germany) [1].

Amlitelimab is a fully human anti-OX40 antibody that inhibits T cell-dependent inflammation without T cell depletion (see Figure) [2,3]. In the phase 2b STREAM-AD study (NCT05131477), the agent showed clinically meaningful improvements in patients with AD at week 24, being given every 4 weeks across 4 different doses [4].

Figure: OX40 Ligand-OX40 axis: a secondary co-stimulatory pathway. Adapted from [2,3]



The second part of STREAM-AD explored the maintenance of clinical response over 28 weeks (from week 24 to week 52) with continued amlitelimab treatment or amlitelimab withdrawal (placebo) in clinical responders of study part 1, defined as participants achieving Eczema Area and Severity Index improvement by 75% (EASI75) and/or clear or almost clear skin in the Investigator's Global Assessment (IGA 0/1) at week 24.

Of the 390 participants enrolled in part 1 of STREAM-AD, 190 entered part 2. Participants were re-randomised to withdraw from amlitelimab (n=130), continue amlitelimab on their pre-week 24 doses (n=44) every 4 weeks, or continue placebo (n=16), and were followed to week 52 for efficacy evaluations.

At week 52, a high percentage of clinical responders was seen in all groups, both on and off amlitelimab. In the non-responder-imputation analysis, 70.5% of the participants that continued their original amlitelimab dose and 60.6% of the pooled placebo participants still achieved IGA 0/1 and/or EASI75 response. The corresponding overall percentages, regardless of treatment discontinuation and rescue medication use, were 81.8% versus 74.6%, respectively. Those continuing treatment had numerically higher maintenance response rates.

As Prof. Weidinger pointed out, the high efficacy observed across the broad range of amlitelimab doses given every 4 weeks supports an extended dosing interval of amlitelimab (e.g. every 12 weeks). Furthermore, AD-related biomarkers remained suppressed for over 28 weeks; ≥95% of the drug was eliminated from serum for the last 8 weeks. The overall incidence of treatment-emergent adverse events was similar in part 1 and part 2 of the STREAM-AD study.

1. Weidinger S, et al. Efficacy and safety of amlitelimab (an OX40 ligand antibody) in patients with moderate-to-severe atopic dermatitis: 52-week results from a Phase 2b trial (STREAM-AD). LB2, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Fu Y, et al. Acta Pharm Sin B 2020;10:414-33.
3. Haddad EB, et al. Dermatol Ther (Heidelb) 2022;12:1501-33.
4. Weidinger St, et al. Br J Dermatol 2023;189:531-9.

Delgocitinib cream: A promising treatment option for chronic hand eczema

A long-term extension of chronic hand eczema treatment with delgocitinib cream led to favourable safety and efficacy findings in the phase 3 DELTA 3 trial. New

safety signals were not observed and, over time, more patients achieved clear or almost clear (0/1) skin in the Investigator's Global Assessment of chronic hand eczema (IGA-CHE).

"Delgocitinib is a first-in-class topical pan-JAK inhibitor that targets the key mediators of chronic hand eczema pathogenesis," Prof. Melinda Gooderham (Queens University, Canada) introduced the investigated study drug [1]. Following positive results in the phase 3 trials DELTA 1 (NCT04871711) and 2 (NCT04872101), DELTA 3 (NCT04949841) was designed as a long-term, open-label treatment assessment of topical delgocitinib on an as-needed regimen for chronic hand eczema. After completing week 16 in 1 of the parent trials, 801 participants rolled over to DELTA 3. Within the 36-week treatment period, delgocitinib cream 20 mg/g was used twice daily until an IGA-CHE of 0/1 indicated disease control. Subsequently, participants stayed off treatment unless the IGA-CHE increased to ≥2, in which case delgocitinib was re-started. Baseline characteristics in DELTA 3 included a mean age of 45 years, 63.9% women, 43.1% with mild and 30.3% with moderate disease. The primary objective of DELTA 3 was safety.

The analysis of treatment-emergent adverse events (TEAE) was in line with previous findings in the parent trials. "There were no safety concerns over this prolonged 36-week period," underlined Prof. Gooderham. She also pointed out that the most frequent TEAE was COVID-19 (16.7% of the total cohort) as the study was performed during the pandemic. The second most frequent TEAE was nasopharyngitis in 16.0%.

The long-term, as-needed therapy regimen resulted in sustained improvement with, for example, the IGA-CHE 0/1 rate rising from 24.6% at baseline to 30.0% at week 36. Further, at week 36, a 4-point decrease in Hand Eczema Symptom Diary (HESD) itch/pain was observed in 41.3%/43.3% of the participants switching from vehicle and 52.4%/55.4% of those continuing delgocitinib.

Prof. Gooderham concluded that the DELTA 3 findings support the benefit of long-term, as-needed use of delgocitinib cream in moderate-to-severe chronic hand eczema.

1. Gooderham M. Long-term safety and efficacy of delgocitinib cream for up to 36 weeks in adults with Chronic Hand Eczema: results of the Phase 3 open-label extension DELTA-3 trial. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

The Latest in Psoriasis

Robust long-term efficacy of bimekizumab in psoriasis

Consistent response rates through 4 years of bimekizumab therapy were observed in patients with psoriasis from several trials who rolled over into the open-label extension (OLE) trial BE BRIGHT. High response rates of Psoriasis Area Severity Index (PASI) 90 and 100 were consistent throughout the extension study, as was a Dermatology Life Quality Index (DLQI) of 0/1.

In previous study results, bimekizumab displayed efficacy compared with placebo but also compared with, for example, secukinumab [1,2]. Prof. Mark Lebwohl (Icahn School of Medicine at Mount Sinai, NY, USA) presented maintenance data up to week 196 from BE BRIGHT [1]. The OLE trial BE BRIGHT (NCT03598790) included 771 bimekizumab-treated participants with psoriasis from various phase 3 trials (BE SURE, NCT03412747; BE VIVID, NCT03370133; BE READY, NCT03410992) with a 16-week double-blind phase and a maintenance part of 52 or 56 weeks.

Participants entering the OLE with a PASI <90 were treated with 320 mg bimekizumab every 4 weeks with a possibility of a dose switch when reaching PASI ≥90 at weeks 76 or 80. Those with a PASI ≥90 continued on a 320 mg dose every 8 weeks. The new analysis evaluated pooled data through 4 years of continuous bimekizumab therapy. Prof. Lebwohl emphasised that the initial participant characteristics included around 80% with prior systemic therapy, a mean weight close to 90 kg and a DLQI score over 10. "This is a tough group of patients," he commented.

At the end of the double-blinded phases of the parent trials (week 16), PASI90, PASI100, and body surface area ≤1%

responses were present in 90.9%, 65.8%, and 78.5% of the participants. These results more or less plateaued with respective maintained proportions of 86.1%, 64.7%, and 79.8% at week 196. "If you look at other vigorous markers of response, 89% of the participants still had absolute PASI ≤2 at year 4," Prof. Lebwohl noted.

Robust results were also observed for participants achieving a DLQI of 0/1: 71.5% at week 16 to 78.7% at week 196. "Only 10 patients dropped out for lack of efficacy," Prof. Lebwohl underlined. In total, 83% of participants completed week 196 of treatment.

In summary, in patients with psoriasis receiving bimekizumab who enrolled in the OLE trial BE BRIGHT, high rates of clinical and health-related quality-of-life responses were rapidly achieved and durable through 4 years.

1. Lebwohl M, et al. Bimekizumab efficacy from treatment initiation through 4 years in patients with plaque psoriasis: A comprehensive, long-term, pooled analysis from BE BRIGHT. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Reich K, et al. N Engl J Med 2021;385(2):142-152.

Benefit and safety of TYK2 inhibitor ESK-001 for psoriasis in phase 2

ESK-001 demonstrated increasing dose-dependent efficacy over time compared with placebo in primary and secondary Psoriasis Area and Severity Index (PASI) endpoints of the phase 2 STRIDE study. In the open-label extension (OLE), further drug exposure resulted in rising response rates including PASI75 in 90.9% on the highest dose at week 28.

"ESK-001 is a highly selective allosteric TYK2 inhibitor that avoids classic JAK inhibitor liabilities," Dr Kim Papp (Probity Medical Research, Canada) described the agent assessed in the phase 2 STRIDE study (NCT05600036) [1]. The trial included 228 participants with moderate-to-severe plaque psoriasis receiving placebo or ESK-001 in various dosages between 10 mg daily and 40 mg twice daily over 12 weeks. The OLE with 40 mg ESK-001 once daily or twice daily for all participants followed suit, after a withdrawal of 4 weeks. The overall study cohort had a mean age of 47.8 years and 82.5% was White. The mean PASI score was 17.8, and 36.0% of participants had previous experience with biologics or JAK inhibitors.

At week 12, STRIDE met its primary endpoint PASI75 with dose-dependent response rates ranging from 19.4% (P<0.005 vs placebo) to 64.1% (P<0.0001). PASI90 was reached by 25.6% to 38.5% on the highest 3 dose regimens. Measuring achievement of a static Physician Global Assessment (PGA) of 0/1, all dosages demonstrated increasing trajectories over time, with, for example, 17.9% on 40 mg twice daily at week 4 and 59.0% at week 12.

In the washout period, response rates dropped. However, during the OLE up to week 28, PASI75, PASI90, and PASI100 response rates on ESK-001 40 mg twice daily rose over time from 46.3% to 90.9%, 23.2% to 72.7%, and 6.1% to 36.4%, respectively.

Safety assessments during STRIDE revealed proportions of participants with ≥1 treatment-emergent adverse event (TEAE) of 39.5% in the placebo arm and 39.8% to 64.1% in the ESK-001 groups. Overall, TEAE were mainly mild to moderate in severity. Most frequent were headaches, upper respiratory tract infections, and nasopharyngitis. During the OLE, the rate of ≥1 TEAE was overall 44.5%, with 1.2% of TEAEs entailing treatment discontinuation.

Thus, Dr Papp considered ESK-001 to be safe and well-tolerated, having a favourable risk-benefit profile in long-term use. Phase 3 development is therefore supported.

1. Papp KA. Efficacy and safety of ESK-001, a highly selective oral TYK2 inhibitor, in a phase 2 study in adults with moderate-to-severe plaque psoriasis (STRIDE). LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

Durable skin clearance by IL-23 blockers due to reduction of resident memory T cells

In the KNOCKOUT trial, high induction doses of the IL-23 blocker risankizumab led to a significant decrease in resident memory T cells even 36 weeks after the final dosage. This reduction could potentially account for the sustained improvement in skin clearance seen in patients with psoriasis treated with IL-23 inhibitors.

As Prof. Andrew Blauvelt (Oregon Medical Research Center, OR, USA) pointed out, data suggests that one should "hit hard and early" in psoriasis to induce remission [1,2]. One strategy is to target tissue-resident memory cells (T_{RM} cells). These cells are responsible for psoriasis recurrences at the same sites as previous disease [3]. IL-23 plays an essential role not only in psoriasis pathogenesis but also in T_{RM} cell retention and proliferation.

The KNOCKOUT study (NCT05283135) is an ongoing phase 2 study including patients with moderate-to-severe psoriasis receiving high doses of risankizumab (300 mg and 600 mg)

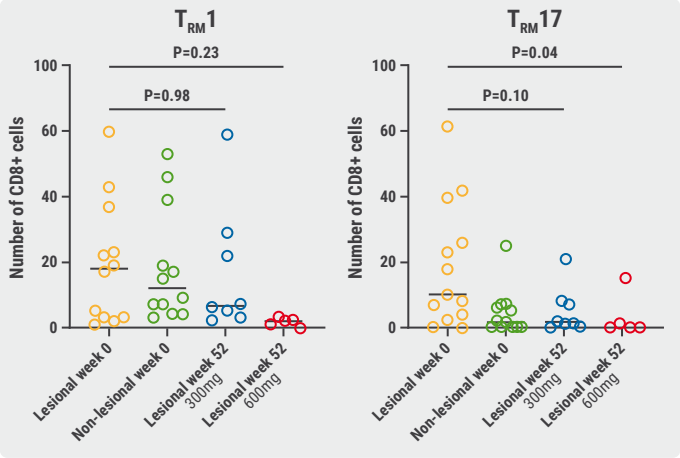
to induce long-term remission by decreasing T_{RM} cell number in skin affected by psoriasis [1]. The primary endpoint of the KNOCKOUT trial is the reduction in the number of T_{RM} cells between baseline and week 52 with these doses of the IL-23 inhibitor. Secondary endpoints evaluated are the clinical efficacy and safety of high induction doses of risankizumab.

All 20 participants were treated with 300 mg or 600 mg risankizumab at weeks 0, 4, and 16, with no further treatment. The 52-week visit was completed by 16 participants. Differential distribution of T-cell subclusters from baseline lesional skin, baseline non-lesional skin, and post-treatment lesional skin were assessed with single-cell RNA sequencing analysis.

The results demonstrated that high induction doses of risankizumab led to a marked reduction in the number of epidermal T_{RM} cells (see Figure). Moreover, lesional inflammatory cells at week 52 returned to levels of T_{RM} cells observed in baseline non-lesional skin. Risankizumab also proved to be well tolerated, and no new safety signals were observed.

Prof. Blauvelt concluded that the T_{RM} reductions noted with high induction dosing of risankizumab may explain the durability of skin clearance noted in patients with moderate-to-severe psoriasis on a cellular level. Larger prospective studies are needed to confirm these results.

Figure: Significant reduction in T_{RM} cells with high induction risankizumab at week 52 [2]



T_{RM}, tissue-resident memory cells.

Lesional baseline (n=13), non-lesional baseline (n=12), and post-treatment low-dose (n=8), and high-dose (n=5) groups.

1. Blauvelt A, et al. High induction dosing of risankizumab in patients with moderate-to-severe plaque psoriasis: 52 week results from the phase 2 KNOCKOUT study. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Schäkel K, et al. P50236, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
3. Blauvelt A, et al. J Psoriasis Pso Arthr 2022;7:157-159.

Hidradenitis Suppurativa: New Treatment Possibilities

HS: Targeting IL-1 pathway potential option after anti-TNF failure

The IL-1α/1β antagonist lutikizumab showed promising results in patients with hidradenitis suppurativa (HS) who had insufficient treatment success with TNF blockers. In 2 out of 3 different regimens tested in phase 2, an HS Clinical Response of 50% (HiSCR50) was reached more often with lutikizumab than placebo.

"We see more and more HS patients in whom TNF blockers fail," Prof. Falk G. Bechara (Ruhr-University Bochum, Germany) stated [1]. This phenomenon contributed to the design of a phase 2 trial (NCT05139602) of lutikizumab in patients with HS with prior unsuccessful anti-TNF therapy. The study included 153 participants randomised to weekly placebo or the IL-1α/1β antagonist at dosages of 300 mg bi-weekly, 100 mg bi-weekly, or 300 mg weekly over 16 weeks.

At baseline, the mean age in the 4 groups varied between 37.0 and 39.5 years, and the rate of women ranged from 53.8% to 67.6%. The highly affected study population included 64.9% to 74.4% of participants with severe HS (i.e. Hurley stage 3).

Compared with placebo, participants in the 2 high-dosed drug arms demonstrated greater rates in reaching the primary endpoint of HiSCR50: placebo 35%, 300 mg bi-weekly 59.5% (nominal P=0.027), and 300 mg weekly 48.7% (nominal P=0.197). HiSCR75 was seen in 17.5%, 45.9% (P=0.005), and 38.5% (P=0.031), respectively.

Skin pain, measured by numerical rating scale (NRS)30, improved in 12.9% of participants on placebo, in contrast to 22.2% (100 mg bi-weekly), 34.5% (300 mg bi-weekly), and 34.8% (300 mg weekly) of those on lutikizumab. Prof. Bechara also described that the improvement in draining fistula count was greater on both 300 mg regimens than on placebo.

Lutikizumab was considered safe and well-tolerated. The percentage of treatment-related events was similar between both treatment groups and placebo, with HS, diarrhoea, and headache being the most common. There were 2 serious adverse events in each of the study drug arms and 1 in the placebo group.

"For quite a long time, the IL-1 pathway has been assessed, but we did not really have clinical data; now, with lutikizumab, we have a new molecule to address this pathway," Prof. Bechara highlighted.

1. Bechara FG. A phase 2 multicentre, randomised, double-blind placebo-controlled study to evaluate the safety and efficacy of lutikizumab in adult patients with moderate to severe hidradenitis suppurativa who have failed anti-TNF therapy. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

BTK signalling as a novel target in hidradenitis suppurativa treatment

Treating hidradenitis suppurativa (HS) with the Bruton's tyrosine kinase (BTK) inhibitor remibrutinib is a novel treatment approach that was examined in a phase 2 study. The results suggest that this new mode of treatment could be both safe and effective for HS.

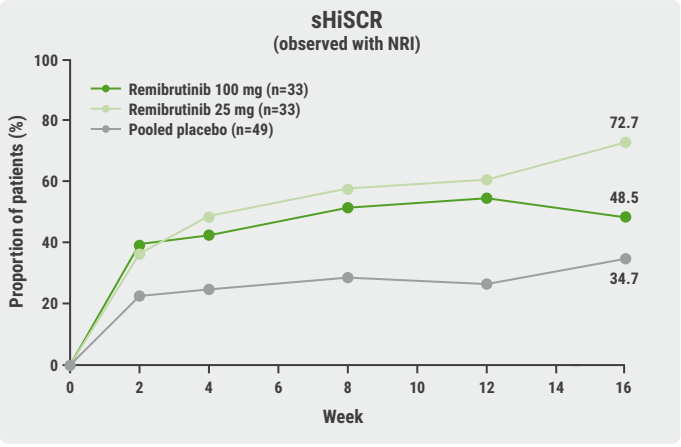
Research on pathogenesis has identified that HS lesions contain B cells and plasma cells that are linked to immunoglobulin generation and complement activation [1,2]. Also, activation of BTK and spleen tyrosine kinase pathways are involved in central signal transduction.

Prof. Alexandra Kimball (Harvard Medical School, MA, USA) presented a study that investigated therapy with the selective BTK inhibitor remibrutinib for moderate-to-severe HS over 16 weeks [1]. The trial forms part of a phase 2b multicentre platform study with 5 cohorts (A to E) that assessed various agents for this indication. The rationale for cohort D, testing remibrutinib against placebo, stems from findings that point to a role of BTK activation in HS [1,2].

Cohort D included 77 participants; 33 participants were randomised to remibrutinib at either 25 mg or 100 mg twice daily over 16 weeks, 11 patients received a placebo; the pooled placebo group of all cohorts included 50 participants [1]. The primary endpoint was a simplified HS Clinical Response (HiSCR) that stands for a ≥50% reduction in abscess and nodule (AN) count with no increase in draining tunnels.

At week 16, the results revealed higher rates of participants on the BTK inhibitor achieving simplified HiSCR50 with 72.7% (25 mg) and 48.5% (100 mg) versus 34.7% (pooled placebo; see Figure). Remibrutinib in both doses was also superior to pooled placebo regarding higher HiSCR response rates: HiSCR75 was achieved by 42.4% (25 mg) and 27.3% (100 mg) versus 18.4% (pooled placebo), and HiSCR90 by 36.4% (25 mg) and 15.2% (100 mg) versus 8.2% (pooled placebo). Also, greater reductions were observed in draining tunnels and AN counts along with ameliorations in skin pain in favour of remibrutinib.

Figure: Primary study endpoint of simplified HiSCR at week 16 [1]



NRI, non-responder imputation; sHiSCR, simplified Hidradenitis Suppurativa Clinical Response.

As for safety, remibrutinib was deemed well tolerated. One grade 4 adverse event occurred in each of the remibrutinib arms, but, overall, adverse events were mainly mild to moderate.

"We are very much looking forward to how this mode-of-action will perform in the future," Prof. Kimball concluded.

Due to the novel mode-of-action, it might be possible to combine BTK inhibitors with other biologics in this indication.

1. Kimball AB. Efficacy and safety of the oral Bruton's tyrosine kinase inhibitor, remibrutinib, in patients with moderate to severe hidradenitis suppurativa in a randomized, phase 2, double-blind, placebo-controlled platform study. LB1, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Gudjonsson JE, et al. JCI Insight. 2020;5(19):e139930.

Topical ruxolitinib shows promise in milder stages of hidradenitis suppurativa

In patients with milder hidradenitis suppurativa (HS), treatment with ruxolitinib cream led to significantly superior reductions in the abscess and inflammatory nodule (AN) count compared with vehicle application. The topical JAK inhibitor also led to more pronounced results in both HS Clinical Response (HiSCR) and International HS Severity Score System (IHS4).

With no approved treatment and unsatisfactory responses to standard therapies, treatments for patients with milder stages of HS are needed [1,2]. "There are no options for these patients," Prof. Martina Porter (Beth Israel Deaconess Medical Center, MA, USA) underlined in her talk [1]. Treatment success with topical ruxolitinib in skin diseases like atopic dermatitis and vitiligo contributed to the rationale for investigating the compound for milder stages of HS.

In a 16-week phase 2 trial (NCT05635838), ruxolitinib 1.5% cream twice daily was compared with vehicle in 69 adult patients with Hurley stage 1 or 2. To be eligible, the AN count had to be 3–10 and the affected body surface area could not exceed 20%. Prof. Porter further explained that the participants did not apply the cream as a field therapy but only on the lesions.

The study met its primary endpoint with a significantly greater change in least-square means of the AN count in the ruxolitinib arm (-3.61 vs -2.42 on vehicle; P<0.05). At week 16, a reduction of at least 50% in AN (AN50) was seen in 79.2% on ruxolitinib cream and 56.3% on vehicle. Proportions for reaching HiSCR were similar (ruxolitinib 79.2% vs vehicle 50%). Furthermore, a mean decrease in IHS4 was depicted by a delta of -4.46 on ruxolitinib compared with -2.66 on vehicle. This was also reflected by bigger drops on the scales for skin pain and itch for participants receiving the JAK inhibitor treatment.

The safety assessment revealed treatment-emergent adverse event rates of 38.2% (ruxolitinib) and 42.9% (vehicle). However, treatment-related adverse events occurred in 11.8% and 11.4%, respectively. On ruxolitinib, nasopharyngitis and COVID-19 were the most common treatment-emergent adverse events, on vehicle this was nausea. There were no serious adverse events noted in the active treatment arm.

1. Porter MJ, et al. Efficacy and safety of ruxolitinib cream in patients with hidradenitis suppurativa (Hurley Stage I and II): results from a randomised, double-blind, vehicle-controlled phase 2 study. LB2, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Sabat R, et al. Nat Rev Dis Primers. 2020;6(1):18.

Best of the Posters

Children with atopic dermatitis may be smaller and heavier than healthy children

Comparing paediatric patients with atopic dermatitis (AD) to a healthy reference population found a lower mean height and a higher mean weight in those affected with AD. For example, among the boys, 38% and 69% were above the 50th percentile for height and body mass index (BMI).

PEDISTAD (NCT03687359) is a prospective 10-year observational study assessing paediatric patients aged <12 years old with moderate-to-severe AD who have indications for systemic therapy due to insufficient disease control with topical management [1]. Prof. Amy Paller (Northwestern University's Feinberg School of Medicine, IL, USA) presented an analysis of the ongoing trial comparing the growth and weight of 1,329 children with AD under the age of 12 and the CDC Learning Management System reference healthy population.

At baseline, the AD cohort had a mean age of 5.98 years, and 53.2% were boys. The mean age at onset of AD was 1.5 years.

The average percentile among boys was 46th for height, 51st for weight, and 58th for BMI. The corresponding percentiles for the girls with AD were 50th, 50th and 59th.

Evaluating the rate of all participants exceeding the 50th percentile for height, revealed 52% of girls and 38% of boys. For weight and BMI, the fractions above the 50th percentile were at 51% and 71% for girls together with 50% and 69% for boys. In the subgroup of the 5 to under 12-year-olds, the proportions of boys over the 50th percentile were 28% (height), 56% (weight), and 70% (BMI) with 47%, 52%, and 70% of the girls. Taken together, these results demonstrated lower means for height and higher means for weight compared with the reference population.

Prof. Paller and her fellow researchers proposed that the hindered growth within the studied cohort was possibly due to factors like sleep deprivation and prolonged use of topical or systemic glucocorticoids and immunosuppressants. They suggested that early intervention with effective targeted therapies may mitigate this negative impact on growth in children with AD.

1. Paller AS, et al. Growth analysis in children aged less than 12 years with moderate-to-severe atopic dermatitis. P51363, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

JAK inhibitors have similar incidence rates of long-term adverse events as traditional immunomodulators

For venous thromboembolic (VTE) events, serious infections, and malignancies, except for non-melanoma skin cancer (NMSC), no significant differences in incidence rates of long-term adverse events were detected during treatment with JAK inhibitors versus non-JAK agents. The only observed disadvantage of the JAK inhibitors was a significantly higher incidence rate of herpes zoster infections. Yet, the incidence rates for NMSC and major adverse cardiovascular events (MACE) were lower on JAK inhibitors.

In the advent of the broadening successful use of JAK inhibitors in dermatology, there is notable interest in potential new indications that could benefit from this class of drugs [1]. In this context, the question of long-term safety is an important topic and a black box warning for long-term adverse events by the FDA has led to concerns. To gain further insight, Ms Olivia Lamberg (University of Michigan, MI, USA) and colleagues gathered and summarised evidence to compare the incidence rates of adverse events per 100 patient-years (PY) of JAK inhibitor use versus other immunomodulators. They looked at the JAK inhibitors baricitinib, tofacitinib, upadacitinib, ruxolitinib, and filgotinib, and non-JAK agents cyclosporine, methotrexate, etanercept, adalimumab, and prednisone.

For serious infections, VTE, and malignancies in general, no significant difference in incidence rates was identified between JAK and non-JAK drugs. However, NMSC showed a lower incidence rate in the JAK group compared with the non-JAK group: 0.4/100 PY versus 0.6/100 PY (P<0.0001). Significantly lower incidence rates per 100 PY in favour of JAK inhibitors were also detected for MACE with 0.3 versus 0.6 (P<0.0001). However, serious and non-serious events of herpes zoster were significantly fewer in the non-JAK category (3/100 PY vs 0.5/100 PY; P<0.001).

The research also included results for single agents and different daily dosages. Depending on these variations, the meta-analyses and single study estimates for malignancies (incidence rate/100 PY) on JAK inhibitors ranged from 0 (baricitinib) to 0.9 (tofacitinib). Corresponding findings for MACE, VTE, and serious infections were, for example, 0 (15–20 mg ruxolitinib) and 0.5 (5 mg tofacitinib), 0 (30 mg upadacitinib) and 0.5 (4 mg baricitinib), and 1.1 (15 mg upadacitinib) and 3.1 (100 mg filgotinib), respectively.

In their conclusion, the authors mention a therapeutic advantage of JAK inhibitors with their more precise mechanism of action than the broader-acting immunomodulators, and consider it safe to use JAK inhibitors, based on these valuable insights into the safety profile.

1. Lamberg O, et al. Long-term adverse event risks of systemic Janus kinase (JAK) inhibitors versus traditional immunomodulators. P53329, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

Baricitinib maintains regrowth of hair, eyebrows, and eyelashes over 3 years

Patients with alopecia areata (AA) continued to show a response to therapy in a long-term extension of the BRAVE-AA studies. Over 80% of responders to therapy with baricitinib at week 52 maintained their response until week 152.

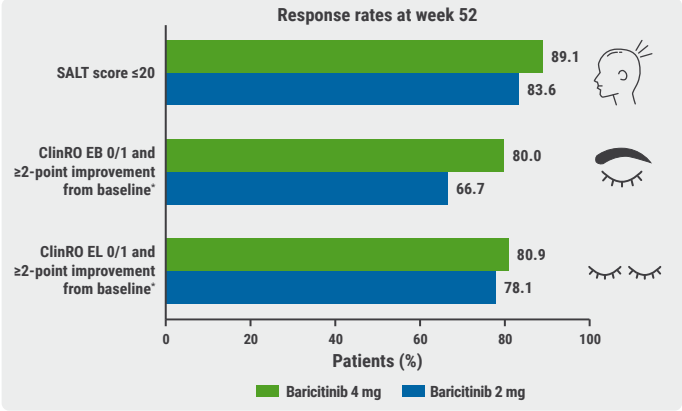
In severe AA, the disease tends to run a chronic course that often requires long-term therapy [1]. Moreover, it considerably affects quality-of-life, particularly in its severe form [2,3]. The oral, selective JAK1/2 inhibitor baricitinib is the only approved

therapy by European Authorities for AA following the positive results of the phase 3 BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259) trials. In these studies, 1,200 adults with ≥50% hair loss in the Severity of Alopecia Tool (SALT) score were randomised to 2 mg or 4 mg of baricitinib once daily, or a placebo. In the 4 mg group, SALT ≤20 was achieved by 34% of the participants, SALT ≤10 by 24.9%.

The rationale for the extension of the BRAVE-AA studies was to test the long-term efficacy of baricitinib. Prof. Maryanne Senna (Harvard Medical School, MA, USA) presented the 3-year results from BRAVE-AA1 and BRAVE-AA2 [4]. Treatment results after 3 years were presented for week 52 responders, defined as participants treated with 4 mg and 2 mg baricitinib who achieved a SALT score ≤20 at week 52.

In total, 89.1% of the participants treated with the high baricitinib dose and 83.6% treated with the low dose maintained a SALT score ≤20 at week 152 (see Figure). Moreover, the proportion of participants achieving full or nearly full eyebrows and eyelashes increased from week 52 through week 152: 70% in the 4 mg baricitinib group and 68.4% in the 2 mg group had full or nearly full eyebrows at 52 weeks. This percentage increased to 80% in the 4 mg group and to 66.7% in the 2 mg group at week 152. At 52 weeks, 70.8% of participants treated with 4 mg and 68.3% of those treated with 2 mg baricitinib had full or nearly full eyelashes, these percentages increased to 80.9% and 78.1% at week 152, respectively.

Figure: Key findings of the extension of the BRAVE-AA studies after 3 years of treatment [4]



ClinRO, clinician-reported outcomes; EB, eyebrows; EL, eyelashes.

* Among participants with ClinRO ≥2 at baseline.

1. Lintzeri DA, et al. J Dtsch Dermatol Ges 2022;20:59-90.
2. Pratt C, et al. Nat Rev Dis Primers 2017;3:17011.
3. Rencz F, et al. Br J Dermatol 2016;175:561-71.
4. Senna M, et al. Long-term efficacy of baricitinib in alopecia areata: 3-year results from BRAVE-AA1 and BRAVE-AA2. P49690, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.

Hidradenitis suppurativa treatment with secukinumab linked to low immunogenicity

Treatment-emergent anti-drug antibodies (TE-ADA) were found in under 1% of patients on IL-17A inhibition with secukinumab for hidradenitis suppurativa (HS). On further analysis, the discovered TE-ADA were non-neutralising.

Since anti-drug antibodies may occur as an immune response to treatment with biologics, possibly altering properties such as pharmacokinetics, inducing side effects, and decreasing efficacy, Prof. Martina Porter (Beth Israel Deaconess Medical Center, MA, USA) and colleagues were interested in the immunogenicity of secukinumab in patients with HS [1,2]. The analysis was based on data from the phase 3 SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) trials, in which secukinumab demonstrated positive efficacy and safety results in patients with moderate-to-severe HS [1,3]. Testing for TE-ADA was performed at baseline and study weeks 16, 52, and 60 (i.e. follow-up period). When TE-ADA were identified, they were further evaluated for potential drug-neutralising abilities and influence on, for example, pharmacokinetics.

Overall, low immunogenicity of secukinumab treatment was found, with TE-ADA rates of 0.6% (SUNSHINE) and 0.8% (SUNRISE) in participants who had had no baseline manifestation of ADA. At week 60, 3 participants on a 300 mg every 4 weeks regimen of secukinumab developed TE-ADA in SUNSHINE. In SUNRISE, 2 participants on bi-weekly medication and 2 receiving secukinumab every 4 weeks had TE-ADA. No loss of efficacy was observed, except for 1 of the TE-ADA-positive participants. Furthermore, pharmacokinetics stayed overall normal in the presence of TE-ADA. Aside from 1 participant, serum trough levels were also within the range of participants negative for TE-ADA. Moreover, no association was observed with immunogenicity-related adverse events.

1. Porter M, et al. Secukinumab demonstrates low immunogenicity in patients with moderate-to-severe hidradenitis suppurativa: Results from placebo-controlled, double-blind, Phase 3 SUNSHINE and SUNRISE trials. P52241, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.
2. Jahn EM, Schneider CK. N Biotechnol. 2009;25:280-6.
3. Kimball AB, et al. Lancet. 2023;401:747-61.

GUIDE demonstrates: Hit hard and early in psoriasis

Patients with moderate-to-severe psoriasis who were treated with guselkumab at an early stage of their disease had a considerably longer treatment-free interval than

those with more established or long-standing disease in the phase 3b GUIDE trial. Thus, very early therapy could pave the way to disease modification.

The ongoing phase 3b, randomised, double-blind GUIDE study (NCT03818035) assesses the efficacy of the IL-23 inhibitor guselkumab in patients with moderate-to-severe psoriasis. Previous interim results demonstrated the benefit of early intervention with guselkumab for achieving super responder status, defined as patients who achieve complete healing of their psoriatic lesions (i.e. absolute Psoriasis Area Severity Index [PASI]=0) at both week 20 and week 28 with a dose of 100 mg guselkumab every 8 weeks [1]. Part 3 of the GUIDE trial (week 68–220) was a withdrawal phase in which treatment with the IL-23 inhibitor was stopped in participants with an absolute PASI <3.

Prof. Knut Schäkel (University Clinic Heidelberg, Germany) presented another interim analysis (week 68–140) of the GUIDE trial [2]. In this analysis, the participants with short disease duration (i.e. ≤2 years from symptom onset) were divided into evenly-sized subgroups of participants with ultra-short disease duration (i.e. <15 months from symptom onset) and those with intermediate-short disease duration (i.e. ≥15 to ≤24 months); these groups were then compared with participants with long disease duration (>24 months), regarding PASI outcomes and median treatment-fee duration after withdrawal.

At week 116, maintenance of disease control (PASI <3) was significantly higher in the ultra-short disease duration group (40.3%) compared with both the intermediate-short disease duration (21.1%; P=0.0356) and long disease duration (11.9%; P<0.0001) groups. Moreover, a higher proportion of participants achieved PASI ≤1 and PASI=0 at week 115. Participants with disease duration <15 months also remained treatment-free significantly longer than those with longer disease duration: 456 days versus 291 days in participants with intermediate-short duration (P<0.0001) and 259 days (P<0.0001) in participants with long disease duration.

According to the authors, these findings indicate the positive impact of very early intervention with guselkumab on disease modification.

1. Schäkel K, et al J Eur Acad Dermatol Venereol 2023;37:2016–27.
2. Schäkel K, et al. GUIDE trial results after withdrawal in part 3: Long-term remission in patients with psoriasis treated with guselkumab within 15 months from onset of symptoms. P50236, 2024 AAD Annual Meeting, 8–12 March, San Diego, USA.