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29th EADV Congress

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PEER-REVIEWED CONFERENCE REPORT

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Editor Prof. Peter van de Kerkhof, Radboud University Medical Center, the Netherlands

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Letter from the Editor

Prof. Peter CM van de Kerkhof

Dear Colleagues,

The EADV 2020 as virtual meeting was a new experience. Who could have anticipated one year ago that the next EADV would be entirely virtual? The clear disadvantage of virtual meetings is that we miss the contact with our colleagues. The advantage is that it is possible to follow lectures and see posters not only during the few days of the congress, but for several months afterwards, which enables us to be informed on many more lectures.

In this EADV report, we selected topics on COVID-19 and some major innovations in dermatology. New insights into the course of COVID-19 during immunosuppressive treatments was a central theme at this congress. Highly relevant communications have provided us with evidence on which to base our decisions in patient care.

The various Janus kinase inhibitors are an important development, bringing us innovations in the treatment of atopic dermatitis, psoriasis, hand eczema, and other inflammatory diseases. Several Janus kinase inhibitors with selectivity for JAK 1, 2, and 3 and TYK 2 inhibitors are in development.

The development of biologics has not come to an end in psoriasis with an anti-IL-17A-F (bimekizumab) and an anti-IL-23 treatment (mirikizumab). Furthermore, several presentations provided new insights in the treatment selection in psoriasis with 11 biologics available in most European countries. Also in atopic dermatitis, biologics targeted at IL-4 and 13, IL-22, and IL-31 hold promise for the future. In urticaria, results of ligelizumab were presented as a next biologic.

Personalised medicine received attention with the development of biomarkers in several inflammatory diseases, including urticaria, atopic dermatitis, and psoriasis. Moreover, bacterial resistance in infectious diseases bacterial resistance is a growing concern. Due to the rise in bacterial resistance, it has been advised to restrict the use of topical antibiotics to treatment and to refrain from antibiotics as prevention. Attention for refugees and homeless people is important with respect to scabies.

The experience of this virtual meeting had taught us to use the positive aspects of virtual congress communication. In the future, innovative virtual offerings can enrich the classical face-to-face meetings. It is important to make the best of the real and virtual worlds.

Peter C.M. van de Kerkhof

Biography

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

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

Dermatology in Times of COVID-19

Interview with EADV president
Prof. Carle Paul, MD, PhD.

Past President of the European Academy of Dermatology and Venereology (EADV) and Chair of the Department of Dermatology at Paul Sabatier University in Toulouse, France.

How has the pandemic influenced the field of dermatology?

In many dramatic ways. Of course, COVID-19 has influenced the work of everybody. Survey data about the impact of COVID-19 in Europe has shown that one-third of dermatologists had to work in a COVID unit, and most dermatologists had to cancel many appointments in spring. There was an increase in tele-dermatology consultation. This was prevalent until the summer when people started to come into the practice again. Most dermatologists, including myself, feel that tele-dermatology does not have all the advantages of face-to-face consultations.

During the pandemic, we observed that many patients delayed treatment and consultations or even stopped their treatment. Many patients with inflammatory skin diseases stopped their immune modulators because they feared this medication would render them more susceptible to a COVID-19 infection. Now we have evidence that some of these patients relapsed.

Are there skin manifestations of COVID-19 that dermatologists need to know about?

The most familiar manifestation of COVID-19 is what we call pernio, the pernio-like eruptions that show on hands and feet. They usually manifest a few weeks after the COVID-19 infection and can last for several months. Data was presented in the late-breaking session by a US colleague, Prof. Esther Freeman from Harvard. She did excellent work on analysing an international COVID-19 registry from 39 countries and showed that these dermatologic manifestations can sometimes persist for several months. There are also less specific dermatologic manifestations like morbilliform rashes, urticaria, and purpura.

This is the first year the EADV goes virtual. What are the highlights of the congress?

It was back in May when we first realised that we had to do a virtual meeting due to the pandemic. The EADV office led by Martine de Sutter with the expertise of Kimberly Zimmerman, head of the congress, selected the best providers of virtual event platforms and paved the way for a successful experience. The scientific committee, led by Prof. Brigitte Dréno, put together a massive amount of new data presented by over 550 speakers in over 700 lectures. We selected 1,600 abstracts that describe the most significant advances in our specialty.

There are vast amounts of new data and innovation with a lot of progress in the treatment of psoriasis. You will also find presentations on novel, breakthrough therapy in atopic dermatitis, not only with systemic but also with novel topical drugs; this is a quickly evolving field. We also see novel treatment possibilities in alopecia areata, which has been a neglected indication, and now we have both oral and topical novel drugs.

Last but not least, tremendous progress has been made in rare diseases like epidermolysis bullosa (EB). A novel compound was presented that allows the lesions to heal more rapidly. Usually, blisters in EB can take months or years to heal. So, taken together, I think this year was a very interesting rich congress with a lot of innovation.

Which sessions are not-to-be-missed?

Of course, this primarily depends on one's interest, e.g. psoriasis or sexually transmittable disease or skin oncology. We have several interesting plenary sessions with excellent speakers, e.g. a talk from the general director of the World Health Organisation.

We also must learn how to cope with the current difficulties due to the pandemic. A survey performed by the EADV communication committee has shown that the pandemic has a huge impact on the general population: about 50% of patients report anxiety but also anger and a feeling of uselessness. This also impacts the doctor because these emotions of our patients are contagious. It is a real challenge, but there is a way to learn how to cope with this difficult situation. There is a fascinating talk by Ms Michele Nevarez, the CEO of the

emotional intelligence coaching company Goleman EI, who together with the EADV executive committee developed a leader-level emotional intelligence training and certification programme for European dermatologists. In her presentation, she explained how physicians can reduce the impact of these negative developments on their own situation and how we can best cope with the COVID-19 pandemic.

How will the congress landscape develop? Will virtual conferences replace in-person conventions or will there be dual events?

Experience shows that it is more difficult to engage virtually than face-to-face. I think the future will be a dual approach with a physical congress once we can control the pandemic, probably after the first semester of 2021. We simply cannot replace an in-person congress. But alongside the physical meeting will be a virtual component for the people that cannot travel or those with a limited amount of time. I am a strong believer in this dual approach. It will expand the reach of the congress and by now we have the tools to increase the quality of virtual meetings. But nothing can replace the face-to-face contact.

Late-Breaking News

Selective IL-23 blocker shows potential in psoriasis treatment

The IL-23p19 class antibody mirikizumab demonstrated superiority to placebo and non-inferiority to secukinumab in the treatment of psoriasis up to 52 weeks.

"Mirikizumab is a humanised, IgG4-variant monoclonal antibody binding to p19, thereby blocking IL-23," explained Dr Kim Papp (Probity Medical Research, Canada). He reported on the primary and major secondary efficacy and safety outcomes of mirikizumab versus secukinumab and placebo in the treatment of psoriasis at week 52 [1]. The phase 3, randomised, multicentre OASIS-2 study (NCT03535194) included over 1,400 adult patients with moderate-to-severe plaque psoriasis. The study consisted of an induction period to week 16 and a blinded maintenance period lasting to week 52. Patients were initially randomised 4:4:4:1 to receive either 250 mg mirikizumab every 4 weeks in 2 arms, or secukinumab or placebo every 4 weeks. In the maintenance period, 1 of the mirikizumab arms switched to 250 mg every 8 weeks and the other to 125 mg every 8 weeks, while the secukinumab group remained on the per-label dosage. Patients initially treated with placebo, continued with mirikizumab 250 mg every 4 weeks from week 16 to week 32 and subsequently switched to an 8-weekly dosing.

Primary endpoints were defined as the proportions of patients reaching static Physician Global Assessment (sPGA) 0/1 (i.e. clear or almost clear skin) and a psoriasis area and severity index (PASI) 90 improvement at week 16. Among the major secondary endpoints were the proportion of patients achieving PASI 75 and PASI 100. "Regarding age, gender, and weight, the distribution of patients was well balanced across all groups," stated Dr Papp. The study arms also had a similar distribution regarding disease duration, sPGA, body surface area (BSA), PASI, and presence of psoriatic arthritis (PsA) at baseline.

Throughout the induction phase, overall treatment-emergent adverse events (TEAEs) were 60.7% under placebo, 57.8% in the secukinumab arm, and 58.1% in the mirikizumab arms. The corresponding rates during the whole study period (week 0-52) were: placebo 71.2%, secukinumab 78.3%, and combined mirikizumab groups 77.1%; most of them being mild to moderate. The most common TEAEs were nasopharyngitis and upper respiratory tract infections. Serious AEs happened in 1.9% of the placebo group, 5.6% in the secukinumab group, and 3.9% in the mirikizumab groups.

"We see that during the induction period, secukinumab maintains a slight lead over mirikizumab in terms of PASI 90 response, but at approximately week 12 there is a diminishing capability of secukinumab to achieve higher levels of PASI 90 response and mirikizumab quickly catches up, surpassing secukinumab at week 16," Dr Papp indicated. PASI 90 at this point was achieved by 74.4% of the mirikizumab every 4 weeks arm and 72.8% of the secukinumab arm. "Secondly, we see in the secukinumab cohort a somewhat diminishing response over time, leading to an even superior response level maintained by mirikizumab," he continued. At week 52, the proportions achieving PASI 90 were 82.4% and 81.4% in the 2 mirikizumab arms versus 69.4% in the secukinumab group, and 75% in the placebo arm. The sPGA and PASI 100 results followed a similar pattern.

In summary, the novel IL-23 blocker mirikizumab was judged significantly superior to placebo in the primary endpoint and non-inferior and superior to secukinumab in the secondary endpoints. "All this combined indicates that mirikizumab certainly warrants further evaluation in the treatment of chronic plaque psoriasis," Dr Papp concluded.

1. Papp KA, et al. Efficacy and safety of mirikizumab versus secukinumab and placebo in the treatment of moderate-to-severe psoriasis: 52-week results from OASIS-2, a multicenter, randomized, double-blind study. D1T03.3A, EADV 2020 Virtual Congress, 29-31 Oct.

Promising results with nanobody treatment in psoriasis

A phase 2b trial showed significant and clinically meaningful benefits of sonelokinab compared with placebo in moderate-to-severe chronic plaque psoriasis.

"Sonelokinab is a trivalent camelid nanobody comprised of 2 active elements, an IL-17F moiety and an IL-17A/F moiety, bound to albumin as central moiety. Binding with albumin prolongs the half-life to 10-12 days," explained Dr Kim A. Papp (Probity Medical Research, Canada) [1]. The multicentre,

double-blind, phase 2b trial investigated the efficacy and safety of sonelokinab (formerly known as M1095) in the treatment of moderate-to-severe chronic plaque psoriasis. Participants (n=313) were randomised into 6 arms: 3 groups received sonelokinab subcutaneously at doses 30 mg, 60 mg, and 120 mg (at weeks 0, 2, 4, and subsequently every 4 weeks); 1 group received an enhanced loading dose of sonelokinab 120 mg every 2 weeks through to week 12; 1 group received a placebo; and 1 group received secukinumab according to the labelled dosage.

From week 12 to week 24, dose escalation was performed. "Patients in the 30-mg and 60-mg arms were treated according to their week 12 Investigator Global Assessment [IGA] response: those achieving IGA ≤1 continued on the original dose; patients with IGA response >1 received 120 mg at week 12 and every 4 weeks thereafter," described Dr Papp. Sonelokinab recipients with a normal loading dose of 120 mg continued with 120 mg every 8 weeks. Patients with 120 mg enhanced loading stayed on the same dose, administered every 4 weeks, and placebo patients were switched to sonelokinab 120 mg at week 12, 14, 16, and every 4 weeks thereafter. The secukinumab arm continued per the labelled dose. The mean age of the 313 participants was 46 years, 27% were women, they had 18.3 years of disease duration, and 16% had had prior exposure to biologics. Mean baseline PASI was 20.8, 74% had IGA 3 and 26% IGA 4. The primary endpoint was IGA 0/1 at week 12 compared with placebo.

All comparisons for sonelokinab versus placebo were significant for superiority of sonelokinab at week 12 (summary P≤0.002). At week 12, rates for the highest dose of sonelokinab were: 88.2% IGA 0/1 (95% CI 76.1-95.6), 76.5% PASI 90 (95% CI 62.5-87.2), 33.3% PASI 100 (95% CI 20.8-47.9). At week 24, percentages of patients achieving IGA 0/1 were between 80.4% and 94.2% in the higher-dose sonelokinab cohorts. The corresponding rates for PASI 90 and PASI 100 varied from 79.2% to 90.4% and 40.4% to 56.9%, respectively. "Patients treated with secukinumab experienced a progressive improvement in PASI 90 to about 80% by week 24; patients treated with sonelokinab 120 mg every 8 weeks had a response trajectory very similar to that of secukinumab, and patients in the sonelokinab 120 mg enhanced load every 4 weeks achieved superior responses at all timepoints," Dr Papp pointed out.

Commenting on the results, Dr Papp made 2 general observations: "Looking at the overall response through 12 weeks for IGA 0/1, PASI 90, and PASI 100, there appears to be a clear dose response across the sonelokinab arms, with secukinumab running roughly in the middle. If I draw your attention back to the first 3 weeks, for the IGA 0/1 or PASI 90 responses, sonelokinab-treated patients consistently showed more rapid responses. This very rapid response may reflect the ability of sonelokinab to get to the target tissue faster because of its low molecular weight."

As for safety, 51.4% of study subjects had a treatment-emergent adverse event (TEAE). "We see that in all dose groups, the occurrence of TEAE is similar with a trend to a slightly higher incidence in the treatment groups compared with placebo. Nasopharyngitis and upper respiratory tract infections were the dominant adverse events. Consistent with the mechanism of action, there was a trend of an increased incidence of candidiasis with increased IL-17 blockade," evaluated Dr Papp.

"These results support the emerging role of the IL-17A/F mechanism of action and other first important steps in exploring the nanobody platform for the treatment of inflammatory conditions," concluded Dr Papp.

1. Papp KA, et al. A Phase 2B, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Assessing the Efficacy, Safety, and Tolerability of Sonelokinab (M1095), an IL-17A/F Nanobody, in Patients with Moderate-to-Severe Chronic Plaque Psoriasis: Results from 24 Weeks. D1T03.3B, EADV 2020 Virtual Congress, 29-31 Oct.

Light at the end of the tunnel for chronic hand eczema

Both topical and oral JAK inhibitors led to rapid and sustained improvement in skin status in patients with chronic hand eczema, an indication with limited therapeutic options. In two phase 2b trials, delgocitinib, a topical pan-JAK inhibitor, and gusacitinib, and oral JAK inhibitor, demonstrated remarkable efficacy and a fast onset of action in hand eczema [1,2].

Hand eczema is characterised by painful, pruritic, non-infectious inflammatory skin changes on the hands and wrist. The disease is considered chronic when it lasts ≥3 months or relapses at least twice a year. Current topical treatment options are limited to emollients, topical corticosteroids, and calcineurin inhibitors.

The novel, topical pan-JAK inhibitor delgocitinib prevents inflammation by blocking several cytokine-mediated signalling cascades involved in the pathophysiology of

chronic hand eczema. This explains the motivation for a recent phase 2b, dose-finding study in chronic hand eczema patients assessing the safety and efficacy of this agent [1]. Participants (n=258) were randomised to delgocitinib cream in 4 different doses (i.e. 1 mg/g, 3 mg/g, 8 mg/g, and 20 mg/g) or a vehicle cream. All treatments were applied twice daily. The participants had mild-to-severe chronic hand eczema (Investigator´s Global Assessment [IGA] ≥2) and had shown an inadequate response to topical corticosteroids within 1 year before screening. "Most of the 258 patients had moderate chronic hand eczema, reflected by a Hand Eczema Severity Index [HECSI] score of 44.5," Prof. Margitta Worm (Charité – Universitätsmedizin Berlin, Germany) explained during the presentation of the study. The primary study endpoint was an IGA for chronic hand eczema (IGA-CHE) score of 0 (i.e. clear) or 1 (i.e. almost clear) with at least a 2-step improvement from baseline to week 16. A key secondary endpoint was a change in HECSI from baseline to week 16.

A statistically significant response was observed in the primary endpoint for participants receiving delgocitinib 8 mg/g and 20 mg/g (P<0.0004 vs vehicle). This significant effect was consistently demonstrated from week 4 for the 8 mg/g delgocitinib group and week 6 for the 20 mg/g delgocitinib group. IGA-CHE treatment success was achieved by 37.7% of patients treated with 20 mg/g delgocitinib and 36.5% of patients treated with 8 mg/g delgocitinib.

In addition, a statistically significant dose-response was established for the change in HECSI from baseline to week 16; all active arms had a significantly greater change in HECSI from baseline to week 16 than vehicle (P<0.05), which was most pronounced in the 2 highest doses. A significant treatment effect of delgocitinib 8 mg/g and 20 mg/g was already noticed at week 2 (P<0.05). Delgocitinib also showed a favourable safety profile. The majority of adverse events were non-serious, mild, or moderate, and not considered treatment related. The most frequently reported adverse events were nasopharyngitis, eczema, and headache.

As Prof. Worm mentioned in the discussion, the number of patients in the different treatment groups was too small to discriminate between different subgroups of hand eczema and their response. "We have to wait for phase 3 data, but delgocitinib is definitely interesting in a disease where we have hardly any options," Prof. Worm concluded.

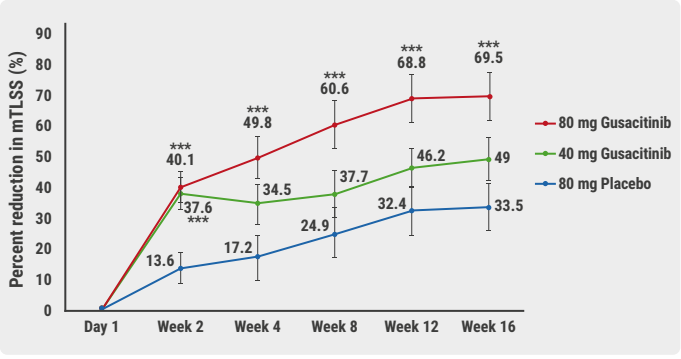
Oral JAK inhibitor achieves fast reduction of target lesions by almost 70%

A second phase 2b study (NCT03728504) in patients with chronic hand eczema assessed the oral JAK inhibitor gusacitinib [2]. This agent has a broad spectrum of action blocking JAK1, JAK2, JAK3, TYK2, and SYK. Thus, gusacitinib targets both the Th1 and Th2 cytokine pathways, the Th17 and Th22 cytokine pathways as well as the SYK-mediated IL-17 signalling in keratinocytes.

Prof. Howard Sofen (University of California, Los Angeles, USA) presented the results. All study participants (n=97) had moderate-to-severe chronic hand eczema and were refractory to corticosteroids (locally and/or systemic). The participants were randomised to gusacitinib 40 mg, gusacitinib 80 mg, or placebo. At 16 weeks, placebo-treated patients could switch to the higher dose of gusacitinib for continued treatment. The primary endpoint was the percentage change in the modified Total Lesion Symptom Score (mTLSS) at week 16.

Gusacitinib in the higher dose reduced the mTLSS by almost 70% (see Figure). A significant difference with placebo was seen as early as after 2 weeks. The lower dose was only significantly more effective than placebo at 2 weeks. At this time, almost a third of patients treated with the higher dose achieved the secondary endpoint of Physician Global Assessment (PGA) 0-1 (i.e. clear/almost clear). "31.3% achieved a minimal disease activity, a 5-fold difference in response compared with placebo," explained Prof. Sofen. In addition, gusacitinib provided a rapid and significant improvement in pruritus.

Figure: Percentage reduction in mTLSS at week 16 (primary endpoint) [1]



mTLSS, modified Total Lesion Symptom Score. *P<0.05; **P<0.01; ***P<0.005.

Adverse events evaluated were mostly sporadic and mild or moderate in severity. No significant changes were seen in haematology lab values or changes in total cholesterol, no

opportunistic infections, thromboembolic events or major adverse cardiovascular event, malignancies, or deaths.

1. Worm M, et al. The topical pan-JAK inhibitor delgocitinib cream demonstrates dose response in a 16-week phase 2b trial in chronic hand eczema. D1T03.4A, EADV 2020 Virtual Congress, 29-31 Oct.
2. Sofen H, et al. A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Gusacitinib (ASN002) in Subjects with Moderate-to-Severe Chronic Hand Eczema. D1T03.4C, EADV 2020 Virtual Congress, 29-31 Oct.

Epidermolysis bullosa: Novel wound treatment on the horizon

Oleogel-S10 has shown great promise as a topical treatment for epidermolysis bullosa. In a multicentre, phase 3 study, complete wound closure was reached by 41.3% of wounds treated with Oleogel-S10 versus 28.9% of those treated with a control gel.

"Epidermolysis bullosa [EB] is a chronic genetic skin fragility disorder characterised by the presence of recurring healing and breaking down of wounds as well as chronic wounds," Prof. Dedee F. Murrell (St George Hospital, University of New South Wales, Australia) told the audience [1]. A specific treatment for EB has been lacking, and the standard of care until now comprised non-adhesive bandages and topical treatments (i.e. anti-microbials, corticosteroids).

The agent that is expected to address this need for a specific treatment is Oleogel-S10. Oleogel-S10 is derived from the bark of the birch tree. It consists of 10% dry extract from this bark with 90% of pure sunflower oil and can be applied directly to the open wound during dressing changes at least every 4 days [2,3].

The phase 3 EASE trial (NCT03068780) enrolled 252 patients from 58 sites in 28 countries [1]. The target wound had to be a partial-thickness wound aged ≥21 days and <9 months; median wound age was 35.5 days. The age of participants ranged from 21 days to adults, with about 70% being under 18 years; 60.1% were male and 51.6% underweight, which can be expected in EB patients according to Prof. Murrell. The majority of study subjects (78.5%) suffered from recessive dystrophic EB. Participants underwent a stratified randomisation to consider the different subtypes of EB. The double-blind treatment with either Oleogel-S10 or a sunflower oil gel as vehicle gel (1:1), both with standard-of-care, lasted 90±7 days and was continued in an open-label extension. The primary endpoint was complete wound closure rate within 45 days.

Complete wound closure was achieved by 41.3% of the target wounds in the Oleogel-S10 group versus 28.9% of wounds in the vehicle gel group (P=0.013). "This is the first time that a phase 3 trial in EB has met its primary endpoint," Prof. Murrell pointed out. Looking at the subgroups, she explained that the treatment benefit was driven by the acceleration in the group with recessive dystrophic EB. This subtype had the greatest benefit with the difference between Oleogel-S10 and vehicle gel reaching high statistical significance (P=0.008). "The wound healing trajectories demonstrate that Oleogel-S10 accelerates wound healing in a subset of wounds; however, as expected with good wound care, the vehicle group began to catch up later by 90 days," said Prof. Murrell. She added that the control arm never overtook the Oleogel-S10 arm.

Looking at itch reduction in the age group 4–13 years, an overall improvement was observed but the control group had better results than the Oleogel S-10 group. In terms of pain during the changing of dressing, Oleogel-S10 outperformed the vehicle gel in a statistically significant manner at day 14 but not at day 90. Prof. Murrell thought this result was probably influenced by the small sample size.

In general, 81.2% of the patients had some sort of adverse event (80.7% Oleogel-S10; 80.7% vehicle gel), mostly mild and moderate. "A low number of target wound infections occurred. Only 8 overall, 5 patients had target wound infections reported as adverse events, with 4 of these occurring in the control group," Prof. Murrell informed.

In conclusion, she saw Oleogel-S10 as a well-tolerated and potentially important advancement for patients and their families, especially in recessive dystrophic EB.

1. Murrell DF, et al. Efficacy and safety of Oleogel-S10 for epidermolysis bullosa – results of 3 months double-blind treatment during the phase 3 study 'EASE'. D3T03.3B, EADV 2020 Virtual Congress, 29-31 Oct.
2. Grysko M, Daniels R. Pharmazie. 2013;68:572-7.
3. Schwieger-Briel A, et al. Dermatol Res Pract. 2017;2017:5068969.

Efficacious non-steroidal topical for psoriasis

Once-daily tapinarof 1% cream has shown highly significant treatment success in a substantial proportion of psoriasis patients in the identical, multicentre, phase 3 PSOARING 1 and PSOARING 2 trials.

"In psoriasis, we have a significant need for effective topical therapies that do not restrict the amount of time we can apply them or the locations on the body where we can apply them," stated Prof. Mark Lebwohl (Icahn School of Medicine

at Mount Sinai, USA) [1]. He referred to restrictions of high-potent topical corticosteroids that cannot be used, for example, in the face or intertriginous sites.

Tapinarof is a first-in-class, non-steroidal topical aryl hydrocarbon receptor-modulating agent, which moderates pro-inflammatory pathways implicated in psoriasis (i.e. IL-17A, IL-17F) and atopic dermatitis (i.e. IL-4, IL-5, IL-13). "Tapinarof enters the cell where it binds to the aryl hydrocarbon receptor. That complex then enters the nucleus where it joins with the aryl hydrocarbon receptor nuclear translocator and that entire complex regulates gene expression, resulting in a reduction in inflammatory cytokines and an increase in barrier proteins," Prof. Lebwohl explained the mode of action.

Tapinarof was evaluated in the identical multicentre PSOARING 1 (PSO1; NCT03956355) and PSOARING 2 (PSO2; NCT03983980). The studies included a total of 1,025 adults with a mean age between 49.1 and 50.0 years, the proportion of males was 50.6% and 62.2%, the mean weight was 89.6 kg and 92.9 kg, and the participants had a Physician Global Assessment (PGA) of 2-4, respectively. Roughly 80% had moderate disease and almost 10% mild or severe psoriasis, respectively. The mean Psoriasis Area Severity Index (PASI) ranged from 8.7 to 9.3. In both trials, patients were randomised 2:1 to either tapinarof 1% or vehicle once daily. The primary endpoint was a PGA response of 0 or 1 with a ≥2-grade improvement at week 12.

In PSO1 and PSO2, 35.4% and 40.2% in the tapinarof group achieved this PGA goal versus 6.0% and 6.3% in the vehicle group (P<0.0001 for both comparisons). At week 12, the results for the key secondary endpoint, defined as the rate of patients with PASI 75, were similar: 36.1% and 47.6% in the tapinarof group versus 10.2% and 6.9% in the vehicle group with again P<0.0001 for both differences.

The safety parameters of PSO1 and PSO2 were in line with previous studies [2,3]. Most adverse events (AEs) were mild or moderate in severity with a low study discontinuation rate due to AEs of 5.6% and 5.8% in PSO1 and PSO2 [1]. The most common treatment-related AEs were folliculitis, contact dermatitis, headache, and pruritus.

"Tapinarof has the potential to be a first-in-class topical therapeutic aryl hydrocarbon receptor modulating agent and will provide physicians with a novel non-steroidal topical treatment option that is highly effective and well-tolerated," Prof. Lebwohl concluded.

1. Lebwohl M, et al. Tapinarof Cream 1% Once Daily for the Treatment of Plaque Psoriasis: Efficacy and Safety in Two Pivotal Phase 3 Trials. D3T03.3D, EADV 2020 Virtual Congress, 29-31 Oct.
2. Robbins K, et al. J Am Acad Dermatol. 2019;80:714-721.
3. Gold SL, et al. J Am Acad Dermatol. 2020 May 21: S0190-9622(20)30957-9. DOI: 10.1016/j.jaad.2020.04.181.

Oral JAK 1 inhibitor leads to fast itch relieve and remarkable skin clearance in AD

Monotherapy with the oral Janus kinase (JAK)1 inhibitor upadacitinib showed a remarkable efficacy and speed of response in patients with moderate-to-severe atopic dermatitis (AD) in 2 replicate, multicentre, phase 3 trials [1].

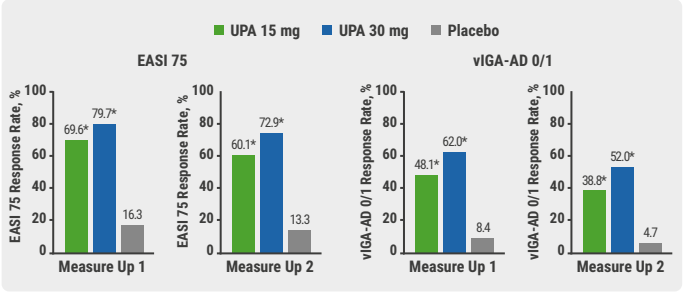
The JAK inhibitor upadacitinib was specifically developed for therapy of AD because key cytokines involved in the pathogenesis of AD signal via the JAK1 pathway [2,3]. A previous phase 2b trial demonstrated that upadacitinib monotherapy was efficacious with a favourable benefit-risk profile compared with placebo in adults with moderate-to-severe AD. The 2 replicate, randomised, double-blind, phase 3 trials Measure Up 1 (NCT03569293) and Measure Up 2 (NCT03607422) aimed to evaluate the efficacy and safety of monotherapy with upadacitinib versus placebo in adolescents and adults with moderate-to-severe AD [1].

Prof. Emma Guttman-Yassky (Icahn School of Medicine at Mount Sinai, USA) presented the results of both trials [1]. Participants were 12-75 years old and had AD symptoms for at least 3 years. Their Eczema Area and Severity Index (EASI) was ≥16 and they had a worst pruritus score on a numerical rating scale (NRS) of ≥4. In the double-blind treatment phase, participants were randomised to upadacitinib in 2 doses (i.e. 15 mg or 30 mg once daily) or placebo. Co-primary endpoints of the trials were a ≥75% reduction in EASI and a validated Investigator´s Global Assessment of 0 or 1 (vIGA-AD 0/1; i.e. clear or almost clear skin) with ≥2 grades of reduction.

Data from 847 participants in Measure Up 1 and 836 participants in Measure Up 2 were analysed at the end of the double-blind phase. At week 16, significantly more patients treated with upadacitinib in the Measure Up 1 and 2 studies achieved the co-primary endpoints EASI 75 and vIGA-AD 0/1 (P<0.001 for all doses and endpoints; see Figure). In addition, both studies met all ranked secondary endpoints. The higher dose of upadacitinib achieved numerically better results, but both doses were significantly superior to placebo. "An EASI

100 response was achieved in 27% of patients treated with the high dose," said Prof. Guttman-Yassky. Regarding the co-primary endpoints, a noticeable difference was already seen at week 1, which reached a plateau at week 4.

Figure: Co-primary endpoints EASI 75 and validated IGA-AD 0/1 at week 16 [4]



* P≤0.001 vs placebo (multiplicity controlled).
EASI, Eczema Area and Severity Index; UPA, upadacitinib; PBO, placebo; vIGA-AD, validated Investigator's Global Assessment for atopic dermatitis.

Really early significant improvement in worst pruritus NRS was already seen at days 2 and 3. The proportion of patients achieving a clinically meaningful itch reduction was significantly higher than placebo from day 2 on. The effect reached a plateau at week 4 and was maintained through week 16.

Concerning safety, acne was the most frequently reported treatment-related adverse event, reported in 19 patients treated with the low dose and 49 patients with the high dose, but only 2 patients discontinued treatment due to acne. "We saw some eczema herpeticum in the higher dose group, but no patient discontinued," added Prof. Guttman. No new safety signals and no death were reported in the treatment arms. "The speed and the magnitude of response are really characteristic features of upadacitinib," Prof. Gutmann-Yassky concluded.

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COVID-19: What Dermatologists Need to Know

Biologic psoriasis treatment and COVID-19 risk: Contradictory results

SARS-CoV-2 infections confront physicians with an ongoing number of puzzles. Two studies assessing the risk of developing COVID-19 for psoriasis patients treated with biologics presented contradictory results at the EADV 2020 Virtual Congress [1,2].

Systemic and biologic psoriasis treatments have been associated with an increased risk of infection. Thus, Dr Anne-Claire Fougerousse (Military Teaching Hospital Bégin, France) and her team assessed the frequency of severe COVID-19 in psoriasis patients receiving systemic or biologic treatment during the 4 months following treatment initiation [1]. This national, multicentre, cross-sectional study included 1,418 adult psoriasis patients, who received systemic psoriasis treatment from 27 April to 7 May 2020. Besides data on the psoriasis treatment and the treatment period (initiation or maintenance), data on comorbidities such as hypertension, obesity, and diabetes was collected. Where possible, probable cases of COVID-19 were confirmed by polymerase chain reaction.

Of the participants, 23.27% were treated with conventional disease-modifying drugs, 70.87% with biologics, and the remaining patients received apremilast or a combination of methotrexate and biologics. Five patients (0.35%) had a COVID-19 disease course that required hospitalisation, 2 of them required intensive care, and no patient died. The 2 patients requiring intensive care had known risk factors for severe COVID-19; both were obese and 1 patient was 71 years old. A total of 60% of patients had other risk factors for

severe COVID-19. There was no difference in the number of severe cases of COVID-19 according to the treatment period.

"Our study revealed that there is no additional risk of hospitalisation or intensive care in patients receiving systemic or biological treatment for psoriasis when compared with the general population," concluded Dr Fougerousse.

Different results in a single-centre Italian study

A second study performed in the San Donato Hospital in Milan, Italy, compared the risk of SARS-CoV-2 infections in 1,193 psoriasis patients treated with biologics and small molecules with the general population of the Lombardy Region from 21 February until 9 April 2020 [2]. Compared with the general population, patients receiving biologics were at a higher risk of testing positive for COVID-19 (unadjusted OR 3.43; 95% CI 2.25-5.73; P<0.0001), being self-quarantined at home (OR 9.05; 95% CI 5.61-14.61; P<0.0001), and being hospitalised (unadjusted OR 3.59; 95% CI 1.49-8.63; P=0.0044). However, their risk of being admitted to intensive care (unadjusted OR 3.41; 95% CI 0.21-54.55; P=0.3861) and of dying (unadjusted OR 0.41; 95% CI 0.03-6.59; P=0.5306) was not statistically significant compared with the general population.

Thus, Dr Giovanni Damiani (University of Milan, Italy) concluded that biologics seem to be protective against a COVID-19 poor prognosis but not infection preventive. The better prognosis of patients treated with immunosuppressants may be due to immunosuppressants improving the third inflammatory phase of a COVID-19 infection characterised by a cytokine storm and hypercoagulation that is associated with severe disease and death.

1. Fougerousse AC. Systemic or biologic treatment in psoriasis patient does not increase the risk of a severe form of COVID-19 FC02.03, EADV 2020 Virtual Congress, 29-31 Oct.
2. Damiani G, et al. The impact of COVID-19 in a large population of psoriatic patients undergoing biologics. FC01.07, EADV 2020 Virtual Congress, 29-31 Oct.

Much to be learned about COVID-19 and the skin

The global COVID-19 Dermatology Registry is collecting data on skin manifestations of COVID-19. The latest analysis of 900 cases from 39 countries presented insights with a focus on symptom duration including in long-term COVID-19 patients.

Launched in April 2020, the COVID-19 Dermatology Registry was developed and supported by the American Academy of Dermatology and the International League of Dermatological Societies to track skin manifestations of COVID-19 [1,2]. It is important to consider what the registry with a global reach can and cannot do. Prof. Esther Freeman (Director of the COVID-19 Dermatology Registry; Harvard Medical School, USA) explained, "The registry allows us to bring together the different skin manifestations that as single observations may not mean that much, but when you bring them together, they start to tell a story and will allow us to form hypotheses about how COVID-19 is presenting in the skin." She also suggested that the registry should be seen as a giant series of case studies rather than a population-based cohort study that could tell anything about, for example, incident rates of dermatologic COVID-19 manifestations or causations.

The presented analysis was done in August 2020 when the registry already comprised 900 cases from 39 countries, of which 330 were lab-confirmed by PCR or antibody testing [1]. The providers were contacted for follow-up data and this led to 224 cases with dermatologic symptom duration data. The aim of this analysis was to shed light on the existence and duration of long-term COVID-19 symptoms of the skin. "This is particularly relevant because cutaneous manifestations are visible to the naked eye, so they are for all to see and cutaneous manifestations could be a sign of underlying pathophysiology or underlying larger-scale inflammation of the body," said Prof. Freeman.

In terms of duration, the dermatologic symptoms lasted a median time of 12 days, but differences were observed according to the type of morphology. For example, urticaria, as may be expected, had a median duration of 5 days and papulosquamous disorders lasted a median of 20 days. Furthermore, Prof. Freeman stressed that it was also interesting to look at the outliers and 5 of those outliers with pernio qualified as "long haulers" because their symptoms lasted ≥60 days. Prof. Freeman remarked that she suspects patients with long-term COVID-19 are underrepresented in the registry. She presented an example of a patient with a dramatic clinical course of COVID toes, starting with a subtle erythema a week after the onset of cough and fatigue that worsened over time to a state with some toes being persistently violaceous and symptomatic even after over 133 days. Interestingly, the IgA levels of this patient were more in line with those seen in more severe cases with systemic symptoms than with those with short-term pernio.

"We encourage dermatologists caring for patients with long-hauler symtoms or long-term COVID-19 to enter their data

in the registry so that we can better capture this population," said Prof Freeman and asked them to submit their data under www.aad.org/covidregistry, as there is still much to study about COVID-19.

1. Freeman E. COVID-19 "long-haulers" in Dermatology? Duration of dermatologic symptoms in an international registry from 39 countries. D1T03.3D, EADV 2020 Virtual Congress, 29-31 Oct.
2. Freeman E, et al. J Am Acad Dermatol. 2020;83:1118-1129.

JAK Inhibitors – A Fascinating Novel Drug Class

JAK inhibitors in AA: re-establishing the immune privilege of hair follicles

Janus kinase (JAK) inhibitors are a promising novel treatment option for patients with moderate-to-severe alopecia areata (AA). They seem able to address the immunologic changes noticed in this disease.

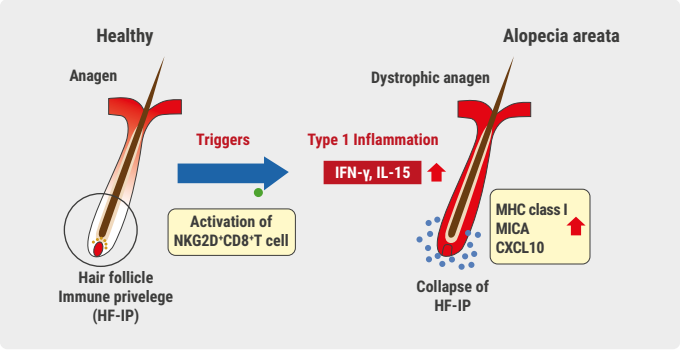
AA is a poorly treatable autoimmune disease that affects women, men, and children of all ages. This chronic, relapsing, inflammatory disorder is characterised by non-scarring hair loss on the scalp and/or body and has a remarkable negative impact on quality of life. Prof. Taisuke Ito (Hamamatsu University School of Medicine, Japan) explained that hair follicles of healthy subjects have an immune privilege, and that loss of this immune privilege leads to the disease [1]. Certain triggers can lead to activation of NKG2D-expressing $CD8^+$ cytotoxic T lymphocytes, which are necessary for induction of disease. They lead to a type 1 inflammation with upregulation of interleukin (IL)-15 and interferon (IFN) γ in the outer root sheath of the hair follicle. Upregulation of IL-15, NKG2D ligands, and major histocompatibility complex (MHC) class 1 molecules leads to a collapse of the immune privilege, and thus ultimately to AA (see Figure) [2-4].

AA is sometimes triggered by viral infections, such as influenza, which cause excess production of IFNγ. IFNγ is certainly one of the key factors that lead to the collapse of immune privilege [4].

Why JAK-inhibitors?

A possible therapeutic approach for AA is the restoration of this immune privilege by reducing $CD8^+$ T lymphocytes and IL-15. JAK-1/3 signalling mediates IL-15 activation of

Figure: Induction of alopecia areata. Adapted from [1,2]



HF-IP, hair follicle immune privilege; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex.

T lymphocytes [5]. IL-15 is highly expressed in human and murine AA. It drives CD8 killer activation. JAK inhibitors block both IL-15 and IFNγ.

A breakthrough in AA therapy was a study published in 2014 in which the oral JAK inhibitor tofacitinib reversed alopecia universalis in a 25-year-old patient with plaque psoriasis [6]. Complete regrowth of hair was achieved after 8 months. Significant hair growth was also achieved in another case report with tofacitinib treatment [7]. In 2017, a study investigating AA treatment with oral tofacitinib found that 7 out of 13 participants (53.8%) achieved hair regrowth of at least 50% independent of age, disease severity, and disease duration with minimal side effects [8]. Efficacy of tofacitinib was even shown in longstanding AA: After 5 years of previous treatment with little or no response, a patient achieved total hair regrowth after therapy with tofacitinib (5 mg twice daily for a year) [9]. "However, treatment with tofacitinib is not always effective and there is a relapse after initial success in some patients," said Prof. Ito.

AA: Also type 2 inflammation?

A study published in 2018 showed dual efficacy of the IL-4/IL-13 blocker dupilumab in a patient with atopic dermatitis and concomitant AA [10]. Due to severe, refractory AD, a young man was treated with dupilumab. In addition to response to dupilumab, the patient experienced hair regrowth starting at month 3 with almost full recovery at month 6.

JAK inhibitors show effectiveness for both AA and atopic dermatitis and are therefore promising candidates for future therapy of AA. At the moment, many JAK inhibitors are in the clinical development stage for AA.

1 Ito T. JAK family inhibitors – In alopecia areata. D1T06.3B, EADV 2020 Virtual Congress, 29-31 Oct.
2 Ito T, et al. Am J Pathol 2004;164:623-34.
3 Paus R, et al. J Investig Dermatol Symp Proceed 2018;19:S12-17.
4 Ito T. Clin Dev Immunol 2013;2013:348546.
5 Ghoreschi K, et al. J Immunol 2011;186:4234–43.
6 Craiglow BG, King BA. J Invest Dermatol 2014;134:2988-90.
7 Jabbari A, et al. Exp Dermatol 2016;25:642-3.
8 Ibrahim O, et al. JAMA Dermatol 2017;153:600-602.
9 Ferreira RB, et al. Clin Case Rep 2019;7:2539-42.
10 Darrigade A-S, et al. Br J Dermatol 2018;179:534-6.

JAK inhibitors in vitiligo

A mouse-model study suggests that the IFNγ/CXCL10 axis plays a role in the pathogenesis of vitiligo. Moreover, a recently published proof-of-concept study showed that a cream containing the Janus kinase (JAK) inhibitor ruxolitinib is indeed effective in vitiligo [1,2].

Vitiligo patients have increased numbers of autoreactive, melanocyte-specific $CD8^+$ T cells in their skin and blood, which are directly responsible for melanocyte destruction. In addition, gene expression in lesional skin from vitiligo patients revealed an IFNγ-specific signature, including the chemokine CXCL10. Experimental data in a mouse model identified a critical role for CXCL10 in both the progression and maintenance of vitiligo, thereby supporting inhibition of CXCL10 as a targeted treatment strategy for vitiligo patients [3]. Since IFNγ signal transduction occurs through JAK1 and 2, JAK inhibitors could lead to blockade of IFNγ signalling and downstream CXCL10 expression. Indeed, a case report published in 2015 showed a treatment success with tofacitinib in a patient with vitiligo [4]. Another case report showed rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata [5]. "In this case report, skin repigmentation went hand in hand with a significant reduction of CXCL10," explained Dr Mehdi Rashighi (Massachusetts Medical School, USA) during his presentation [1].

The latest proof-of-concept study for JAK inhibition in vitiligo was published recently [2]. In this randomised, double-blind, phase 2 study, adult patients with vitiligo were treated with ruxolitinib cream in different doses (0.15% up to 1.5% twice daily). The primary endpoint was the proportion of patients achieving a 50% or higher improvement from baseline in the facial Vitiligo Area Severity Index (F-VASI) at week 24. In the highest dose group, 30.3% of patients achieved this endpoint, a percentage that increased to 51.5% after 52 weeks. At this time, a third of the patients even gained an F-VASI-90 response. "Clearly, the best response was seen with the 1.5% ruxolitinib cream applied twice daily," Dr Rashighi stated. The tolerability of the cream was good; only acne was seen more frequently than in the vehicle group. Enrolment for a phase 3 trial with this cream is already completed.

"Hopefully, within the next 5-8 years, we will have more therapeutic options in vitiligo," concluded Dr Rashighi.

1 Rashighi M. JAK family inhibitors – In vitiligo. D1T06.3A, EADV 2020 Virtual Congress, 29-31 Oct.
2 Rosmarin D, et al. Lancet 2020;396:110-20.
3 Rashighi M, et al. Sci Transl Med 2014;6:223ra23.
4 Craiglow BG, King BA. JAMA Dermatol 2015;151:1110-2.
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JAK1 inhibition successful in hidradenitis suppurativa

The results of two phase 2 trials with a novel Janus kinase (JAK) 1 inhibitor showed a good safety profile in patients with moderate-to-severe hidradenitis suppurativa (HS).

Patient with HS experience painful inflammatory lesions and have a markedly reduced quality of life. The rationale for using a JAK inhibitor in this indication is that treatments targeting pro-inflammatory cytokine signalling may influence disease pathology and ameliorate symptoms of HS. "There is an unmet medical need for an oral treatment for these patients," said Dr Afsaneh Alavi (Mayo Clinic, USA) during the presentation of the results from two phase 2 studies with the JAK1 inhibitor INCB054707 [1]. INCB054707 is an oral, small-molecule, JAK1 inhibitor with 52-fold greater selectivity for JAK1 versus JAK2.

Study 1 was an open-label, single-arm study (NCT03569371), and study 2 was a placebo-controlled, dose-escalation study (NCT03607487) in which 3 doses of the JAK inhibitor were tested (i.e. 30 mg, 60 mg, and 90 mg). The primary endpoint of both studies was safety and tolerability, but efficacy endpoints were assessed as secondary study outcomes. All

45 participants (age 18-75) had moderate-to-severe HS (i.e. Hurley stage II/III) for at least 6 months. They had lesions in at least 2 different anatomic locations and a total abscess and inflammatory nodule (AN) count of ≥3.

Regarding safety, all occurring treatment-emergent adverse events were mild or moderate. One patient in study 1 discontinued due to upper respiratory tract infection and fibromyalgia. In study 2, 4 patients (15.4%) treated with the highest dose of the JAK inhibitor experienced thrombocytopenia (defined as platelet count <150 x 10^9/L), a known JAK inhibitor-related side effect. These patients interrupted their dose for up to 2 weeks. However, all platelet counts returned to levels above 150 x 10^9/L, and the drug was restarted in these patients without sequelae.

In addition, the JAK1 inhibitor showed remarkable efficacy. An HS complete response was achieved by 43% of patients in study 1 and 88% of patients who received the highest dose in study 2. An HS complete response is defined as a ≥50% reduction in AN count with no increase in either abscess or draining fistula counts relative to baseline. "With regard to the AN count, we could even show a better dose-dependent response," said Dr Alavi. An AN count of 0-2 was achieved by 63% of patients in the highest dose group. "All quality-of-life measures improved very nicely and significantly in a dose-dependent way," according to Dr Alavi.

The researchers also performed a biomarker analysis of inflammatory mediators. According to this analysis, a significant drop in inflammatory markers was seen with increasing doses of the JAK inhibitor. "An improvement was seen as early as week 1," Dr Alavi concluded. Further larger studies are warranted to back these preliminary results.

1. Alavi A. INCB054707, a Janus Kinase 1 inhibitor, for patients with moderate-to-severe hidradenitis suppurativa: Results from two 52-week phase 2 studies. Abstract 2665, EADV 2020 Virtual Congress, 29-31 Oct.

Topical JAK inhibition: a novel treatment option for patients with mild-to-moderate AD

According to a phase 2b study, brepocitinib cream could be an interesting novel option for patients with mild-to-moderate atopic dermatitis (AD). The brepocitinib cream showed a significant 75% decrease in EASI score at week 6 compared with a vehicle cream, as well as a higher rate of EASI 90 response and a fast and significant antipruritic effect.

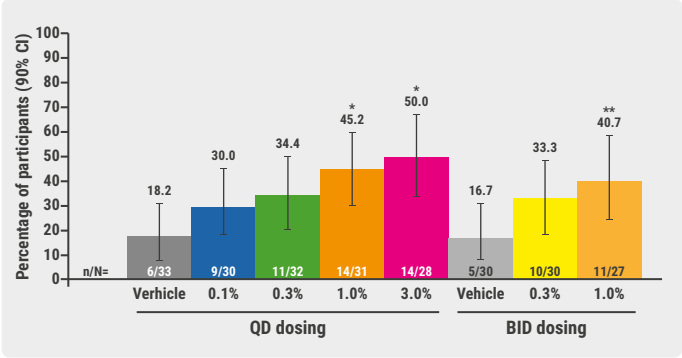
The topical tyrosine kinase (TYK)2/Janus kinase (JAK)1 inhibitor brepocitinib is a single-molecule designed to target 2 key pathways that play a role in both psoriasis and AD. Inhibition of TYK2 blocks the Th17 axis, which is important in psoriasis but also in specific forms of AD, for example in Asian patients with AD and paediatric new-onset AD. In contrast, inhibition of JAK1 blocks the Th2-pathway, the relevant pathway in European and American AD patients.

Prof. Megan Landis (University of Louisville School of Medicine, USA) presented promising results of a double-blind, vehicle-controlled, phase 2b study that assessed the efficacy and safety of topical brepocitinib in patients with mild-to-moderate AD. The study randomised 292 adult and adolescent AD patients with mild-to-moderate disease (i.e. Investigators Global Assessment [IGA] 2-3 and an Eczema Area and Severity Index [EASI] total score of ≥3 to ≤21), who received at least 1 dose of the study drug or vehicle cream. The study period of 6 weeks was completed by 240 patients. The primary endpoint was the percentage change from baseline in EASI total score at week 6. In addition, the EASI 90 response and the proportion of participants achieving an IGA score of clear (0) or almost clear (1) skin and a reduction from baseline of ≥2 points at week 6 were assessed as secondary endpoints.

At week 6, a significant decrease from baseline in EASI score was seen with the cream that contained 1% brepocitinib, which was the highest BID dose tested in the study. When brepocitinib was applied twice daily, there was a 75% decrease in EASI score compared with 47.6% in the vehicle group. A significant treatment response was also seen in the secondary endpoints. Participants treated with the cream containing 0.3%, 1.0%, and 3.0% brepocitinib twice daily achieved significantly more often an EASI 90 response compared with the vehicle group. A significantly higher percentage of patients in all brepocitinib groups achieved an IGA 0/1 response at week 6.

The influence on pruritus, a symptom particularly bothering AD patients, was also assessed as the percentage of participants achieving a ≥4-grade reduction from baseline (among those with baseline ≥4 in severity on the peak pruritus numerical rating scale). "A significant effect on pruritus was observed in the 2 highest doses," Prof. Landis said. This reduction was achieved by 50% of the participants treated once-daily with the 3.0% brepocitinib cream (see Figure).

Figure: Participants achieving ≥4-grade reduction from baseline among those with baseline ≥4 in PP-NRS at week 6 (FAS, NRI) [1]



Unadjusted, one-sided P-values: *P≤0.05 versus vehicle once daily; ** P≤0.05 versus vehicle twice daily. BID, twice daily; CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.

"With regard to safety, we noticed no side effects that increased with dose. We also had no serious adverse events and no lab changes," Prof. Landis reported. Of note, more patients in the vehicle group had side effects or discontinued the study due to treatment-emergent adverse events than in the brepocitinib groups. "This trial supports the use of this novel agent for patients with mild-to-moderate AD," Prof. Landis concluded.

1. Landis M, et al. A Phase 2b study to evaluate the efficacy and safety of the topical TYK2/JAK1 inhibitor brepocitinib for mild-to-moderate atopic dermatitis. Late-breaking abstract D1T03.4D, EADV 2020 Virtual Congress, 29-31 Oct.

Urticaria – What's new

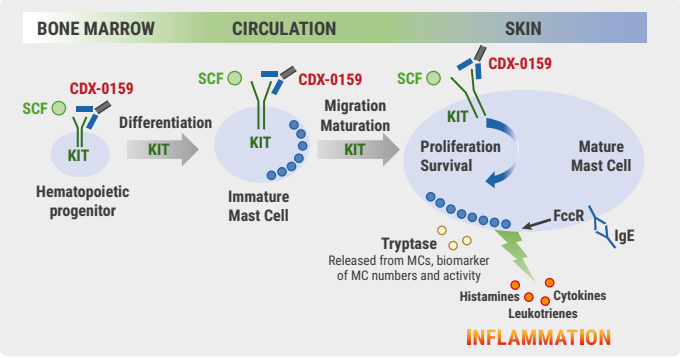
Chronic inducible urticaria can require some detective work

Chronic inducible urticaria (CindU) is less common than spontaneous urticaria but can also have a dramatic negative impact on quality of life. Novel treatment options aim at depleting or silencing mast cells [1].

"About 1 in 4 patients suffers from CindU, the most common being symptomatic dermographism, cold urticaria, and cholinergic urticaria," Prof. Marcus Maurer (Charité Universitätsmedizin Berlin, Germany) explained [1]. COLD-CE is an international, multicentre, prospective, cross-sectional academic study aiming to better understand cold-induced urticaria. In this study, real-world data is collected on still ill-defined characteristics, such as subforms of cold-induced urticaria. The researchers found subforms like food-dependent CindU. One patient only suffered from cold-induced urticaria after a specific meal: steak. "There are rare subforms that require our detective work and these projects are in the process of identifying and characterising them," Prof. Maurer said.

Regarding therapy, omalizumab seems to be effective in cold urticaria, although it is not an approved indication. At the moment, many different biologics are developed for CindU and other forms of urticaria. An interesting novel approach is CDX-0159, an anti-KIT monoclonal antibody that aims to starve mast cells by inhibiting differentiation, migration, and maturation of mast cells (see Figure).

Figure: CDX-0159, an anti-KIT monoclonal antibody, aims to treat CindU by mast cell depletion [2]



CindU, chronic inducible urticaria; IgE, Immunoglobulin E; MC, mast cell; SCF, stem cell factor.

Cholinergic urticaria is brought on by raised body temperature or sweating and entails a significant burden for affected patients. "We put patients on a treadmill and challenge them because then we can determine thresholds before wheals start to come," Prof. Maurer explained. This can greatly help patients to cope with the situation. Antihistamine treatment is often ineffective in cholinergic urticaria. Sometimes, a response can be gained by updosing but a little more than

60% of patients with cholinergic urticaria do not respond sufficiently to elevating antihistamines. "So, clearly, we have to develop better treatment options," stated Prof. Maurer. A complete response to omalizumab standard dose was shown by 13% of patients, and 47% had at least a major response. "If you change the dose and interval of omalizumab, you get up to two-thirds of patients to respond," Prof. Maurer recommended. However, even with optimised dosing, there are non-responders, particularly in the male population. Furthermore, the standard dose is often not sufficient in patients with cholinergic urticaria.

Another novel approach is the silencing of mast cells with Siglec-8, an inhibitory mast cell silencing receptor antibody. In a phase 1b study, 7 patients that were treated with this agent showed a very good response. In addition, there is an ongoing study with dupilumab, the CHED study (NCT NCT03749148), in patients with cholinergic urticaria.

There are also new tools to assess disease activity and disease control in CindU, the most important being the urticaria control test. "Let's use these tools in clinical practice to better treat patients," Prof. Maurer concluded.

1. Maurer M. News in inducible urticarias. D2T05.1C, EADV 2020 Virtual Congress, 29-31 Oct.
2. Maurer M, et al. CDX-0159, an anti-KIT monoclonal antibody, demonstrates dose-dependent reductions in serum tryptase and a favorable safety profile in a phase 1a healthy volunteer study. Abstract 1829, EAACI Digital Congress 2020, 6-8 June.

Chronic spontaneous urticaria: hives, wheals & biomarkers

Chronic spontaneous urticaria (CSU) has numerous biomarkers. Some of these biomarkers appear to be useful in monitoring disease activity and severity as well as in predicting treatment response.

CSU is a mast cell driven disease characterised by the presence and recurrence of wheals and angioedema [1]. "In patients with high disease severity, angioedema, positivity of the autologous serum skin test [autoreactivity] or a combination with physical urticaria, the overall duration of CSU tends to be longer," said Prof. Ana Giménez-Arnau (Autonomous University of Barcelona, Spain). In her presentation, Prof. Giménez-Arnau shed light on the long list of potential biomarkers.

Bench-to-bedside

Prof. Giménez-Arnau listed a seemingly limitless list of potential biomarkers including: TAT, fibrinogen, FVIIa, FXIIa, FVIII, FIX, FII, C-reactive protein (CRP), vitamin D, B12, prolactin, DHEA-S, cortisol, histamine, anti-IgE, IgG, IFNγ, TNF, histamine, tryptase, platelet, and basophil or eosinophil count [2]. Today, the most widely accepted biomarkers of disease activity with great potential are D-dimers, IL-6, and CRP [1,3].

Besides biomarkers of disease activity, researchers have studied clinical biomarkers of severity and prognosis. For example, the presence of angioedema has been associated with a less favourable prognosis. Prof. Giménez-Arnau pointed out that angioedema has a substantial impact on the afflicted who seem to be suffering from a more active disease. She further stressed that angioedema is underdiagnosed in patients with CSU, which was shown in analyses of the ASSURE-CSU study [4].

Other scientists have looked at a subtype of CSU, namely autoimmune CSU, in which functional IgG autoantibodies to IgE or its high-affinity receptor (i.e. FcεRI) induce mast cell degranulation, leading to subsequent symptoms [5]. These patients had significantly higher IgG anti-TPO levels and lower total IgE levels as demonstrated by the authors of the PURIST trial (NCT01637116). This trial showed that a positive basophil activation test was 69% predictive of autoimmune CSU and a positive basophil histamine release assay was 88% predictive. Thus, including these tests in the diagnostic workup may help identify patients with this condition who would have remained undetected by routine clinical parameters. The afflicted have a different prognosis and may benefit from specific management [5].

1. Giménez-Arnau A. Phenotypes of CSU and their biomarkers. D2T05.1A, EADV 2020 Virtual Congress, 29-31 Oct.
2. Kolkhir P, et al. Clin Exp Allergy 2017;47:19-36.
3. Folci M, et al. J Immunol Res 2018;2018;5615109.
4. Sussman G, et al. Allergy 2018;73:1724-34.
5. Schoepke N, et al. Allergy 2019;74:2427-36.

Ligelizumab for chronic spontaneous urticaria: a new star on the horizon

Results of a novel analysis of a previously published phase 2b trial, comparing ligelizumab with omalizumab in the treatment of chronic spontaneous urticaria (CSU), showed numerical superiority for ligelizumab in terms of speed of onset and duration of action [1,2].

Ligelizumab is a high-affinity, humanised, monoclonal, anti-IgE antibody, which has previously been assessed for treatment of patients with CSU who do not adequately

respond to H1-antihistamines [1]. The phase 2b dose-finding trial (NCT02477332) with 382 patients did not only find superiority to placebo but also to omalizumab [1]. "In the present analysis we look at how long it takes before patients experience a beneficial response and how sustained this response is over the first 12 weeks of treatment," Prof. Marcus Maurer (Charité Universitätsmedizin Berlin, Germany) told his audience [2]. For this purpose, 3 of the 6 treatment groups were separately analysed, namely ligelizumab 72 mg, ligelizumab 240 mg, and omalizumab 300 mg, all administered every 4 weeks.

Using an electronic diary, patients with moderate-to-severe CSU that were enrolled in the study collected their daily urticarial symptoms. This data was used to determine the Urticaria Activity Score summed over 7 days (UAS7). A UAS7 0 was defined as complete disease control and well-controlled disease as UAS7 1-6. As of week 2, numerically more participants in the 2 ligelizumab groups already reached a score of UAS7 0 than those treated with omalizumab. At week 12, UAS7=0 was achieved by 45.7% of participants treated with ligelizumab 72 mg, 43.6% of participants in the ligelizumab 240 mg arm, and 28.6% of participants in the omalizumab 300 mg arm. Overall, more patients reached the goal of a well-controlled disease (UAS7 1-6) in the ligelizumab groups. At week 2, the results were 43.4% for ligelizumab 72 mg, 36.1% for ligelizumab 240 mg, and 28.6% for omalizumab 300 mg. These results rose to 60.5% for ligelizumab 72 mg, 52.6% for ligelizumab 240 mg, and 51.9% for omalizumab 300 mg at week 12. Evaluating durability in terms of cumulative urticaria-free weeks over the duration of the study, the ligelizumab groups demonstrated mean values of 56.0% (72 mg) and 60.6% (240 mg) versus 38.1% with omalizumab.

Prof. Maurer concluded with 2 key messages based on these results: "Number 1, the onset of action with ligelizumab is faster than with omalizumab, with higher rates of patients achieving well-controlled and even completely controlled disease as soon as week 2. In addition to that, over the course of the first 12 weeks, patients experienced higher rates of complete control and well-controlled disease with ligelizumab than with omalizumab." The ongoing phase 3 PEARL 1 (NCT03580356) and PEARL 2 (NCT03580369) studies will provide further efficacy and safety data of ligelizumab for up to 1 year.

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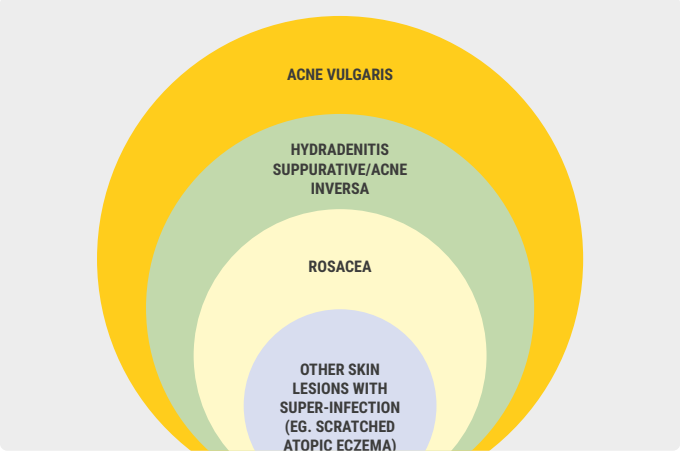
Infectious Diseases: Novel Developments

Bacterial resistance in skin infections – a challenging threat

Resistant bacterial strains are on the rise. Therefore, topical antibiotics should be used to treat rather than prevent clinically manifested superinfections.

Prof. Domenico Bonamonte (Bari University, Italy) discussed the various indications for topical antibiotics, which are widely used in clinical practice [1]. Besides for impetigo, topical antibiotics are also key components in the management of mild-to-moderate skin infections (see Figure). According to Prof. Bonamonte, an ideal topical antibiotic should penetrate the skin efficiently, reach adequate therapeutic doses, minimise cross-resistance, and have a weak sensitisation potential.

Figure: Conditions besides impetigo that may also require topical antibiotics [1]



Fusidic acid became a first-choice treatment option in primary and secondary skin infection due to its efficacy, safety, sensitisation potential, resistance profile, and spectrum selectivity. After topical application, it reaches high antimicrobial concentrations in deep skin layers. Fusidic acid has a high bactericidal activity against *S. epidermidis, Streptococcus pyogenes, Propionibacterium acnes, Corynebacterium, Clostridia,* and *S. aureus,* including methicillin-resistant strains [2]. Fusidic acid can not only be used to treat superinfected atopic dermatitis but also for the management of non-infected atopic skin. Since *S. aureus* releases antigens that sustain the inflammatory reactions in atopic patients, fusidic acid may be applied in combination with corticosteroids in the management of patients with atopic dermatitis. However, studies have not demonstrated any benefits from antibiotic treatment in reducing atopic dermatitis flare-ups.

1. Bonamonte D. Indications for topical antibiotics. D1T04.3C, EADV 2020 Virtual Congress, 29-31 Oct.
2. Bonamonte D, et al. G Ital Dermatol Venereol 2014;149:453-9.

Borreliosis: A multifaceted disease

Lyme disease is often disguised and may occur long after the tick has left its host. In tick-borne Lyme disease, the bacteria are transmitted by vectors and may lead to various symptoms and skin manifestations.

Lyme disease can be caused by various *Borrelia* species, leading to neurological symptoms or possibly affecting the joints. Dr Markus Starink (Amsterdam University Medical Centre, the Netherlands) pointed out that these bacteria all depend on vectors for transmission to humans [1]. They are known to cause tick-borne illnesses and are transmitted by the Ixodes ricinus in Europe or the Ixodes scapularis in the USA.

In the early stages of Lyme borreliosis (i.e. days to weeks after an infectious tick bite), the Lyme disease is localised, and one may notice erythema migrans. Erythema migrans is the most prominent manifestation of Lyme disease, occurring in 77-89% of cases. It is an erythematous macule or papule/plaque, spreading centrifugally within days to months –on average 2-3 weeks– after the initial tick bite. Recently, more homogeneous patterns are seen, such as an erythematous macule and, less often, of an annular shape. The lesions are usually asymptomatic and vary in size upon presentation (>5 cm). In adults, erythema migrans is predominantly found in or around the flexor side of the great joints, mostly inguinal/legs. In children, preferred sites are the head and the neck. The lesions usually disappear after several weeks or months (4 weeks on average). Atypical manifestations may be evident in skin folds, where the shape of the erythematous region is no longer circular but is rather an incomplete ring related to local haemorrhage. Within weeks to months, early disseminated disease manifests as borrelial lymphocytoma and multiple erythema migrans.

Borrelial lymphocytoma occurs in 2-3% of the infections and more often in children, often at the earlobe and scrotum, than in adults, often at the areola. Smooth, asymptomatic, blue-red nodules and plaques, 1 to several centimetres in size may be detected in the vicinity of the original tick bite. If left untreated, these lesions can persist for months. In 50% of the cases, they may be detected together with or directly after the resolution of erythema migrans.

Early signs of neuroborreliosis may present as radiculitis, meningitis, and peripheral facial paresis. Further manifestations include Lyme-arthritis, carditis, uveitis, hepatitis, myositis, and orchitis. Late stages of the illness (>1 year) are characterised by acrodermatitis chronica atrophicans, chronic neuroborreliosis, and chronic arthritis. Acrodermatitis chronica atrophicans typically occurs 6 months to 10 years after infection in 1-3% of all cases. In 70% of those cases, one or both (lower) legs are affected. In starts with red/purple "inflammatory" colouration, which is slowly progressive and reversible after treatment. Later, red/blue atrophy is observed, and sometimes localised scleroderma or lichen sclerosus-like changes, or fibrous plaques. Acrodermatitis chronica atrophicans is often accompanied by irreversible treatment-resistant symptoms, including peripheral neuropathy (in 60% of the cases), hyperalgesia (50%), joint involvement, muscle weakness and cramp, headache, and tiredness.

Dr Starink advised not to rule out Lyme disease in people with no history of a tick bite because some tick bites go unnoticed or transmission might have occurred long before skin manifestations have become apparent. Checking for Lyme disease is based on serology, PCR (sensitivity up to 90% in skin), culture (sensitivity 40-80%), and histology. Serology will still render negative results in early stages of the disease and may not be helpful in the erythema migrans phase. Antibody titers, such as IgG, remain positive after successful treatment and are, therefore, not suitable for follow-up. The treating physician should also consider that

PCR results may remain positive after treatment. Regarding borrelial lymphocytoma, serology is positive in 70-90% of the cases and PCR sensitivity is up to 90%. For acrodermatitis chronica atrophicans, sensitivity is 75% for PCR and 98% for serology (high IgG).

Therapeutic options differ per country

When it comes to treatment, the Dr Starink advised the audience to stick to regional guidelines as national recommendations may vary tremendously.

Prophylactic treatment after a bite generally consists of one 200-mg doxycycline dose. Data from the USA has indicated that it might prevent erythema migrans, but there is no data available on later stages of the illness.

For primary erythema migrans, doxycycline (100 mg twice daily for 10-14 days) is typically prescribed. In case of allergies, pregnancies, or in children, amoxicillin or azithromycin may both serve as alternatives. Disseminated/ multiple erythema migrans, borrelial lymphocytoma, and acrodermatitis chronica atrophicans can be treated with doxycycline or, alternatively, ceftriaxone. In Germany and in the UK, amoxicillin is recommended for acrodermatitis chronica atrophicans. However, not all patients will notice a marked improvement after treatment because of irreversible skin changes. For this group, recent studies showed no improvement after prolonged treatment or re-treatment.

"Tick"-home message

Recognising Lyme borreliosis and treating it as early as possible can prevent chronic and disabling disease. Dr Starink stressed that erythema migrans does not only present as a ring and should be considered when detecting any kind of centrifugally spreading erythema. Further, there is no indication for serology in erythema migrans. Acrodermatitis chronica atrophicans may be suspected in patients presenting with red/purple/blue discoloration on one or more extremities. Lastly, Dr Starink strongly advised his listeners to consult their local guidelines for adequate treatment.

1. Starink M. Borreliosis: How to diagnose and treat. D1T04.3D, EADV 2020 Virtual Congress, 29-31 Oct.

Scabies – A global health challenge

Scabies has endemic proportions among many refugees, homeless, and people in developing countries, but occur worldwide and may affect people of all social classes.

As Prof. Olivier Chosidow (University Paris-est Creteil Val de Marne Teaching Hospital Henri Mondor, France) emphasised, for a long time, scabies has been a truly neglected disease [1]. Scabies in humans is caused by an infestation of the skin by mites (*Sarcoptes scabiei var. hominis*). The parasite burrows into the upper layer of the skin where it lays its eggs. The afflicted suffer from severe itching (especially in the evening and at night) and a rash, caused by hypersensitivity reactions to the faeces of the mites. Scabies usually starts between the fingers, wrists, or armpit while the face is usually spared in adults. Prof. Chosidow stressed the fact that major sleep disturbances, psychosocial stigma and complications might add to the burden of disease. Scratching triggers skin infections as the mites inhibit complement pathways, leading to *Streptococcal* and *Staphylococcal* infection of the skin. Impetigo in turn might lead to haematuria and may affect the kidneys (post-streptococcal glomerulonephritis) and trigger acute rheumatic fever or rheumatic heart disease [2]. Skin scrapings may reveal mites or eggs under the microscope and confirm any suspected diagnosis.

Scabies is more than a common parasitic skin disease. Thus, the speaker welcomed that –in response to the high burden of scabies and its complications– the World Health Organization (WHO) added scabies on the list of neglected tropical diseases in 2017. A study performed in the Netherlands in asylum seekers revealed that scabies prevention was feasible, he added. Risk of reinfection and development of scabies complications were effectively reduced [3]. Scabies has been added as an indication for ivermectin (the most commonly used derivative of avermectin) to the "WHO Model List of Essential Medicines". Ivermectin is able to significantly reduce the level of scabies and is highly effective in controlling scabies epidemics, although it is not able to kill eggs. Prof. Chosidow further mentioned moxidectin which, like avermectin and its derivatives, has activity against arthropods but has properties suited to long-acting formulations. In 2015, the Nobel Prize was granted for the discovery of avermectin; its derivatives have saved millions of lives.

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2. Chosidow O, Hay RJ. Lancet 2019;19:P454-6.
3. Beeres DT, et al. PLoS Negl Trop Dis 2018;12:e0006401.

Upcoming Treatments

Bimekizumab in psoriasis: up-and-coming

In the multicentre, randomised phase 3 BE VIVID trial, bimekizumab led to higher rates of psoriasis improvement compared with ustekinumab in the treatment of moderate-to-severe plaque psoriasis. These results were consistent across subgroups stratified by weight, baseline PASI, and prior biologic therapy.

The novel antibody bimekizumab inhibits IL-17A and IL-17F [1]. "IL-17A and IL-17F are key drivers in the pathogenesis of psoriasis," Prof. Bruce Strober (Yale University, USA) pointed out. "The response to psoriasis therapy varies based on patient demographics, disease characteristics, and prior treatment exposure. Therapies that provide a consistent and durable response, regardless of these variables are needed."

The double-blinded, 52-week, phase 3 BE VIVID (NCT03370133) trial was designed to evaluate the efficacy and safety of bimekizumab compared to placebo and ustekinumab for the treatment of moderate-to-severe chronic plaque psoriasis. The 567 adult participants were randomised 4:2:1 to bimekizumab 320 mg (n=321) every 4 weeks, ustekinumab (n=163) in a weight-adjusted dose (45 mg or 90 mg) at baseline, week 4, and subsequently every 12 weeks, or placebo. After 16 weeks, patients in the placebo cohort were switched to bimekizumab. "Just over a third of patients had been previously exposed to biologic therapy," said Prof. Strober. The current analysis evaluated outcomes for bimekizumab versus ustekinumab only.

At week 16, a Psoriasis Area and Severity Index (PASI) 90 response was achieved by 85.0% of patients with bimekizumab and 49.7% with ustekinumab. At week 52, the corresponding proportions were: 81.9% with bimekizumab and 55.8% with ustekinumab. Looking at differences between weight groups with a cut-off point of 100 kg, results were consistent in both subgroups of bimekizumab with rates over 80% versus around 56% in the ustekinumab groups. Also, stratifying according to PASI <20 or ≥20 led to similar results for achievement of PASI 90. With regard to prior exposure to biologic DMARDs, PASI 90 was achieved by 50.8% in ustekinumab recipients with previous biologics and 59% without history of biologic treatment. For patients treated with bimekizumab, these percentages were 86.6% and 79.1%, respectively.

The secondary endpoint of a PASI 100 response at week 16 was observed in 58.6% of patients treated with bimekizumab and 20.9% with ustekinumab. After 1 year, 64.5% reached PASI 100 with bimekizumab and 38.0% with ustekinumab. Similar to the PASI 90 results, the PASI 100 results were consistent across subgroups stratified by weight, baseline PASI, and prior biologic therapy.

"Bimekizumab demonstrated greater skin clearance that was durable in patients with moderate-to-severe plaque psoriasis as compared with ustekinumab, regardless of patient subgroup," stressed Prof. Strober. "These results support bimekizumab as a psoriasis treatment suitable for a wide variety of patients given its consistent efficacy across all subgroups analysed."

1. Strober B, et al. Bimekizumab versus ustekinumab efficacy across subgroups of patients with moderate to severe plaque psoriasis: Results from the multicentre, randomised, double-blinded phase 3 BE VIVID trial. FC03.06, EADV 2020 Virtual Congress, 29-31 Oct.

Meaningful sleep improvement with IL-13 inhibition

A post-hoc analysis of the pivotal phase 3 ECZTRA 1 and 2 trials on tralokinumab treatment for atopic dermatitis observed early and significant ameliorations in various sleep assessing tools.

Tralokinumab is an anti-IL-13 monoclonal antibody that has previously demonstrated significant superior efficacy in reducing signs and symptoms of atopic dermatitis (AD) in the pivotal phase 3 trials ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) [1]. As sleep loss plays a major role in the decreased quality of life of AD patients, Prof. Jonathan Silverberg (George Washington University School of Medicine and Health Sciences, USA) and his fellow researchers performed a post-hoc analysis of these studies with a focus on the impact of tralokinumab on sleep loss [2,3]. The identically designed, international studies randomised over 1,500 adult patients to receive either tralokinumab 300 mg every 2 weeks over 16 weeks or placebo [3]. In ECZTRA

trials, 3 different kinds of sleep measures were evaluated: the eczema-related sleep Numeric Rating Scale (NRS) with a 24-hour recall, the Scoring Atopic Dermatitis (SCORAD) sleep score with a 3-day recall, and the Patient Oriented Eczema Measure (POEM) sleep score with a 7-day recall. The NRS data was collected in an e-diary filled out by the patients themselves, data for SCORAD and POEM was gathered during the study visits.

"Baseline characteristics were similar between the groups, really everything was well balanced across trials and across treatment arms," said Prof. Silverberg. For example, in ECZTRA 1, the mean Eczema Area and Severity Index (EASI) was 32.9 in the placebo arm versus 32.2 in the tralokinumab arm. The respective measures for sleep were: 6.8 versus 6.9 for the sleep NRS, 6.4 versus 6.5 for the sleep SCORAD, respectively, and 3.3 for POEM. The mean age of the participants was 39, about 60% of patients were male.

The results for eczema-related sleep disturbance in the NRS showed greater improvements in both tralokinumab arms. "The curves for tralokinumab show early separations already by week 1 compared with placebo, and that separation continues to widen even further and continues out to week 16 and it is really statistically significant at all endpoints," Prof. Silverberg highlighted. The P-values at every week versus placebo were all either P<0.01 or P<0.001. At week 16, changes from baseline were -2.6 for tralokinumab versus -1.9 for placebo in ECZTRA 1, and -2.9 for tralokinumab versus -1.5 for placebo in ECZTRA 2. Results in SCORAD sleep score were similar: at week 16, the difference was -2.6 and -3.0 for tralokinumab versus -1.8 and -1.8 for placebo with a P<0.01 and P<0.001 in ECZTRA 1 and ECZTRA 2, respectively.

POEM is a categorical scale placing the days of sleep disturbance in 5 different classes starting at 0 days, then 1-2 days, and further up to every day. "At baseline almost everybody had really profound sleep disturb with ≥3 nights of disturbed sleep," said Prof. Silverberg. At week 16, there were higher proportions of patients who even achieved 0, or only 1 or 2 night of sleep problems in the tralokinumab groups, without much amelioration in the placebo arms. For example, in ECZTRA 2, at baseline, 14% of patients reported up to 6 days and 65.4% everyday sleep disturbance within the tralokinumab arm. The corresponding proportion in the placebo arm were 11% and 68%, respectively. At week 16, the percentage of tralokinumab recipients with everyday sleep problems declined to 33.3%, and 39.1% even reported 0 or only 1-2 disturbed nights, while the matching placebo rates were 51.5% and 21.5%.

"Early improvement in sleep measures as early as week 1 with tralokinumab is consistent with its effects on the signs and troublesome symptoms of atopic dermatitis, including pruritus," concluded Prof. Silverberg.

1. Wollenberg A, et al. Br J Dermatol. 2020 Sep 30. DOI:10.1111/bjd.19574.
2. Chang YS, et al. J Allergy Clin Immunol. 2018;142:1033-40.
3. Silverberg J, et al. Specifically targeting interleukin-13 with tralokinumab improved sleep in two Phase 3, randomised, double-blind, placebo-controlled trials in patients with atopic dermatitis. FC08.05, EADV 2020 Virtual Congress, 29-31 Oct.

Preventing foot odour with zinc oxide coated socks

A Thai, double-blind, randomised controlled trial revealed that wearing socks coated with nanoparticles of zinc oxide led to less bromodosis and pitted keratolysis in military cadets during field training.

"While completing an internship as a naval officer in the medical department, I saw a high number of foot infections in military personnel. I wanted to find a way to prevent and treat these fungal and bacterial infections and those conditions associated," Dr Punyawee Ongsri (Siriraj Piyamaharajkarun Hospital, Mahidol University, Thailand) explained the motivation for the presented study [1].

Metal oxides have shown antibacterial action for a wide range of bacteria, including antibiotic-resistant species. They act by generating reactive oxygen species that may destroy bacterial walls and, for example, induce bacterial DNA damage. "Antibacterial efficacy is determined by size and concentration of the particles," stated Dr Ongsri. Previous studies have shown that several metal oxide particles like zinc, titanium, silver, or silica can have antibacterial effects and some are already used in different industrial fields [2-5]. Special features of zinc oxide nanoparticles (ZnO-NP) are their photocatalyticity and the lack of evidence of environmental toxicity in contrast to, for example, silver oxide.

The double-blind, randomised controlled trial included more than 140 cadets of the Thai Naval Rating School, who took part in a 2-week field training course and had no history of bromodosis or abnormal foot lesions like pitted keratolysis. The cadets were provided with 2 pairs of either ZnO-NP-

coated socks or uncoated socks. The groups were not statistically different in baseline characteristics.

Before the training, a self-assessment of foot odour and a dermatologic, intervention-blinded examination was performed along with the completion of a questionnaire on behavioural risk factors by the cadets. During training, the provided socks had to be worn ≥8 hours a day and the use of any foot treatment such as deodorant was not allowed. After the training, the same assessments followed.

The results showed significantly less cases of pitted keratolysis (15.7% vs 40.5%; P=0.05) and a reduction in foot odour (-0.34 vs -0.14; P=0.34; see Table). The ZnO-NP-coated socks were also associated with high satisfaction in use by the cadets compared with the uncoated socks (95.9% vs 83.8%; P=0.01). "Persons in the uncoated-sock group complained of a more intense foot odour, which had a moderate to large effect on their daily life," stated Dr Ongsri. He concluded: "We propose that wearing these socks could be adopted as a primary prevention in populations at risk, especially in military personal."

Table: Results after the 2-week field training course [1]

	ZnO-NP coated socks (n=74)	Uncoated socks (n=74)	P-value
Pitted keratolysis development after training, n(%)			
Yes	19 (15.7)	30 (40.5)	0.05
No	55 (74.3)	44 (59.5)	0
VAS of foot odour, n(%)			
Before training	2.6 (0.6)	2.6 (0.6)	0.32*
After training	2.2 (1.1)	2.5 (1.6)	0.20*
After - Before	-0.34 (1.1)	-0.14 (1.5)	0.34**
Disturbing foot odour affecting daily quality of life after training, n(%)			
Moderate to large effect	3 (4.1)	10 (13.5)	0.04
No to minimal effect	71 (95.9)	64 (86.5)	
Satisfaction with using socks, n(%)			
High	71 (95.9)	62 (83.8)	0.01
Low	3 (4.1)	12 (16.2)	

*Mann-Whitney U test; **unpaired t-test. ZnO-NPs, zinc oxide nanoparticles; VAS, visual analogue scale.

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3. Fiedot-Toboła M, et al. Materials (Basel). 2018;11:707.
4. Padmavathy N, Vijayaraghavan R. Sci Technol Adv Mater. 2008;9:035004.
5. Gao J, et al. Chemosphere. 2015;119:948-52.

Baricitinib in AD: Efficacy paired with consistent long-term results

In the phase 3 BREEZE-AD3 trial, baricitinib demonstrated reliable long-term response maintenance in patients with moderate-to-severe atopic dermatitis (AD) for up to 68 weeks.

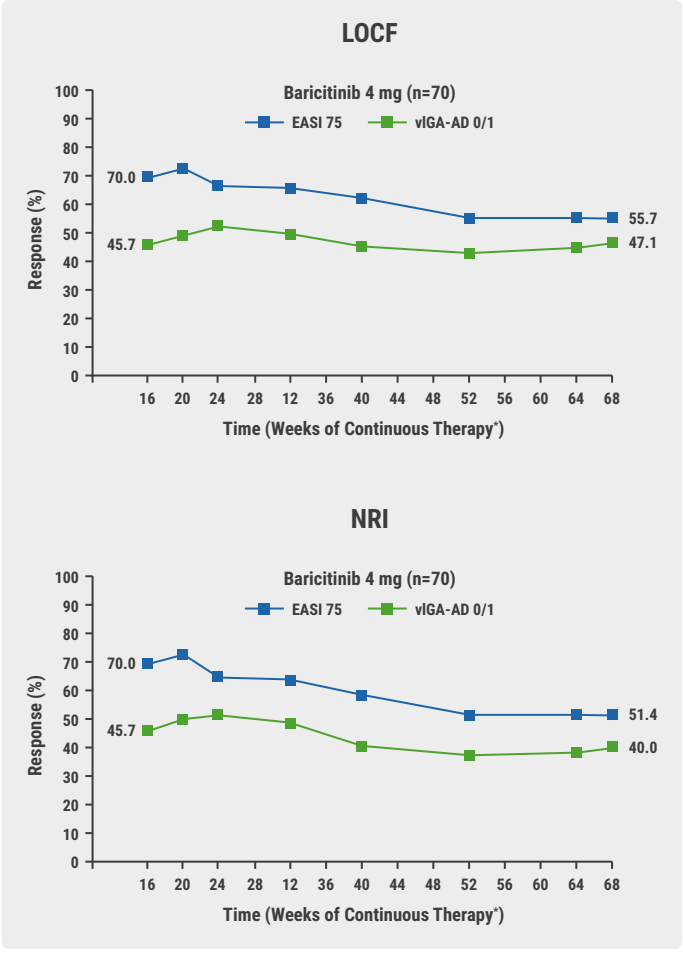
The oral JAK1/JAK2 inhibitor baricitinib has shown significant efficacy in improving signs and symptoms of AD in the 2 independent monotherapy trials BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422) [1]. Patients completing these studies were eligible for enrolment into the presented BREEZE-AD3 (NCT03334435), a double-blind, long-term extension trial to assess baricitinib in patients with moderate-to-severe AD up to 68 weeks [2].

The trial design differed depending on the participant's outcome at the end of the parent studies. Responders and partial responders, identified by a validated Investigator´s Global Assessment (IGA) for AD of 0, 1, or 2 at week 16, would continue receiving the same agent as in BREEZE-AD1 and BREEZE-AD2. As a result, there were 4 arms with either placebo or 1 mg, 2 mg, or 4 mg of baricitinib. Non-responders, who ended the previous studies with an validated IGA AD score of 3 or 4, were re-randomised and switched from once daily placebo, 1 mg, or 2 mg of baricitinib to either 2 mg or 4 mg of baricitinib in the extension study. Non-responders in the 4 mg baricitinib group continued their previous dosage. Efficacy outcomes were measured by the rate of patients achieving a validated IGA AD of 0/1 (i.e. clear or almost clear) as the primary endpoint and an Eczema Area and Severity Index (EASI) 75 improvement up to 68 weeks. The investigators used 2 different approaches for imputing missing data: last observation carried forward (LOCF) and non-responder imputation (NRI). Results were compared between both methods.

Independent of the applied approach, baricitinib 4 mg accounted for an overall consistent efficacy that was more or less maintained from week 16 on, with a validated IGA AD 0/1 starting at 45.7% at week 16 and reaching 47.1% (LOCF) and 40.0% (NRI) at week 68. Furthermore, the EASI 75 of 70.0% at week 16 decreased slightly to 55.7% (LOCF) and 51.4% (NRI) at week 68 (see Figure page 23). Similar outcomes were seen in the evaluation of itch NRS (≥4-point improvement), skin pain NRS (≥4-point improvement), and AD symptom score (ADSS) item 2 (≥1.5-point improvement)

with baricitinib 4 mg. "You see a consistent pattern across all those endpoints regardless of using LOCF or NRI," said Prof. Jonathan Silverberg (George Washington University School of Medicine and Health Sciences, USA). The rates measured at week 32 (LOCF) were: 45.9% (itch NRS), 54.5% (skin pain NRS), and 71.4% (ADSS item 2) versus 52.5%, 61.8%, and 75.0%, respectively, at week 16. In the baricitinib 2 mg treatment arms, validated IGA AD and EASI 75 percentages at week 16 were 46.3% and 74.1%, and even mounted to 59.3% and 81.5% (both with LOCF) at week 68. Also, the patient-related outcomes were suggestive of stable response through week 32.

Figure: Results for validated IGA-AD 0/1 and EASI 75 with baricitinib 4 mg from week 16 to 68 [2]



* Total weeks includes the 16 weeks of treatment in the original studies BREEZE-AD1 and BREEZE-AD2.
EASI, Eczema Area and Severity Index; LOCF, last observation carried forward; NRI, non-responder imputation; vIGA-AD, validated Investigator's Global Assessment for atopic dermatitis.

Reassuring safety data in over 2,500 treated patients

Since the patients enrolled in BREEZE-AD3 originated from different parent studies, Prof. Silverberg presented a unique safety summary that was published, which contained integrated data from 2,531 patients from 8 clinical trials (7 phase 3 trials and a phase 2 trial) [2,3]. The data includes adverse event information from responders, partial responders, and non-responders within the placebo-controlled data sets until week 16, as well as the extended analyses. All AD trial patients treated with baricitinib equalled a total of 2247.4 patient-years of exposure. "What you can appreciate overall is that the safety is pretty consistent to what we have seen in the individual studies, but now in the pooled analyses there is maybe a little bit of an increase in terms of any treatment-related adverse events with baricitinib 2 mg and 4 mg doses, although we don't see any kind of dose-dependent responses," Prof. Silverberg pointed out. Especially in the placebo-controlled treatment phase up to week 16, there were no deaths, no gastro-intestinal perforations, and no major adverse cardiovascular events. In all patients treated with baricitinib (n=2,531), herpes zoster had a study size-adjusted incidence rate of 2.3 and herpes simplex an incidence rate of 10.3. All in all, authors of the safety analysis observed no new safety concerns. In conclusion, Prof. Silverberg highlighted that baricitinib 2 mg and 4 mg demonstrated sustained long-term efficacy in moderate-to-severe AD.

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Best of the Posters

Effects IL-13 blocker improves with longer treatment duration

Patients with atopic dermatitis (AD) who initially only showed partial response to tralokinumab showed progressive improvements when treated beyond week 16. This was the results of a pooled analysis of two phase 3 trials.

In the pivotal phase 3 ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) trials in adults with moderate-to-severe AD, tralokinumab monotherapy provided significant and early improvements in clinically relevant endpoints. In both trials, significantly more patients receiving tralokinumab monotherapy than placebo achieved the primary endpoints of Investigator's Global Assessment (IGA) 0/1, equivalent to clear or almost clear skin, and 75% improvement in Eczema Area and Severity Index (EASI 75). However, these are stringent endpoints; hence, achievement of mild disease severity (IGA 2) and a 50% improvement in EASI could already be considered clinically relevant for most patients. The current post-hoc analysis evaluated the treatment results of patients who did not achieve the primary endpoint at week 16 and continued to receive open-label tralokinumab plus optional topical corticosteroids (TCS) for an additional 36 weeks [1].

After 52 weeks, 20.1% of patients treated with tralokinumab plus optional TCS achieved an IGA 0/1 response, and 42.9% achieved an EASI 75 response (see Figure). More than half of the responder proportions at week 52 were achieved within 8 weeks of starting open-label treatment.

Late response not due to TCS therapy

To determine whether the improved response over time was due to TCS or tralokinumab, another analysis was performed in which participants who used concomitant anti-inflammatory treatment (49.3%) were considered non-responders. In this alternative analysis, the response rates were 13.9% and 25.7% for IGA 0/1 and EASI 75, respectively, at week 52 without TCS.

The authors concluded that adult patients who did not achieve IGA 0/1 or EASI 75 at week 16 progressively improved with continued tralokinumab treatment beyond week 16. The clinical response with continued treatment beyond week 16 was mainly driven by continued tralokinumab treatment and not by the addition of optional TCS.

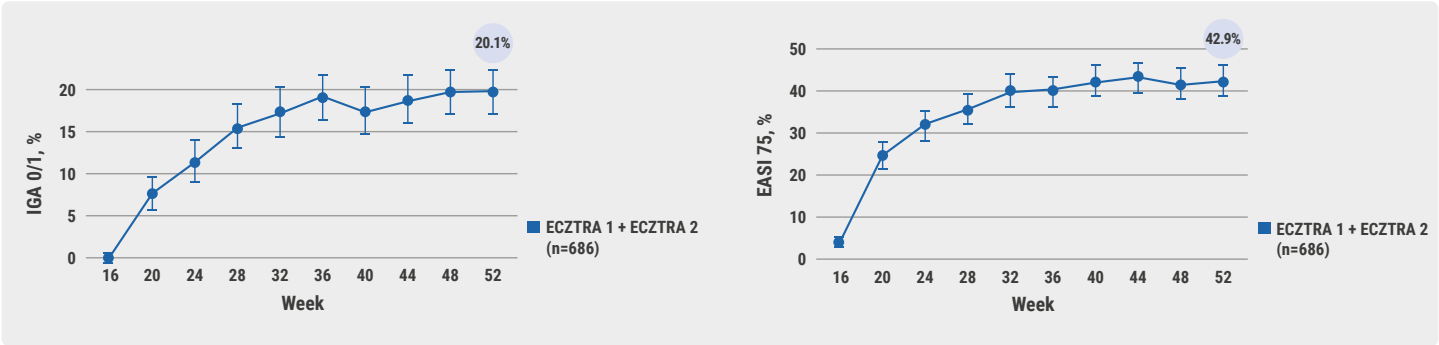
1. Simpson E, et al. Tralokinumab provides progressive improvements beyond week 16 in patients with atopic dermatitis with an initial partial response. Poster P0214, EADV 2020 Virtual Congress, 29-31 Oct.

Risky sexual behaviour and STIs on the rise despite the pandemic

Despite the COVID-19 lockdown restrictions, an Italian study with data from 2 centres for sexually transmitted infections in Milan revealed an increase in sexually transmitted infections (STIs), including gonorrhoea, secondary syphilis, and *Mycoplasma genitalium* in 2020 compared with 2019.

Data for the study was collected in 2 main centres for STIs, which together account for about 80% of STI diagnoses in the Lombardy region in Italy [1]. Both centres limited their access

Figure: Participants achieving (A) IGA 0/1 and (B) EASI 75 at week 52 in the open-label phase [1]



but stayed open during the lockdown that started on 8 March 2020 in Italy. The total attendance of the centres decreased by 70% from 1,696 patients in 2019 to 534 in 2020. In 2019, 86% of patients were male compared with 76% male in 2020. The prevalence of men who have sex with men (MSM) was 31% in 2019 and 35% in 2020. The median age was 37 years in 2019 and 33 in 2020.

In 2019, 233 confirmed STI cases were diagnosed. In the same period in 2020, 147 persons were diagnosed with STIs, a drop of 37%. Yet, this drop was noticed in the non-acute cases, such as genital warts and Molluscum, whereas the number of acute bacterial infections associated with MSM increased: in 2020, more cases of secondary syphilis, gonorrhoea, and *M. genitalium* were diagnosed.

The authors concluded that the COVID-19 pandemic, despite lockdown and advice on social/physical distancing, did not inhibit risky behaviours and that acute STIs even increased. "It was assumed that the lockdown would reduce the opportunity for sexual encounters and STIs. However, I was surprised by the number of new acute infections diagnosed in this short period of time. Gonorrhoea and syphilis are typically more prevalent in people in their 30s, so infections may have increased because the concentration of COVID-19 morbidity and mortality in the elderly made the younger, more active, cohort feel protected and so less risk-averse," concluded Dr Marco Cusini (Policlinico of Milan, Italy).

Although it is unrealistic to prevent people from having sex, close contact during sexual intercourse inevitably involves an increased risk of SARS-CoV-2 infection. Dr Cusini concluded that these findings highlight the importance of ongoing screening for STIs and the importance of having these types of services open and available during pandemic restrictions.

1. Cusini M, et al. COVID-19 and STIs. P1534, EADV 2020 Virtual Congress, 29-31 Oct.

Real-world data on brodalumab affirms efficacy and fast onset of action

A German study investigated the performance of brodalumab for the treatment of psoriasis in real-world conditions. They found meaningful responses as of week 2 and the highest clearance rates was observed in biologic-naïve patients.

Brodalumab has shown remarkable efficacy and fast onset of action in psoriasis patients in clinical phase 3 trials [1,2]. The current LIBERO trial aimed to assess how these results translate into a patient population encountered in the daily practice [1]. The ongoing, prospective, non-interventional study investigates the real-world evidence of brodalumab in disease management of psoriasis after 12 and 52 weeks. Data of over 500 patients was obtained between November 2017 and January 2020 from 216 German study centres on the effect of brodalumab on the absolute Psoriasis Area Severity Index (aPASI). Dr Ralph Von Kiedrowski (Germany) presented the 12-week results of the study at the 29th EADV Congress [3].

The mean age of the study subjects was 50 years, mean duration of disease 20 years, and 64.9% of the patients were male. Baseline grades of psoriasis severity were 28% mild, 41% moderate, 19% severe, and 12% very severe. More than half of the patients had never received biologics before (57.2%). Of those who received preceding biological therapy, 39% were changed within 3 months from IL-17A antagonists, 47% from TNF blockers, and 17% from IL-23/12 or IL-23 antagonists.

At week 12, 77.2% of the patients met the primary endpoint of aPASI ≤3. Interestingly, the mean aPASI already dropped from 16.9 at baseline to 9.1 by week 2 and continued to decrease to 4.8 at week 4. PASI 75 and PASI 100 were achieved by 82.3% and 37.0% of the biologic-naïve patients compared with 64.8% and 27.8% with previous TNF-blocker treatment, respectively. After 12 weeks, complete clearance (PASI 100) was reached by a quarter of the patients in the baseline category of very severe psoriasis (mean PASI 30.5).

In conclusion, this large study on real-word evidence confirms that brodalumab induces swift ameliorations of aPASI with a high grade of efficacy.

1. Lebwohl M, et al. N Engl J Med. 2015;373:1318-28.
2. Lebwohl M, et al. Am J Clin Dermatol. 2019;20:863-871.
3. Von Kiedrowski R, et al. Management of moderate-to-severe psoriasis with brodalumab in daily practice conditions – first real-world-evidence (RWE) results from the LIBERO trial. P1307, EADV 2020 Virtual Congress, 29-31 Oct.

Heightened risk for psychiatric comorbidities in hidradenitis suppurativa patients

A substantially increased risk for several psychiatric disorders as well as for substance and alcohol abuse was detected in patients with hidradenitis suppurativa (HS) in an Australian meta-analysis. The chronic inflammatory skin disease HS is known to reduce quality of life and has also been linked to factors such as

smoking and comorbidities like obesity and metabolic syndrome [1-3].

Since previous studies have shown that chronic inflammatory skin diseases could be connected to psychiatric disorders, Dr Kevin Phan (Liverpool Hospital, Australia) and colleagues were interested in a possible association of HS with psychiatric comorbidities like depression, schizophrenia, or suicidal tendency [4-6]. They also looked at alcohol and substance abuse in this population. The researchers performed a meta-analysis of studies identified by an electronic database search and direct review of articles together with data about cases and controls [4].

Regarding psychiatric diagnoses, the study found significantly elevated risks for HS patient to suffer from schizophrenia (OR 1.66; 95% CI 1.53-1.79; P<0.00001), anxiety (OR 1.71; 95% CI 1.51-1.92; P<0.00001), bipolar disorders (OR 1.96; 95% CI 1.65-2.33; P<0.00001), depression (OR 1.75; 95% CI 1.44-2.13; P<0.00001), and personality disorders (OR 1.50; 95% CI 1.18-1.92; P=0.001). The likelihood of suicide was around 2 times higher (OR 2.08; 95% CI 1.27-3.42; P=0.004) and in about the same order of magnitude as alcohol abuse (OR 1.94; 95% CI 1.43-2.64; P<0.0001). The odds for substance-related disorders were almost 3 times higher (OR 2.84; 95% CI 2.33-3.46; P<0.00001) when HS patients were compared with those without HS.

In view of these results, Dr Phan highlighted the need for dermatologists treating HS patients to consider integrating psychological and psychiatric support to the multidisciplinary management. The authors endorse future studies to evaluate a general screening policy in order to identify suicide risk.

1. Menter A. Semin Cutan Med Surg. 2014;33:S54-6.
2. Kohorst JJ, et al. J Am Acad Dermatol. 2015;73:S27-35.
3. Shlyankevich J,et al. J Am Acad Dermatol 2014;71:1144-1150.
4. Phan K, et al. Hidradenitis suppurativa and relationship with psychiatric comorbidities, suicides and substance abuse. P0019, EADV 2020 Virtual Congress, 29-31 Oct.
5. Onderdijk AJ, et al. J Eur Acad Dermatol Venereol. 2013;27:473-478.
6. Shavit E, et al. J Eur Acad Dermatol Venereol. 2015;29:371-376.