**Late-Breaking News**
Two JAK inhibitors show promising results in patients with alopecia areata. Preliminary data suggest that IL-17 blockade might be effective in hidradenitis suppurativa, and IL-36 blockade in pustular psoriasis.

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**Spotlight on Urticaria**
Many patients with chronic urticaria have to live with their symptoms, despite the availability of effective therapies. The motto ‘treat the disease until it is gone’ is also highlighted in the novel treatment guidelines.

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**What’s New in Atopic Dermatitis?**
Patients with AD are more prone to skin infections compared to healthy controls due to the immune dysfunction that plays a key role in AD pathogenesis. A novel topical approach addressing this immune dysfunction proved remarkably effective.
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Dear Reader,

This year’s EADV provided a wealth of new information. Insights into the pathogenesis of complex inflammatory diseases are developing rapidly, with an important practical impact. Discovering treatment targets in these diseases, invention of new medications, targeting and implementing these innovations is the reality of dermatology of today: INVENTIONS, INNOVATIONS, AND IMPLEMENTATION characterise dermatology as a rapidly developing specialty. This was also visible at the 27th EADV Congress in Paris, France.

In psoriasis, important new treatments have become available: anti-IL-17 treatments and, more recently, anti-IL23. These treatments have clearly raised the bar for efficacy: we can be ambitious in the treatment of psoriasis. Current important questions are the positioning of biologics in the treatment of psoriasis: Should we treat forever, or can we reduce the dosage or stop treatment? Is true disease modification possible? Which treatment for which patient? What about early intervention? An important new lead in this area is the registration of certolizumab, which means that we can treat women in pregnancy safely.

New opportunities are also available in atopic dermatitis. Blockade of IL-4 and IL-13 by dupilumab has provided a new horizon for patients with this disease. Important is that new drugs are in development for atopic dermatitis, with JAK inhibitors as a promising development. A remarkable observation was the demonstration that two JAK inhibitors are effective in alopecia areata; a new perspective for this often difficult-to-treat condition.

In this EADV Medicom Conference Report you will find the highlights of innovations presented at the 27th EADV Congress, including developments in the management of urticaria, new aspects of allergic contact dermatitis, new insights into skin fragility syndrome, and new aspects in paediatric dermatology.

The future of dermatology is bright.

Prof. P.C.M. van de Kerkhof
Chair of the scientific programming committee of EADV and director and chair of the Department of Dermatology at the University of Tübingen, Germany.

Among the numerous interesting data presented during this meeting, what are your highlights of the EADV 2018, what is not to miss?
Prof. Röcken: The highlights this year were probably the plenary lectures, where we had world famous clinicians who brought us the latest insights into HIV infection, atopic dermatitis and infection, melanoma therapy, microbiome of the skin diseases, and then the classical and new treatment options. Every indication is done on three different levels: one for beginners, one for practising dermatologists, and, of course, one for teaching experts. In this way, every participant can choose a programme tailored to his or her specific needs and will get the appropriate and highest training possible.

Do you think it is still worth visiting a congress despite all the online training possibilities that exist nowadays?
Prof. Röcken: Very much so. And the dermatologists obviously feel the same. During the previous two years, we have seen an increase of 3,000-4,000 participants, and 2,000 more EADV members. Our annual meeting was the largest worldwide congress in dermatology with a total of 13,000 participants. So, this was a clear success, and more and more people are attending our meeting.

How can the problem of undertreatment be solved?
Prof. Röcken: The problem is that many patients are not taken care of by dermatologists, or they are with dermatologists who lack up-to-date training. This is why we created classes at three levels at the EADV meeting. Train the dermatologist in order to bring them up-to-date with novel treatments. Better education is a successful approach to solve the problem of undertreatment. First, the patient should really see a dermatologist, and then the dermatologist has to be well trained.

Are there new features in EADV 2018 in the way this meeting is organised?
Prof. Röcken: In principle, we more or less preserved the structure we established for this meeting four years ago. Normally, congresses are organised in different workshops and symposia, without a specific structure. In contrast, we set up a structured training according to different indications, e.g. atopic dermatitis, psoriasis, non-melanoma skin cancer, HIV, or skin infections. Attending dermatologists get the full insight into this indication starting from early epidemiology, diagnosis histology, microbiology of the skin diseases, and then the classical and new treatment options. Every indication is done on three different levels: one for beginners, one for practising dermatologists, and, of course, one for teaching experts. In this way, every participant can choose a programme tailored to his or her specific needs and will get the appropriate and highest training possible.

With so many new biologics entering the treatment arena (at the moment in psoriasis, and in atopic dermatitis in the near future), how do you choose the right agent for the patient?
Prof. Röcken: For psoriasis, we now have more than a dozen different drugs, and also increasingly more drugs for atopic dermatitis. And there are the IL-1 antagonists and TNF-α antagonists for other inflammatory diseases. The goal in teaching healthcare professionals is exactly this: what to do first, and how to develop a treatment algorithm; what are the classic treatments, what is the initial treatment and what is the maximal treatment – when to do what. And how and which biological to use under certain conditions. The worst thing to do is to just exchange one biologic with another, without a plan. We will need an escalation ladder, and the idea is to train people to make the correct treatment decisions, and to gradually move from the regular treatments to the more aggressive/expensive ones.
The late-breaking news session was one of the highlights of this year’s EADV meeting. More and more biologics and small molecules will enter the stage in dermatology, not only in psoriasis and atopic dermatitis but also in rare diseases.

**JAK-inhibitor successful in alopecia areata**

Two experimental janus kinase (JAK) inhibitors proved to be active in alopecia areata in a phase 2a study [1]. This trial investigated hair regrowth and adverse events (AEs) in subjects with alopecia areata treated with PF-06651600 (a potent JAK3 inhibitor, given in a dose of 200 mg once daily [QD] for 4 weeks, followed by 50 mg QD for 20 weeks) and PF-06700841 (an inhibitor of JAK1 and tyrosine kinase 2 [TYK2], given in a dose of 60 mg QD for 4 weeks, followed by 30 mg QD for 20 weeks).

A total of 145 adults with moderate-to-severe alopecia areata were included, which was defined as hair loss affecting more than 50% of the scalp that had persisted for more than six months. The primary efficacy endpoint was mean change from baseline in Severity of Alopecia Tool (SALT) score at week 24. In addition, the proportion of participants achieving 30%, 50%, 75%, 90%, and 100% SALT improvement from baseline (SALT30, SALT50, SALT75, SALT90, and SALT100, respectively), and eyelash and eyebrow responders (1 grade improvement on the respective assessment scale [range 0-3] among patients with the condition at baseline) were assessed. The trial included 62 patients with alopecia totalis, and 42 patients with alopecia universalis. Further, 62 patients had no or minimal eyelashes.

Spontaneous and treatment-induced recovery occurred in up to 50% of cases. Both JAK inhibitors met week 24 primary endpoints by improving hair regrowth scoring 33.6 of 100 points on SALT scale and 49.5 of 100 points for JAK3 and TYK2/JAK1, respectively (both changes P<0.01). There was a statistically significant separation from placebo occurring at week 6 and week 4, respectively, and greater improvement in the PF-06700841 group (Figure 1).

At week 24 (vs baseline), SALT30 was achieved in 48% of the PF-06651600 group and in 36% of the PF-06700841 group. Significant improvements were also seen in SALT50, 75, 90, and 100 responses, and in patients who experienced eyelash and eyebrow improvement. The patients with areata totalis and areata universalis also showed benefit of the treatment.

**Acceptable safety profile**

The most common AEs were infections, gastrointestinal complaints, and subcutaneous tissue disorders, and most were mild. Rhabdomyolysis was observed in two cases in the PF-06700841 group, and this was resolved after discontinuation. No other major adverse events were recorded.

“These JAK inhibitors are well-tolerated in patients, including those with areata universalis and areata totalis. Both treatments achieved the primary and secondary endpoints, and safety and tolerability, and I think that our patients with alopecia areata now have reason to be optimistic,” concluded Prof. Rodney Sinclair (Sinclair Dermatology, Melbourne, Australia), who presented the trial results.

Despite a global lifetime incidence estimated at about 2%, alopecia areata has lacked effective treatment options and there is an unmet medical need for a reliable therapy in moderate-to-severe cases. This autoimmune disease results from damage

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**Figure 1 SALT change from baseline over time compared to placebo for PF-06651600 (red) and PF-06700841 (blue) [1]**

**LS Mean Change from BL within 90%CI**

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<th>Week</th>
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**P<0.01, ***P<0.001 vs Placebo**

BL, baseline; CI, confidence interval; LS, least squares.
of the hair follicle by cytotoxic T lymphocytes, a process that can be reversed by JAK inhibition [2].

Since 2014, an increasing number of case reports have demonstrated that oral JAK inhibitors are an effective treatment for chronic alopecia areata. However, few randomised controlled trials have examined the efficacy and safety of JAK inhibitors.

**Secukinumab: the upcoming therapy for hidradenitis suppurativa?**

Therapy for hidradenitis suppurativa (HS) can be very demanding and has a substantially negative impact on the quality of life (QOL) of the ones affected. This inflammatory condition can, among other things, lead to abscess formation, fistulas, and scarring of great extent [3]. It has been found that HS lesions present an increased ratio of T-helper 17 (Th17) cells to regulatory T-cells within the T-cell population. Additionally, elevated IL-17 in skin and serum of HS patients, as well as case reports of effective HS treatment with the IL-17A blocker secukinumab contributed to the objective of further investigation of this treatment option.

The current open-label trial included 18 patients with moderate to severe HS for testing two different dosing frequencies of secukinumab. Study subjects all started with weekly doses of secukinumab 300 mg in week 0-4 and continued with the same subcutaneous dosage every two (Q2) or four (Q4) weeks up to week 24. The primary endpoint was defined as clinical response with no increase in draining fistulas or abscesses plus a 50% decrease in inflammatory nodules from baseline. Furthermore, changes in Dermatology Quality of Life Index (DLQI) and Sartorius Score values were measured. The Sartorius Hidradenitis Suppurativa Score is a standardised tool to assess the anatomic region involved, the number and scores of lesions, and the distance between relevant lesions in HS [4].

Patients had a mean age of 33, weight of 103 kg, DLQI of 12, Sartorius Score of 166, and 61% had smoked. About one third of them had a history of treatment failure with TNF inhibitors. Within the Q4 group 7 patients completed week 12 and four week 24, patient’s numbers in the Q2 group were nine and six respectively. This interim study analysis showed that 78% of the patients attained clinical response with no increase in draining fistulas or abscesses plus a 50% decrease in inflammatory nodules from baseline. Furthermore, changes in Dermatology Quality of Life Index (DLQI) and Sartorius Score values were measured. The Sartorius Hidradenitis Suppurativa Score is a standardised tool to assess the anatomic region involved, the number and scores of lesions, and the distance between relevant lesions in HS [4].

In general, the drug was well-tolerated at both dosing regimens. No cases of inflammatory bowel diseases occurred.

Despite the rather small sample size of this trial and a big drop-out rate, the authors conclude that secukinumab may be seen as a promising new treatment modality for HS. The results warrant further investigations in a randomised controlled clinical trial.

**IL-4/IL-13 blockade shows remarkable efficacy in adolescents**

Adolescents with moderate-to-severe atopic dermatitis have a distinct treatment benefit from the antibody dupilumab. This was the key message of a phase 3 trial presented by Prof. Eric Simpson (Oregon Health and Science University, Portland, USA) [5].

This randomised, placebo-controlled, double-blind, parallel-group study included 251 adolescents aged 12 to <18 years old (mean age 14 years) with moderate-to-severe atopic dermatitis that was inadequately controlled by topical therapies. Their mean disease duration was 12 years. After a washout period, subjects were randomly allocated to dupilumab every 4 weeks (Q4) treatment group (300 mg; n=84), or dupilumab every 2 weeks (Q2) treatment group (200 mg or 300 mg for adolescents weighing >60 kg; n=82), or placebo (n=85). Endpoints were measured at baseline and at week 16.

At week 16, both dupilumab groups showed a significantly higher proportion of patients with clear or almost clear skin according to the Investigators Global Assessment (IGA) than the placebo group, with slightly stronger responses seen in the Q2 group (Q4 group: 17.9%; Q2 group: 24.4%; placebo group: 2.4%; both dupilumab groups P<0.01 vs placebo). The proportion of patients reaching a 75% improvement in the Eczema Area and Severity Index (EASI 75) at week 16 was 38.1% in the Q4 group, and 41.5% in the Q2 group, compared with only 8.2% in the placebo group (both dupilumab groups P<0.001 vs placebo) (Figure 2). Dupilumab also significantly improved peak pruritus numerical rating scale (NRS) scores from baseline to week 16. A significantly higher proportion of dupilumab-treated than placebo-treated patients achieved ≥3-point improvement in peak pruritus NRS at week 16 and ≥4-point improvement at week 4 and week 16.

**Higher effect size in adolescents**

“The effect sizes seen in the change in EASI scores from baseline were larger than those seen in the previous adult
"trial," Dr Simpson said. Of note, the higher effect size could be demonstrated despite the fact that the adolescents included in this study had more severe atopic dermatitis than that of the previous study with adults, with higher mean EASI scores, a larger proportion exhibiting severe atopic dermatitis, and a high atopic comorbidity (92%). Rates of conjunctivitis and injection-site reactions were higher in the dupilumab groups, but atopic dermatitis exacerbation and non-herpetic skin infections were higher in the placebo group. None of the events seen with dupilumab was serious or severe. The safety profile was similar to that observed in adults, with no new safety signals.

This data is of particular importance because no effective treatment options currently exist for adolescents not adequately treated with topical steroids or calcineurin inhibitors. At present, there are no systemic biologic medications approved for this growing patient population.

Tildrakizumab: consistent treatment benefit over three years

A pooled analysis of the reSURFACE1 and reSURFACE2 trial showed that Psoriasis Area and Severity Index (PASI) 75 responses gained after 28 weeks were maintained with continued treatment in 9 out of 10 patients up to week 148 [6]. Tildrakizumab is a high-affinity selective IL-23 blocker that demonstrated efficacy in the treatment of chronic plaque psoriasis in the two phase 2 studies reSURFACE1 and reSURFACE2 [7]. In the reSURFACE2 trial, there was also a study arm with the active comparator etanercept.

Prof. Diamant Thaçi (University of Lübeck, Germany) presented the current post-hoc analysis, which was performed to report long-term 148-week efficacy and safety in patients who were responder (PASI≥75%) at week 28 and who continued treatment with the same dose of tildrakizumab. All included patients had moderate-to-severe chronic plaque psoriasis. The efficacy of 200 and 100 mg tildrakizumab was evaluated for 64 weeks in the reSURFACE1 and for 52 weeks in the reSURFACE 2 trial.

Patients who completed the base studies and had achieved PASI≥50% were eligible to take part in open-extension studies, in which the end-of-base study treatment was continued (administered every 12 weeks). Maintenance of PASI75 response was observed in 91% and 92% of patients who received 100 mg and 200 mg tildrakizumab, respectively. Over this cumulative 3-year treatment period, both doses of tildrakizumab were well tolerated with a low rate of adverse events and discontinuation rates. "Injection site reactions were rare with tildrakizumab and occurred much more often in etanercept compared to tildrakizumab," said Prof. Thaçi during the presentation.

Approximately 50% of PASI75 responders did not relapse after switching to placebo in part 3 of the study, where reSURFACE1 responders were randomised to continue the same tildrakizumab dose or placebo. “What is really interesting is the long median time of seven to nine months to relapse,” said Prof. Thaçi.

Psoriasis and pregnancy: patients need better information

Nearly 5% of French women aged 18-65 are affected by psoriasis and many of them are of childbearing age [8]. A great part of the drugs that are used to treat psoriasis are either contraindicated or at least not endorsed during pregnancy. So, how are women counselled on this topic by their dermatologists and what are the doctor’s standpoints on the different issues that pregnancy and psoriasis bring along? A French multicentre survey sought answers to these questions by collecting data from 361 special questionnaires filled in by 152 dermatologists in 2018, who worked in either a private practice, hospital, or both. The investigators distinguished information given from doctors who got their diploma ≥2004, the so-called ‘biological agent generation’, from those who were more senior.

Of the mean 28.6% of women at childbearing age, significantly more were treated by dermatologists working in a practice
setting or in practice plus hospital than by doctors working in hospitals only (31.9% vs 25.3%). Three quarter of the doctors talked about sexual function and psoriasis with their patients, with a higher portion of female dermatologists to take the initiative. However, 55% only did so at the patient’s request. The short-term wish for a child was discussed in 83.1% of the young women when diagnosed with psoriasis. Contraception was a topic with 70.7% of female and 61.2% of male patients. The greatest concerns about pregnancy were foetal risks (49%), possible transmission of disease (54%), and the compatibility of treating psoriasis during pregnancy (64%). Many dermatologists stated that they have been confronted with unplanned pregnancies that occurred with ongoing treatment. In 66% of the cases, their reaction mostly depended on the medication taken by the patient. Only 28% of the dermatologists knew about the current recommendations concerning psoriasis treatment for women of childbearing age [9]. With 12.5%, the youngest doctors with a seniority of diploma <10 years were less often informed than the older ones (42.3%). Of those familiar with the existing recommendations, only 21% were satisfied with them meeting all their issues. As a result, the investigators concluded that awareness of recommendations needs to be increased, and that education on discussing sexual topics is needed to provide better counselling on the matter.

Dose reduction of biologics is possible in majority of psoriasis patients

Treatment of psoriasis with biologics has led to a stable and enduring disease control for a considerable portion of patients and a substantial advance in care of this immune mediated disease [10,11]. Unfortunately, biologics do not offer a cure but need to be taken as continuous long-term treatment. However, long-term treatment may entail augmented health risks, and the incurring costs for the drugs constitute a substantial burden to society.

Dr Juul van den Reek (Radboud University Medical Center, Nijmegen, the Netherlands) presented the CONDOR study, which was designed to find out whether tapering the dosage of biologics in stable patients is possible without losing disease control. This multicentre, non-inferiority trial randomised 120 patients with stable low disease activity under treatment with etanercept, adalimumab, or ustekinumab to either a dose reduction or a standard care group. Low disease activity over ≥6 months was determined by PASI ≤5 and DLQI ≤5. Tapering in the dose reduction group was performed by gradually extending the treatment intervals while keeping close contact with the patient. The first step of reduction led to a decrease of 67% of the original dose. If PASI and/or DLQI stayed ≤5 after 3 months, the next step was initiated and the patient received only 50% of the original dose. The margin for non-inferiority was set at a difference in PASI of 0.5 at 12 months. Secondary endpoints included PASI and DLQI at different times, and rates of patients with flares, as well as serious adverse events (SAE). Monitoring took place every 3 months. In case of PASI and/or DLQI mounting over 5, patients returned to their original dose when entering the trial.

At baseline, mean values were: 56.45 for age, 25.95 for disease duration, 1.65 for PASI, and 0 for DLQI. 20% of patients in the normal care and 32% in the dose reduction group also suffered from psoriatic arthritis. After correcting for baseline PASI, the mean intergroup PASI difference between normal care and dose reduction at month 12 was 1.1. So, the PASI result did not prove non-inferiority. However, there was no significant difference in median DLQI scores at month 12, nor in persistent flares. After 1 year, 68% of the patients were still on low-dose treatment (Figure 3). Intervention-related serious AEs did not occur. Dr van den Reek critically questioned the clinical relevance of a mean PASI difference of 1.1 between the groups, as 3.2 can be seen as the minimal clinically important difference. In her conclusion, she stressed that in 7 out of 10 patients a dose reduction was possible without entailing important related risks plus median PASI and DLQI remaining ≤5. Further analyses of CONDOR addressing cost-effectiveness, serum drug levels, and antibody formation will be done. Determining factors to predict successful dose reduction could be a focus of future investigations.

![Figure 3 Percentage of patients with original and reduced doses up to month 12](image-url)
Blockade of IL-36: a potential novel treatment option in generalised pustular psoriasis

The generalised pustular form of psoriasis (GPP) is an uncommon subtype of the disease. Due to the rarity of the condition and the questionable link to the common, plaque-type psoriasis, numerous therapies have shown variable results and pustular psoriasis remains difficult to treat [12].

The few that are affected, face a potentially life-threatening condition with frequent compromise of different organs and general symptoms. GPP, presenting with primary sterile pustules and disseminated erythema, may also be accompanied by plaque psoriasis in other parts of the skin. The pathogeneses of these two diagnoses do not overlap, which may be one of the reasons why GPP currently lacks approved biologic therapy. Current genetic knowledge links GPP strongly to the IL-36 signalling and IL-36 is also highly expressed in GPP skin lesions [13].

BI 655130 is a monoclonal anti-IL-36 receptor antibody that has been tested in an open label, phase 1, proof-of-concept study with 7 adults between 22 and 58 years of age. The inclusion criteria included a moderate-to-severe GPP flare with ≥10% body surface area (BSA) with erythema and pustules plus a GPP Physician Global Assessment Score (GPPGA) score ≥3. A single dose of intravenous BI 655130 (10 mg/kg) was given at day 1. Thereafter patients were monitored until week 20 by evaluating GPPGA and the GPP Area and Severity Index score (GPPASI), both modifications of the Physician Global Assessment (PGA) and PASI used for plaque psoriasis. Additional laboratory investigations and skin biopsies were also performed. Primary endpoint included safety and tolerability of BI 655130. Secondarily, clear skin and almost clear skin with a GPPGA of 0 or 1 and changes from baseline in PASI were assessed.

Rapid onset of activity

All patients reached a GPPGA score of 0/1 by week 4, 71.4% already in week 1 and 2. Over 40% of the patient were free of pustules within 2 days of treatment, 85.7% at week 2. Likewise, improvements in GPPASI were swift. Blood work found substantial reductions of C-reactive protein (CRP) and absolute neutrophil count. At week 1, gene expression within the pustules achieved near non-lesional skin levels. The mutational status did not influence the effect of BI 655130.

Drug-related AEs that were of mild to moderate grade occurred in 57.1% of the patients. No severe AEs occurred. After these promising results, pivotal trials with BI 655130 are presently being prepared.

References:

Novel Treatment Options for Skin Fragility Syndromes

Genetic or acquired destabilisation of the epidermis or the dermis evokes injury-driven and inflammation-driven skin fragility. Insights into the pathogenesis opens the door for novel treatment modalities including gene therapy.

Skin fragility is characterised by fragile, non-healing skin with an inadequate adherence of the skin layers. Consequences of skin fragility are function deficits, blistering, and chronic wounds, and fragile skin is often complicated by infections. "Inherited epidermolysis bullosa (EB) is a paradigmatic skin fragility disorder, which has been intensively investigated
to understand the causes and mechanisms of fragile skin," said Prof. Leena K. Bruckner-Tuderman (University Medical Center Freiburg, Germany) [1]. Structures of the epidermis and the dermal-epidermal junction area are targeted in skin fragility – both in autoimmune and genetic syndromes. "Therefore, by studying one group, we learn about the other," said Prof. Bruckner-Tuderman. Studies of EB have generated abundant new information on not only genetic causes but also on cellular and molecular mechanisms of skin fragility.

EB is associated with mutations in 20 genes, and there are dominant and recessive forms [2]. "A genetic diagnosis is important, and all patients with a precise diagnosis should take part in a trial," recommended Prof. Bruckner-Tuderman. The genetic analysis itself can be performed by any laboratory. However, interpretation of the results and understanding of the phenotypes requires specialists for bullous disorders.

**Hopeful prospects due to gene therapy**

Recessive dystrophic epidermolysis bullosa (RDEB) is caused by a wide variety of mutations in COL7A1-encoding type VII collagen, which is essential for dermal-epidermal adhesion. In the last 10 years, many reports have shown that gene transfer approaches to target epidermal stem cells are feasible and able to restore the adhesion properties of primary keratinocytes from patients with EB [3]. Such a repair was demonstrated in an experimental study [3]. Grafting of genetically corrected 3D skin equivalents onto nude mice showed up to 26% re-expression and normal localisation of type VII collagen, as well as anchoring fibril formation at the dermal-epidermal junction [4]. Gene modification in combination with advanced tissue-engineering techniques could therefore represent a realistic option for RDEB therapy in the future.

**Epidermolysis bullosa: a systemic disease**

Curing EB is challenging because skin fragility often represents a systemic disease. In many cases, there is an unexpected organ involvement. This knowledge is important to develop novel evidence-based therapies. An example for such an organ involvement is the so-called Kelch-deficient skin fragility, caused by a KLHL24 mutation. In childhood, it is characterised by extensive skin defects, blistering, and nail dystrophy. In adulthood, there is less skin fragility, skin atrophy, and nail changes [5]. This year, a study demonstrated that Kelch-deficient skin fragility is also associated with dilatative cardiomyopathy and neurological involvement [6]. A second example of organ involvement is the fact that RDEB is not only associated with skin fragility, blistering, and scarring, but also with squamous cell carcinoma. In addition, patients frequently suffer from bacterial superinfections. Due to the lack of collagen VII in the spleen, macrophages that usually combat bacteria cannot be activated [7].

**Losartan: old drug with a new indication**

A study demonstrated an alternative evidence-based approach to ameliorate fibrosis and relieve symptoms in patients with RDEB [8]. This approach was based on the findings that TGF-β activity is elevated in injured RDEB skin due to an increase in TGF-β signalling. This process ultimately leads to tissue fibrosis and stiffening, and carcinoma conversion. "We asked ourselves, whether, if a cure is not yet possible, and we cannot stop blistering, we could at least ameliorate fibrosis, or prevent cancer," said Prof. Bruckner-Tuderman. The antihypertensive losartan is an antagonist of TGF-β signalling. In a proof of concept study, Prof. Bruckner-Tuderman and her group treated RDEB mice, a mouse model for RDEB, with losartan [8]. This approach led to an efficiently reduced TGF-β signalling in chronically injured forepaws and halted fibrosis and subsequent fusion of the digits. In addition, losartan reduced inflammation and diminished TNF-α and IL-6 expression in injured forepaws. This data supports the hypothesis that fibrosis is a consequence of a cascade encompassing tissue damage, TGF-β-mediated inflammation, and matrix remodelling [8].

After this promising data, the phase 1 and 2 trial REFLECT was started in 30 children with moderate-to-severe RDEB in the age of 2-16 years who are treated with a losartan suspension. "This trial is ongoing and performed in collaboration with paediatric cardiologist, since losartan is an antihypertensive drug," explained Prof. Bruckner-Tuderman. So far, two participants have completed the study, and first results are promising. "There will be no miraculous cure for genetic skin disease, but depending on the constellation, mutations, and disease mechanisms, we will be able to find individualised combinations of different biologically valid modalities: gene and cell therapies, protein therapies plus small molecules and repurposed drugs, such as losartan as modifiers. Curative and symptom relief therapies have to be combined; this will be the future," concluded Prof. Bruckner-Tuderman.

**References:**

Chronic Urticaria: Many Patients Are Not Treated According to Guidelines

An important treatment motto in chronic spontaneous urticaria is ‘treat the disease until it is gone’. Despite effective therapeutic possibilities, many patients are still not controlled, and suffer from considerable comorbidity.

This year, new treatment guidelines from a joint initiative of the dermatology section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) were published for the definition, classification, diagnosis, and management of urticaria [1]. More than 43 countries took part in developing these guidelines, so it represents a real international perspective on the practical management of chronic urticaria. In her lecture, Prof. Ana Giménez-Arnau (Hospital del Mar, University of Barcelona, Spain) highlighted the novel treatment algorithm for chronic spontaneous urticaria (CSU) [2]. Key symptoms of CSU are recurring itchy wheals and/or angioedema ≥6 weeks, the latter are present in about 70% of patients. As patients with CSU experience a high degree of psychological strain, it is important to move patients to an effective treatment fast.

Rapid treatment escalation
This novel approach for CSU is highlighted in the current treatment algorithm, where step-up treatment is already initiated if symptoms cannot be controlled after 2-4 weeks. As Prof. Giménez-Arnau pointed out, urticaria cannot be cured, but it can be treated until the disease is gone. The right approach is to use as much medication as needed but as little as possible. The guidelines recommend either the Urticaria Activity Score (UAS) or the Urticaria Control Test (UCT) to judge disease activity. The UAS is based on the assessment of key urticaria signs and symptoms (i.e. wheals and pruritus), which are documented by the patient. The UCT was developed and validated to determine the level of disease control in all forms of chronic urticaria, the cut-off value for a well-controlled disease being 12 out of 16 possible points. The UCT is a valuable tool to guide treatment decision [2].

Intensive therapy often necessary in patients with high baseline UAS score
In an observational study, factors associated with a worse prognosis in terms of duration and/or CSU activity included multiple episodes of CSU, late-onset (i.e. after the age of 45 years), concomitant inducible urticaria, and functional serum autoreactivity [3]. Baseline CSU activity was the only factor found to be predictive for refractoriness to treatment with H1-antihistamines: the higher the UAS-score was, the higher the likelihood that patients required ciclosporin or omalizumab therapy to achieve symptom control. Most patients suffer from CSU for more than a year; a considerable number of patients even seem to be affected for longer than 5 years.

The first step in the treatment algorithm consists of prescription of 2nd generation antihistamines (Figure 4). “Do not give antihistamines of the first generation to avoid sedative effects,” recommended Prof. Giménez-Arnau. In addition, combinations of antihistamines are not recommended. If this therapy is not effective enough and symptoms are intolerable, after 2-4 weeks, or even earlier, the dose of the antihistamines should be elevated up to fourfold. In clinical practice, many physicians avoid this step because it is not an approved dose. Literature suggests that this approach is very effective: the estimated relative risk for improvement by increasing the antihistamine dosage was 2.27 (95% confidence interval [CI] 1.68-3.06); however, there was significant heterogeneity [4]. The proportion of non-respondent patients with CSU who responded to antihistamine updosing was 63.2% (95% CI 57-69.6). Updosing antihistamines significantly improved control of pruritus but not wheal number. However, the relative weakness of the studies and the significant heterogeneity among them make it difficult to reach a definitive conclusion [4]. “Further high-quality studies on updosing anti-H1 histamines are therefore urgently needed,” said Prof. Giménez-Arnau. Unfortunately, in real-world conditions, first generation antihistamines are often prescribed because patients sleep better. Many CSU patients are still treated with a combination of antihistamines or with long-term low doses of oral corticosteroids.
treatments were most evident at the first visit, with an increase in patients receiving omalizumab vs prior therapy from 3.0% to 19.4%, and a decrease in those receiving no treatment from 38.9% to 10.3%. Between months 12 and 24, few changes in treatment patterns were observed: nearly a third of patients was treated with omalizumab and nearly half of patients with H1-antihistamines. Early changes in treatment pattern were associated with greater QOL and symptom improvements compared with later visits. However, after 2 years, 47.8% of patients still reported that they experienced hives and 14.5% experienced angioedema at least once within the previous 3 months (compared with 58.4% and 16.8%, respectively, after a year). Nearly 30% of patients had still uncontrolled disease (defined as an UCT score <12) and 20.6% reported a moderate-to-severe negative impact on their QOL.

Although improvements were observed, the current data of AWARE confirmed that many patients are not receiving guideline-recommended treatments. The authors conclude that greater awareness of current guideline recommendations for CSU is needed to ensure better management of patients with high disease burden [10].

**High psychiatric comorbidity**

A second poster showed that psychiatric comorbidities of patients with chronic urticaria are common, particularly depression and somatoform disorders [11]. Data from 2,554 adult patients and 216 paediatric patients with confirmed CSU, and 911 adult and 76 paediatric patients with CIndU were included in the analysis. About 21.6% of adults with CSU and 24.7% of paediatric patients with CIndU had a single episode of depression. This rate was considerably lower in paediatric patients with CSU (3.7%). Of the adult patients, 23.3% CSU and 23.7% with CIndU suffered from somatoform disorders, which were also the most common psychiatric comorbidity in paediatric patients with CSU (7.4%). Other comorbidities associated with chronic urticaria included asthma and atopic dermatitis. The authors conclude that in addition to the already bothersome CSU symptoms, these comorbidities negatively impact the quality of life of these patients and demand an interdisciplinary therapeutic management [11].

**References:**

Treating Psoriasis in 2018

There is a whole new armamentarium of effective drugs to treat psoriasis. Despite this fact, undertreatment is still very common, particularly in moderate-to-severe disease.

A multicentre, cross-sectional study performed in Germany revealed that 77% of all psoriasis patients and 55% of patients with a Psoriasis Area and Severity Index (PASI) ≥20 have never been treated with a systemic therapy (Figure 5) [1]. Recent data from the USA confirms that most patients with moderate and severe psoriasis are treated with topical therapy only or even no therapy at all [2]. Although there are many effective biologics approved for psoriasis, only 6% of patients receive them [2]. The World Health Organization (WHO) published a resolution on psoriasis and came to the conclusion that too many people in the world suffer needlessly from psoriasis due to incorrect or delayed diagnosis, inadequate treatment options, and insufficient access to care [3]. “Obviously, we are not efficient, it appears that only 6% of patients receive new drugs,” said Prof. Antonio Costanzo (Humanitas University, Milan, Italy) in his spotlight presentation on psoriasis therapy in 2018 [4]. An important reason for the vast undertreatment might be that patients do not believe that doctors can help them, as was shown in the MAPP study [2]. More than a third of patients believe that healthcare professionals cannot help them, and about 25% think their symptoms are not severe enough. Obviously, there is a mismatch between patient perceptions and treatment goals.

Are current treatment goals still justified?

Current European Guidelines still recommend a treatment target of PASI≥75. A PASI≥75 together with a DLQI≤5 are considered an adequate response [5]. However, these guidelines were published before newer trial data were published with more effective biologics. “PASI75 is a threshold that is also used for the approval of drugs, but it is questionable whether this is still a good goal,” said Prof. Costanzo. The psoriasis group of the Spanish Academy of Dermatology and Venereology proposes a higher PASI response, as clearance is closely related to QOL of patients [6]. They propose a first-line therapy for moderate-to-severe psoriasis, concurrently with conventional systemic drugs and phototherapy. As ideal therapeutic goals, the Spanish group defined a PASI90 response, a PGA≤1, or alternatively a minimal and controllable localised involvement with topical treatments, DLQI≤1, prolonged remissions without loss of efficacy, and no worsening of comorbidities.

Today, absolute PASI may be a better therapeutic target than a PASI-response relative to baseline. Objective measures of psoriasis involvement are clinically meaningful only if they correlate with significant improvements in patients perceived health-related QOL [7]. “Trials have shown that an absolute PASI is better, due to a stronger correlation between absolute PASI and QOL of patients,” said Prof. Costanzo. Trials have shown that approximately 55% of patients with a PASI≤2.5 at week 24 had a DLQI=0, compared to less than 5% with PASI≥5 [8,9]. During the previous years, there were numerous advances in the treatment possibilities of psoriasis.
**Topical therapy: enhanced efficacy of a foam preparation**

In his presentation, Prof. Costanzo also gave an update on topical therapy, since it is still the mainstay of psoriasis management, especially in mild disease. Vitamin D3 analogues like calcipotriol play an important role in psoriasis pathogenesis: they inhibit keratinocyte proliferation and induce keratinocyte differentiation. They also enhance immunosuppressant properties of regulatory T-cells and inhibit dendritic cell differentiation and maturation. Their efficacy can be enhanced by combination with a steroid. A combination of a topical steroid with calcipotriol is not only more efficacious than monotherapy, but also causes less skin atrophy compared with monotherapy with a steroid. Choosing the right vehicle is of key importance in topical therapy. “The most important progress in topical therapy was the introduction of a betamethasone propionate calcipotriol foam vs ointment – this is the only new topical that really provided better efficacy,” said Prof. Costanzo. In a clinical trial, a calcipotriene and betamethasone dipropionate aerosol foam showed not only superior efficacy compared with a vehicle but also compared with an ointment with the same active substances in patients with psoriasis vulgaris [10,11]. In the phase 3 PSO-ABLE trial, after 4 weeks of treatment, significantly more patients using the combination aerosol foam achieved treatment success compared with patients using a calcipotriene and betamethasone dipropionate gel formulation after eight weeks (38% vs 22%; P<0.001). 52% of patients treated with the foam compared with 35% of the patients treated with the gel achieved at least a 75% reduction in modified PASI (P<0.001). The tolerability was comparable in both groups.

**Pathogenesis-based approach in systemic therapy**

“In 2018, we are able to define specific targets in psoriasis and, thus, use a pathogenesis-based approach,” explained Prof. Costanzo (Figure 6). All new biologics target cytokines. The IL-12/IL-23 blocker ustekinumab showed better efficacy compared to TNF-blockers. Up to 80% of patients reach PASI75 and maintain this response. Data from the BADBIR registry show that ustekinumab has a long retention in daily practice and a higher probability of drug survival compared to TNF-blockers [12].

“What really changed the therapeutic landscape was the ability to block IL-17. With secukinumab we shift from 80% of patients reaching PASI75 to 80% reaching PASI90,” explained Prof. Costanzo. These drugs are also superior to ustekinumab. The second IL-17 blocker, ixekizumab, maintained efficacy over 3 years in the UNCOVER-3 study [13]. Brodalumab is another IL-17 blocker with a slightly different mode of action: it does not block IL-17A but the receptor, and, thus, has a broader mode of action. According to the experience of Prof. Costanzo, brodalumab is characterised by a fast onset of action: genital psoriasis resolved after only one week in one of his patients treated with brodalumab.

Selective blockade of IL-23 is as effective as the IL-17 blockers, but administration of the IL-23 blockers is only necessary once every 8 weeks. 60% of patients that do not respond to ustekinumab still achieve a response with the selective IL-23 blocker guselkumab as could be shown in the NAVIGATE trial [14]. A novel interesting selective IL-23 blocker is risankizumab. In a phase 2 trial, only 3 administrations were necessary to achieve a PASI90 response after 48 weeks. “When a patient is on an IL-23 blocker, there is a long time to relapse, so hitting IL-23 is probably a good strategy to reach long resolution of symptoms,” said Prof. Costanzo [15].

In general, new drugs are also safer than old drugs because they act very skin specific. With IL-17 inhibitors, there is a low incidence of mild-to-moderate candidiasis, and they should not be used in patients with inflammatory bowel disease since they can potentially cause exacerbation of the disease. Tuberculosis screening should be performed before therapy with TNF-blockers, IL-17 and IL-23 blockers. Common side effects are upper respiratory tract infections. “At present, we have many therapeutic options with high efficacy. Despite this fact, few patients deserving active therapies are actually being treated. We should therefore focus our efforts on getting access to treatment for more patients rather than on new drugs,” concluded Prof. Costanzo.

*Figure 6 Psoriasis therapy 2018: A pathogenesis-based approach [4]*
Risankizumab also effective in obese patients
New data presented during the EADV meeting highlighted the high efficacy of novel cytokine blockers – even in patients with characteristics commonly associated with a lower response. In an integrated analysis of three phase 3 trials, the selective IL-23 inhibitor risankizumab showed to be significantly more effective than placebo across different subgroups [16].

Data derived from the UltiMMA-1, UltiMMA-2, and IMMhance trial were integrated. Patients stratified by body weight and prior TNF inhibitor-exposure at randomisation received either 150 mg risankizumab at week 0 and 4 or matched placebo. Co-primary efficacy endpoints assessed at weeks 16 across subgroups were PASI90 response and sPGA 0/1 responses. “Regardless of body weight, sex, initial PASI score, or anything else, you are going to get high responses from this particular drug,” said investigator Prof. Charles Lynde (University of Toronto, Canada) during the oral e-poster presentation of the analysis.

Among 1,305 patients included in the integrated analysis, baseline demographics and disease characteristics were generally similar between the two treatment arms. At week 16, significantly more patients treated with risankizumab than with placebo achieved a reduction in PASI score of at least 90% (74.3% vs 3.0%; P<0.001), and significantly more patients in the risankizumab group achieved a static Physician Global Assessment score of 0 or 1 (84.9% vs 6.7%; P<0.001). These results are impressive because patients had characteristics associated with an unfavourable treatment outcome: many participants were obese (mean weight was 90.8 kg) or had failed treatment with multiple other drugs. Risankizumab was also effective in these patients. Another benefit of risankizumab is its long dosing interval. The drug has to be given only once every 3 months.

Ixekizumab beats ustekinumab in clearing psoriatic nail lesions
Patients who undergo treatment with ixekizumab experience greater nail psoriasis improvement than individuals treated with ustekinumab. These were the results of the phase 2b study IXORA-S presented during the EADV meeting [17]. In this head-to-head trial, patients with moderate-to-severe psoriasis were randomised to receive ixekizumab or ustekinumab. At baseline and at 52 weeks, fingernail bed lesions were analysed according to the Nail Psoriasis Severity Index (NAPSI). At baseline, 61.8% of ixekizumab patients and 63.3% of ustekinumab patients had nail psoriasis. At 16 weeks, ixekizumab patients had greater resolution (NAPSI=0) than ustekinumab patients (31% vs 16.2%, P=0.227). At 52 weeks, ixekizumab improvement expanded (61.9% vs 28.6%, P<0.0001). After 52 weeks, the average NAPSI score improvement was significantly larger in ixekizumab patients (-22.4; 95% CI -24.8, -20.0) than in ustekinumab-treated patients (-15.6; 95% CI -17.8, -13.4) (P<0.0001). Longer periods of observation will be required to determine whether nail lesions continue to improve beyond 1 year of treatment.

Insights into the pathomechanism of atopic dermatitis (AD) might lead to novel treatment options like microbiome transplantation. During the EADV meeting, promising study results with JAK inhibitors were presented that might enrich the therapeutic armamentarium in AD.

“"We encounter frequent skin infections in patients with AD, and some patients also have a problem with candida infection," said Prof. Tilo Biedermann (Technical University Munich, Germany) [1]. There are a couple of underlying reasons for a higher susceptibility of AD patients to infections.

References:
3. WHO Global report on psoriasis
For a long time, we believed in dry skin and barrier defects, a pathogenetic factor that has been confirmed by filaggrin mutations, but AD patients also have a disturbed immune function and AD is a Th2 disease," said Prof. Biedermann. All AD patients have dry skin and a damaged epithelial barrier. Filaggrin is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier. Studies have shown that two independent loss-of-function genetic variants (i.e. R510X and 2282del4) in the gene encoding filaggrin are very strong predisposing factors for AD and allergic disease [2,3]. Due to the barrier defect, allergens penetrate the skin and lead to initiation of a Th2 immune response, thus linking the barrier defect and the altered immune response. AD skin is characterised by the overexpression of the two Th2 cytokines of IL-4 and IL-13 [4]. In addition, there is a deficiency in the expression of antimicrobial peptides in patients with AD that may account for the susceptibility of patients with AD to skin infection with Staphylococcus aureus, and the cutaneous S. aureus overgrowth [5]. Another trial assessed the association of S. aureus colonisation in patients with AD with and without filaggrin gene mutation [6]. In this study, increased S. aureus colonisation was found in lesional skin of patients with AD and filaggrin mutation. “The more severe AD is, the more likely is a S. aureus colonisation,” said Prof. Biedermann.

Loss of diversity in the skin microbiome
A microbiome is defined as all the microorganisms in an environment and their interactions with each other and with that environment. Healthy subjects have a diverse skin microbiome. This diversity is lost in AD patients, as could be demonstrated in a trial that assessed the composition of bacterial communities during AD disease states to identify characteristics associated with AD flares and improvement post-treatment [7]. In this trial, microbial community structures at sites of disease predilection were dramatically different in AD patients compared with controls. Microbial diversity during AD flares was dependent on the presence or absence of recent AD treatments, with even intermittent treatment linked to greater bacterial diversity than no recent treatment. The proportion of Staphylococcus, particularly S. aureus was greater during disease flare and correlated with worsened disease severity [7]. “However, if we treat AD successfully, diversity comes back,” said Prof. Biedermann.

Increased risk of systemic infections
Many AD patients also suffer from other atopic diseases. A cross-sectional study sought to determine whether adult AD is associated with systemic infections, and whether this association is strengthened in those with AD plus another atopic disease [8]. Data came from the National Health Interview Survey (NHIS) 2010 and 2012, where patients with AD with or without an additional atopic disease, asthma, or allergic rhinitis were asked whether they had a systemic infection. Trial results showed an increased risk of sinusitis, head or chest cold, gastrointestinal illness, pneumonia/influenza, and infectious disease [8]. “There is a clear-cut higher risk of other infections in atopic patients: the more atopic you are, the more susceptible you become to infection because you are more Th2-prone,” concluded Prof. Biedermann.

Another trial confirmed that risk of systemic infection was even higher in patients with two atopic diseases [9]. A trial published this year showed that there are clear differences between adult AD patients that are commonly colonised by S. aureus and noncolonised AD patients [10]. AD patients colonised by S. aureus on their skin had more severe disease, greater type-2 immune deviation, allergen sensitisation, barrier disruption, and serum lactate dehydrogenase level elevation than noncolonised patients with AD [10]. With regard to pathogenesis, there is a crucial triangle of dry skin, reduced barrier, allergy and Th2 disease, and cutaneous dysbiosis favouring infections,” said Prof. Biedermann (Figure 7).

IL-4/IL-13 blockade: the most effective therapy
Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, is the first approved biologic to treat AD and has demonstrated its efficacy as a monotherapy and together with topical steroids [11,12]. In addition, a meta-analysis of randomised controlled trials of dupilumab revealed that use of dupilumab is associated with a decreased incidence of skin infections and eczema herpeticum in adults with moderate-to-severe AD. Figure 7 The crucial triangle of AD: A reduced barrier function, an immunologic disbalance, and a cutaneous dysbiosis act as a vicious circle [1]
AD [13]. The mechanism underlying this association is unclear but is likely related to improvement in AD severity. “Especially with chronic treatment, infections decrease when using dupilumab – with the exception of conjunctivitis,” said Prof. Biedermann.

Another mode of action that could be responsible for the lower risk of infection is the restoration of microbiome. In another trial in 6-month-old infants with a family history of atopy, skin diversity improved after application of an emollient [14]. The number of bacterial taxa in the emollient group, particularly streptococcus salivarius, was higher than in the control group at all sites. This year, a trial was published that for the first time assessed a topical microbiome transplantation with Roseomonas mucosa. This commensal, collected from healthy volunteers, improved outcomes in experimental models of AD [15]. In this proof-of-concept study, 10 adult and 5 paediatric patients received a cutaneous treatment with R. mucosa. This approach led to a significant decrease in measures of disease severity (e.g. regional pruritus score), topical steroid requirement, and S. aureus burden in 10 weeks after transplantation. “I think that applying good bacteria might be a new promising strategy; however, we require more clinical data. With more clinical data I see a promising perspective for microbiome modulation,” concluded Prof. Biedermann.

**JAK-inhibitors: promising new treatment options for severe AD**

New data with Janus Kinase (JAK) inhibitors show that this class of drugs could also be a promising treatment for patients with moderate-to-severe AD. JAK-signal transducer and activator of transcription (JAK-STAT) is an intracellular signalling pathway in which many different proinflammatory signalling pathways converge. Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signalling [16]. JAK inhibitors also modulate inflammatory cytokines involved in the pathogenesis of AD, such as IL-4 and IL-13. In addition, JAKs may also modulate itch associated with AD. At present, JAK inhibitors are approved for the treatment of rheumatoid arthritis. Another advantage of JAK-inhibitors is that they can be taken orally.

A trial presented during the EADV meeting by Prof. Emma Guttmann-Yassky (Icahn School of Medicine at Mount Sinai, New York, USA) showed that ASN002, a dual inhibitor of JAK and SYK, improves symptoms in patients with moderate-to-severe AD, and improved the lesional skin phenotype towards non-involved skin [17]. By targeting SYK, IL-17 signalling and B-cell signalling involved in skin immunity are inhibited in addition to the JAK inhibition. In the study, 36 adult patients with moderate-to-severe AD were included and treated with the JAK/SYK inhibitor ASN002. In addition, a biomarker profile was assessed and correlated with the clinical efficacy of the drug. Therefore, biopsies of lesional and non-lesional skin were taken at baseline, and those of lesional skin also at day 15 and 28. No other topical or systemic treatment was allowed.

The JAK/SYK inhibitor showed an early treatment response within 2 weeks. In the highest dose, 88% of patients gained an Eczema Area and Severity Index (EASI) 50 response and 50% an EASI75 response at day 29. In addition, the genomic profile showed progressive improvements towards uninvolved skin in patients treated with the JAK/SYK inhibitor. Noticeable differences were seen in the 80 mg and 40 mg treatment groups as early as day 15. At day 29, the genomic profile of patients treated with these doses resembled non-lesional phenotype, whereas both 20 mg and the placebo group did not show significant changes. Pruritus, assessed in a numeric rating scale, was reduced by about 80%.

Treatment also led to a significant reduction in Th2-related cytokines, such as IL-13, CCl13, and CCL18. Markers of the Th17/Th22 axis were especially downregulated in the 40 mg group. Therapy with the 40 mg and 80 mg dose also led to a reversal of the barrier defect, namely to an increase of epidermal thickness and K16mRNA expression. ASM002 also reversed the epidermal pathology (including hyperplasia and terminal differentiation) in skin lesions. In addition, inflammatory markers in the serum were significantly reduced with the higher doses, which shows that the agent also fights circulatory inflammation.

“We currently do not have effective and safe oral treatments for our moderate-to-severe AD patients, as available immune suppressants harbour many side effects. It is exciting to have a novel oral therapeutic option such as ASN002 that can achieve rapid control of clinical disease activity in patients with moderate-to-severe AD. Also coupled with significant improvements in the AD lesional skin molecular profile that reverses towards the non-lesional skin fingerprint,” concluded Prof. Guttmann-Yassky. Now it will be interesting to see whether these results are confirmed in the ongoing phase 2b study with ASN002 after longer treatment.
Promising topical JAK1/2 inhibitor

Another trial presented during the meeting showed activity of a topical formulation of the JAK1/2 inhibitor ruxolitinib in 307 adult patients with moderate-to-severe AD [18]. Treatment with a cream containing the highest dose of the JAK1/2 inhibitor ruxolitinib (1.5%) administered twice daily led to 71.6% improvement in the EASI at 4 weeks compared to a 15.5% improvement in baseline EASI score in a vehicle control group. All four dosages of ruxolitinib cream (0.15% once daily (QD), 0.5% QD, 1.5% QD, and 1.5% twice daily) significantly outperformed the vehicle control and achieved numerically better results compared with a second group of patients who received the active comparator topical triamcinolone (0.1% twice daily) for 4 weeks, followed by 4 weeks of vehicle (Figure 8).

Ruxolitinib cream provided dose-dependent efficacy in all arms, and ruxolitinib 1.5% twice daily was non-inferior vs triamcinolone, with a trend toward being better. In addition, rapid and sustained reductions in pruritus, assessed in a numeric rating scale, were observed in all treatment arms with changes as early as within a day from the initiation of therapy. Importantly, the reduction in itch was faster and more pronounced with the 1.5% ruxolitinib (once and twice daily) dose than with the steroid. Ruxolitinib was not associated with any significant safety or tolerability findings. “These findings show that ruxolitinib cream may represent a novel and effective topical treatment for patients with atopic dermatitis,” concluded Prof. Brian Kim (Washington University School of Medicine in St Louis, USA) during his presentation.

In Europe, oral ruxolitinib is already approved for the treatment of myelofibrosis and polycythemia vera.

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There are distinct differences between the skin of newborns and adults. Early barrier protection might be a successful strategy to avoid the atopic march. Further, psoriasis is rare in children and can be easily overlooked, and children with severe disease need a systemic therapy.

“Baby skin is unique; it has a higher water content but less skin surface lipids and lower levels of natural moisturising factor than adult skin, which has consequences for the therapy,” said Prof. Regina Fölster-Holst (University Hospital Schleswig Holstein, Kiel, Germany) in her presentation on special aspects of skin in neonates and infants [1]. During the first year of life, baby skin continues to develop with regard to structure, composition, and function [2]. Infant stratum corneum was found to be 30% and infant epidermis 20% thinner than in adults. Infant corneocytes were found to be 20% and granular cells 10% smaller than adult corneocytes indicating a more rapid cell turnover in infants. These differences in microstructure help explain some of the functional differences; in particular the weaker skin barrier function encountered in early life. “Primary prevention studies underline the importance of use of emollients in early life,” said Prof. Fölster-Holst. In a trial, regular usage of emollients in 124 high-risk infants lead to a 50% lower relative risk of developing atopic eczema at 6 months [3]. A similar result could be seen in a study including Japanese high-risk babies [4]. Therefore, the use of emollients for the supplementation of the skin barrier is now recommended for all infants, not only for those with atopic dermatitis (AD).

Interactions among the skin microbiome (i.e. bacteria, fungi, and viruses), resident cells in the skin (i.e. keratinocytes, fibroblasts, adipocytes, neural elements, and vasculature), and bone marrow-derived cells of the immune system (i.e. dendritic cells, lymphocytes, and granulocytes) are essential for homeostasis in healthy skin [8]. In atopic dermatitis, molecular or cellular defects in these systems are associated with disease (Figure 9).

**Psoriasis in childhood: Rare and easily overlooked**

“Psoriasis is uncommon in children – you have to be more aware as it is easily overlooked,” said Prof. Kim Papp (Probity Medical Research, Ontario, Canada). Despite this fact, psoriasis has a significant impact on the QOL by interfering with children’s self-esteem, family and social relationships in children, and possible depression [9]. Although children present with the same clinical subtypes of psoriasis seen in adults, lesions may differ in distribution and morphology [10]. Currently, no international standardised guidelines exist for medical treatment of paediatric psoriasis. To date, treatment is primarily based on published case reports, guidelines for adult psoriasis, expert opinions, and experience with these drugs in other paediatric disorders [10].

One paediatric study assessed the use of adalimumab in children with severe chronic plaque psoriasis [11]. In this trial, 32% of patients treated with adalimumab reached PASI75 at week 16. Adalimumab was dosed according to tolerance with the median dose being 7.5 mg. Hardly any side effects were observed during treatment with adalimumab. Of note, time to loss of response was rather long (6 months). According to Prof. Papp, “40% of the children we treated in this study were overweight or had other cardiovascular risk factors. This was not the case 20 years ago, and drugs are more complicated to use.” Data from the literature confirms that children with

**Microbiome diversity protects against atopic dermatitis development**

Another protective factor with regard to development of AD is a diversity of the skin microbiome. A study published last year showed that early colonisation with commensal *staphylococci* at two months is associated with a lower risk of AD at one year [6]. “We need a strong diversity of the microbiome in early life,” said Prof. Fölster-Holst. Babies born naturally have a more diverse microbiome compared to those after a Caesarean section. Preterm infants had also a lower diversity and greater enrichment with *Staphylococcus* species compared to full-term infants [7].

Data from the literature confirms that children with...
Psoriasis have a higher prevalence of comorbidities, including obesity, diabetes mellitus, and hypertension [12,13].

In another trial, phototherapy proved to be effective in the treatment of psoriasis [14]. “But why should we give children a carcinogen early and later an immunosuppressant. I would not be surprised if we see skin cancer, but they do not get it with 12, but with 40 years of age,” says Prof. Papp. Therefore, he avoids using phototherapy, and, if it is used, only short term. Likewise, there are tolerability issues with methotrexate. In particular now, with many obese children being treated who already have fatty liver disease. “But what is bothering me most with methotrexate, is an impaired response to vaccination. This is a problem with a maturing immune system – there is an unknown risk when I give them an immunosuppressant whether they will have the same robust immune response as other children,” says Prof. Papp.

Acitretin is also not an easy drug to use. Ciclosporin is even worse and was never intended for continuous therapy. There is a small retrospective trial in children [15]. Ciclosporin really blocks reactions to vaccines. “In addition, this drug kills glomerula. So by treating a 5-year-old we transform his or her kidney into that of a 35-year-old. I therefore only use it as a rescue option and only briefly – sometimes you just cannot help it,” recommends Prof. Papp.

**Biologics in children: Friends or foe**

Regarding the use of biologics in children, only small studies exist. “Naturally, we are extremely cautious in children and you have to treat the parents too” says Prof. Thaçi. In addition, at the moment, there is a lack of paediatric specific treatment guidelines. According to a recommendation of the British Association of Dermatologist guideline for biologic therapy for psoriasis 2017, adalimumab can be offered for children ≥4 years, etanercept ≥6 years, and ustekinumab ≥12 years [16]. “On the other hand, you cannot give patients with severe disease only a topical treatment,” explained Prof. Thaçi. Many children are stigmatised in school, they need a more effective therapy. The study with adalimumab also showed a significant improvement of quality of life [11]. In the CADMUS trial, the standard ustekinumab dose provided response in 12- to 17-year-old patients comparable with that in adults, with no unexpected adverse events [17]. “In general, the risk of adverse events is lower with biologics compared with conventional systemic treatments,” said Prof. Thaçi. At the moment, there are many ongoing paediatric psoriasis trials with different biologics, such as IL-17 and IL-23 blockers.

“I think there are a couple of new diseases where we urgently need to use biologics, for example bullous pemphigoid. Indeed, we only have a few patients, but they are in desperate need of an effective therapy,” concluded Prof. Thaçi.

**References:**

There is still a lack of awareness of the risk of hand eczema, even for hairdressers and other at-risk professions. Patient education on how to protect their skin is a key element to reduce the frequency of hand eczema.

In general, patients with atopic dermatitis (AD) and/or filaggrin defects have a higher risk to develop hand eczema. A study showed that subjects with AD were at an approximately three times higher risk of developing an irritant contact dermatitis than controls [1]. Individuals with concurrent filaggrin mutations and AD are at an even higher risk. Many people working in risk professions already develop hand eczema during their apprenticeship, as was shown in a study including 533 nurses [2]. In this study, the 1-year period prevalence of hand eczema was 23% in the first year, 25% in the second year, and 31% in the third year of follow-up. Even healthy persons that wash their hands more than eight times a day have an elevated risk.

According to Prof. Swen Malte John (University of Osnabrück, Germany), there is a lack of risk awareness, even in persons that work in risk professions [3]. In a trial, hairdressers showed unable to take protective gloves off without contamination [4]. After a demonstration on how to use gloves correctly, only 55.8% were contaminated [4]. "We need to educate people in risk professions. Practical experiences are important," said Prof. John. An example of a practical demonstration is the sugar cube test: a sugar cube with and without protective cream is submerged in water – after a couple of minutes, only the unprotected cube dissolves.

**Extensive patch testing in secondary prevention**

The etiology of patients with occupational dermatitis is extremely heterogeneous [5]. Unfortunately, there is no simple relationship between clinical type of hand eczema and etiological diagnosis. Therefore, in secondary prevention, a dermatologist should be consulted as soon as possible to patch test intensively. In addition, exposure analysis is mandatory. Patients with contact dermatitis can be a risk for others because they have an elevated risk for S. aureus, but also for other nosocomial infections.

"Although hand eczema is so frequent, there are hardly any trials to assess treatment efficacy," criticised Prof. John. In the guidelines, topical corticosteroids are recommended as first-line treatment; however, continuous long-term treatment beyond six weeks is recommended only when necessary and under careful medical supervision. Alitretinoin is recommended as a second-line treatment (relative to topical corticosteroids) for patients with severe chronic hand eczema [6]. For all other treatments, results from randomised controlled trials are missing. However, one study showed that by treating hand eczema with topical steroids, the barrier defect is increased, even if therapy is only performed short term [7]. In Germany, a tertiary individual prevention programme is offered to patients with severe occupational skin disease. A study including 1,410 patients over a 3-year follow-up showed that this approach is extremely successful [8]. The severity of occupational skin disease, the use of topical corticosteroids, and days of absence from work were significantly reduced 3 years after the programme, and the quality of life and skin protective behaviour were significantly improved. At the end of the follow-up, 73% were still working in the same place, and 80% in the same profession. “This is what dermatology can do, it can save peoples’ jobs. Severe hand eczema can be rehabilitated, and this process is also economic,” concluded Prof. John.

**Pitfalls in diagnosis**

Irritant dermatitis, occupational dermatitis, and contact allergy can mimic each other perfectly," said Dr Jonathan White (St John’s Institute, Guy’s and St Thomas' Hospitals, London, UK) [9]. In addition, genetic disease has to be excluded: keratolysis exfoliativa can mimic hand eczema but is not directly related to the workplace. Not all skin problems at work are caused by work and there is also home exposure to irritants and allergens. “It is important to prove your case, for example by provocation testing, because your patient’s job may depend on it,” recommended Dr White.

**References:**

In six oral poster sessions the most interesting posters of the 2018 EADV meeting were presented to the audience. This chapter describes a selection of the highlights of the poster sessions.

**Ligelizumab: a novel future therapy for chronic spontaneous urticaria**

More patients with chronic spontaneous urticaria (CSU) inadequately controlled by H1-antihistamines achieved a complete hives response with ligelizumab than with the active comparator omalizumab or placebo [1]. Enrolled in this phase 2 dose-finding study were 382 patients with an urticaria activity score (UAS) of ≥16, corresponding to moderate-to-severe CSU. After randomisation, patients received their study medication every 4 weeks over a period of 20 weeks. Medication consisted of either placebo, omalizumab 300 mg, or ligelizumab at a dose of 24, 72, or 240 mg. By the end of this phase, patients were followed-up without treatment for another 24 weeks. All those with UAS ≥12 qualified to continue in an extension study of week 32. The primary endpoint was defined as reaching a Hives Severity Score (HSS) of 0 at week 12, but changes in HSS and itch were also assessed.

A significant dose response connection was found at week 12. By week 20, 43% and 40% of patients receiving the two highest doses of ligelizumab (72 and 240 mg) achieved an HSS of 0, compared with 23% receiving omalizumab, 8% receiving ligelizumab 24 mg, and 5% receiving placebo. “Furthermore, more patients receiving ligelizumab at 72 and 240 mg remained symptom-free throughout the 20-week treatment period,” explained Prof. Marcus Maurer (Charité Universitätsmedizin, Berlin, Germany) during the presentation of the study.

Investigations at week 20 discovered UAS=0, equivalent to a complete response rate in 4.7% of patient in the placebo group and 30.6% of those treated with omalizumab. In comparison, patients receiving ligelizumab at doses of 24, 72, or 240 mg had UAS=0 in 18.6%, 39.3%, or 40.0% respectively. This complete response lasted over 10.5 weeks (median value) after the treatment was stopped when the highest ligelizumab dosage had been administered.

Furthermore, improvements in pruritus, measured by an itch severity score were noted. At week 20, mean improvements in UAS from baseline were -18.2 for omalizumab 300 mg, and -23.1 and -22.5 for ligelizumab 72 mg and 240 mg respectively (Figure 10).

The ligelizumab benefit was more rapid, with high complete response rates observed as early as week 4. Ligelizumab induced neither anaphylactic reactions nor new or unexpected side effects. Incidence of adverse events was comparable between the treatment groups.

**Targeting IL-13 improves QOL in atopic dermatitis patients**

A very recent phase 2b study has already revealed the efficacy of tralokinumab symptom improvement in patients with moderate-to-severe atopic dermatitis (AD) while exhibiting an acceptable safety profile [2]. The trial randomised 204 patients with confirmed AD (BSA ≥10%) to 4 equally sized groups receiving either different doses of tralokinumab (45, 150, or 300 mg) or placebo every 2 weeks over 12 weeks. As part of this study, the effect of tralokinumab on health-related quality of life (HRQoL) was evaluated in 52 adult patients treated with 300 mg of tralokinumab on a background of topical corticosteroids (TCS) and 49 under placebo [3].
HRQoL was measured using the Short Form 36 version 2 form, comprising not only health-related questions but also physical and mental component summary scores.

Tralokinumab in combination with TCS showed statistically significant and clinically relevant improvements in virtually all aspects of HRQoL in adult patients with moderate-to-severe AD over TCS with placebo at week 12. Improvements were shown not only in physical but also in mental aspects of the disease (mental component summary in SF-36v2). Mean change in this summary after 12 weeks was 5.41 for tralokinumab vs 1.18 for placebo (P=0.011). In addition, further areas such as vitality, social functioning, physical functioning, and general health revealed significant advantages in favour of tralokinumab, suggesting that tralokinumab can meaningfully reduce the burden of disease. Phase 3 trials are currently in progress.

**Specific comorbidity in young psoriasis and atopic dermatitis patients**

Health insurance information of nearly 300,000 German children and adolescents, including 1,313 psoriasis patients and 30,354 being diagnosed with AD, were analysed on concomitant conditions [4]. Concomitant diseases varied in their prevalence according to diagnosis. Children with psoriasis suffered significantly more often from obesity (7.08% of children with psoriasis vs 3.61% of children without psoriasis), hyperlipidemia (1.14% vs 0.64%), arterial hypertension (0.91% vs 0.44%), and diabetes (0.61% vs 0.31%). The most frequent concomitant diagnoses in AD turned out to be allergic rhinitis (15.16%), and bronchial asthma (12.19%). According to the authors, looking explicitly for the identified comorbidity can, thus, be helpful to detect the need for co-medication early, thereby reducing long-term consequences.

**Early treatment with adalimumab reduces long-term radiographic progression**

Adalimumab can slow radiographic progression. This was shown by a post-hoc analysis of an open label extension study over 120 weeks, where the influence of adalimumab on radiographic progression in patients with psoriatic arthritis (PsA) depending on time since diagnosis and time of treatment was evaluated [5]. All 285 patients included had completed the phase 3 ADEPT randomised controlled trial testing of adalimumab vs placebo over 24 weeks. In the open extension, adalimumab was given at a dosage of 40 mg every 2 weeks. Existence of radiographic damage at baseline or radiographic progression from baseline was defined by change in modified total Sharp score (mTSS) over 0.5. Results were presented including stratification according to duration of disease, type of treatment sequence, and existence of radiographic damage at baseline. Already at baseline, 81% of study subjects presented with radiographic joint damage. Patients being diagnosed ≥2 years ago were affected more often than those with PsA <2 years. In comparison with placebo, treatment with adalimumab during the ADEPT trial led to less radiographic progression by week 144 for patients without initial radiographic damage (placebo 24.3% vs adalimumab 11.8%). Also, at all control visits, significantly fewer progression was present in patients not suffering from pre-existing radiographic damage. Moreover, study subjects had lesser radiographic progression at week 48 and week 144 when receiving adalimumab in both ADEPT and the open extension than those with placebo in ADEPT and adalimumab only during extension. Starting with adalimumab from the beginning of ADEPT entailed significantly less mean radiographic progression at week 24. All in all, the results are in favour of an early start with adalimumab treatment of patients with moderate-to-severe PsA to reduce radiographic progression.

**Dentist follow-up indicated in psoriasis patients**

Due to mutual risk factors for psoriasis and chronic periodontitis, a new study investigated the frequency of dental disease as comorbidity to psoriasis [6]. Chronic periodontitis is characterised by gingival pockets and recessions as well as loss of bone substance. Chronic periodontitis was defined when ≥2 sites with a probing depth of ≥5mm or ≥2 sites with periodontal attachment level ≥4mm with X-ray evidence of bone loss could be documented. A total of 40 adults >18 with plaque psoriasis and an equal amount of healthy controls were matched for sex and age. Of the psoriasis patients, 62.5 % were overweight compared with 32.5% of the controls. The associated BMI came up to 27 and 25, respectively. In 82.5% of the psoriasis cases, severe chronic periodontitis was diagnosed, significantly more than in controls (37.5%, P=0.001). A multivariate analysis that controlled for various confounders, such as diabetes, age, smoking, and obesity, revealed that psoriasis patients had a nearly 22 times higher relative risk to get chronic periodontitis compared with controls. As a result, investigators strongly advised for a close dental monitoring of psoriatic patients.

**References:**