2018 AAD Annual Meeting

American Academy of Dermatology

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PEER-REVIEWED CONFERENCE REPORT

Late Breakers
New agents are in the pipeline for the treatment of moderate to severe atopic dermatitis: The JAK inhibitor upadacitinib showed promising results, but also dual JAK/SYK inhibition is an interesting option.

read more on PAGE 3

Atopic Dermatitis
Sleep disturbance is an AD comorbidity, which is often overlooked, but always warrants step up therapy. New study data hint to the fact that antihistamines should be used more critically in minors.

read more on PAGE 12

Spotlight on Acne
Not only AD patients, also acne patients have a barrier defect. Therefore, patients benefit from the use of suitable moisturisers that should always be recommended by the dermatologist.

read more on PAGE 15

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Editor Prof. dr. Peter van de Kerkhof, University Medical Centre, Radboud, The Netherlands

Letter from the Editor

Prof. Peter van de Kerkhof

Dear Reader,

It is my pleasure to present the report on 2018 -AAD Annual meeting held in San Diego, USA on February 16-20. The Meeting was a huge success and the programme covered all aspects of dermatology, incorporating both explorative research and clinical studies.

This report compiles several studies from late breaker session, Psoriasis, Atopic dermatitis, Acne management, Alopecia Areata, Melanoma related to risk-factor identification, innovative therapeutic approaches, presented in this meeting. We have selected the clinically relevant topics and key outcomes that may be most interest to the practicing clinicians.

I hope that you enjoy our selections.

With best regards,
Peter

Biography

Peter van de Kerkhof is Professor in Dermatology and Chairman of the Department of Dermatology of the University Medical Centre St. Radboud, Nijmegen. Professor van de Kerkhof graduated in Medicine from the Catholic University of Nijmegen in 1978 and trained in Dermatology at the Radboud University Nijmegen Medical Centre, Nijmegen. Since his first publication on psoriasis in 1980, Professor van de Kerkhof has kept a long-standing commitment to research on the pathogenesis and treatment of psoriasis. He serves as Editor or Associated Editor for 7 dermatological journals and has published over 700 publications in peer-reviewed journals. Professor van de Kerkhof is a member of 12 international dermatology organisations and is past President of the European Society for Dermatological Research, the European Dermatology Forum and the International Psoriasis Council.

Contents

COLOPHON

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Interview with

Dr. Erik Joseph Stratman

Marshfield Clinic, Marshfield, chair of the AAD Scientific Assembly Committee

Interview taken on 17 February 2018 by Susanne Kammerer

Living in the golden age of psoriasis and atopic dermatitis therapies

What are the highlights from AAD 2018?

Dr. Stratman: "First of all, it is very exciting that we have one of the largest groups of registrants ever, with physicians from every state in the US and over 99 other countries. As for the highlights, we are surely living in the golden age of psoriasis therapies. There is a large number of new psoriasis drugs and as dermatologists want to learn about new therapies, that is certainly one of the hot areas. Furthermore, new therapies for very severe atopic dermatitis (AD) are being discussed. There are also some practice management topics dermatologists have to face; for example, access to drugs which are becoming incredibly expensive over the last five to ten years. We have to ask why they have to be so expensive and what can we do to get access to those therapies for our patients. The "hot topics in dermatology" are also very popular as this session looks at new developments in a variety of different areas like drug therapy, disease management, diagnosis and basic science. Those are always very exciting because we learn not only about what's ready for practice today but what's coming down the pipeline. In addition, the well-being of dermatologists is discussed as we are facing increasing rates of burnout amongst our colleagues."

Can dermatology stay affordable in view of all these new medications?

Dr. Stratman: "I think we are living in a very important time, where we are having more and more conversations about the value of care. But value isn't just the costs but also quality of life gained. We know that there are many studies that show that we may sometimes be undertreating our patients with severe skin disease due to ignorance about options of therapy and, sometimes, due to a bit of discomfort in prescribing medicines that are somewhat more aggressive. But what we know is that many of these new drugs have an incredibly good rate of clearance and so patients are experiencing a dramatic improvement in quality of life. That's a big part of what's in the numerator of the value equation as it is: quality of life over costs. If you can impact the quality of life, you may end up keeping the patient out of the dermatology office or even the hospital: and both can also be very expensive."

How should we select the right treatment for a patient?

Dr. Stratman: "I am sure that there is some variability across the globe on how that happens but, in most places in the US, insurance companies that are usually the ones paying for medicines or helping the patient pay for the medicines often want you to go through a step ladder approach with the more expensive drugs being higher up. So, most of the time we do start with frontline therapy that may have been around a little while longer. Many of the more expensive therapies are second-line. In my opinion, the great news is that we have so many options. Even if we go through the therapies that are lower on the ladder, if they don't work there are many more choices, and I think this variety of choices is what will help drive the prices down. It is just the market forces of drugs sales."

What is your wish for future AAD meetings?

Dr. Stratman: "My idea of a meeting is one where physicians leave the meeting and immediately have an impact in how they practice medicine. There are many studies that show that if you attend a meeting not doing anything but sit in a seat and listen to lectures, this won't change much or anything that you will do in your practice. But what we need to be impacting with our education is: what are we doing and, also, what are we overdoing or underdoing and therefore should change? So, I'd like sessions that are more hands-on, meaning a real chance for kinaesthetic practice—for example, learn a new technique. I would also like to see more high-fidelity simulation models, where you can learn to do a surgery here at the meeting or actually perform a laser procedure. These simulation models should help the attending physicians to train to be better in their clinical practice. We already have several of those sessions but I'd like to see them more. As I said, we can't change practice in a traditional lecture setting. We have to improve audience engagement during the presentation in order to not have a passive audience. So, e.g. an audience response system, where you have to click an answer or give an opinion, are both very powerful ways of engaging the audience. Learning with case-based scenarios also helps all clinicians to do a better job when they go back to practice. They will see a similar case and the learning that they did here will click in their mind."

Late Breakers

As in every year, the late breaker sessions were one of the main attractions of the AAD meeting. A clear focus was on the indications of atopic dermatitis and psoriasis. Biologics will play an increasingly important role in the management of these diseases.

IL-17C Inhibition in AD: a new treatment approach

Last autumn, the first biologic for atopic dermatitis (AD) was approved in Europe. But more is yet to come! Another interesting approach is blockade of interleukin (IL)-17C, which was shown to be remarkably effective in a randomised controlled, dose-escalation, phase-1 trial presented by Prof. Diamant Thaçi MD, University Clinic Schleswig-Holstein [1]. "In moderate-to-severe AD we have a clear unmet medical need for treatments that are safe and efficacious", Prof. Thaci emphasised during the presentation of the data. The rationale for this trial was experimental evidence that IL-17C induces expression of proinflammatory cytokines, mediators and antimicrobial peptides in epithelial cells and is thus closely related to dermal inflammation. This has been shown to be distinct from other members of the IL-17 cytokine family. In the trial, 25 subjects with moderate-to-severe AD received four weekly infusions with three different doses, and then a 10-week follow-up period. 83% of patients (five out of six) at the highest dose reached at least 50% improvement on the Eczema Area and Severity Index (EASI-50) at Week 4. The onset of activity occurred within two to four weeks, depending on the dose administered. Pooled data across all three dose cohorts showed a 72% improvement of AD symptoms at Week 12 compared to baseline in patients treated with the IL-17C blocker. Even at Week 4, 58% had already reached EASI-50 response (compared to 32% with the placebo). The agent was well-tolerated with no safety signals detected. All adverse drug reactions observed were mild-to-moderate and transient in nature. It is notable that activity was maintained more than two months after the last treatment. "Both the first signs of clinical activity and the sustained response, lasting up to two months after treatment discontinuation, support further clinical development of this antibody," concluded Prof. Thaci. A Phase 2 trial will commence in 2018.

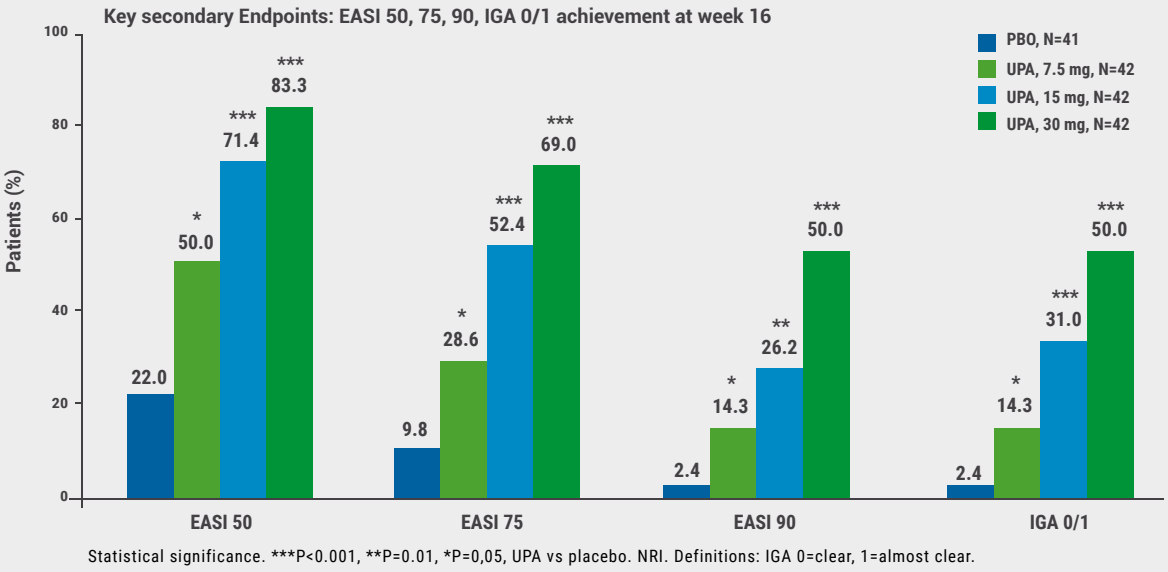
But also new oral treatments on the horizon

The selective Janus kinase (JAK)-1 inhibitor, upadacitinib, is currently being investigated for the treatment of patients with AD and other inflammatory indications. A Phase 2b trial, presented by Prof. Emma Guttmann-Yassky of Mount Sinai Hospital, showed promising results in patients with moderate-to-severe atopic dermatitis [2]. Patients who were inadequately controlled by topical treatment, or for whom topical treatments were not medically advisable, were randomised to once-daily upadacitinib monotherapy 7.5, 15, or 30 mg, or placebo. The primary endpoint of this dose finding study was a mean percentage improvement in EASI score from baseline to Week 16. Janus kinase upadacitinib showed a clear dose-response effect and good differentiation between doses of 7.5, 15 and 30 mg, and placebo. At Week 16, all upadacitinib dose groups experienced statistically significant improvements compared to placebo. Mean EASI scores improved 23% for placebo vs. 74.4% for the 30 mg dose upadacitinib over the 16-week trial. Upadacitinib was also effective in relation to a couple of key secondary endpoints such as EASI 75 or EASI 90 response, or clear or almost-clear skin, according to the investigator´s global assessment (IGA 0/1) (Figure 1). "Even the lowest dose gave us good EASI 90 results, while 50% of patients on the highest dose showed EASI 90," said Prof. Guttman-Yassky. "And we saw no serious adverse events." The agent displayed a rapid onset of action with significant differences compared to placebo after only two weeks; maximum efficacy was reached after four weeks and maintained until Week 16. Upadacitinib successfully lowered pruritus (assessed on a numerical rating scale) compared to placebo. The most common adverse events were upper respiratory tract infections in >10% of patients and exacerbations of AD. No herpes zoster, malignancies, death or cases of pulmonary embolism or deep vein thrombosis were reported. "I think these are quite exciting data", concluded Prof. Guttman-Yassky. A 72-week extension of this trial will be reported later this year.

First promising data for a dual JAK/SYK inhibitor

"This is the first clinical study with ASN002, a novel JAK/SYK inhibitor" said Dr. Robert Bissonnette of Innovaderm Research at the presentation of this Phase 1b trial [3]. According to Dr. Bissonnette, ASN002 is an interesting molecule and somewhat different from other JAK inhibitors, because it also affects spleen tyrosine kinase (SYK). This

Figure 1 Upadacitinib was effective in a dose-dependent way regarding EASI response in moderate-to-severe AD [2]



Statistical significance. ***P<0.001, **P=0.01, *P=0,05, UPA vs placebo. NRI. Definitions: IGA 0=clear, 1=almost clear.

intracellular kinase inhibits IL-17 signalling/CC chemokine ligand 20 production in keratinocytes, increases terminal differentiation of keratinocytes, and inhibits B-cell signalling, which plays a role in skin immunity. AS002 thus diminishes production of Th2 and Th22 cytokines. The dysregulation of Th2 and Th22 cytokine pathways are a hallmark of the pathogenesis of AD. Although safety was the primary target of this trial there were also several efficacy targets. The 36 study participants represented the typical AD population with moderate-to-severe disease. They were separated into three 12-patient groups. In each group, nine received the active drug every day in a dose of 20, 40 or 80 mg for 28 days, followed by a 14-day safety period. No concomitant administration of topical corticosteroids or other immunosuppressants was permitted during or prior to the study. ASN002 was well-tolerated: the most common adverse event was headache, which occurred at equal rates among the groups. At Day 29, 100% of patients taking 40 mg ASN002 and 88% taking 80 mg had achieved an EASI50 response, and 63% and 50% an EASI75 response. Itch (assessed in a Numeric Rating Scale) was reduced by 19–51%. There were no clinically significant changes in chemistry lab parameters. Skin biopsies and microbiome analysis will be also performed in this trial, but these data will be presented later this year. According to Dr. Bissonnette, ASN002 shows "…clear efficacy in patients with moderate-to-severe atopic dermatitis, with rapid symptom improvement". In addition, a significant reduction in patient-reported itch was observed as early as Day 2 of treatment. The agent allows a convenient once-daily dosing. After this encouraging data, a Phase 2b trial will be initiated this year.

Proof of concept trial regarding anti-IL-33 blockade

Prof. Graham Odd of Oxford University presented a small trial with an anti-IL33 antibody that was effective in patients with AD [4]. All 12 patients who received one intravenous infusion of ANB020 achieved at least a 50% reduction in their EASI-Score by Day 29. The agent also displayed a rapid onset of action: most of the improvement occurred in the first two weeks. Pruritus was also reduced. All effects were largely sustained for two months, then gradually began to fade. IL-33 is produced by keratinocytes and epithelial cells and is highly expressed in AD lesions. As Dr. Ogg pointed out, IL-33 is an alarm molecule predominately produced after damage to keratinocyte—for example, after an allergenic challenge to the skin. The antibody was well-tolerated with no drug-related safety signals.

Psoriasis: unprecedented activity with selective IL-23 blocker

The IL-23 blocker risankizumab was superior to both placebo and ustekinumab over 52 weeks in two identical, double-blind, placebo- and ustekinumab controlled Phase 3 trials (ultiMMa-1 and ultiMMa-2) [5]. Both trials compared the IL-23 inhibitor risankizumab with placebo and ustekinumab over 52 weeks in a total of 797 patients with moderate-to-severe plaque psoriasis. Patients in the placebo arm were switched over to risankizumab after 16 weeks. The primary targets were a reduction of the Psoriasis Area and Severity Index (PASI) by 90% (PASI 90) and clear or almost clear skin, according to the static Physician´s Global Assessment (sPGA

0/1). In addition, 15 secondary targets were assessed at different time points during the 52-week study. Risankizumab met all: the difference in efficacy between the drugs were all statistically significant at 16 and 52 weeks (P<0.001). At 52 weeks, when the placebo group had crossed over to risankizumab, the percentage of patients whose symptoms were completely cleared increased in both groups but risankizumab was still more effective than ustekinumab. "We saw 75% of patients achieving PASI 90 vs. 5% on placebo, and 88% sPGA clear or almost clear compared to 8%," said lead author Prof. Kenneth Gordon of the Medical College of Wisconsin. The PASI 100 response was among the highest ever reported—60% at Week 52 in the risankizumab group vs. 30% for ustekinumab. "This is where we see the real difference between these new biologics and drugs we used to use", said Prof. Gordon. As expected, quality of life (QoL) improved with higher clearance rates: more than 70% of the patients treated with risankizumab reached a 0/1 response in the Dermatology Life Quality Index (DLQI), which means that their disease no longer has an impact on their QoL. About 15% of patients experienced adverse events related to the drugs, but they were similar for risankizumab and ustekinumab with no unexpected safety signals. The most frequently reported risankizumab-emergent adverse event was upper respiratory tract infection.

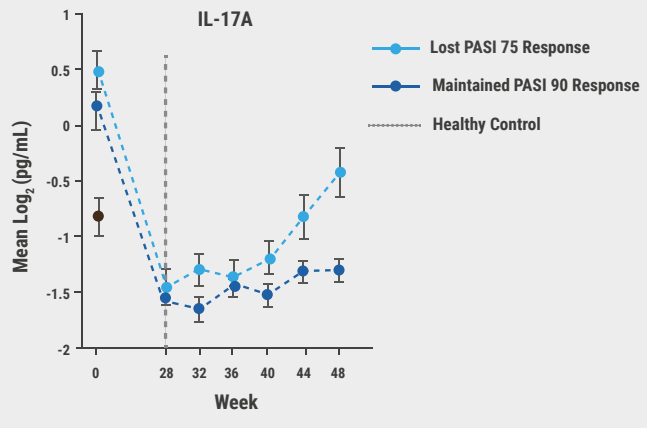
Analysis of the VOYAGE-2-trial: a first glimpse into disease modification?

An analysis on the long-term efficacy of guselkumab after drug withdrawal and retreatment in patients with moderate-to-severe psoriasis showed that this agent had an amazing durability of response [6]. This analysis included patients who were originally randomised to guselkumab in the Phase 3 VOYAGE-2-trial and achieved a PASI 90 response at Week 28. Patients were then either re-randomised to placebo/withdrawal (with retreatment upon loss of ≥50% PASI improvement achieved at Week 28 or at Week 72 if retreatment criteria were not met) or continued guselkumab treatment (every eight weeks) through to Week 72. Of patients who remained on treatment during the 76-week study, 86% showed PASI 90 or better. When they were taken off the drug, only 37% of patients displayed PASI 90 20 weeks later and 12% displayed it at the end of the study, 44 weeks later. "We know that if you withdraw from the drug, you open the door to the return of disease," said lead author Prof Kristian Reich of the Sciderm Research Institute. "However, the median time to loss of PASI 90 response was 15 weeks—23 weeks after the last guselkumab dose—for patients randomised to the withdrawal group; with adalimumab, this happens much earlier." According to him, this is an amazingly durable response. Patients who were randomly withdrawn from guselkumab and re-treated had a response similar to continuous treatment, with 88% achieving PASI 90 six months after retreatment. This was also reflected in high DLQI 0/1 scores after patients were re-treated with Guselkumab. "When patients are treated with guselkumab we see a dramatic fall of IL-17A, but now comes the interesting part—even in patients that are off the drug but maintain their PASI 90 response, there is no reoccurrence of IL-17A, IL-17F, and IL-22 in contrast to patients that lost PASI 75 response [Figure 2]: in these patients, IL-17 goes up quickly. This might be our first glimpse into disease modification," concluded Prof. Reich.

Dual IL-17 inhibitor active in patients with moderate-to-severe Psoriasis

According to the 12-weeks results of a Phase 2 trial, the dual IL-17 inhibitor bimekizumab is an interesting novel treatment option for patients with moderate-to-severe psoriasis [7]. Bimekizumab is a humanised monoclonal IgG1 antibody that selectively neutralises IL-17F in addition to IL-17A. The rationale for developing this drug was that simultaneous targeting of both IL-17 subgroups might increase efficacy. IL 17A and 17F are key cytokines that jointly express in the inflammation contributing to tissue impairment (Figure 3). Lead author Dr. Kim Papp of Probity Medical Research found that, at 12 weeks of treatment with the highest bimekizumab dose, up to 86% of patients achieved a PASI90 response (primary target), and 60% achieved a PASI 100 response: a complete clearance of their psoriatic lesion. In the study, 250 patients were randomised to different doses of bimekizumab

Figure 2 Maintenance of PASI 90 Response after drug withdrawal is associated with continued suppression of IL-17A, IL-17F and IL-22 [6]



Serum cytokine levels were determined by Singulex high-sensivity immunoassay.
Data are presented as mean $\log_2$ (pg/mL) over time. Error bars represent SEM.
P<0.01 vs Week 28; P<0.05 PASI 75 lost vs PASI 90 maintained
IL-17A, interleukin 17A; IL-17F, interleukin 17F; IL-22, interleukin 22

(64 mg, 160 mg, 160 mg with a 320 mg loading dose, 320 mg, 480 mg) or placebo every four weeks, for 12 weeks. Treatment with bimekizumab also provided an improvement in psoriasis severity, as measured by an Investigator's Global Assessment (IGA) 0/1 ("clear" or "almost clear") response. "Looking at the curves, I think we have not yet reached the maximum response," said Dr. Papp. The most frequently reported treatment-emergent adverse events were nasopharyngitis and upper respiratory tract infections.

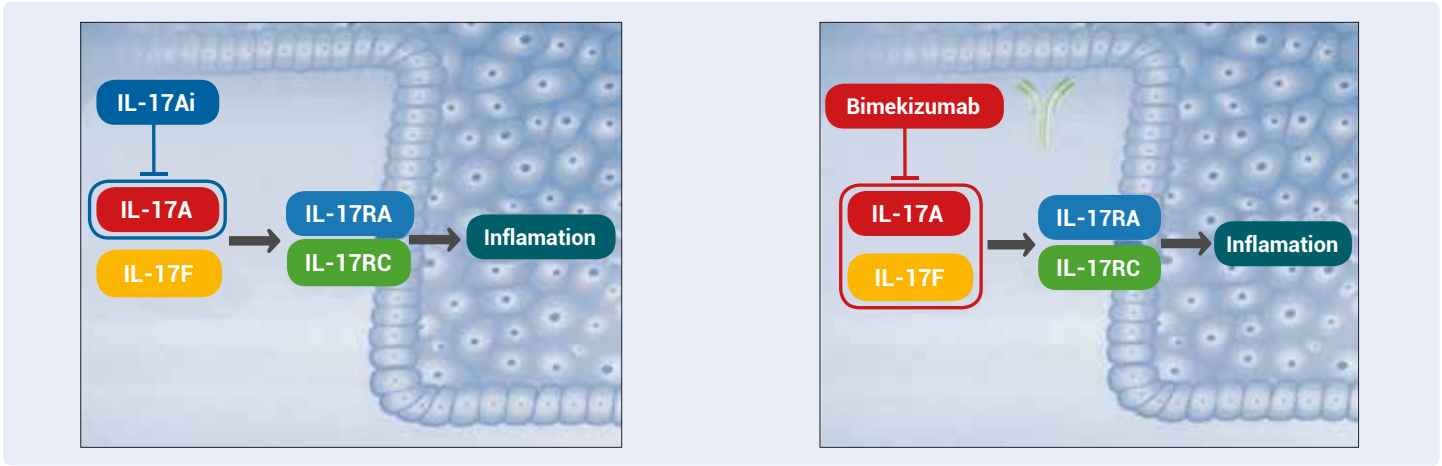
Ustekinumab lowers risk of aortic inflammation

Patients with moderate-to-severe psoriasis have a significantly elevated cardiovascular risk [8]. This is particularly true in patients with a body surface area (BSA) of >10%: they have an 80% increased risk of mortality, independent of major risk factors [9]. There is preliminary evidence that some psoriasis treatments improve cardiovascular biomarkers and the incidence of cardiovascular risk [8]. Systemic inflammation is regarded as the link between psoriasis, obesity, and other cardiovascular diseases. A trial presented by Prof. Joel Gelfand of the University of Pennsylvania Perelman School of Medicine tried to determine whether therapy with the IL-12/23 blocker ustekinumab can reduce aortic inflammation and whether this will translate into lower cardiovascular risk [10]. Previous studies have demonstrated that as the PASI score goes up, so does the aortic inflammation. Patients with severe psoriasis therefore develop a high risk of atherosclerotic plaques. At the meeting, the 12-week data of the "Vascular Inflammation in Psoriasis (VIP-U)" trial were presented. 43 randomised patients received placebo or two injections of ustekinumab. At Week 12, a PET/CT was performed, after which all patients were treated open-label with ustekinumab for up to one year. The efficacy of ustekinumab was as expected: 77.3% of patients gained a PASI 75 response (compared to 10.5% with placebo; P<0.001) after 12 weeks, and 63.6% gained clear or almost clear skin in the PGA, reported Prof Gelfand. However, the significant reduction of vascular inflammation, measured by fluorodeoxyglucose positron emission tomography (FDG-PET), came as a surprise: effect sizes were in a similar range as those seen with statin therapy. In just 12 weeks, therapy with ustekinumab was followed by a 6.6% reduction in total aortic inflammation, whereas a 12.1% increase in inflammation occurred in the placebo group. The results were independently confirmed by a separate imaging laboratory. Whether the reduction of vascular inflammation will also lead to a reduced cardiovascular risk is a matter of debate. The study will go to open label at one year and biomarker assays will be presented in future meetings. According to Prof. Gelfand, this might be a class effect of the IL-12/23 blocker, because an earlier trial with the TNF blocker adalimumab failed to display an effect on aortic inflammation [11]. To resolve this issue, longer-term effects for ustekinumab as well as the biomarker analyses have to be awaited. As Prof. Gelfand indicated, additional trials are necessary to determine whether this effect is due to inhibition of IL-12, IL-23 or a combination of them. Only a cardiovascular event trial will be able to fully determine the clinical implications of the effect on vascular inflammation.

Soft molecule highly efficacious in hyperhidrosis

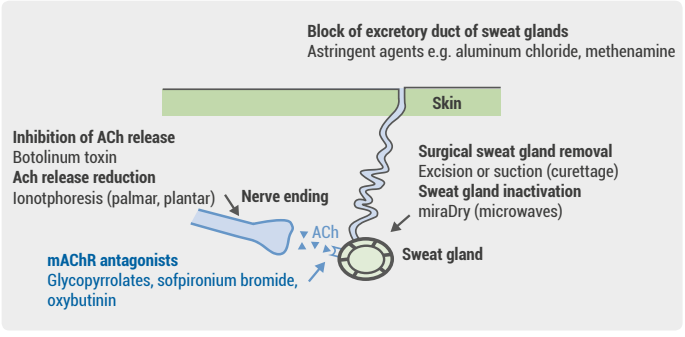
Hyperhidrosis has an impact on QoL comparable to, or greater than, psoriasis or eczema [12]. According to the International Hyperhidrosis Society, sweat production of >100 mL/5 min. in males, and >50 mL/5 min. in females is defined as hyperhidrosis. A new gel with a soft molecule

Figure 3 Both IL-17A and IL-17F contribute to tissue inflammation in psoriasis [7]



was shown to be effective in reducing hyperhidrosis after a treatment period of only eight days [13]. "The anticholinergic drug sofpironium bromide is a soft molecule, which means that it is easily broken down and rapidly metabolised in the bloodstream" explained Dr. Stacey Smith, a dermatologist in Encinitas, California. It inhibits acetylcholine-driven sympathetic and parasympathetic actions on various exocrine glands, including sweat glands (Figure 4). This new molecular entity has the advantage of a better local therapeutic effect with fewer systemic side effects. The efficacy and safety of this agent was assessed in a dose finding study, where a topically applied gel with three doses of sofpironium bromide was compared against a vehicle gel in 227 subjects with primary axillary hyperhidrosis. "We did not only a sophisticated questionnaire but also a combined axillary gravimetric sweat production test. To be successful in hyperhidrosis, you must do well in both," said Dr. Smith. At baseline, all subjects had scores of ≥3 (scale, 0-4) in the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax), a validated patient-reported outcome measure for hyperhidrosis and a combined axillary gravimetric sweat production (GSP) of ≥150 mg/5 min. A one-point improvement in the HDSM-Ax has been established as being clinically meaningful. After 42 days of once-daily application to the axillae, patients treated with sofpironium bromide gel (5% and 15%) had statistically-significant higher response rates as measured by the HDSM-Ax from Day 8 until the end of therapy. In addition, sofpironium bromide-treated subjects demonstrated statistically significant reductions in GSP. The gel was also effective in a combined responder analysis. Treatment success was seen as both a HDSM-Ax improvement of at least one point and a ≥ 50% reduction in GSP. Nearly 60% of patients treated with the gel gained treatment success. "Hyperhidrosis significantly impacts the social, occupational and emotional well-being of those affected, and there are currently very limited therapeutic options," said Dr. Smith. "I am excited by the prospect of

Figure 4 Mode of action of Acetylcholine receptor antagonists and other treatment modes for hyperhidrosis. Ach = acetylcholine, mAChR = muscarinic acetylcholine receptor



sofpironium bromide, to offer my patients a well-tolerated, effective and convenient first-line treatment option." The gel was well-tolerated at all doses, with side effects that were transient and primarily mild-to-moderate in severity. The most common anticholinergic adverse event was dry mouth.

Anticholinergic towelettes safe and effective in paediatric hyperhidrosis

Hyperhidrosis is largely undertreated and underdiagnosed, particularly among paediatric patients [14]: "It would not be fair to exclude paediatric patients because hyperhidrosis often starts at an age of 9," said Dr. Adelaide Hebert, of the University of Texas Health Science Center in Houston, during the presentation of a subgroup analysis of the randomised controlled Phase 3 trials ATMOS-1 and ATMOS-2 [15]. The analysis showed that about 80% of paediatric patients had at least a 50% decrease in sweat production when using towelettes containing glycopyrronium tosylate, with a similar treatment benefit as adult patients (mode of action, see Figure 4). The subgroup analysis focused on 44 patients from ages 9 to 16, with 25 randomised to use the towelettes with the anticholinergic agent. The remaining 19 patients were assigned wipes containing an inert vehicle substance. After four weeks, axillary sweat production decreased by 64 mg/5 min (from a baseline mean of 146 mg/5 min). 79.9% of children assigned to the anticholinergic wipes had at least a 50% reduction in axillary sweat production, compared with 54.8% assigned to the control groups. Corresponding rates in the older patients were 74.3% and 53.0%. This was also true for the impact on QoL. "In all endpoints, the paediatric group responded equally well as the adult group," said Dr. Hebert. "We did not just reduce the sweat, we increased QoL even in paediatric patients." The safety profile was likewise similar in all age groups: some children had headache, some had specific anticholinergic effects such as mydriasis. Only one paediatric patient in the verum group discontinued therapy due to side effects. "Even though the patients had some systemic cholinergic side effects, they did not want to leave the study because their QoL improved so much," said Dr. Hebert. The subgroup analysis was the first study in paediatric patients with hyperhidrosis. Topical glycopyyronium tosylate treatment provides a much-needed treatment option for paediatric patients with hyperhidrosis.

Apremilast effective in Behcet´s Syndrome

The oral phosphodiesterase (PDE)4 inhibitor apremilast displayed a significant effect on ulcers and ulcer pain associated with Behcet´s syndrome in the RELIEF trial [16]. Behcet´s syndrome is a rare, chronic, multi-system

inflammatory disorder characterised by oral and genital ulcers, skin lesions, uveitis, arthritis, with vascular, central nervous system, and gastrointestinal involvement. A key symptom occurring in nearly all patients is painful recurrent oral ulcers that can be disabling and have a substantial effect on QoL: there are currently no effective treatment options for them. The oral PDE4 inhibitor apremilast modulates inflammatory mediators and has demonstrated efficacy in a Phase 2 Behcet´s syndrome study. These preliminary data were the reason for a Phase 3trial with apremilast. In the RELIEF study, a total of 207 patients were randomised to apremilast (30 mg twice daily) or placebo. At Week 12, the area under the curve (AUC) for the number of oral ulcers had a statistically significant reduction in apremilast compared to placebo (129.5 vs. 222.1; P<0.0001). The AUC was chosen as the trial's primary endpoint because it assesses the change in the number of oral ulcers over time, accounting for the clinical characteristic of oral ulcers repeatedly remitting and recurring in Behcet´s syndrome. "Apremilast had also a significant effect on the ulcer pain and overall disease activity measures, and improved QoL of patients with Behcet´s syndrome," said Dr. Yusuf Yazici of the New York University School of Medicine during the presentation of the data. QoL improved significantly in patients taking apremilast (P=0.0003). The most common adverse events observed in the trial were diarrhoea (41.3% with apremilast, 19.4% for placebo), nausea (19.2% with apremilast, 10.7% for placebo), headache (14.4% for apremilast, 9.7% for placebo) and upper respiratory tract infections (11.5% for apremilast, 4.9% for placebo). The safety profile was consistent with the known safety profile of apremilast in studies with psoriasis patients.

First specific therapy for patients with Hidradenitis suppurativa

An antibody against a split product of the complement system was safe and showed impressive clinical efficacy in an open-label Phase 2a study in patients with severe Hidradenitis suppurativa [17]. C5a is a split product of complement that has been shown to be increased in hidradenitis suppurativa [18]. A high expression of C5a is also associated with the severity of the disease and stimulates overproduction of TNF-α and, therefore, may be a future therapeutic agent. IFX-1 is a humanised monoclonal IGG4K antibody that specifically binds to the soluble human complement split product C5A. Twelve patients with hidratenitis suppurativa were treated with weekly infusions of 800 mg IFX-1 for eight weeks and followed up for another 12 weeks. IFX-1 was well-tolerated. "For us, it was important to see that the antibody blocks only the split product C5a, which is responsible for the inflammatory action, but not the fragment C5b, which is needed for host defence", explained Prof. Evangelos Giamarellos-Bourboulis, of the National and Kapodistrian University of Athens Medical School in Greece, during the presentation of the data. Although half of the participants experienced adverse events, these were not related to the drug but to the disease itself. The antibody displayed a remarkable efficacy (secondary endpoints): at the end of the treatment period on Day 50, 75% of patients showed a clinical response. This response was maintained and was even better at the end of the follow-up period, 84 days after the last treatment. At that time, 83% of participants were responder. Patients also improved according to the PGA. In addition, there was a significant change of the abscess and nodule count, which was also maintained during the follow-up period. "We did also notice that the dimensions of the lesions diminished," said Prof. Giamarellos-Bourboulis. C5 levels showed a complete blockade during the entire treatment period. Due to these results, a larger Phase 2 study is currently being planned to confirm these results.

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Psoriasis: An Update

There is currently an ever-increasing number of innovative psoriasis treatments that specifically target underlying pathomechanisms. Novel combinations and an individualised treatment approach are important contributors to therapeutic success.

Dr. John Koo, of the Phototherapy and Skin Treatment Clinic at the University of California San Francisco, gave an update on new data on oral therapeutics in psoriasis [1]. Apremilast appears to have lower efficacy than some biologic agents. However, its ease of administration as an oral agent, coupled with a mild side-effect profile, make it an attractive option for many psoriasis patients. A poster presented at the annual meeting of the European Academy of Dermatology and Veneorology (EADV) in Geneva provided more insight into the mode of action of this small molecule: it assessed the influence of apremilast on different cytokines compared to placebo [2]. Data came from the ESTEEM 2 trial, which confirmed the therapeutic concept that apremilast works as a cytokine modulator. It has a distinct effect on the proinflammatory cytokines IL-17A, IL-17F and IL-22, but lowers TNF-α to only a minimal amount. "I think it is therefore a good idea to combine apremilast with a TNF-α blocker, if a monotherapy does not show enough efficacy, because in this way you get an influence on all cytokines," said Dr. Koo. This approach is backed by a case report of a patient with recalcitrant psoriasis who gained near-complete remission after therapy with a combination of adalimumab and apremilast [3]. According to a retrospective study, apremilast can also be combined with phototherapy, systemic, and/or biological agents in patients with plaque psoriasis who do not respond adequately to these agents alone [4]. Gastrointestinal side-effects were manageable in the majority of patients, 81% of whom achieved PASI-75 response at Week 12 after apremilast was added to an existing therapy. Another open-label observational study assessed the efficacy of apremilast in combination with narrowband ultraviolet-B therapy [5]. Patients with moderate-to-severe plaque psoriasis received apremilast and increasing doses of NB-UVB (310-312 nm) three times per week for 12 weeks. In this way, 73% of patients achieved a PASI 75 response at Week 12. NB-UVB may therefore be an option to enhance an initial therapeutic response to apremilast. In this trial, the combination had an impressive effect on pain and itch, assessed as an improvement in a VAS-Score (Figure 5).

Supersaturation to enhance topical therapy

Applying active ingredients in an aerosol instead of an ointment can enhance local therapy This is shown in a study that compared an aerosol foam formulation of fixed combination calcipotriene plus betamethasone dipropionate with the same ingredients in an ointment [6]. "The reason is that the aerosol goes away, and you achieve a higher penetration of the active ingredients," said Dr. Koo. In this trial, 54.6% of patients using the aerosol foam gained controlled disease according to IGA, compared with 43% using the ointment (Figure 6). The aerosol was also superior in reducing the itch [6]. A penetration study after topical application to pig-ear skin confirmed that about double amounts of calcipotriene and betamethasone dipropionate were found in the skin after application of the aerosol compared to the ointment [7]. "I think this supersaturation is a nice way to enhance efficacy of topical treatment. In addition, it is also easier to use for our patients," concluded Dr. Koo.

Figure 6 A combination aerosol foam Is more efficacious than a combination ointment [6]

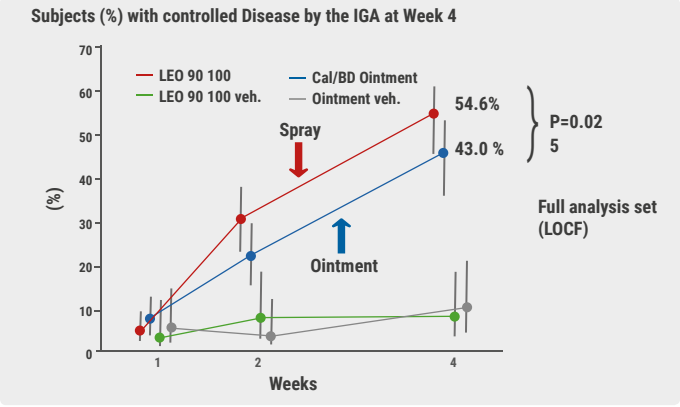
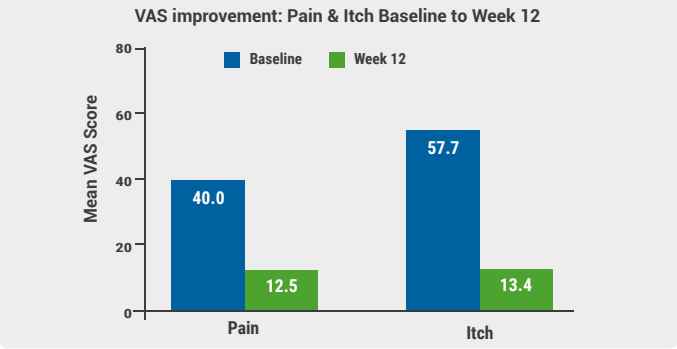


Figure 5 Improvement of pain and itch by the combination of apremilast and narrowband UV-B therapy [5]



Excimer laser treats faster than UVB box

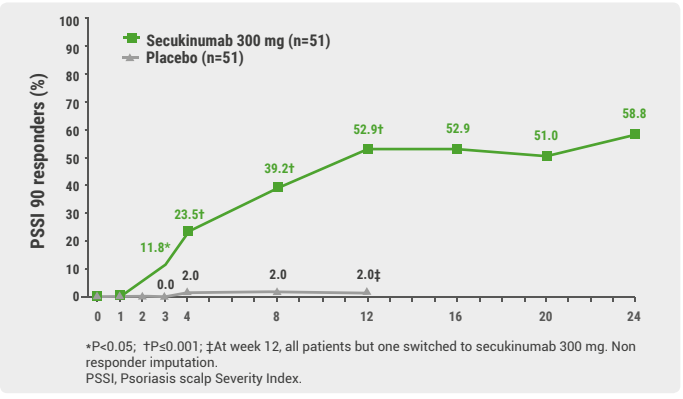
A drawback of phototherapy with a UVB box is that approximately 36 sessions (three per week for three months) are necessary for a marked improvement. "UVB phototherapy using excimer laser is targeted. Therefore, you can treat much more aggressively because thick plaques are more tolerant than normal skin whereas, in phototherapy, you can only use the minimal erythema dose—otherwise, you cause sunburn," explained Dr. Koo. The 308-nm excimer laser takes only 10–15 sessions. The protocol for the laser is based on skin type and plaque induration. A case report demonstrated that, by applying an aggressive protocol by using plaque-based sub-blistering dosimetry, a PASI-75 response can be reached in only two sessions [8]. In traditional full-body phototherapy, the maximum dose is the minimal erythema dose (MED). "Plaques can take more light than normal skin; the applied dose is higher than the MED. On plaques, the lighter you give, the more effective it is, and erythema disappears quickly," explained Dr. Koo. According to his experience, this is not even painful for patients. By applying high doses, T cells producing TNF-α are selectively and effectively decreased; the same applies for IL-2 producing cells. This probably explains the fact that laser treatment also enables a long remission of about six months without further treatment [9]. This novel way of enhanced phototherapy is important because, in the experience of Dr. Koo, many people nowadays have no time to undergo the traditional phototherapy regime.

Spoiled for choice regarding biologics in psoriasis

Biologics have revolutionised the management of moderate-to-severe psoriasis and allow clear or almost-clear skin in many patients. All biologics yield superior PASI 75 responses (ranging from 40% to >90%) when compared with methotrexate, cyclosporine, and acitretin, with better overall tolerability. "From the IL-17 inhibitors, we have data over a treatment period of more than five years: they show that the efficacy stays the same over this period of time," said Dr. Jashin Joaquin Wu of Kaiser Permanente Los Angeles Medical Center, in his update on biologics in psoriasis [10]. He referred to the SCULPTURE five-year data that were published recently [11]. A poster presented during the meeting established the high efficacy of secukinumab in difficult-to-treat regions: palmoplantar psoriasis, nail psoriasis and scalp psoriasis [12]. This showed the results from three prospective Phase 3 studies, the GESTURE study that included patients with palmoplantar psoriasis, the TRANSFIGURE study with patients with nail psoriasis, and the SCALP study that included patients with scalp psoriasis. In the GESTURE study, more than half of all patients treated with secukinumab achieved clear or almost-clear palms and soles by Week 132. The mean percentage change in the palmoplantar PASI (ppPASI) score from baseline to 2.5 years reached -74.7% and -61.6% for secukinumab 300 mg and 150 mg, respectively. The IL-17 blocker showed comparable efficacy in the treatment of nail psoriasis in the TRANSFIGURE study: both doses of secukinumab demonstrated a large sustained improvement in mean Nail Psoriasis Severity Index (NAPSI) scores from baseline to Week 16 and Week 132. After 2.5 years, NAPSI scores decreased by 63.6% with 150 mg secukinumab and by 73.3% with 300 mg secukinumab [12]. In the SCALP study, almost 60% of patients treated with secukinumab had clear or almost clear scalps as early as Week 24 (Figure 7) [12].

"However, you should not use IL-17 inhibitors in patients with pre-existing inflammatory bowel disease," Prof. Wu recommended. Secukinumab is also clearly superior in comparison to the IL-12/IL-23 blocker ustekinumab, as the recently published one-year data from the CLEAR trial have shown [13]. Curves separated as early as Week 8 until Week 52. Along with ixekizumab, the second IL-17 blocker was approved in September 2017 for adults with active psoriatic arthritis. The agent may be administered alone or in combination with a conventional Disease Modifying Antirheumatic Drug (DMARD); for example, MTX. Brodalumab is another biologic that interacts with IL-17 in a slightly different way, binding not to the cytokine IL-17A itself but to the IL-17A receptor. Brodalumab also proved to be significantly superior to ustekinumab in the AMAGINE-2 and AMAGINE-3 trials [14]. However, it has a boxed warning about suicidal ideation and behaviour: four suicides occurred in subjects treated in the psoriasis clinical trials but not in the 12-week placebo-controlled period. There are also some interesting new agents in the pipeline: an example is the selective IL-23 blocker guselkumab. In the VOYAGE 1 trial, 96.8% of patients reached a PASI 75 response, 83.8% a PASI 90 response and 50% a PASI 100 response, meaning completely clear skin [15]. Certolizumab is not a new drug—it is approved for rheumatoid arthritis—but it is new in psoriasis and

Figure 7 SCALP-study: Almost 60% of patients receiving secukinumab had clear/almost clear scalps by week 24 [12]



*P<0.05; †P≤0.001; ‡At week 12, all patients but one switched to secukinumab 300 mg. Non responder imputation.
PSSI, Psoriasis scalp Severity Index.

psoriatic arthritis: it showed remarkable efficacy in a Phase 3 psoriasis trial (CIMPASI-2) [16]. "This drug is important, because certolizumab is no problem in pregnancy as there is no placental transfer, which is important for female patients of child-bearing age," explained Dr. Wu. This has been demonstrated in the CRIB trial that was designed to measure the potential level of placental transfer of certolizumab from pregnant women to their infants [17]. A total of 16 women (≥ 30-week gestation) who were already receiving the agent for approved indications (rheumatoid arthritis, Crohn´s disease, psoriasis artritis and axial spondylarthritis) were followed in the study. Blood samples were collected from each woman, the umbilical cords, and their infants at delivery, and again from infants at Weeks 4 and 8 post-delivery. Certolizmab blood concentration was measured with a sensitive, specific electrochemiluminescence immunoassay with an extremely low level of quantification of 0.032 µg/mL. Certolizumab levels were below this level in 13 out of 14 infant blood samples at birth, and in all samples at Weeks 4 and 8 post-delivery. One infant had a minimal certolizumab level of 0.042 µg/mL.

New selective IL-23 blockers

Another interesting agent in the pipeline is tildrakizumab, an agent that targets interleukin23p19. It proved to be active in the reSURFACE 1 and 2 trials [18]. "The safety of this biologic looked pretty good, so this will be a valuable additional treatment option," said Dr. Wu. Another agent targeting IL-23, risankizumab, showed impressive one-year data [19]. "Nearly half of the patients (47%) reached complete clearance (PASI 100) at Week 16 in the ultiMMA-1 and ultiMMA-2 trials," said Dr. Wu. As he pointed out, we are "spoilt by choice" with eight biologics and four oral medications. "Adalimumab and ustekinumab are my first-line biologics," he said. "If monotherapy or combo with MTX is not successful, then I switch to secukinumab, ixekizumab, brodalumab, or guselkumab." But it´s all about individualisation of therapy: in patients where there is concern about adverse events, acitretin, UVB or apremilast are good choices. Severe flares are most effectively managed by cyclosporine (5 mg/kg/day). In patients where quicker clearance of psoriasis is needed or patients with concomitant psoriatic arthritis or palmoplantar psoriasis, Dr. Wu advocates IL-17 inhibitors: "Otherwise, I rather give IL-23 inhibitors based on dosing and fewer adverse events, as I do not have to worry about candida infections and inflammatory bowel syndrome", he said.

Psoriasis management online?

A glimpse into the future care of psoriasis patients was given at a trial presented by Prof. April Armstrong of the Keck School of Medicine [20]. According to her trial, an online care model for psoriasis patients was just as good as traditional in-person care. "After the year 2020, there will be more people above the age of 65 than below nine years. The demand in dermatology care will outstrip the supply in future," she said. In years to come, more and more patients with chronic skin diseases will lack regular access to dermatology providers, but teledermatology could eventually relieve the pressure of this demand. The researches decided to assess this model in psoriasis patients because it is a chronic skin disease with a number of co-morbidities, where a team approach by a primary care practitioner (PCP) together with a dermatologist might be particularly valuable. For the study, either PCP or psoriasis patients took standardised photographs of their skin. The photos were uploaded to a connected site where dermatologists could access the images, evaluate them, and provide recommendations directly to the patient and the PCP. The study enrolled 300 patients randomised 1:1 with online to in-person care. A change in the PASI index was the primary study outcome. Over 12 months, the difference in the average change in the PASI between the online and in-person groups was -0.271. The average change in BSA between the two groups was -0.053%. Between-group differences in PASI and BSA were within the pre-specified equivalence margins, which means that the two interventions were equivalent for this endpoint. "It was really astonishing for us how small the difference between the groups was," said Prof. Armstrong. In addition, the online model fared better in the PGA. As Prof. Armstrong pointed out, the online group was believed to have lower disease activity during the study compared to the in-person group and had less side effects. "With our trial, we demonstrated that this model really works," said Prof. Armstrong. For physicians, it will be equally important to know whether they get paid for their cooperation and whether they could be sued more. These questions will be crucial to making online care successful.

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What´s Hot in Atopic Dermatitis

New medications for AD are entering the field. Effective therapy also has a positive impact on comorbidities such as sleep disturbances.

AD is not only skin deep but can have a profound influence on the life of AD patients. As Prof. Jonathan Silverberg of Northwestern University's Feinberg School of Medicine pointed out, a substantial proportion of patients will also have sleep disturbance due to the intense itching associated with AD [1]. This is demonstrated by a US survey of 91,642 children up to the age of 17. About 10% of children with only mild to moderate AD had more than four nights of disturbed sleep per week, a percentage that climbed to more than 20% for children with severe AD [2]. Severe eczema was also associated with a higher prevalence of other comorbid chronic health disorders including asthma, hay fever, and food allergies (P<0.0001). In addition, the severity of eczema was directly related to the severity of the comorbidities [2]. Are adult AD patients better off? Obviously not, as a 2012 US Health Interview Survey of 34,500 adult patients demonstrated: "Even adult patients with mild AD can suffer from fatigue, daytime sleepiness and insomnia," said Prof. Silverberg [3]. This relationship was still evident after controlling for sleep duration, history of allergic disease, sociodemographics, and body mass index. Fatigue, sleepiness, and insomnia were also predictors of poorer overall health status, number of sick days, and doctor visits. Eczema plus any of the sleep symptoms were associated with higher odds of poorer outcomes than either eczema or sleep symptoms alone [3]. "Patients have difficulty in a variety of activities, hobbies and even with their finances when they are tired," said Prof. Silverberg. Besides sleep disturbances, other mental health comorbidities are increased in patients with more severe AD. A telephone survey conducted in >91,000 households across the US showed that children with AD have a significantly higher rate of depression and anxiety compared to healthy controls: even conduct disorder and autism seem more frequent in children with AD [4]. One in five adult US patients has symptoms of depression or is treated for depression. Whether or not there is a genetic correlation with AD is unclear. "Many comorbid conditions will vanish if we treat patients properly," said Prof. Silverberg.

Are we too comfortable using antihistamines?

A study published this year suggests a relation between antihistamine use and the development of attention-deficit/hyperactivity symptoms (ADHD) [5]. In this prospective clinical trial, four groups of children aged 6–12 years were compared using a factorial design: AD-only (without ADHD), ADHD-only (without AD), AD+ADHD, and healthy controls. Compared to the controls, children with AD-only, ADHD-only and comorbid AD+ADHD had significantly increased behavioural problems and decreased QoL. Interestingly, in AD-only children, previous use of antihistamines was significantly associated with increased ADHD symptoms (OR 1.88; 95% CI 1.04-3.39), although current clinical signs and AD symptoms were unrelated to the level of ADHD symptoms. "I think we are too comfortable using antihistamines at the moment and this study calls for further investigations to determine whether early antihistamine exposure is a risk factor for ADHD," said Prof. Silverberg

Sleep disturbances warrant step-up therapy

"At the very least, improving sleep and mental health should improve the QoL of our patients," said Prof. Silverberg. Therefore, patients with AD should be asked about their sleep and mental health. "Patients with a major component of sleep and/or mental health disturbances may require more aggressive treatment. These are the patients where you should consider systemic agents," recommended Prof. Silverberg. Adjunctive treatments for sleep and mental health—such as gabapentin, mirtazapine and selective serotonin reuptake inhibitors—have demonstrated efficacy for itchiness as well [6,7]. According to Prof. Silverberg, high dose melatonin is an alternative sedative without the safety issues observed with antihistamines. In many cases, it might be sufficient to improve sleep hygiene or to start relaxation therapy or meditation.

Osteoporosis: another neglected AD comorbidity

Another US survey comprising 4,972 adult patients ages 20–85 showed that eczema is also associated with osteoporosis and fractures in adults with AD [8]. This relationship was confirmed in a database from Taiwan [9]. In this Taiwanese cohort, risk factors included older age, being female, increased comorbidity, depression, and systemic corticosteroid use. "What we can do to reduce this risk is really to minimise

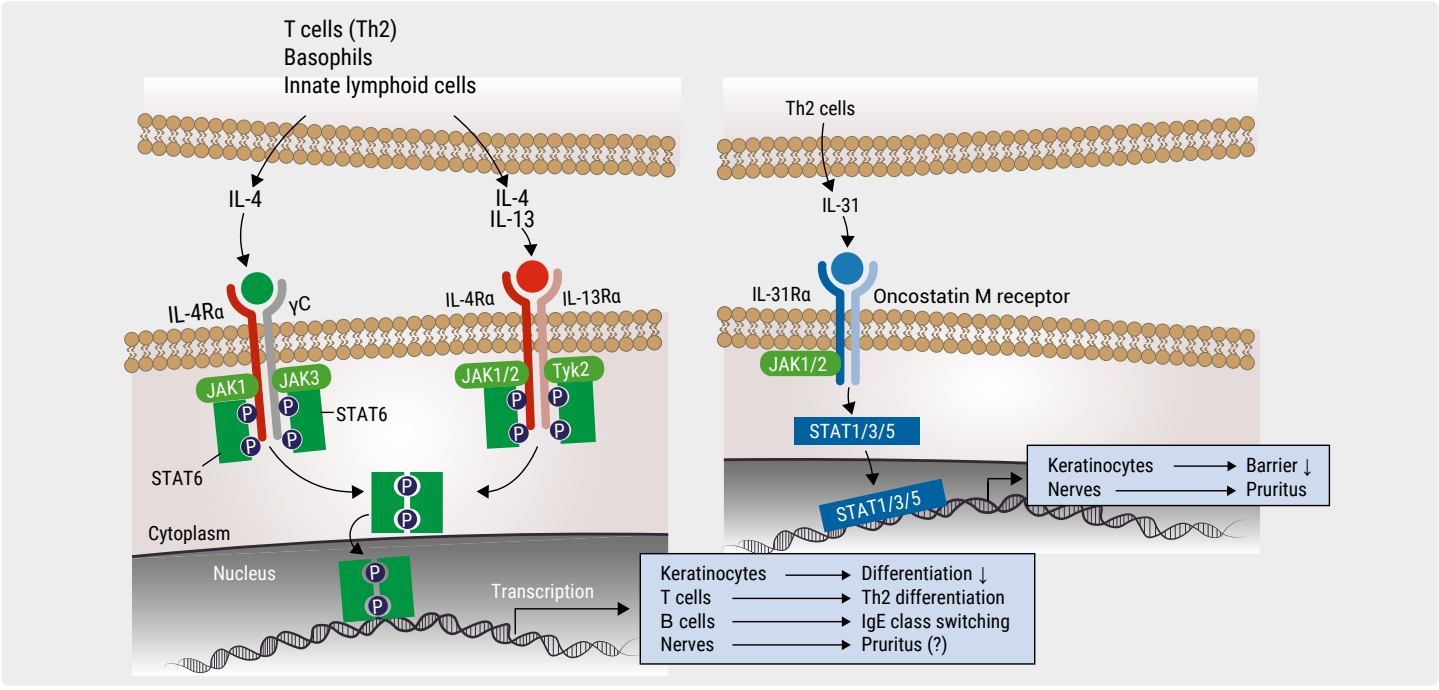
systemic steroids and rather use other systemic agents or phototherapy. In addition, we should try to motivate patients to an active lifestyle," said Prof. Silverberg. In addition, sweat and heat can lead to a flare-up of the disease. "We have to decrease ambient temperature and treat underlying itch effectively to enable patients to be active," recommended Prof. Silverberg.

New topical and systemic treatments

"It is mind-blowing how much is going on with respect to new treatments for AD," said Prof. Eric Simpson of Oregon Health & Science University [10]. An emerging topical treatment is the PDE4 inhibitor crisaborole, a cream that contains borone. A trial published last year found that nine to 14 patients need to be treated to get one more patient clear or almost clear compared to placebo [11]. "The problem with this medication, which has the potency of low-to-mid-potency topical corticosteroids is the price: a 60g tube costs 600 US dollars," said Prof. Simpson. Other topical PDE4 inhibitors are also in development. "JAK inhibitors are definitely entering dermatology, locally and systemically," said Prof. Simpson. JAKs are key mediators in the signalling pathway of numerous cytokines implicated in the pathogenesis of AD, which include IL-4, -13, and IL-31 (Figure 8). [12,13].

A topical PAN-JAK inhibitor, JTE-052, displayed remarkable efficacy in Japanese patients with moderate-to-severe AD in improving the EASI, the primary endpoint of this trial [14]. Patients were randomised to receive the topical JAK-Inhibitor at 0.25%, 0.5%, 1%, and 3%, as well as the vehicle ointment, or tacrolimus (0.1%); these ointments were applied twice daily for four weeks. Patients in all JAK-Inhibitor groups experienced a significant change in modified EASI score from baseline, compared with the vehicle group. The improvements appeared to be dose-dependent. "A rapid improvement of pruritus was observed already at Day 1 for the three higher dosing groups," said Prof Simpson. All adverse events were considered mild or moderate in severity, the majority of them mild; no serious adverse events were reported. It is notable that no clinically significant changes in laboratory parameters or vital signs were reported. Clinical results were similar to tacrolimus ointment 0.1%, but with fewer side-effects and burning. This study suggests that JAK inhibitors in AD are very promising and can provide increased opportunity to tailor treatment to the needs of each individual patient. The International Eczema Council considered when AD should warrant systemic therapy [15]. "We came to the conclusion that systemic treatment should only be advocated if aggressive topical therapy does not achieve adequate control of the disease," said Prof. Simpson. A systematic and holistic approach is recommended to assess patients with severe AD and the impact on QoL before systemic therapy. Steps taken before commencing systemic therapy include considering alternate or concomitant diagnoses (e.g. allergic contact dermatitis), avoiding trigger factors, optimising topical therapy, ensuring adequate patient/caregiver education, treating coexistent infection, assessing QoL, and considering phototherapy. "In many cases, phototherapy is a safe and effective way to enhance topical therapy," said Prof. Simpson.

Figure 8 JAK inhibitors influence numerous cells in Atopic Dermatitis [12,13]



IL-4/IL-13 inhibition: key factor in the AD pathogenesis

In the pathogenesis of AD, an immune dysfunction with an enhanced Th2 inflammation is as important as the epidermal barrier dysfunction. Dupilumab, a potent blocker of IL4 and IL13, is the first biologic approved for the treatment of AD. Both cytokines are key mediators of TH2 inflammation, but also lower epidermal barrier proteins [16,17]. Dupilumab impacts both the inflammation and the barrier dysfunction in AD, thus targeting two key factors in AD pathogenesis. As Prof. Simpson pointed out, about 50% of patients in the SOLO trial treated with a monotherapy of dupilumab gained an improvement in the EASI by 75% [17]. The efficacy is even higher when combined with topical steroids: 69% of patients gained an EASI 75 response, as was shown in the CHRONOS trial [18]. The one-year data of the CHRONOS trial have shown that the effect persists over a year. In addition, dupilumab is effective in itch reduction. All improvements are well beyond a minimal clinically important difference.

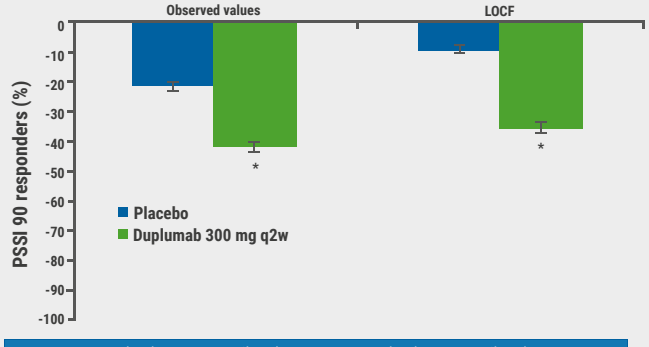
Even non-responders benefit from the treatment

A post hoc analysis of the SOLO trial presented during the AAD meeting indicated that even patients on dupilumab that could not achieve clear or almost clear skin according to Investigator´s Global Assessment (IGA) still had a clinically relevant treatment benefit from the biologic [19]. In the SOLO1 and SOLO 2 trials, 36–38% of adults with moderate-to-severe AD treated with dupilumab 300 mg every two weeks (and 8–10% of patients who received placebo) achieved an IGA score of 0 or 1 and a ≥2-point reduction in IGA score from baseline. This endpoint represents an exceptionally good clinical outcome, particularly in a population of patients with moderate-to-severe AD not adequately controlled with topical treatments. However, this endpoint may be missing important, clinically-meaningful treatment benefits. Therefore, patients who did not reach this endpoint at Week 16 were analysed with other disease severity measures: the percent change from baseline in EASI, the proportion of patients achieving a ≥ 50% improvement in EASI from baseline, and the percent change from baseline in peak pruritus numerical rating scale (NRS) and compared to placebo. The IGA scale has important limitations compared to the EASI: It does not capture changes in BSA affected by AD lesions and is typically limited to signs of acute skin inflammation (erythema and induration/papulation). At Week 16, dupilumab induced a greater improvement from baseline against placebo in the EASI score (-57.8% vs. -28.8%; P<0.0001) in patients not achieving IGA 0 or 1. In addition, a greater proportion of patients receiving dupilumab vs. placebo achieved EASI-50 (68.7 % vs. 32.4%; P<0.0001)

Significant itch reduction

Dupilumab also induced a greater improvement from baseline compared with placebo in peak pruritus NRS score (−41.9% vs. −21.3%; P<0.0001; Figure 9) The positive results of therapy with dupilumab in IGA non-responders is also mirrored in the patients' global assessment of the treatment: a greater proportion of patients receiving dupilumab compared to placebo rated the treatment as being "good", "very good", or "excellent". "Overall, the IGA scale underestimated the efficacy of dupilumab in these patients," concluded Prof. Simpson. While IGA 0 or 1 can be a valid clinical outcome as a disease state consistent with clinical remission, the upper portion of the scale (IGA 2-4) lacks the sensitivity to discern important and significant differences between study groups. "The only frequent side effect of therapy with dupilumab is conjunctivitis, but most of the time it resolves without intervention and it is mild or moderate", said Prof. Simpson. In the future, JAK inhibitors will play an increasingly important role also in AD treatment. "But JAK-inhibitors block many interleukins; we are still not sure about their safety. These agents definitely need close monitoring," said Prof. Simpson. Many agents are currently in Phase-2-trials.

Figure 9 Dupilumab significantly improves itch in a NRS score at Week 16 in patients not achieving IGA 0 or 1 [19]



IGA at Week 16	Placebo (Observed values), N	Dupilumab 300 mg q2w (Observed values),N	Placebo (LOCF), N	Dupilumab 300mg q2w (LOCF), N
2, 3 or 4	360	255	395	275

Error bars indicate SE *P<0.0001 vs placebo

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Acne Management: Generous with Moisturiser, Restrictive with Antibiotics

In acne, just as in AD, a barrier defect exists that must be addressed properly, particularly during winter. Antibiotics should be used only in combination and for a limited duration.

There is increasing evidence that acne pathophysiology may include a barrier defect. Acne medications are also often drying. An improvement of the barrier may improve acne, a fact that is often not addressed in acne therapy. "The distinct vehicle response often seen in trials with topical medications may be due to improvement of barrier," said Prof. Hillary Baldwin of the Acne Treatment and Research Center [1]. In to her experience, this barrier improvement is part of a successful acne management. "Patients are happier when physicians also address the dryness of their skin," she said. Patients with moderate-to-severe acne have a higher transepidermal water loss (TEWL) compared with control subjects [2]. An impaired water barrier function may be responsible for comedo formation, since barrier dysfunction is accompanied by hyperkeratosis of the follicular epithelium. A current trial showed that ceramides in the stratum corneum undergo seasonal variations over the course of a year [3]. In this trial, ceramides in the stratum corneum of healthy and acne skin were assessed using ultraperformance liquid chromatography, and seasonal variation was studied over the course of a year.

Acne often worsens in winter

Acne-affected skin demonstrated overall lower levels of ceramides compared to healthy controls. However, this difference was more apparent in the winter months. Lower ceramide levels reflected an increase in TEWL in acne compared with healthy skin, which partly resolved in the summer. Certain ceramide species with 18-carbon 6-hydroxysphingosine bases were significantly reduced in acne skin, suggesting that these species may be particularly important in a healthy skin barrier. Indeed, acne patients often report a worsening of acne during winter months [3]. A poster presented during the meeting confirmed these seasonal changes in epidermal ceramides in acne patients [4]. In addition, TEWL was assessed in the course of the year. Compared to healthy skin, acne skin showed increased TEWL year-round, but this difference reached statistical significance only from December to June [4]. The microflora of the skin also differs significantly between acne patients and healthy controls [5]. This was evident in a poster presented during the meeting that analysed the microbiome from ten healthy young women and compared it to ten patients with acne vulgaris [6]. There was no difference in the actinobacteria and proteobacteria, but a relative increase in firmicutes species in acne vulgaris. Patients with a high percentage of firmicutes species had a threefold elevated risk of having acne compared to the low firmicutes group [6]. During puberty, alteration of the sebaceous lipid profile, stress, irritation, cosmetics and potential dietary factors lead to inflammation and formation of different types of acne lesions. Skin barrier damage also significantly increases between the ages of 6 and 13. The proliferation of P. acnes strains is another important process that triggers acne. P. acnes activates the innate immunity via the expression of proinflammatory cytokines and matrix metalloproteinases by keratinocytes, resulting in the hyperkeratinisation of the pilosebaceous unit [5]. Optimal skin health and innate immunity are maintained when the microbiome and the immune system of the skin are balanced. "Therefore, quality moisturisation is essential in our acne patients," Prof. Baldwin recommended. By using adequate moisturisers, TEWL can be improved, ceramides normalised, and the microbiome restored. This is of particular importance because acne therapy further damages the stratum corneum. "Many patients notice the dryness of their skin and use moisturiser, but maybe the wrong ones," warned Prof. Baldwin. No acne visit is complete without discussion of skin care. At the moment, coconut oil is "in fashion" but, due to its comedonic effect, is not suitable for acne patients. Quality moisturisers contain ceramides or hyaluronic acid.

Early therapy prevents scarring

"Acne is not a cosmetic problem: it has to be treated effectively to prevent scarring," said Prof. Baldwin. Studies have shown that scarring can occur with any severity of acne. Even in mild acne, more than 20% of patients will have a presence of acne scars [7]. Risk factors for developing scars is the time elapsed between acne onset and the first effective treatment: ≥3 years vs. <3 years [8]. A trial presented recently confirmed

the positive effect that effective treatment has on acne scar formation. In this split-face study conducted over six months, patients were either treated with the combination of adapalen 0.1%/benzoyl peroxide (BPO) 2.5% gel or a vehicle. All participants had at least ten atrophic scars at baseline [9]. After six months of treatment, scar counts remained stable with adapalen/BPO while they increased by approximately 25% with vehicle. The percentage of subjects with barely-visible scars increased from 9.7% to 45.2% with adapalen/BPO, whereas it did not change with vehicle (p=0.0032) [9].

Restrictive antibiotic use to fight resistance

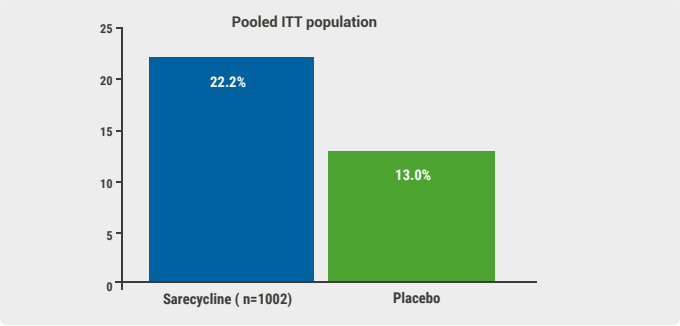
Dr. Neal Bhatia critically discussed the use of oral antibiotics for acne vulgaris [10]. The majority of published guidelines and consensus statements support antibiotic use for inflammatory acne to limit proliferation of P. acnes on the skin. Tetracyclines are recommended as "first-line" agents. However, the use and duration of antibiotics should be limited due to antibiotic resistance concerns [11]. As Dr. Bhatia pointed out, dermatologists use more oral antibiotics per prescriber than any other medical specialty, with the main indication being acne vulgaris. Dr. Bhatia proposed a more critical use of antibiotics. Systemic antibiotics are only recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments [11]. Monotherapy should be avoided, and use should be always combined with topical therapy (e.g. retinoids or BPO). A current publication also deals with measures to limit the development of antibiotic resistance associated with oral antibiotic use for acne. The authors recommend avoiding oral antibiotics when other effective options are available, limiting the use of systemic oral antibiotics to three to four months, and considering sub-antimicrobial doses of antibiotics with anti-inflammatory action, such as doxycycline [12].

Novel tetracycline effective in acne

A novel antibiotic, sarecycline, in the tetracycline family is in clinical development for the treatment of moderate-to-severe inflammatory lesions of acne vulgaris and has been shown to be highly effective in acne treatment. "A promising characteristic is its limited activity against enteric gram-negative species. In contrast to traditional members of the tetracycline class, sarecycline does not affect the gut microbiome," said Dr. Leon Kircik of the Indiana University School of Medicine [13]. This could translate into a better gastrointestinal tolerability. He presented pooled data from two identical randomised, double-blind, placebo controlled, Phase 3 studies. The studies comprised 2,002 patients (mean age 19.9 years) with moderate-to-severe facial acne. All patients had an IGA score ≥3 as well as 20–50 inflammatory lesions, ≤100 non-inflammatory lesions, and ≤2 nodules. The patients were randomised and treated with sarecycline 1.5 mg/kg/day, or placebo, for 12 weeks. Of the patients were treated with sarecycline, 22.2% experienced a ≥2-grade improvement on the IGA and a score of 0 ("clear") or 1 ("almost clear") skin at the end of 12 weeks (defined as therapeutic success), compared with only 13.0% of patients taking the placebo (P<0.0001; Figure 10). In addition, inflammatory lesions at Week 12 were reduced by 50.4% among patients taking sarecycline and 34.7% among those on placebo (P<0.0001). Starting at Week 3, sarecycline was statistically superior to placebo for inflammatory acne. A post hoc analysis of patients with more than ten non-inflammatory lesions at baseline revealed a reduction of 34.8% in the number of non-inflammatory lesions at Week 12 with sarecycline, compared with 26.9% with placebo (P<0.0001). "Over time, both inflammatory and non-inflammatory lesions' difference to placebo gets wider," said Dr. Kircik.

The most commonly observed treatment-emergent adverse events were nausea, headache, and nasopharyngitis. "For us, it was important to see that sarecycline has only mild gastrointestinal side effects," said Dr Kircik. Side effects particularly common to tetracyclines—including sunburn, dizziness, photosensitivity, and urticaria—occurred in <1% of sarecycline patients.

Figure 10 Significantly more patients treated with sarecycline gained therapeutic success (a ≥2-grade improvement on the IGA and a score of 0/1) compared to placebo [13]



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Alopecia Areata: A Glimpse into the Future

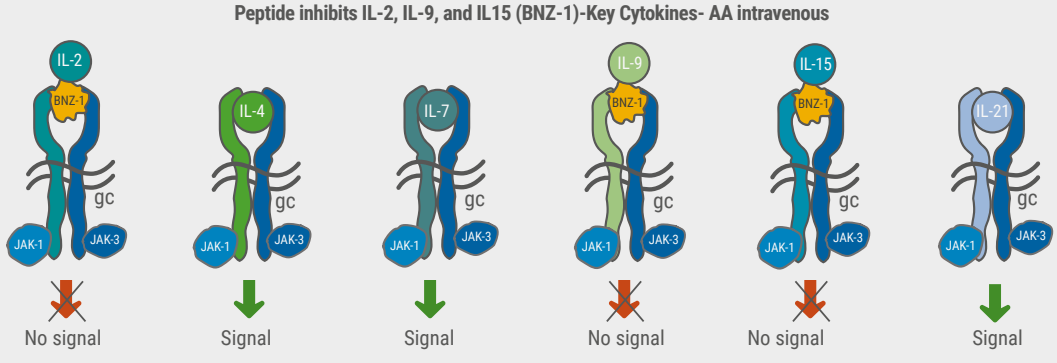
Alopecia areata is responsible for up to 4% of all patient visits to a dermatologist. JAK inhibitors and IL-15 antagonists are novel therapies that may even enable a complete reversal of this condition in the future.

Alopecia areata (AA) is a chronic relapsing inflammatory disorder characterised by non-scarring hair loss on the scalp and/or body. As Prof. Wilma Bergfeld of the Cleveland Clinic indicated, in healthy subjects there is an immune privilege of the hair follicle [1]. A loss of this immune privilege leads to AA. Genome-wide association studies implicated ligands for the Natural Killer Group 2D (NKG2D) receptor (a product of the KLRK1 gene) in disease pathogenesis [2]. In a murine model of AA, a type I cytotoxic pathway has been demonstrated as responsible for the disease state, with NKG2D-expressing CD8+ cytolytic T-lymphocytes necessary for the induction of the disease. Upregulation of IL-15 in the outer root sheath of the hair follicle activates cytolytic T-lymphocytes, which in turn produce Interferon (IFN)γ, leading to activation of the hair follicle and upregulation of IL-15, NKG2D ligands, and major histocompatibility complex (MHC) molecules, all of which target the hair follicle for attack [3]. A possible therapeutic approach is the restoration of this immune privilege by restoring the defective function of CD4+/CD25+ cells and by reducing CD8 T lymphocytes and IL-15. JAK 1/3 signalling mediates IL-15 activation of T-lymphocytes [4]. IL-15 is highly expressed in human and murine AA and drives CD8 killer activation. IFN γ is a second important player in the AA pathogenesis: it is produced by killer T cells and drives inflammation. JAK inhibitors block both IL-15 and IFNγ. A breakthrough in AA therapy was a publication in 2014 where, in a patient with plaque psoriasis, the oral JAK-inhibitor tofacitinib reversed alopecia universalis [5]. An open trial where AA was treated with oral tofacitinib confirmed that the majority of patients experience a regrowth of hair independent of age, disease severity, and disease duration with only minimal side effects [6]. 47% of patients experience a regrowth of hair by 12 months. In addition, the JAK inhibitor also improves nail dystrophy that was reported in 23% of patients. This and other work has spawned so much interest that there are now many JAK inhibitors in the clinical development for AA.

Many new agents in the pipeline

Another interesting agent is a novel peptide that inhibits the cytokines IL-2, IL-9, and IL-15 (BNZ-1). Signalling of IL-4, IL-7, and IL-21 are unaffected by this peptide, which preserves immunological function (Figure 11). The agent BNZ-1 was effective in a mouse model of immune-mediated hair loss. It led to a reduction of the inflammatory cytokines IL-6, TNF-α and IFNγ and was able to restore hair growth. It proved to be safe in healthy volunteers and a Phase 2 randomised double-blind placebo-controlled dose ranging study in AA is planned in 2018. "Many pharma companies are now interested in hair disorders and in the hair follicle as a model to study inflammatory pathways, so there is more to come in the next years," said Prof. Bergfeld.

Figure 11 Mode of action of the peptide BNZ-1



Signaling of IL-4, IL-7 and IL-21 are unaffected, which preserves immunologic function

Combination therapy to enhance topical steroids

The efficacy of conventional therapy (topical steroids) can be improved by its combination with narrowband-UVB (NB-UVB) phototherapy [7]. This was shown in a randomised trial among adult Filipinos aged 18–60 that was presented as a late-breaking trial. 33 patients were randomly allocated into two treatment groups. Group A (n=17) applied clobetasol propionate 0.05% ointment twice daily and underwent NB-UVB thrice weekly for eight weeks. Group B (n=16) was treated with clobetasol alone. Therapeutic response was assessed at Weeks 2, 4, and 8 based on hair count. At Week 8, Group A had a significantly higher mean hair count than Group B (P<0.0001). It was believed by 87.5% of patients in the intervention group that the intervention was markedly effective, compared to 18.75% from the placebo group (P<0.0001). Group A observed that their alopecic patches had improved notably while Group B failed to see significant improvement from baseline (P<0.0001). No adverse reactions were identified in both groups. The authors conclude that NB-UVB phototherapy is a safe and effective adjuvant therapy for AA as it works synergistically with topical steroid in promoting hair growth without phototoxic reactions.

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Melanoma: A Growing Disease Burden in Europe

The incidence of malignant melanoma continues to rise in Europe. Even for advanced disease, combination immunotherapy enables a survival of more than five years in selected patients.

A retrospective study compared the incidence and mortality rates of melanoma across 45 countries in 2012 and the change in incidence between 2000 and 2012 in each country [1]. Data sources were the World Health Organization´s recently released 2012 GLOBOCAN cancer databases and 45 countries with the highest quality incidence and mortality data. The highest melanoma incidence (per 100,000 individuals) was found in New Zealand (35.8), followed by Australia (34.9), Switzerland (20.3), the Netherlands (19.4), and Denmark (19.2). Females had a higher incidence than males in 23 of 45 countries. A female predominance was particularly common in Europe (in 21 of 27 countries). A slightly different result was found with regard to melanoma mortality (per 100,000 individuals). Again, the leading countries were New Zealand (4.7) and Australia (4.0), but followed by Norway (3.6), Slovenia (3.1), and Sweden (2.8). Mortality was higher in males than in females in the majority of countries (41 of 45), including all countries in Europe. Melanoma incidence between 2000 and 2012 increased in almost all countries, but an increase by >100% was found in both sexes in Italy and the United Kingdom, in females only in Japan, and in males only in Spain and Switzerland. "Although the burden of melanoma is greatest in New Zealand and Australia, it appears to be stabilising in these countries, eventually due to public health campaigns for sun-safety and early detection," observed medical student Emily Dando, of the University of Pittsburgh School of Medicine, during the presentation. However, incidence and mortality remain high and a continuing increase is seen in many European countries.

Atypical lesions in paediatric patients

"Malignant melanoma in minors is a rare event", said Dr. Ryan Kelm of the Feinberg School of Medicine [2]. Despite

this fact, efforts for prevention are still important. Recent reports have observed an increasing rate of paediatric melanoma up to 2004, followed by a decrease in the United States [3,4]. Paediatric melanoma decreased by 11.58% per year from 2004–2010 [4]. A similar trend was noticed in the Netherlands [5]. Therefore, current incidence rates from the National Surveillance, Epidemiology, and End Results (SEER) cancer database were assessed in a population-based study. The SEER database, providing data from 2000–2014, was searched for data from patients aged 0–19 years, and a diagnosis of malignant melanoma. A total of 1,796 cases (in 218 children aged 0–9 years, and in 1,578 adolescents aged 10–19) of melanoma were detected. Although the overall incidence rates for melanoma were only five per one million, there was a marked increase in the incidence rate of adolescents (from 1.3 in the 0–9-year-olds compared to 8.7 in the 10–19-year-olds). Auperficial spreading melanoma is more common in adolescents than nodular and other manifestations. In children and adolescents, incidence rates were significantly higher in females. Incidence trends were significantly decreased in adolescents (by an annual per cent change of -4.5; $P<0.05$), but not in children. The five-year survival rate was higher in adolescent females (97.1%) compared to adolescent males (92.6%). "Our findings are congruent with recent studies suggesting that there continues to be a decrease in the incidence of overall paediatric melanoma, "concluded Dr. Kelm. In addition, five-year survival improved compared to earlier reports.

Lower melanoma risk in coffee addicts?

Two meta-analyses assessed a possible correlation of coffee drinking and melanoma risk [6,7]. In one meta-analysis, two case-control and five cohort trials were evaluated. The pooled relative risk of malignant melanoma was reduced by 19% in the highest vs. the lowest consumption of coffee. Strikingly, there was no association between the drinking of decaffeinated coffee and melanoma risk [6]. The authors conclude that caffeinated coffee might have chemo-preventive effects against melanoma. Another analysis included 23 studies with 2,268,338 participants. Compared to the lowest-level consumption, total coffee reduced the relative risk of melanoma by 20%, caffeinated coffee by 15%, and decaffeinated coffee by only 8%. In addition, a clear dose-response relationship could be observed: the melanoma risk decreased for each cup/day by 3% for all coffee, and by 4% for caffeinated coffee [7]. Another protective habit after diagnosis of melanoma is the use of acetyl salicylic acid (ASS) [8]. Researchers evaluated data from a retrospective cohort of 1,522 patients who were diagnosed with melanoma between 2000 and 2014 and were followed up through September 2016. In patients diagnosed with a melanoma Stage II or III, ASS use was associated with a survival benefit. ASS use was associated with longer overall survival in univariate analysis and after controlling for age, sex, stage, and treatment modalities. In turn, patients taking ASS before diagnosis were less likely to be diagnosed with Stage III or IV disease. Therefore, the therapeutic potential of ASS will now be evaluated in a clinical trial.

Better diagnosis with deep convolutional neural networks

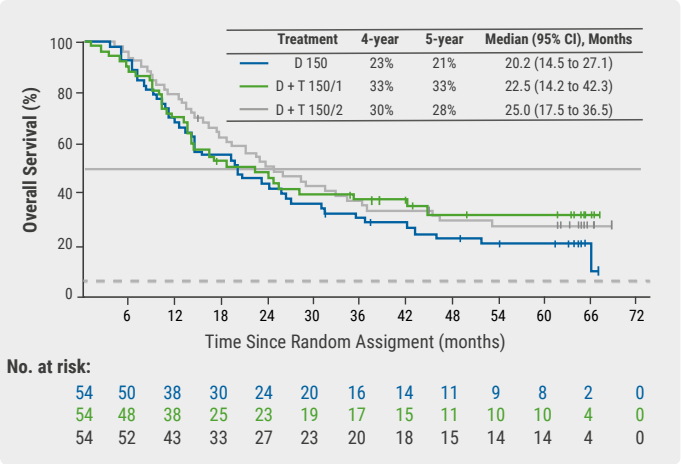
"Malignant melanoma is primarily diagnosed visually, beginning with an initial clinical screening," said Dr. Allan Halpern [9]. This step is than followed by dermoscopic analysis, a biopsy and histopathological examination. Artificial intelligence—deep convolutional neural networks (CNNs) —may help in diagnosis, according to a recent publication [10]. CNNs are feed-forward artificial neural networks and learn the filters that, in traditional algorithms, were hand-engineered. This makes them independent of prior knowledge and human effort. The working group at Stanford University in California trained this system with a dataset of 129,450 clinical images consisting of 2,032 different diseases (two orders of magnitude larger than previous datasets). The CNN was then tested against 21 board-certified dermatologists on biopsy-proven clinical images. The result was astonishing: the CNN achieved a performance on par with all tested experts, and classified melanoma with a level of competence comparable to the dermatologists. Even regarding the biopsy decision, the dermatologists did not outperform the CNN. According to the authors of the study, deep neural networks deployed on mobile devices can potentially extend the reach of dermatologists outside the clinic. This technique could provide low-cost universal access to vital diagnostic care [10]. "The digital ability to monitor lesions over time is going to be the state of the art in the future: the technology is already there," said Dr. Halpern.

Survival benefit of targeted combination therapy

New data are also available about therapy of metastatic melanoma. A trial published in 2017 confirmed that patients with BRAF600-mutant metastatic melanoma have a persistent overall and progression-free survival benefit when they are treated with the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib [11]. Overall survival was 30% at four years and 28% at five. Survival was higher among patients with normal baseline

LDH levels. This five -year analysis represents the longest follow-up to date with BRAF + MEK inhibitor combination therapy in BRAF V600-mutant melanoma. It shows that this therapy really elicits durable plateaus of long-term overall and progression-free survival that can last more than five years in some patients (Figure 12) [11]. However, treating physicians have to deal with the different toxicities of this regime. According to Dr. Halpern, checkpoint inhibitors are also relevant in the adjuvant setting: in December 2017, FDA granted regular approval to the immune checkpoint inhibitor nivolumab for patients with melanoma involving lymph nodes or in patients with metastatic disease who have undergone complete resection [12]. Nivolumab was previously approved only for the treatment of patients with unresectable or metastatic melanoma. Approval was based on improvement in recurrence-free survival in the CHECKMATE-238 trial that included 906 patients with completely resected, Stage III B/C or Stage IV melanoma [13]. Patients were randomly allocated (1:1) to receive nivolumab 3 mg/kg every two weeks or ipilimumab 10 mg/kg every three weeks for four doses, then every 12 weeks beginning at Week 24 for up to one year. Patients in the nivolumab arm experienced significantly fewer recurrences/deaths compared with the ipilimumab arm (34% vs. 45.5%; P<0.0001) [13]. "The problem with immunotherapy is the toxicity like hypophysitis, but rash is also a big piece of it," concluded Dr. Halpern.

Figure 12 Overall survival of patients with malignant melanoma in the intention-to-treat-population: D = Dabrafenib; D + T 150/1 = dabrafenib 150 mg twice a day plus trametinib 1 mg once daily: D + T 150/2 = dabrafenib 150 mg twice a day plus trametinib, 2 mg once a day [11]



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Pearls of the Posters

The "Pearls of the Poster" session enabled dermatologists to become familiar with the most recent breakthroughs in dermatological research. The selected posters covered a wide range of topics in clinical dermatology.

Better gastrointestinal tolerability with biologics than the conventional therapy

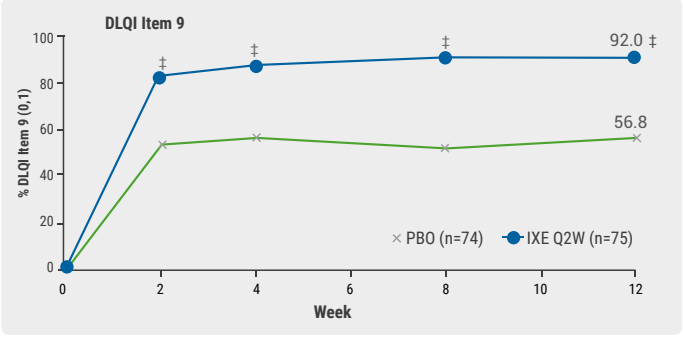
In Switzerland, consenting patients with moderate-to-severe psoriasis enter the SDNTT (Swiss Dermatology Network for Targeted Therapies) Psoriasis Registry when they start systemic treatment. The purpose of adding the outpatient data to the non-interventional registry lies in obtaining long-term evidence for the efficacy and safety of these therapies in psoriasis and comparing adverse and serious adverse events between biological and non-biological drugs. In the evaluation presented, 473 patients were included until December 2016: this corresponds to 264 patient years of biological and 272 years of non-biological systemic therapy [1]. Their mean age was 46.7 years, 65% were male and more than a third not only suffered from psoriasis but also from psoriatic arthritis. Rates of serious adverse events and non-serious infection rates were not significantly different between the two treatment groups. The most reported non-serious adverse events were ineffectiveness of the drug with 15.8 % of patients treated with biologics and 16.6%

in the non-biological group. Non-serious gastrointestinal side effects were significantly higher in the non-biological cohort compared to biological regimes (14.1 vs. 4.3/100 patient years; P≤0.05). All in all, serious adverse events were uncommon and without a different distribution among the two kinds of treatment.

Improvement in impact of genital psoriasis on sexual activity with use of ixekizumab

Genital lesions are not rare in psoriasis; however, often overlooked is their severe impact on the patient's QoL [2,3]. Psoriasis in this location is seen as especially embarrassing and is, moreover, often mistaken for a sexually transmitted disease [4]. A substantial proportion of patients experiences increased problems after sexual activity. In an observational, multicentre study of 354 participants, 87% reported itch, 39% pain, 42% dyspareunia, 32% a worsening of their genital psoriasis after intercourse, and 43% a decreased frequency of intercourse [5]. The current Phase 3b randomised controlled trial by Dr. Jennifer Cather of the Aesthetics Center in Dallas and her colleagues therefore investigated whether treatment of genital psoriasis with the IL-17 blocker ixekizumab has a positive influence on the sexual activity of patients [6]. 149 participants were randomised to receive either a placebo over 12 weeks or 80 mg of ixekizumab subcutaneous every two weeks after a starting dose of 160 mg. The study subjects all had moderate-to-severe genital psoriasis. Its influence on sexual activity was evaluated by extracting specific questions from the Genital Psoriasis Sexual Frequency Questionnaire. At 12 weeks, 92% of patients treated with ixekizumab compared to 56.8% of patients treated with placebo reported no (0) or little (1) sexual difficulties caused by skin symptoms (P<0.001; Figure 13). 78.4% of patients treated with ixekizumab, compared to 21.4% of patients treated with placebo (P<0.001), reported the frequency of sexual activity was either never (0) or rarely (1) limited by genital psoriasis.

Figure 13 Proportion of patients treated either with ixekizumab or placebo whose skin did not cause any sexual difficulties [6]



Ixekizumab was superior to placebo as early as Week 1 regarding the limitations on the frequency of sexual activity due to genital psoriasis (P<0.05) and Week 2 for the sexual difficulties caused by skin symptoms (P<0.001). A greater number of patients under ixekizumab stated considerably more often that they never or rarely avoided sexual activity owing to their genital psoriasis at Week 12 (76.7% IXE vs. 25.7 placebo, P<0.001). The ixekizumab group also experienced a markedly reduced worsening of local psoriasis symptoms during or following sexual activity at Weeks 2, 4 and 8. The most common (greater than 4%) adverse events observed in patients treated with ixekizumab in this study were upper respiratory tract infections, injection-site reactions, headache, oropharyngeal pain and pruritus. The safety outcomes were consistent with the overall safety profile of the agent in previous clinical trials.

Intralesional cryosurgery effective for keloids

Extreme cold is a novel treatment approach for hypertrophic scars or keloids [7]. Prof. dr. Yaron Har-Shai of the University of Technion treated 380 Caucasian patients with keloids by inserting a cryo-needle into the core of the scar, applying liquid nitrogen, and thus freezing the HSK from the inside. His patients were aged 3 to 67 years and 204 were female. In total, these patients suffered from 448 keloids in different locations of their bodies for over six months, originating, for example, from trauma, surgery, burns, piercings and acne. After the procedure, the change of scaring was followed over 18 months for objective transformation in volume, hardness, redness and pigmentation. Furthermore, clinical symptoms such as pain or tenderness, itch or other discomfort were monitored. Biopsies were evaluated for changes in collagen structure and the post-interventional blister fluids analysed for their proteome. As a result, keloids on the ear lost 67% of their volume after a single session. The reduction of lesions on chest and upper back/shoulders were 50% and 60%. A significant decrease in both clinical and objective symptoms was reached with a non-responder rate of only 3%. The histological work-up revealed a rejuvenation of the treated tissue, demonstrated by reorganisation of collagen fibres, amongst other signs. The proteomic examination revealed specific proteins known to be linked to cell and stem cell differentiation and response to stress and injury.

Itching in psoriasis: More important than often thought

While pruritus occurs in the majority of psoriasis patients, it is rarely in the centre of efficacy control during trials [8]. An

Australian, observational, cross-sectional study included 179 patients to look for prevalence and exacerbating factors of itching in psoriasis. The study subjects were predominantly Caucasian and 45% were female. 65% had a PASI <10 and 89% suffered from plaque psoriasis. The mean age was 52.3 years. 24% were being treated with biologics and 47% by phototherapy [9]. Altogether, 49% reported having itching most or all of the time while, in 11%, itching never occurred [8]. Dr. Philippa Dickison of the University of Sydney proposed a seasonal difference in itch severity, the worst time being winter. Pruritus, for instance, also went up during flares, under stress, and after taking a shower. Interestingly, in patients with nail psoriasis, itching was less often omnipresent. Dr. Dickison hypothesised this may be due to scratching in this area being difficult; thus, maybe making the occurrence of a scratch-itch cycle less likely. It was noted before that, in psoriasis, the disease severity is not necessarily associated with the intensity of itching, but the itch has great influence on QoL [10]. Although itch was 2.2 times more likely in patients with PASI >10, the improvement of PASI did not always lead to a reduction in itching to the same extent [8].

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