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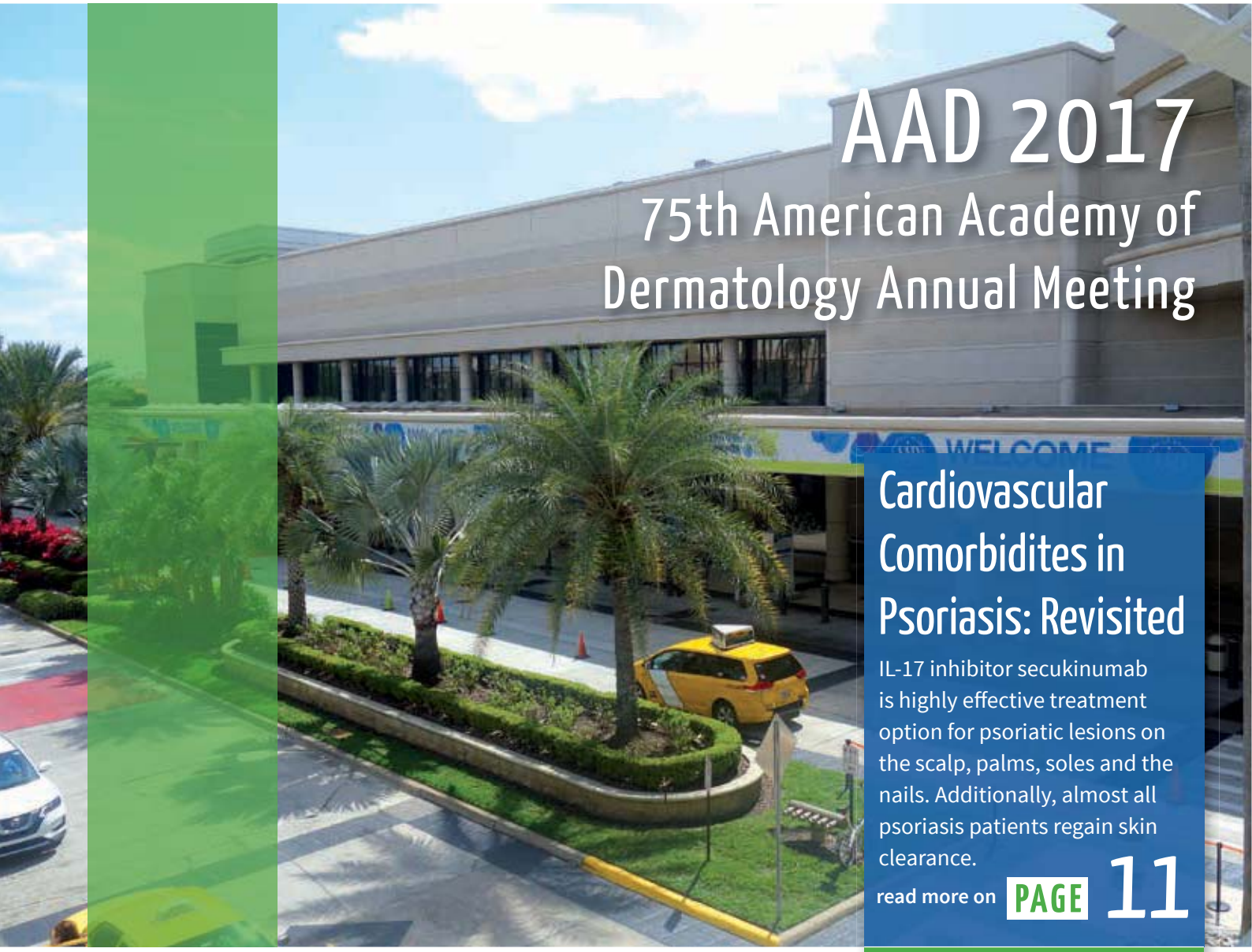

AAD 2017

75th American Academy of Dermatology Annual Meeting

Cardiovascular Comorbidites in Psoriasis: Revisited

IL-17 inhibitor secukinumab is highly effective treatment option for psoriatic lesions on the scalp, palms, soles and the nails. Additionally, almost all psoriasis patients regain skin clearance.

read more on PAGE 11

Late Breakers

This year's late-breakers were highly competitive: Benvitimod was found superior to calcipotriol in handling mild-to-moderate plaque psoriasis, likewise ixekizumab exceeded ustekinumab on treating mode-to-severe plaque psoriasis and certolizumab also significantly improved the condition.

read more on PAGE 3

Spot light on Aesthetic Medicine

Graceful Aging-thanks to minimal invasive procedures. Its never too late for an effective treatment.

read more on PAGE 26

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

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Letter from the Editor

Prof. dr. Peter van de Kerkhof

Dear Reader,

I am pleased to announce that the 75th American Academy of Dermatology- Annual meeting in Orlando was successfully conducted this year. Our report has covered all the scientific programme about new developments, with deep discussions.

We have chosen few highlights which we are presenting in the report; including late breaking session, atopic dermatitis, cardiovascular comorbidities in psoriasis, skin cancer, hair loss and Aesthetic medicines.

In Addition, I am delighted to welcome new advisory board members who have invested their valuable time in reviewing and providing expert opinions.

We hope that you enjoy our report and see you again next year at AAD.

Thanks for reading!

With Best Regards,
Prof. dr. Peter van de Kerkhof

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.

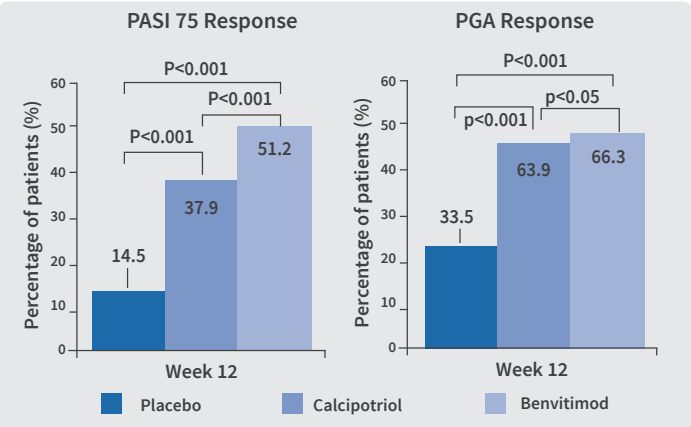
Late Breakers

As every year, the late breaking clinical trial sessions attract most of the attendants. This year's late-breakers were competitive: only 48 of 180 submitted abstracts got accepted. Enclosed a selection of the most interesting or possibly practice changing trials.

New topic shows promising results in psoriasis

Since Vitamin D analogs were approved in the 1980, there has not been a breakthrough in topical treatment of psoriasis. This could change with the advent of the first-in-class drug benvitimod, a novel nonsteroidal cream, which showed superiority not only to placebo but also compared to calcipotriol ointment in patients with mild to moderate plaque psoriasis [1].
In the randomized, multicentre, placebo- and comparator-controlled phase 3 trial 1% benvitimod cream was compared to calcipotriol 0.005% and placebo over 12 weeks of treatment and a 48-week open label follow-up phase. All 686 participants were adults with mild-to-moderate psoriasis for at least 6 months, and a body surface area (BSA) of less than 10%. At week 12, significantly more patients treated with benvitimod showed a Psoriasis Area Severity Index (PASI) 75 response (51.2%) compared to calcipotriol (37.9%) and placebo (14.5%; P<0.001 for each comparison; (Figure 1). In addition, significantly more patients treated with the new topical reached a PASI 90 response compared to calcipotriol or placebo (32.6% vs 20.1% vs. 3.5%). After discontinuation of benvitimod, 59 patients completed a 40-week follow-up period. Of these, 29 patients (49.2%) remained in remission and 30 (50.8%) had recurrence at 40 weeks. Median recurrence time was 36 weeks.

Figure 1 Efficacy of benvitimod compared to calcipotriol at week 12 [1]



"Benvitimod is a new small molecule that regulates immune function. However, we do not know the exact mode of action of this drug," said Dr. Jianzhong Zhang, department of dermatology at Peking University People's Hospital in Beijing (China) during the presentation of the data.
The new topic caused a higher rate of side effects (44.5%) compared with calcipotriol (19.5%) and placebo (20.2%). However, most commonly reported adverse events were restricted to the application site (transient mild-to-moderate erythema, sting or a burning sensation). No systemic side effects were seen in the trial.
"There is an unmet need regarding topical treatment that is better tolerated and more effective than the options we have today for patients with milder forms of psoriasis," concluded Dr. Zhang.

Certolizumab pegol effective in psoriatic patients

The tumour necrosis factor alpha (TNF-a) inhibitor certolizumab pegol led to significant improvements in moderate to severe chronic plaque psoriasis, compared with placebo: About three-fourth of patients reached a PASI 75 response. These were the main results of the phase 3 CIMPASI 1 and CIMPASI 2 trials, in which more than 450 patients with moderate-to-severe psoriasis were included [2].
The primary endpoint of CIMPASI 1 was the percentage of patients who achieved a 75% improvement (PASI-75) score. There was a striking difference between patients treated with the TNF-Blocker and placebo in patients reaching this endpoint: 66.5% of patients on certolizumab 200 mg taken every 2 weeks and 75.8% of patients on certolizumab 400 mg administered every 2 weeks gained a PASI-75 response compared to 6.5% of the patients in the placebo group (P<0.0001 vs placebo for both active arms). In the CIMPASI 2 trial, 11.6% of people on placebo achieved a PASI-75 compared with 81.4% of patients on certolizumab 200 mg and 82.6% of patients on certolizumab 400 mg (P<0.0001). The results were similar when the researchers considered Physicians Global Assessment (PGA) scores of 0/1, which equals clear or almost clear skin. In CIMPASI 1, that goal was reached by 4.2% of subjects on placebo but 47.0% of patients on certolizumab 200 mg and 57.9% of patients on certolizumab 400 mg (P<0.0001). At week 16, the percentage of patients who achieved a PASI 90 was 43.6% in the 400-mg dose group, 35.8% in the 200mg dose group, and 0.4% in the placebo group.

The CIMPAZI 2 trial led to comparable results: 66.8% of patients on certolizumab 200 mg and 71.6% of patients on certolizumab 400 mg compared to only 2% in the placebo group showed a PGA scale improvement of at least two points over baseline toward a final score of clear or almost clear skin at week 16 was (P<0.0001 for each comparison). In the CIMPASI 2 trial, more than half of the patients in the active arms had a PASI 90 (55.4% of patients and 52.6% respectively), compared with only 4.5% of the placebo group.

Significant improvement of quality of life

"In addition, at week 16 patients in the 400 mg and 200mg groups showed significant improvements over baseline Dermatology Life Quality Index (DLQI) average scores, compared with placebo," explained lead author Prof. Alice Gottlieb, MD, PhD, New York Medical College, Valhalla, New York (NY/USA). DLQI-scores showed a 10.2 decrease in the 400-mg group and a 9.3 decrease in the 200-mg group, compared with a 3.3 decrease in the placebo arm (P<0.001) in the CIMPASI-1 study. In the CIMPASI-2 study at week 16, there was a drop of 10.0 DLQI in average scores in the 400-mg group, 10.4 in the 200-mg group, and an average drop of only 3.8 in controls (P<0.001). Treatment with certolizumab pegol proved to be tolerable: there were no cases of tuberculosis, one case of vulvovaginal candidiasis, and equal distribution of herpes zoster across the study. "There is clinically meaningful and statistically significant improvement with certolizumab," Dr. Gottlieb concluded.

IL-17 inhibitor beats ustekinumab

"We dermatologist are great in developing all these new drugs, but whether they are really better we can only judge according to head to head trials," said Prof. Kristian Reich, Dermatologikum Hamburg (Germany) at the presentation of the urgently awaited results of the IXORA-S-trial that were presented during a late breaking session [3]. As Prof. Reich pointed out, the comparison of a new agent with the second generation biologic ustekinumab is considerably more challenging than the comparison to etanercept. Ixekizumab mastered this crucial test in the IXORA-S-trial: the agent demonstrated to be superior to ustekinumab not only for the primary but also for several secondary outcomes after 24 weeks of treatment in patients with moderate-to severe psoriasis.

Primary endpoint of this trial was the percentage of patients that reached a PASI 90 response after a treatment period of 24 weeks. The majority of patients of the IXORA-S trial were from Western Europe. At baseline the mean PASI score was about 20. 83 % of psoriasis patients treated with ixekizumab achieved a PASI 90 response compared to 59% of the patients on ustekinumab (P<0.001). In addition, 50% of patients reached clear skin in the static Physician´s Global Assessment (sPGA), an enormous effect as Prof. Reich pointed out. There was no significant difference in overall adverse events in the treatment groups. Treatment-emergent adverse events occurred among 75% of the patients on ustekinumab and 70% of the patients treated with ixekizumab (P=0.299).

Patients on ixekizumab will take part in an extension trial that will continue for 52 weeks. In contrast to the CLEAR study, in which the IL-17 inhibitor secukinumab was compared to ustekinumab, in the IXORA-S-trial only second line patients were included.

Clear skin means better quality of life

Ixekizumab was also significantly superior regarding quality of life, measured with the DLQI. "In this questionnaire, there are also questions that have nothing to do with PASI 100, e.g. the question does therapy bother you. In this questionnaire, we have also seen a clear-cut advantage for ixekizumab," concluded Prof. Reich. After 24 weeks, 66.3 % of patients treated with ixekizumab compared to 53% of patients treated with ustekinumab showed a DLQI 0/1 response, which means that the disease has no effect on the life of the patients.

Iodine containing gel effective against molluscum contagiosum

A dimethyl sulfoxide gel containing povidone-iodine was effective in a study of 12 patients that were treated over 8 weeks [4]. Patients in the study were treated with the gel formulation twice a day and evaluated after 4 weeks. All 12 had complete or partial resolution of the condition. Of 115 lesions treated, 103 (90%) had resolved at eight weeks. Mild skin irritation and dryness were the only adverse effects reported. "We have found remarkable success with this novel combination that has not been previously reported in the literature, warranting further investigation to elucidate clinical utility," said Dr. Kara Capriotti, a dermatologist at Bryn Mawr Skin and Cancer Institute in Bryn Mawr (PA/USA).

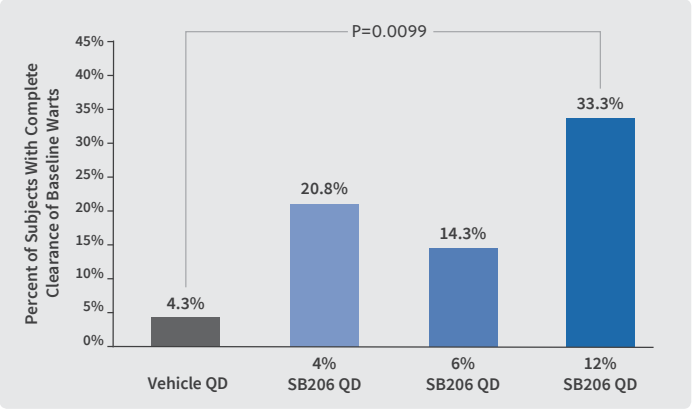
Povidone-iodine is a resistance-free, broad-spectrum biocidal agent that eradicates micro-organisms, including bacteria, viruses, yeasts, molds, fungi, and protozoa. Dimethyl sulfoxide is an effective vehicle that works by enhancing percutaneous penetration of povidone-iodine. "Our results may have far-reaching impact in dermatology, offering well-tolerated at-home treatment, along with eliminating morbidity from current treatments and frequent office visits," concluded Dr. Capriotti.

Nitric oxide effective against genital warts

A study of 30 patients with genital or perianal warts showed promising results regarding the efficacy of a nitric oxide-releasing topical gel [5]. Participants of the trial had 2 to 20 genital or perianal warts, but were otherwise healthy. In this dose finding trial, a dose response was seen with 12% gel. With this concentration, 33.3% of the patients gained complete clearance of baseline warts in the intention-to-treat analysis (Figure 2) and 42.1% in the per protocol analysis after 12 weeks compared with 6.7% of patients who used a vehicle gel (P=0.02).

There was a low discontinuation rate. “At the moment, we speculate, that the mode of action is more inflammatory than cytotoxic,” explained Prof. Stephen Tyring, University of Texas Health Science Center in Houston. Therefore, the agent is targeting more the viral infected than the normal cells.

Figure 2 Complete clearance of baseline warts after application of a nitric oxide-releasing gel at week 12 in the intention-to-treat analysis (Primary endpoint) [5]



In the dose-ranging phase 2 trial, a 4% and 8% gel was also tested and reduced warts. However, the difference compared to placebo failed statistical significance. The twice daily dosing of SB206 was too toxic and was discontinued. Therefore, future trials will use the 12% gel. Prof. Andrew Blauvelt, Oregon Medical Research Center in Portland, who moderated the session, called the results "compelling. I think that nitric oxide has promise for many dermatologic conditions."

New antifungal highly effective in candida nail infections

Phase 2 results for a novel fungal CYP51 inhibitor indicate the agent is safe and effective in eliminating Candida albicans nail infections [6]. The phase 2b trial RENOVATE (Restoring Nail: An Oral VT-1161 Tablet Evaluation), compared four formulations of the next generation tetrazole VT-1161 against placebo for 48 weeks. An ongoing follow-up phase will overlook a treatment period of up to 96 weeks. “The long half-life of VT-1161 enables once-weekly dosing, which is very comfortable for the patients,” said Amir Tavakkol, PhD, chief development officer for Viamet.

All participants received either 300 mg or 600 mg of the new antifungal or a placebo. Patients treated with VT-1161 met the primary endpoint of complete cure of the target toenail at 48 weeks at a rate that was highly statistically significant compared with patients in the placebo group. Complete cure, which requires both a normal appearing nail and negative mycology testing, is the endpoint historically required by the U.S. Food and Drug Administration (FDA) for approval. In the intent-to-treat analysis, complete cure rates were 0% in the placebo arm compared to a range of 32% to 42% in the four VT-1161 arms of the study, with all VT-1161 arms achieving statistical significance vs. placebo. Complete cure rates for evaluable patients through week 48, calculated using an analysis like that used for the FDA approval of terbinafine, the current standard-of-care for onychomycosis, were as high as 51% in the VT-1161 groups. Complete cure rates continued to improve through week 60, with all active arms having a complete cure rate of greater than 40% in the intent-to-treat analysis.

"These data are among the strongest to be reported for onychomycosis, particularly when viewed in comparison to terbinafine, which was approved based on a 31% intent-to-treat and 38% evaluable complete cure rate, and given the significant safety concerns, which limit its use,” said Dr. Tavakkol.

Throughout the study, the new antifungal was very well tolerated. Not a single patient stopped treatment due to an adverse event. “After these encouraging results, phase 3 trials are planned in 2017,” concluded Dr. Tavakkol.

Dupilumab effective in combination therapy

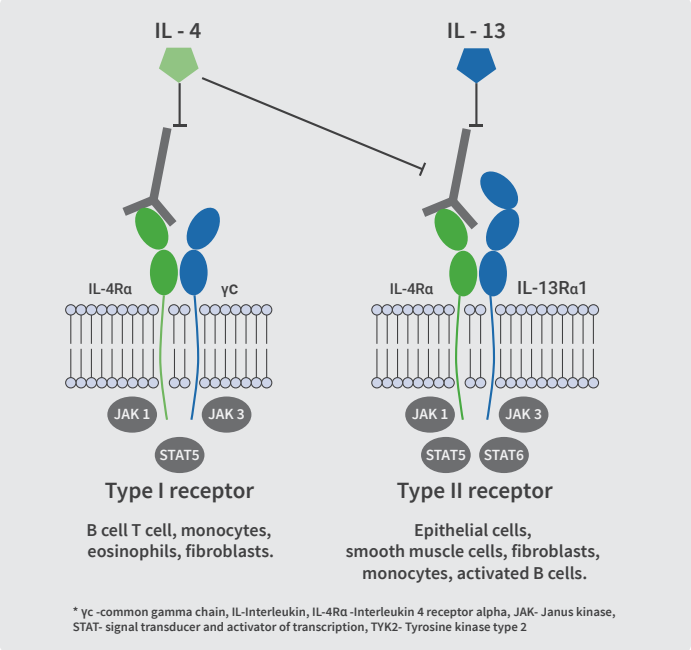
“Atopic dermatitis is the new psoriasis: we finally have new drugs that show excellent treatment results,” said Prof. Blauvelt during presentation of the CHRONOS trial, where the combination of the IL-4 and IL-13 blocker dupilumab with topical cortico-steroids (TCS) was compared to TCS alone in patients with moderate-to-severe atopic dermatitis (AD) [7]. In this trial, the combination achieved significantly improved measures of overall disease severity compared to TCS alone. Dr. Blauvelt and colleagues enrolled 740 subjects (mean age 34 years; 60% male). Patients were randomized to receive dupilumab 300 mg weekly with TCS, dupilumab 300 mg every 2 weeks with TCS, or placebo with TCS. At 16 weeks, 39% of both dupilumab dosing groups compared to 12% of the placebo group achieved the primary endpoint of CHRONOS, an Investigators Global Assessment (IGA) of 0/1, which means clear or almost clear skin

and at least a 2-point improvement from baseline (P<0.0001). This positive result could be maintained over 52 weeks in 36%-40% of patients on dupilumab compared with 13% of placebo subjects (P<0.0001). In addition, both dupilumab arms were significantly superior to placebo in several secondary endpoints, e.g. regarding the reduction on the "Eczema Area and Severity Index (EASI-75)". The agent also had a positive impact on pruritus, the symptom that bothers AD patients most. As Prof. Blauvelt pointed out, the intensity of patient-reported itch, as measured by the "Pruritus Numerical Rating Scale", came down quickly and showed a continuous response over time. "For us it was important to demonstrate that this effect can be maintained to week 52," concluded Prof. Blauvelt.

IL-4/IL-13 Blockade: also an option for children with AD

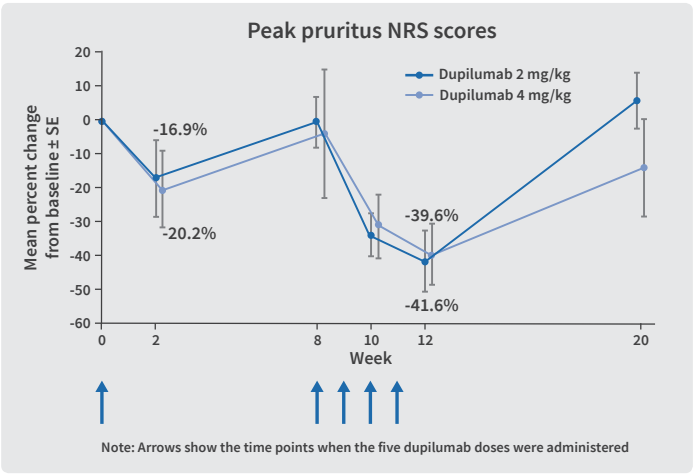
First results from an open-label phase 2a trial show that Dupilumab, an inhibitor of IL-4 and IL-13 (Figure 3) can also be safely used in children [8].

Figure 3 Mode of action of dupilumab. Dupilumab is a potent blocker of IL-4 and IL-13 [8]



"IL-4 and IL-13 are even more the driver of inflammation in pediatric AD, therefore we anticipated that it will be active in children. Now we know, that it is exciting times for AD," said presenter Prof. Michael J. Cork, MD, PhD, a pediatric dermatologist at Children's Hospital, Sheffield in the United Kingdom. All participants were on topical steroids, 20% had failed systemic treatment. In the trial, children were separated into two age groups (6-11 years and 12-17 years) and were treated with two doses of dupilumab. Primary endpoint was the characterization of the pharmacokinetic profile of dupilumab in pediatric patients, but key secondary endpoints were the percentage of change from baseline in the EASI-score and in peak pruritus score, measured in a numeric rating scale. The impressive results: after only one injection, the EASI-score dropped by 50% in the older age group (12-17 years). In addition, there was a distinct improvement of pruritus, which fell by 37% after four injections and by 41.6% in the 6-11 years old (Figure 4). According to this data, the non-linear pharmacokinetic profile of dupilumab was consistent with that seen in adults. These data confirm the significant clinical benefit for the Th2-mediated pathophysiology for AD in children. "The life of these children was changed after only one injection of dupilumab," concluded Prof. Cork. The identical pharmacokinetic profile translates into an impressive clinical efficacy.

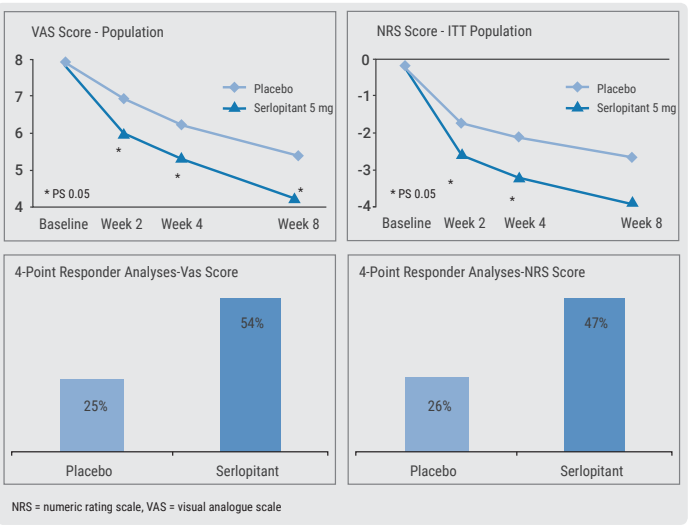
Figure 4 Dupilumab lead to a rapid reduction of pruritus in children aged 6-11 years [8]



New hope for patients with prurigo nodularis

As Prof. Sonja Ständer, Universitätsklinik Münster in Münster (Germany) pointed out, this is the first time that there is a systemic drug for pruritus nodularis [9].
Pruritus nodularis is a chronic skin disease characterized by intensely pruritic papulonodular eruptions. It is frequently associated with systemic diseases such as chronic kidney disease and with atopy-related conditions. However, the aetiology of pruritus nodularis is unclear in most cases. Pruritus nodularis is often refractory to first line treatments, such as topical steroids. Stimulation of the tachykinin neurokinin 1 receptor (NK1-R) is an important pathway for pruritus perception. This receptor is expressed on multiple cell types throughout the body. Serlopitant is a small molecule, that is a highly potent and selective NK1-R antagonist (Figure 5).

Figure 5 Serlopitant lowers average and worst itch



NRS = numeric rating scale, VAS = visual analogue scale

The randomized double-blind, placebo-controlled trial compared serlopitant 5 mg daily to placebo over an 8-week treatment period and 2 weeks of follow-up in 127 patients with refractory notalgia paresthetica. Serlopitant was superior for reducing pruritus at 2 weeks with increasing superiority over the course of the trial. A subgroup analysis revealed that patients with atopic disposition respond better to treatment. "The reason for this might be, because atopic patients have higher concentrations from substance P," explained Prof. Ständler and further he continued - "We hope to have a phase 3 study soon after these encouraging results". Serlopitant was well tolerated, most adverse effects were mild to moderate.

A new skin regimen supports the development of a physiological infant microbiota

"Previously, we demonstrated that after 1 month, the skin microbiota has evolved from birth, where it's dominated by vaginal and/or environmentally acquired microbes, to an infant skin microbial profile," explained lead author Kimberly Capone, PhD, head of the Microbiome Platform, Emerging Science and Innovation at Johnson & Johnson Consumer Inc. [10].
Different factors have been found to delay the development of an infant microbiome e.g. a caesarean section or bottle feeding with possible negative immunological consequences. According to a trial presented by Capone, a specific skin regimen consisting of a baby wash, shampoo and lotion can support the evolution of a physiologic infant-like skin microbial profile within the first week of life. The babies in the intervention group were compared to a control group that continued with their typical use of baby skincare products. The use of the specified baby product regimen was associated with a significant increase in microbial diversity during the first month of life. In this trial, it could be shown for the first time that the skin microbiota in neonates evolves to an infant skin microbial profile within the first week of life. In general, microbial richness was significantly lower in C-section infants at day 3-7 of life, but became indistinct from vaginal-delivered infants by day 11-18 of life.

Novel topical agent reduces IL-17 levels

A topical compound shows promise in improving skin histopathology and in reducing IL-17 levels in an imiquimod-induced psoriasis model. RORγ is a nuclear hormone receptor that controls the differentiation of Th17 cells that play a key pro-inflammatory role in a variety of autoimmune diseases, including psoriasis. The study has identified potent inhibitors of RORγ with greater than 100-fold selectivity against RORγ/RORγ as well as other nuclear receptors. The lead compounds inhibit differentiation of primary mouse/human CD4+ve T cells to Th17 cells without affecting Th1, Th2, or Treg cell differentiation. "Our RORγ inverse agonist lead compound has shown a good safety profile as well as efficacy comparable to the IL-17 antibody in this psoriasis model," said Kavitha Nellore, PhD, associate research director at Aurigene Discovery Technologies. Therefore, RORγ inverse agonists could be candidates for innovative topical therapies for the treatment of psoriasis [11].

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2. Gottlieb A. Certollzumab Pegol Treatment for Chronic Plaque Psoriasis: 16-Week Primary Results from Two Phase 3, Multicentre, Randomized, Placebo-Controlled Studies. Session F056 – late-breaking research: clinical trials presented at the 75th AAD annual meeting. March 3-7 2017, Orlando (FL/USA)
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5. Tyring S. Results from phase 2 study of nitric oxide – releasing SB206 once daily administration show favourable efficacy and safety in genital warts. Session F056 – late-breaking research: clinical trials presented at the 75th AAD annual meeting. March 3-7 2017, Orlando (FL/USA)
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10. Capone K. Longitudinal Development of the Skin Microbiome During the Neonatal Period. Session F072 – late-breaking research: clinical studies/pediatric, presented at the 75th AAD annual meeting. March 3-7 2017, Orlando (FL/USA)
11. Nellore K. Efficacy of RORγ inverse agonists in imiquimod-induced psoriasis model with both oral and topical administration Session F085 – late-breaking research: basic science/cutaneous concology/pathologyF, presented at the 75th AAD annual meeting. March 3-7 2017, Orlando (FL/USA)

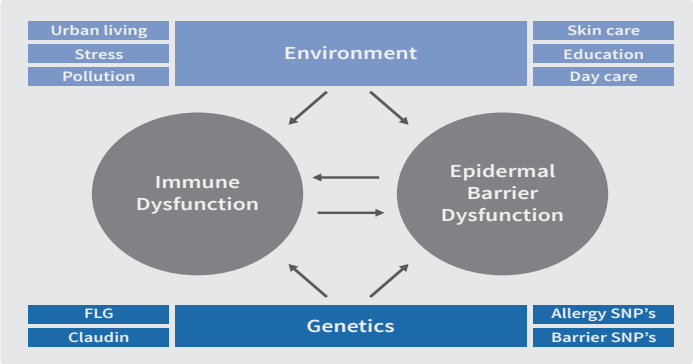
Atopic Dermatitis – A New Psoriasis

Although AD is the most common inflammatory skin disease, treatment options for moderate-to-severe disease have been limited. Recent studies of biologics, led by dupilumab, have opened doors to fascinating therapeutic possibilities in the future.

Immune dysfunction

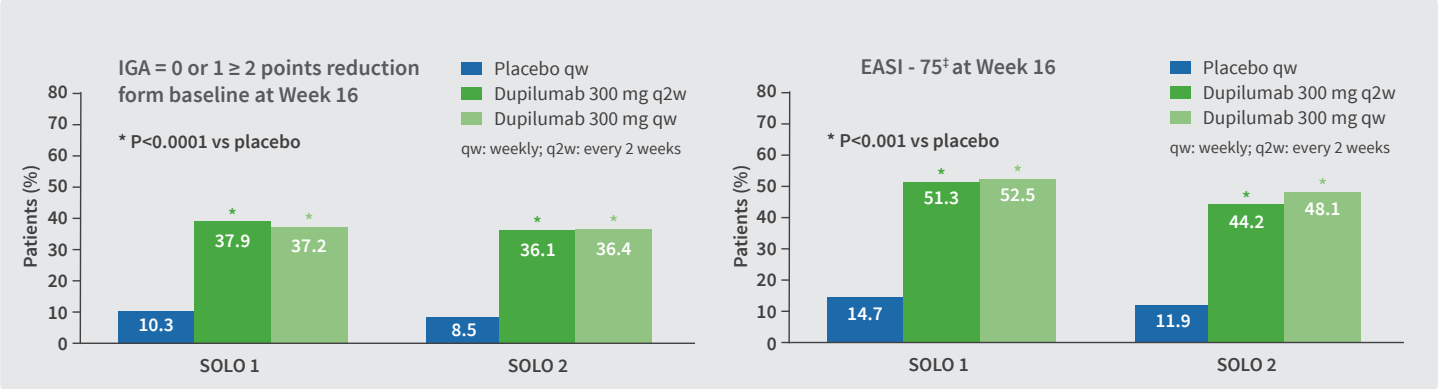
Like psoriasis, AD is not confined to the skin, but a systemic disease with a yet-to-be-defined immunologic background leading to immune deviations. There is increased T cell and circulatory cytokine activation, and its two most important T cells are Th2 and Th22. Today, the focus is shifting clearly toward the immune dysfunction in AD (Figure 1). "Can the psoriasis model be applied to atopic dermatitis? The answer is 'yes,'" said Prof. Emma Guttman-Yassky, department of dermatology and vice chair of the immunology institute at Icahn School of Medicine at Mount Sinai, New York (NY/USA), and co-author of the SOLO 1 and SOLO 2 trial [1]. SOLO 1 and SOLO 2 were two identically designed phase 3 trials conducted on 1,379 patients with moderate to severe AD to examine the efficacy and safety of the drug [2].

Figure 1 Atopic Dermatitis is a Th2-mediated disease



The exiting results: Dupilumab in two doses provided significant improvement in symptoms of AD assessed in the IGA and the EASI-75 response compared to placebo, both primary endpoints of the trial (Figure 2).
In the SOLO 1 trial, in the dupilumab group 37.9% of patients (every week) or 37.2% of patients (every 2 weeks) achieved clearing or near-clearing of skin lesions (IGA 0 or 1) and a reduction from baseline from at least 2 points compared to 10.3% in the placebo group at week 16 (primary endpoint). Results of the SOLO 2 trial were comparable (both P<0.0001 vs. placebo). 51.3% of patients in the dupilumab group (every week) and 52.5% of patients (every 2 weeks) gained a ≥ 75% reduction in their EASI-75, compared to 14.7% in the placebo group. Corresponding results in the SOLO 2 trial were 44.2% and 48.1% vs 11.9% in the placebo group (P<0.0001 vs placebo for each comparison). In the SOLO 1 trial, the percentage improvement in EASI from baseline were -72% and -72.3% for the 2 dosing regimens of dupilumab vs -37.6% with placebo (P<0.0001). Corresponding results in the SOLO 2 trial were -67.1% and -69.1% vs -30.9% with placebo (P<0.0001). The trials also demonstrated that treatment with dupilumab reduced disease severity and itching and improved both quality of life and mental health of the patients.
"These results are very encouraging as they achieved not only the primary, but also all the other endpoints like efficacy on itch, quality of life etc. It all looks very good. The safety data is also very reassuring," said Prof. Guttman. Newer research showed that dupilumab reverses inflammation and AD barrier defects. "This is proof the disease is reversible, an immune-driven disease, like psoriasis. In AD, we are approximately 15 years behind to psoriasis, but I think we will catch up very fast in the next few years." Dr. Guttman-Yassky said. The CHRONOS trial, presented as a late-breaker, confirms the high efficacy of dupilumab also in combination with topical corticosteroids.

Figure 2 Primary endpoints in the SOLO 1 and SOLO 2 trials [2]



IL-13: Key inflammatory cytokine in AD

IL-13 appears to be a central mediator in AD. In the phase 2 trial TREBLE, the effectiveness of the IL-13 inhibitor lebrikizumab in patients with moderate to severe AD, was assessed [3].

The primary endpoint in TREBLE was the percentage of patients who achieved at least a 50% reduction from baseline on the EASI, or EASI-50. A dose-response effect was apparent: the EASI-50 rate was 62.3% in patients on placebo plus daily topical steroids, 69.2% with a single 125-mg dose of lebrikizumab, 69.8% with a single 250-mg dose, and 82.4% with 125 mg of lebrikizumab at weeks 0, 4, 8, and 12. Only the group with monthly dosing of the biologic plus daily triamcinolone 0.1% BID had an EASI-50 response rate significantly better than the controls on placebo plus topical steroid therapy. " However, this trial shows that using topical steroids should be avoided in clinical trials with biologics, as they might confuse results of AD clinical trials due to large placebo effects," she said.

IL-13 is known to be an especially potent promoter of type 1, IgE-mediated inflammation. For this reason, lebrikizumab is also under investigation in the treatment of severe asthma, where large phase 3 trials have been completed, as well as in idiopathic pulmonary fibrosis.

Ustekinumab: also effective in AD

Another study in severe AD was performed with the IL-12/IL-23 p40 antagonist ustekinumab. "Ustekinumab suppresses Th1, Th17 and Th22 activation, and is commonly used for psoriasis patients. "The IL-23/Th17 axis is clearly expressed in AD and might have therapeutic potential," said Prof. Guttman. In this phase 2, double-blind, placebo-controlled study, 33 patients with moderate-to-severe AD were randomly assigned to either ustekinumab (n=16) or placebo (n=17), with subsequent crossover at 16 weeks, and last dose at 32 weeks [4]. Background therapy with mild topical steroids was allowed to promote retention. Study endpoints included clinical (SCORAD50) and biopsy-based measures of tissue structure and inflammation. The ustekinumab group achieved higher SCORAD50 responses at 12, 16 (the primary endpoint) and 20 weeks compared to placebo, but the difference between groups was not significant. Again, the high placebo response due to the TCS could have been responsible. "It did not hit its endpoints, but did show promise," commented Prof. Guttmann-Yasskiy.

Other trials looked at apremilast and both oral and topical tofacitinib, which all showed promise, as did topical JAK inhibitors. In addition, new topical therapies will enrich the therapeutic spectrum. The topical PDE4 inhibitor crisaborole got a FDA-approval in December 2016 for mild-to-moderate AD in patients age 2 and up. More than 1,500 patients were included in two phase 3 trials [5]. The primary efficacy endpoint was success in the ISGA at day 29, defined as the proportion of patients achieving an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. In both trials, treatment with crisaborole met this endpoint (32.8% vs. 25.4% (P=0.038) for Trial 1 and 31.4% vs. 18.0% (P<0.001) for Trial 2[5]. Efficacy results were seen in some patients as early as day 8. "The therapeutic landscape for AD is changing rapidly with testing and development of many therapeutics to provide safer and better long-term disease control," Dr. Guttman-Yassky said.

AD: not only a childhood disease

Many clinicians think of AD as a childhood disease. In contrast, the prevalence of AD in adults is only slightly lower than in children (10% in adults compared to 12% in children). "The similarity in prevalence for adults and children suggests that childhood AD persists more commonly than we think or that adult onset AD occurs more commonly than previously thought, or both," said Dr. I. Silverberg, director of the North-Western Medicine Multidisciplinary Eczema Center and assistant professor of dermatology, preventive medicine, and medical social sciences at North-Western University Feinberg School of Medicine, Chicago (IL/USA) [6]. Childhood AD tends to exhibit on the face, hands, extensors, and flexors, depending on age. Adults tend to exhibit more head, neck, hand, and foot lesions.

As Prof. Silverberg pointed out, differential diagnosis of AD can be difficult in adults. It is often confused with allergic contact dermatitis, which requires prior sensitization, and psoriasis, which generally has thicker scale and darker red colour, but can be difficult to distinguish from AD. Nail findings associated with psoriasis might be a helpful clue. Clinicians should always consider medication history in adults with AD. Possible culprits of drug-induced AD are calcium channel blockers or thiazides. In all AD patients, avoiding triggers is a prerequisite for any treatment. That can include cold and hot temperatures, dry or humid air, tight clothing, fragrances, boredom, and stress.

IL-4/IL-13 blocker dupilumab equally effective in mono and combination therapy

Dupilumab is the first biologic that proofed to be efficacious in AD. New results of the CHRONOS trial build upon these previous positive phase 3 monotherapy data and confirm its activity also in combination with topical steroids.

Dupilumab is a potent blocker of IL-4and IL-13. Both cytokines are key mediators of TH2 inflammation and play a role in other allergic disease such as asthma [7]. Dupilumab impacts

both the inflammation and the barrier dysfunction of AD, thus targeting two key factors in AD pathogenesis. One of the highlights of the AAD meeting was the presentation of the phase 3 trial CHRONOS. In this trial, patients receiving the investigational drug dupilumab with TCS achieved significantly improved measures of overall disease severity compared to TCS alone in adults with uncontrolled moderate-to-severe AD [8].

“Blocking signalling of the type 2 cytokines IL-4 and IL-13 leads to sustained control of moderate-to-severe atopic dermatitis during the 52-week treatment period,” said lead author Andrew Blauvelt, MD, MBA, Oregon Medical Research Centre, Portland, Oregon. Patients were eligible for participation in the CHRONOS study, if their disease was uncontrolled by topical medicines including corticosteroids with or without calcineurin inhibitors.

Dr. Blauvelt and colleagues enrolled 740 subjects (mean age 34 years; 60% male). Patients were randomised to receive dupilumab 300 mg weekly with TCS, dupilumab 300 mg every 2 weeks with TCS, or placebo with TCS. Half of the subjects in this study were diagnosed with severe AD and the other half had moderate disease. The mean baseline score on the DQLI was 14. The primary study endpoint of CHRONOS was achieving an IGA of 0/1, which means clear or almost clear skin and at least a 2-point improvement from baseline. At 16 weeks, 39% of both dupilumab dosing groups compared to 12% of the placebo group achieved this endpoint (P<0.0001).

Results were maintained over 52 weeks

“For us it was important to demonstrate that this effect can be maintained to week 52,” said Dr. Blauvelt. After this time, 36% to 40% of patients on dupilumab achieved this goal compared with 13% of placebo subjects (P<0.0001).
In addition, both dupilumab arms were significantly superior to placebo in several secondary endpoints. 64% of patients who received dupilumab weekly with TCS, and 69% of patients who received dupilumab every two weeks with TCS achieved a 75% reduction on the EASI-75, compared to 23% of patients receiving placebo with TCS (P<0.0001). These results were also similar after a treatment period of one year.
Pruritus is the symptom that bothers AD patients most. As Dr. Blauvelt pointed out, the intensity of patient-reported itch, as measured by the “Pruritus Numerical Rating Scale”, came down quickly in both dupilumab groups and showed a continuous response over time.

Also effective in monotherapy

Last year the results of the SOLO 1 and 2 trials have been published, where dupilumab was assessed as monotherapy [9]. In these identically designed randomised, double-blind trials the efficacy and safety of subcutaneously dupilumab was compared to placebo in adult patients with AD affecting a median 50% of BSA that was not controlled by topical medications. In both trials, dupilumab provided significant improvement in symptoms of AD assessed in the IGA and the EASI-75 response (Figure 3) compared to placebo. "CHRONOS’’ provides now positive long-term data for dupilumab in combination with TCS, which is important given AD is a chronic inflammatory disease. Additionally, the presentation highlights the critical role of IL-4 and IL-13 as drivers of this atopic condition,” concluded Dr. Blauvelt.

As IL-4 and IL-13 are even more the driver of inflammation in children with AD, dupilumab could be especially effective in this age group. First data of a phase 2a trial presented during the meeting confirmed the high efficacy: After only one injection the EASI-score was reduced by 50% in the age group 12-17 years. “Particularly in childhood there is a large unmet need for safe and effective therapeutics,” emphasised Prof. Michael J. Cork, Head of Academic Dermatology at The University of Sheffield (Great Britain) during the presentation of the trial [10]. (Figure 4) Further, the data had to be awaited to determine the importance of dupilumab in paediatric AD.

Figure 3 EASI-75 at week 16 in the SOLO 1 and SOLO 2 trial [9].
qw: weekly; q2w: every 2 weeks.

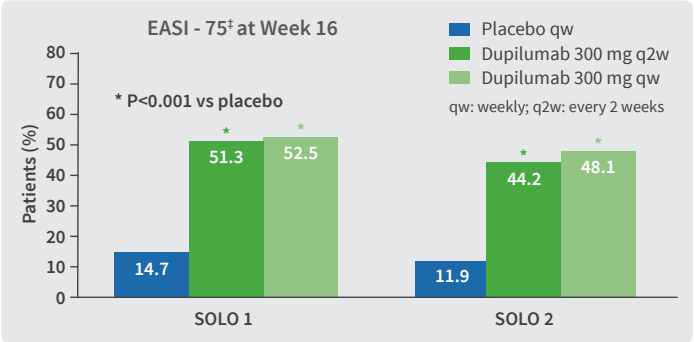
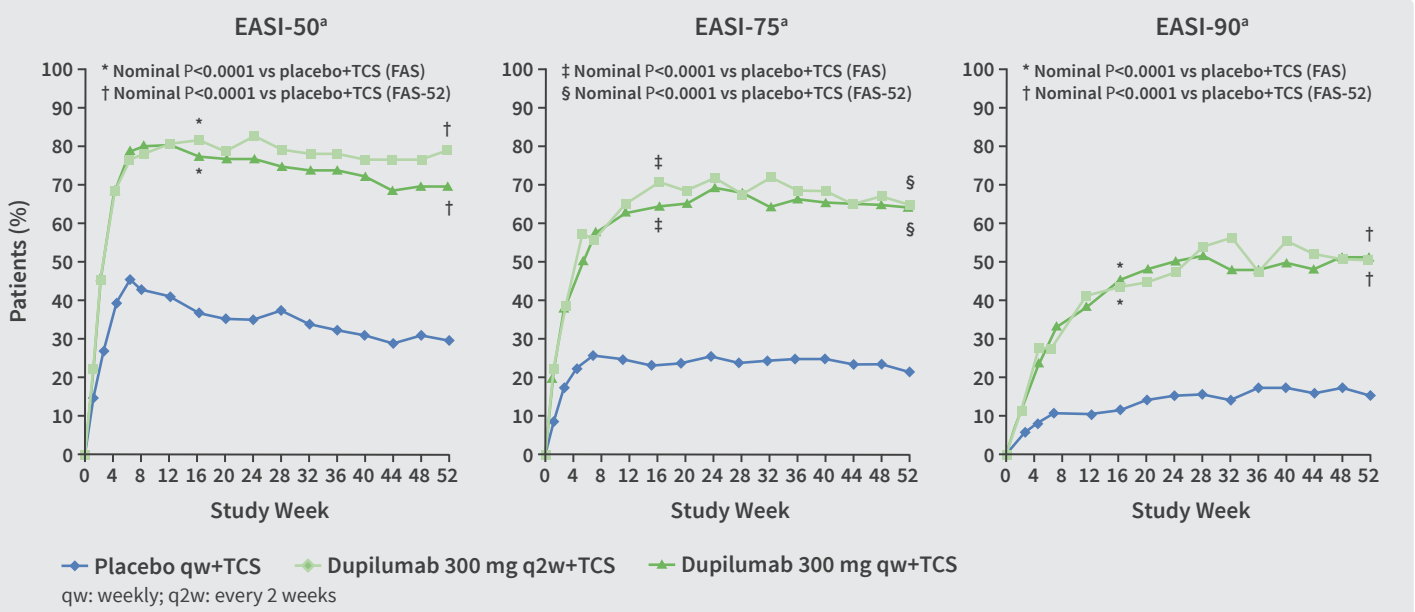


Figure 4 EASI-50/75/90 in the CHRONOS-trial [10]



qw: weekly; q2w: every 2 weeks

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Cardiovascular Comorbidities in Psoriasis: Revisited

Comorbidities, particularly cardiovascular comorbidities, are common in psoriasis. Dermatologist should be aware of these problems and target preventive efforts to psoriasis patients with an affected BSA of more than 10%.

Systemic inflammatory processes

Prof. Joel M. Gelfand, University of Pennsylvania Perelman School of Medicine in Philadelphia (PA/USA), gave an impressive, passionate plea for ''thinking outside the box" during his Marion B. Sulzberger, MD, Memorial Award and Lectureship, [1]. For more than a decade, Prof. Gelfand focused his research on the cardiovascular comorbidity of psoriasis. Already in 2006, he was able to demonstrate that as psoriasis severity increases so does the risk of heart attack, independent of traditional cardiovascular risk factors [2]. Since that time, many studies conducted around the world, including multiple meta-analyses, confirmed the association between severe psoriasis and elevated cardiovascular risk. This risk elevation is presumably caused by systemic inflammatory processes evident in patients with severe psoriasis.

"Strikingly, if you have more than 10% of your BSA involved with psoriasis, you have a 90% higher risk of dying in the next three to four years, independent of concurrent health conditions, smoking, or obesity. That is powerful," Prof. Gelfand said. This showed data from a trial that Prof. Gelfand performed with Dr. Megan Noe, from the same institution [3]. Up to now, no population-based studies evaluating mortality using objective measures of disease severity existed: this trial filled this research gap. All–cause mortality rates for adults with psoriasis were determined, stratified by disease severity, using physician-reported, objective measures of disease. Data came from the Health Improvement Network a database including 11 million individuals. Psoriasis patients were randomly selected, a survey was sent to GPs who confirmed the diagnosis and assessed the extent of disease, by the BSA that was affected. Controls were matched 10:1.
Psoriasis patients with >10% BSA had a significant higher mortality rate compared to controls and psoriatic patients with moderate (3-10% BSA) or mild (less than 3% BSA) psoriasis (Table 1). This excess mortality was similar to other well-established risk factors like diabetes, which emphasizes the importance of targeting patients with more severe psoriasis for preventive health efforts. The results were robust to adjustment for the Charlson comorbidity index, suggesting underlying medical comorbidities are not solely responsible for the increased risk. "Our preventive efforts should be targeted to psoriasis patients with BSA >10%," concluded Prof. Gelfand from this trial.

Table 1 Psoriasis patients with > 10% BSA have a significantly higher mortality rate [3]

Psoriasis patients with > 10% BSA have a significantly higher mortality rate				
	Controls N=90,690	< 3% BSA N=4539	3-10% BSA N=3133	>10% BSA N=1088
Number of Deaths	1233	58	38	29
Average Fllow-Up Time, yrs (SD)	4.17 (1.64)	4.25 (1.56)	4.31 (1.50)	4.16 (1.53)
Mortality Rate, per 1000 person-years (95% CI)	3.25 (3.07 - 3.44)	3.00 (2.32 - 3.88)	2.81 (2.04 - 3.86)	6.39 (4.45 - 9.21)

Increased vascular inflammation in psoriasis

The missing link between severe psoriasis and elevated cardiovascular risk might be vascular inflammation that is increased in patients with psoriasis. But do anti-inflammatory drugs automatically reduce vascular inflammation?
Obviously not, as could be shown in a randomized, double-blind, multicentre study presented during the meeting that evaluated the effects of the TNF-a antagonist adalimumab on vascular inflammation in patients with psoriasis [4], that was simultaneously published [5].
Vascular inflammation was no different in patients with moderate to severe psoriasis after 16 weeks of treatment with adalimumab than in untreated controls. In the double-blind multicentre study, 107 adults with psoriasis were randomized to either adalimumab (80 mg followed by 40 mg at week 1 and 40 mg every other week for 52 weeks), or to placebo for 16 weeks, followed by adalimumab (80 mg at week 16, 40 mg at week 17, and 40 mg every other week until week 52). The mean PASI score among the patients was about 10. All patients were evaluated for vascular inflammation at baseline, at two weeks and after 52 weeks with PET-CT scans of the ascending aorta and the carotid arteries.
After two weeks, there were no significant differences in the change from baseline in vessel wall target to background ratio rom the ascending aorta (P=0.916) and the carotid arteries (P=0.629). At 52 weeks, there was no significant change in target to background ratio from the ascending aorta between baseline and the start of adalimumab, although in the carotid arteries, there was a modest increase in vascular inflammation.

Several previous studies have suggested that reducing inflammation in psoriasis can also reduce the risk of some cardiovascular events. As to why this study did not demonstrate a correlation between vascular inflammation and treatment.

Dr. Bissonnette said – "Either the dose of adalimumab that is used for psoriasis has no impact on vascular inflammation or it may be possible that levels of IL-6, a key cytokine correlated with vascular inflammation, were very low in our study".
Another hypothesis of this unexpected results might be the molecular size of adalimumab. The drug may not be able penetrate the aorta. Finally, psoriasis might be a primarily IL-23 and IL-17 driven disease.

TNF blocker lower cardiovascular endpoints

However, a couple of trials have demonstrated a positive effect of therapy with TNF blockers on clinical outcomes of patients with severe psoriasis. In a previous trial, Dr. Jashin Wu, Kaiser Permanente Medical Group, Los Angeles (CA/USA) showed that intake of a TNF blocker was associated with a significantly reduced risk of myocardial infarction [6]. During the conference, Dr. Wu presented a data analysis regarding the influence of TNF blockers on all-cause mortality [7]. "In our retrospective trial, we used a Kaiser Permanente data set," explained Dr. Wu. Participants had to have at least three core diagnose ICD-9 codes for psoriasis or psoriatic arthritis. The TNF-group received TNF blockers for at least three months, they were compared to a cohort of TNF inhibitor-naïve patients, who got oral agents or phototherapy and to a cohort with only topical therapy.

....as well as all-cause mortality

Therapy with TNF blocker reduced the relative risk to die by 53%. “In our study, phototherapy also reduced the risk by 14%, which was a surprise,” said Wu. However, there is one limitation of the trial, which might have influenced the outcome. “Low-dose aspirin is sold over the counter. We could not exclude this influence in the trial,” said Dr. Wu.
This trial is one of the first studies to look at all–cause mortality in patients with psoriasis or psoriatic arthiritis. According to Dr. Wu, this reduced risk due to TNF blocker use can be explained mainly by a lower cardiovascular risk.

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It´s all in the Genes

An increased knowledge of genetics has identified at least 64 psoriasis genes that are affecting immune pathways. “Patients with psoriasis who have these genetic issues often have autoimmune diseases,” said Prof. Wilson Liao, University of California, San Francisco (CA/USA). Psoriasis is a multifactorial disorder, influenced by both genetic and environmental factors. Its genetic basis has long been established through twin studies and familial clustering. The association of psoriasis with the HLA-Cw6 allele has been shown in many studies. Recent genome-wide association studies have identified many other genes associated with psoriasis. Many of these genes regulate the innate and adaptive immune system [8]. Psoriasis genes cluster to biological pathways, and these psoriasis genes are shared with autoimmune and cardiovascular diseases. Autoimmune diseases that have genes that overlap with psoriasis include celiac disease, lupus, rheumatoid arthritis, and Crohn’s disease.
A focus on the HLA gene system is helping researchers learn more about psoriasis autoantigens that are thought to be triggers for the disease. These increased understanding of the genetic background could lead to whole genome sequencing and learning about interactions among genes and between genes and the environment. This knowledge will be useful for the development of future treatments.

IL-17 Inhibition in Psoriasis

New data presented during the AAD meeting show that the IL-17 inhibition provides significant and sustained improvement in various patient-reported outcomes among individuals with psoriasis.

From the Patient´s Perspective: Better work productivity

The outcomes in the scientific trial program of secukinumab are physician-derived. Are these advantages also evident from the patient´s perspective? This was addressed in analyses of the CLEAR trial, which were presented during the AAD meeting. In the analysis of Strober et al. influence of the IL-17 inhibitor on psoriasis-related pain, itching, and scaling according to patient-reports was examined [1]. All patients rated psoriasis-related pain, itching and scaling at baseline and weeks 1, 2, 3, 4, and then every four weeks until week 52 via numeric rating scale. The complete relief of symptoms was defined as absence of symptoms (item score of 0). According to this analysis, patients treated with secukinumab achieved significantly greater mean improvement (reductions) in psoriasis-related pain, itching, and scaling as early as week 2 until the end of the trial ($P<0.05$ for all three comparisons). Another analysis of the CLEAR trial demonstrated that better symptom control also translates to better work productivity, quality of life and more daily activities [2]. Patients rated their quality of life in the “DLQI”. In addition, they completed the “Work Productivity and Activity Impairment-Psoriasis,” a self-administered questionnaire comprising six questions regarding

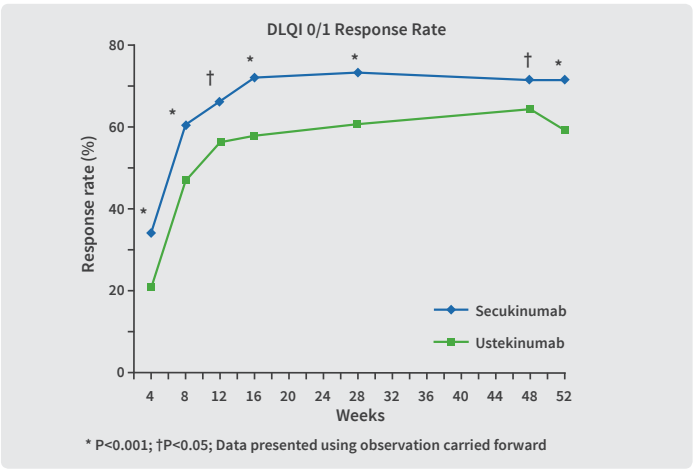
the effects of psoriasis on the subject's ability to work and to perform regular activities. Psoriasis-related pain, itching, and scaling were assessed on an 11-point numeric rating scale (Pruritus Numerical Rating Scale-0-10) by each participant.

Improvement in personal relationships

Compared to ustekinumab, secukinumab had a greater effect on the quality of life. This better quality of life during secukinumab therapy was mediated by improvement in PASI response and psoriasis-related symptoms. Likewise, treatment effected the Work Productivity and Activity Impairment-Psoriasis, but not directly. Improvements in pain and scaling indirectly and significantly reduced activity impairment due to psoriasis and work impairment due to psoriasis. The authors conclude, that secukinumab has a greater and sustained effect on health-related quality of life, work productivity and daily activities compared to ustekinumab.

Another poster shed light on patient-reported assessments of dermatology-specific quality of life, general health status, and work productivity and activity impairment during therapy with ustekinumab and compared it to secukinumab [3]. Again, data derived from the CLEAR 52-week trial. DLQI 0/1 response rates were significantly higher for secukinumab than for ustekinumab at week 52 (71.6% vs. 59.2%; P<0.001). Significant difference could be shown as early as week 4 (Figure 1). Patients were also asked how they judged their current health status in the EQ-5D visual analogue scale. This validated score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). After week 12, subjects treated with secukinumab continued to report improvement in health status over 52 weeks. At the end of the trial, the absolute mean change in EQ-5D VAS was significantly greater (indicating better health) for secukinumab than ustekinumab at week 52 (13.8 vs. 10.6; P<0.05).

Figure 1 Therapy with secukinumab leads to a significantly higher DLQI 0/1 (psoriasis has no impact on the quality of life) response rate compared to ustekinumab starting at week 4 [3]



* P<0.001; †P<0.05; Data presented using observation carried forward

Pronounced activity in difficult to treat regions

The IL-17 inhibitor secukinumab is a new highly effective treatment option for psoriatic lesions on the scalp, the palms and soles, and the nails. 1.5 year updates of clinical trials confirm the long-term efficacy of the IL-17 inhibitor in palmoplantar and nail psoriasis.

Psoriatic lesions at special localizations, namely in the scalp, genital and palmoplantar psoriasis are difficult-to-treat [[4]. Efficient therapy is important, as psychosocial and/or functional impairment of psoriasis involving problem locations is disproportionate compared to other locations [4] [5].

Scalp psoriasis is commonly the initial presentation of psoriasis, and almost 80% of patients with psoriasis will eventually experience it [6]. It causes significant psychosocial disability as it is highly visible and can, on occasion, extend onto the face [7]. Furthermore, topical treatment regimens are messy, time consuming and, in some instances, ineffective, leading to a high level of non-compliance. In cases of severe hyperkeratosis, adherent scales may be required to remove, before a topical may prove efficacious [7]. Therefore, there is a yet unmet medical need for an alternative treatment for moderate to severe scalp psoriasis.

Specific scalp psoriasis trial

In a randomized, double-blind, placebo-controlled, parallel-group, multicentre study efficacy and safety of secukinumab was assessed in 102 patients suffering from moderate to severe scalp psoriasis [8]

This trial was specifically designed to address patients suffering primarily from moderate to severe scalp psoriasis. Therefore, specific severity of body psoriasis was not required for study entry. The effect of treatment with secukinumab on scalp psoriasis-related pain, itching, and scaling was evaluated: patients self-reported these symptoms at baseline and weeks 1, 2, 3, 4, 8, 12, 16 and 20 via a numeric rating scale. In addition, scalp dermatitis-related quality of life was assessed by the patients every 4 weeks up to week 24. This questionnaire evaluates feelings about scalp condition such as hurting or itching sensations and influence of scalp symptoms on stress level and self-consciousness.

Mean scalp surface area involvement of included patients was 60%, mean PASI score was 9.2

Improvement of all scalp-related symptoms

Patients on secukinumab reported significantly greater mean improvement (reductions) in scalp psoriasis–related pain, itching, and scaling vs. placebo as early as week 1 (Figure 2). At week 12, patients treated with the higher dose of secukinumab reported greater reduction in all scalp psoriasis-related symptoms than those treated with placebo (P<0.001 for each comparison).

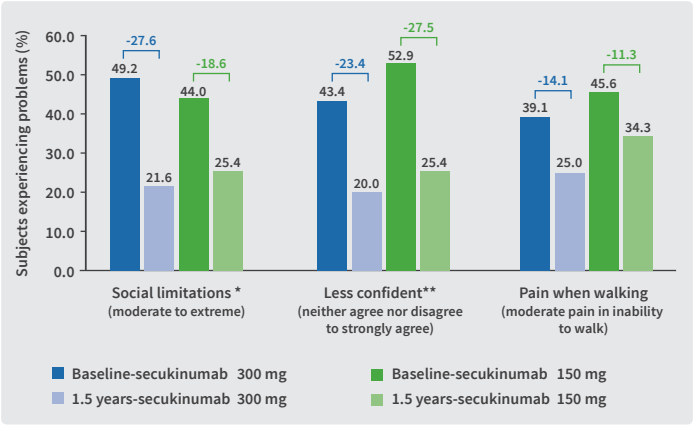
In addition, patients treated with secukinumab reported

greater scalp dermatitis-related quality of life improvement than patients on placebo. These changes got significant as early as week 4. A superiority was seen in all sub scores (total, emotional, symptom, functional) of this quality of life tool particularly designed for patients with scalp psoriasis. This trial shows that secukinumab provides early improvement and has an influence on all scalp related symptoms.

Palmoplantar psoriasis leads to functional and social disability

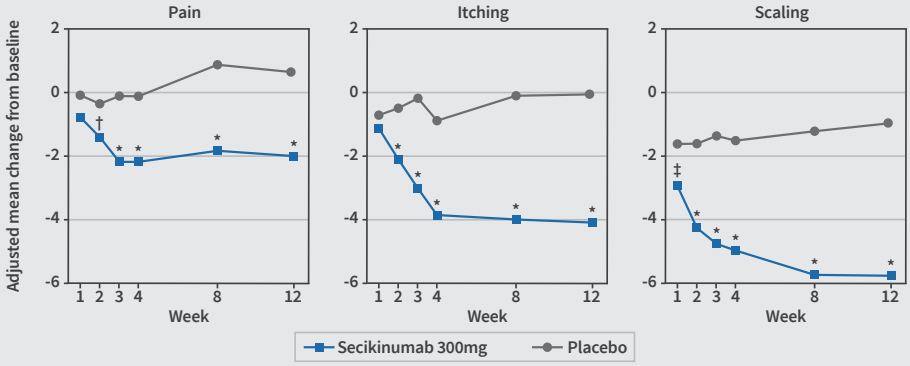
Palmoplantar psoriasis occurs in up to 40% of plaque psoriasis patients [9]. Hyperkeratotic plaques at the soles and palms are associated with significant functional and social disability. Therefore, palmoplantar psoriasis has a severe impact on patient´s quality of life [10]. In addition, these lesions tend to be resistant to treatment [11]. The efficacy and safety of the IL-17 inhibitor secukinumab, in palmoplantar psoriasis was assessed in the GESTURE trial (ClinicalTrials.gov NCT01806597), the only large, randomized, double-blind, placebo-controlled study to report long-term data on efficacy, safety and patient benefits in subjects with palmoplantar psoriasis. In this trial, 202 patients with moderate-to-severe palmoplantar psoriasis were included. About 1/3 of patients achieved clear or almost clear skin on palm and soles after 16 weeks of treatment with secukinumab as assessed using the Palmoplantar IGA (33.3% vs. 1.5% with placebo; P<0.0001) [12]. This result continued to improve with approximately 60% of patients achieving clear or almost clear palms and soles at week 80 (Year 1.5) [13]. At the AAD meeting, the patient reported outcomes of the GESTURE trial after 1.5 years were presented [14]. In this trial, the impact of palmoplantar psoriasis on quality of life was assessed with a questionnaire with 15 hand- and 14 foot related questions. At baseline, 50-60% of patients reported moderate to extreme impairments in this questionnaire. Patients suffer particularly from social limitations and loss of confidence in the use of hand. After 1.5 years, the percentage of subjects with social limitations, loss of confidence, or pain when walking was reduced by approximately 50% in the group that was treated with 300 mg secukinumab (Figure 3).

Figure 3 Quality of life affected by palmoplantar psoriasis greatly improved at 1.5 years in the GESTURE-trial. [14]



In addition, at baseline palmoplantar psoriasis was associated with a very large impairment on subject's lives, assessed in the DLQI. At 1.5 years, 1/3 of patients treated with 300 mg secukinumab stated that the skin problems had no more impact on their life, corresponding to a DLQI 0/1 response. Total DLQI-scores improved by -7.3 score points in the secukinumab 300 mg and – 5.4 points in the lower dose group: both results represent a clinically meaningful improvement. This positive result is mirrored by the results in the patient´s wellbeing, assessed in a 100-mm visual analogue scale in which subjects rated how well they are doing considering all the ways palmoplantar psoriasis affects them. Patient´s well-being in the group that took the higher dose improved by 70% at 1.5 years.

Figure 2 Adjusted mean change from baseline for scalp psoriasis-related pain, itching and scaling over 12 weeks [8]



* P < 0.001; ‡ P<0.01; † P<0.05; data presented using last observation carried forward.
[a]Adjusted for bodyweight, previous systemic therapy, previous biologic therapy, previous tumor necrosis factor α-inhibitor therapy, and baseline score.

Also efficacious in nail psoriasis

Nail psoriasis is also associated with functional disability such as decreased finger mobility and pain and often resistant to available therapy. Importantly, this manifestation correlates with more severe psoriatic disease and is an important predictor of Psoriatic Arthritis (PA) [15] [16] [17] [18]. The efficacy and safety of secukinumab in patients with nail psoriasis was assessed in the double-blind, randomized, placebo-controlled TRANSFIGURE trial. At the AAD meeting, the results after a treatment period of 1.5 years were presented [19]. They showed that fingernail psoriasis improved by almost 70%. Patients showed improvement in a quality of life questionnaire specifically designed for nail psoriasis of -47.7%.

In addition, high levels of skin clearance were achieved and sustained.
The new data confirms the high long-term efficacy of secukinumab in difficult-to-treat areas and the meaningful improvement in quality of life experienced by the patients.

IL-17 inhibitor ixekizumab high showed sustained efficacy – even in difficult to treat areas

New data on the IL-17 inhibitor ixekizumab presented during the conference confirms the significant efficacy in the treatment of moderate-to-severe plaque psoriasis when compared to a second-generation biologic. An extension trial of UNCOVER-3 confirms that the treatment benefit is maintained over a period of 108 weeks.
"We dermatologist are great in developing all these new drugs, but whether they are really better, we can only judge in head to head trials," said Prof. Kristian Reich, Dermatologikum Hamburg (Germany). These eagerly awaited results of the IXORA-S-trial were presented during a late breaking session. As Prof. Reich pointed out, the comparison of a new agent with the second generation biologic ustekinumab is considerably more challenging than the comparison to etanercept. Ixekizumab mastered this crucial test in the IXORA-S-trial: the agent demonstrated to be superior to ustekinumab, in primary as well as secondary outcomes, after 24 weeks of treatment in patients with moderate to severe psoriasis.

High percentage of patients with clear skin

Primary endpoint of this trial was the percentage of patients that reached PASI-90, which equals almost clear skin after a treatment period of 24 weeks. 83 % of psoriasis patients treated with ixekizumab achieved this endpoint compared to 59% of the patients on ustekinumab (P<0.001). "This trial tells you a lot about the response patterns, there is not so much difference at PASI 75 between these agents, but a difference of more than 24% is really relevant after this relatively short treatment period," commented Prof. Reich. In addition, 50% of patients reached clear skin in the sPGA, an enormous effect as Prof. Reich pointed out.
The study assigned 136 patients with psoriasis, to be treated with ixekizumab (160 mg starting dose, then 80 mg every 2 weeks for 12 weeks, followed by 80 mg every 4 weeks). The remaining patients (n=166) were treated with ustekinumab.

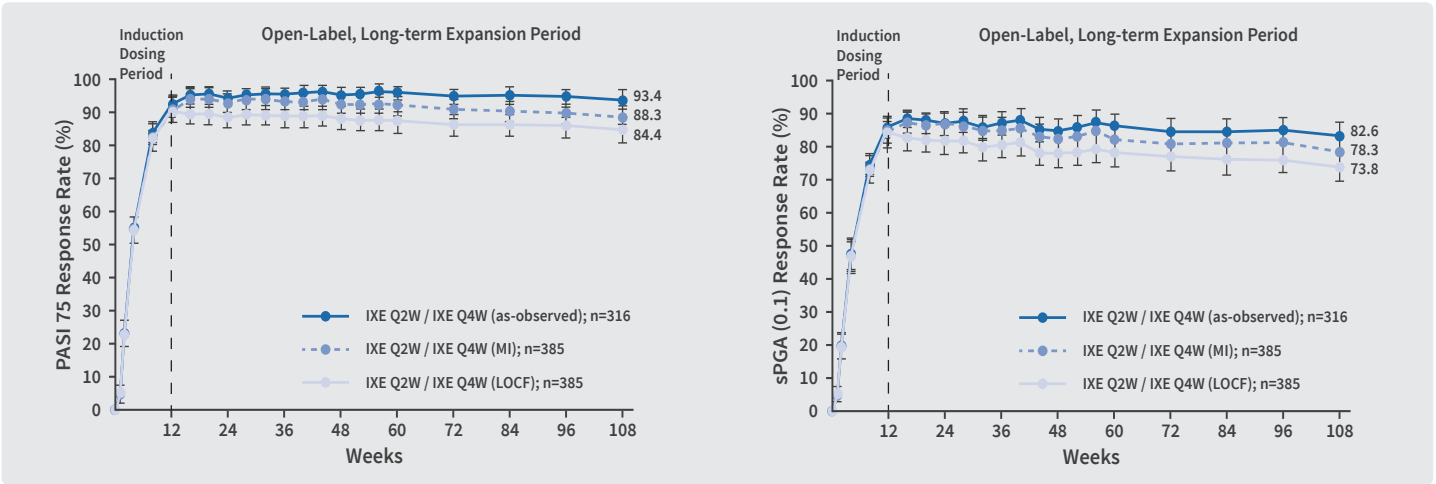
No differences with respect to side effects

There was no significant difference in overall adverse events in the treatment groups. 5 (3%) of the patients on ustekinumab experienced serious adverse events compared with 3 patients (2.2%) taking ixekizumab (P=0.735). 1 individual on ustekinumab and 2 patients on ixekizumab discontinued the trial due to adverse events. Treatment-emergent adverse events occurred among 75% of the patients on ustekinumab and 70% of the patients treated with ixekizumab (P=0.299).
As Prof. Reich pointed out, patients on ixekizumab will take part in an extension trial that will continue for 52 weeks. In contrast to the CLEAR study, in which the IL-17 inhibitor secukinumab was compared to ustekinumab, the IXORA-S-trial only included second line patients. Ixekizumab was also superior regarding quality of life, measured with the DLQI. "In this questionnaire, there are also questions that have nothing to do with PASI 100, e.g. does therapy bother you? In this questionnaire, we have also seen a clear-cut advantage for ixekizumab," concluded Prof. Reich.

Maintained efficacy over 108 weeks

In a poster session, data after 108 weeks of the UNCOVER-3-trial were presented. After completing the double-blind study phase all patients were treated with ixekizumab in a long-term extension period. Efficacy was measured by the percentage of patients achieving a 75%, 90% or 100%

Figure 4 UNCOVER -3-trial: PASI 75 and sPGA (0,1) response rates over 2 years.



improvement from baseline in the PASI and a "sPGA score of 0 or 1, which means clear skin [20]. Over 2 years, ixekizumab showed maintenance of efficacy across all endpoints with high skin clearance rates (Figure 4). The safety profile of ixekizumab over 108 weeks was comparable to shorter treatment periods.

Also effective in difficult to treat areas

Psoriatic lesions on the nails or the scalp are difficult-to-treat as they are often resistant to therapy. In a poster presented during the meeting, scalp and nail psoriasis and health outcomes for patients treated with ixekizumab for 4 years in the open-label extension of a phase 2 trial were assessed [21].

Every 12 weeks, psoriatic lesions on the nails were assessed with the help of the "Nail Psoriasis Severity Index," lesions on the scalp with the "Psoriasis Scalp Severity Index". Patients who received up to 4 years of open-label treatment with ixekizumab gained sustained improvements in the Nail Psoriasis Severity Index and Psoriasis Scalp Severity Index. This lead to a distinct improvement in their health-related quality of life.

Retreatment with the IL-17 inhibitor secukinumab

Although continuous treatment is beneficial, treatment cessation happens frequently in daily practice. A new analysis showed that after a treatment break, almost all patients rapidly regain PASI 75 response, when retreated with secukinumab.

In daily life, invasive surgery, infectious episodes, or changes in healthcare coverage may require temporary cessation of a biologic therapy. In addition, patients take 'drug holidays' because they experience clearance of their skin and believe they no longer need biologic therapy.

In general, psoriasis patients benefit from continuous over intermittent treatment [22]. This showed a meta-analysis, in which 23 trials with 12,617 patients were included. According to this analysis, continuous treatment with anti-TNF agents and anti-IL12/23 agent results in superior efficacy over interrupted therapy. In addition, efficacy from retreatment did not result in equivalent initial response rates for most biologics [22]. During the AAD meeting, retreatment with secukinumab following treatment withdrawal and relapse was evaluated in the extension phase of the phase 3 ERASURE and FIXTURE studies [23]. This new analysis shows that if psoriasis patients relapse during treatment pauses, the majority can achieve previous high levels of efficacy after only 16 weeks of retreatment with secukinumab 300 mg. In this analysis 136 subjects (75.1%) relapsed (defined as a loss of >50% of the maximum PASI gain compared with baseline) for up to 2 years. The median time to relapse following withdrawal from secukinumab 300 mg was 28 weeks. After retreatment, 94% of patients regained a PASI 75 score, 79% of prior PASI 90 responders (n=117) regained a PASI 90 score and 67% of prior PASI 100 response (n=67) regained a PASI 100 score by week 16 (Figure 5) [23]. In addition, no evidence of new or cumulative adverse events or anti-drug antibodies (ADAs) with secukinumab retreatment were seen.

Low immunogenicity explains success after retreatment

Therapy with monoclonal antibodies may be associated with production of ADAs that can affect drug pharmacokinetics, diminish response or cause hypersensitivity reactions. The reason for the positive outcome after retreatment with secukinumab is the extremely low immunogenicity of this agent, as demonstrated previously [24]. In this publication, the immunogenicity of secukinumab across 6 phase 3 clinical trials in which patients with plaque psoriasis were treated with secukinumab for up to 52 weeks and additionally followed up at week 60 was investigated. Among 2842 patients receiving secukinumab and evaluated for ADAs, only 11 of the 2,842 subjects (0.4%) developed treatment emergent ADAs. In accordance with this data, in the current analysis no anti-secukinumab antibodies were observed during retreatment (Table 1) [23]. The new data demonstrates a close to inexistent low immunogenicity of secukinumab with the result that nearly all patients regain treatment response after a treatment break, as is often encountered in real life.

Figure 5 Secukinumab response is rapidly recaptured on retreatment [23]

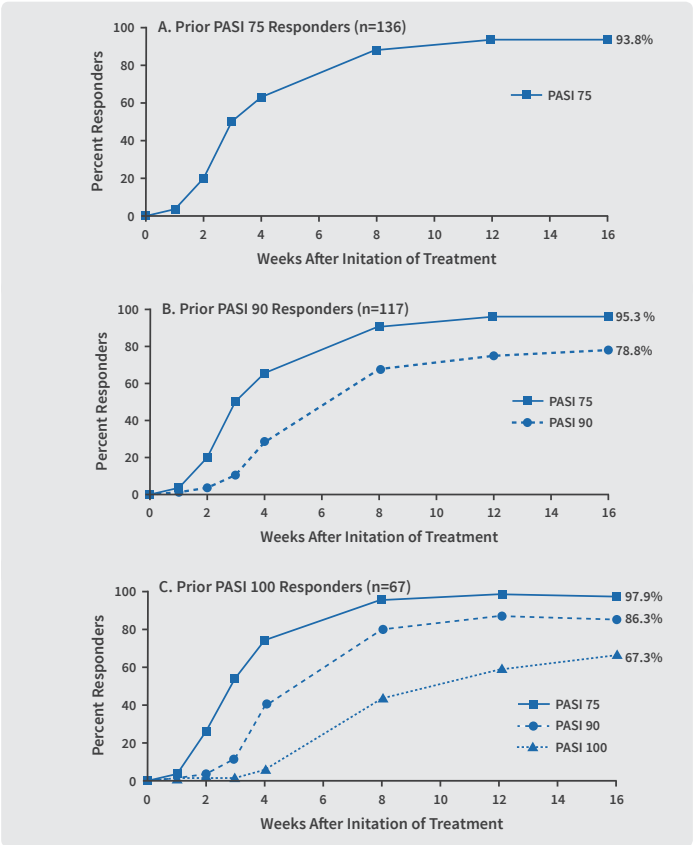


Table 1 Treatment-emergent adverse events or anti-drug antibodies with secukinumab retreatment

Frequencies of Treatment-emergent Adverse Events	
	Secukinumab 300mg - Placebo (n=181)
Subjects with any AE(s), n(%)	107 (59.1)
Deaths	0
SAEs, n(%)	11(6.1)
Infections and infestations, n(%)	4(2.2)
Most common AEs by preferred term, IR per 100 subject-years	
Nasopharyngitis	20.7
Arthralgia	12.6
Upper respiratory tract infections	12.4
Presence of anti-drug antibodies	
Positive, n(%)	0(0)

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Psoriasis in Childhood

A diagnosis of psoriasis in childhood implies the opportunity to prevent comorbidities and early intervention. In severe cases, TNF blockers offer an effective treatment option.

Childhood psoriasis associated with obesity

Even in paediatric patients, comorbidities should be taken into account. In a trial, the overall rate of comorbidity in subjects with psoriasis aged under 20 years was twice as high as in subjects without psoriasis [1]. There is a strong, global association of psoriasis with obesity. Particularly children with central obesity have a greater cardiovascular risk. Obesity may precede psoriasis. In addition, abnormal lipid function has been found in psoriatic patients vs. controls. "In paediatric psoriasis, we have a unique opportunity for prevention and early intervention, we should not miss," said Prof. Kelly M Cordoro, University of California (CA/USA) [2]. She suggested to remain vigilant at each visit and identify children at greatest risk, particularly overweight and obese kids and those with severe disease. In these children, weight loss and lifestyle interventions are the key beside an efficient therapy. In this process, the entire family should be involved.

A trial published last year [3] showed that psoriatic children of all severities have no difference in fasting lipid levels vs. controls. However, higher concentrations of the (atherogenic) apolipoprotein B, fewer large HDL particles, and lower HDL

efflux capacity were evident in the psoriatic children. The authors conclude that patients with paediatric psoriasis have a more atherogenic cardiometabolic risk profile, with evidence of insulin resistance and lipoprotein dysfunction. These findings may provide a basis for the observed link later in life between psoriasis and cardiovascular disease, and support the need to screen and educate young patients to minimize later complications. In addition, a couple of psychiatric and emotional diseases, e.g. anxiety, depression or eating disorders seem to be more common in psoriatic patients [4]. It is not yet fully clarified, whether psychiatric and emotional comorbidities are situational or intrinsic. "Our role as dermatologists is to be aware of these risks and comorbidities in children with psoriasis," concluded Prof. Cordoro.

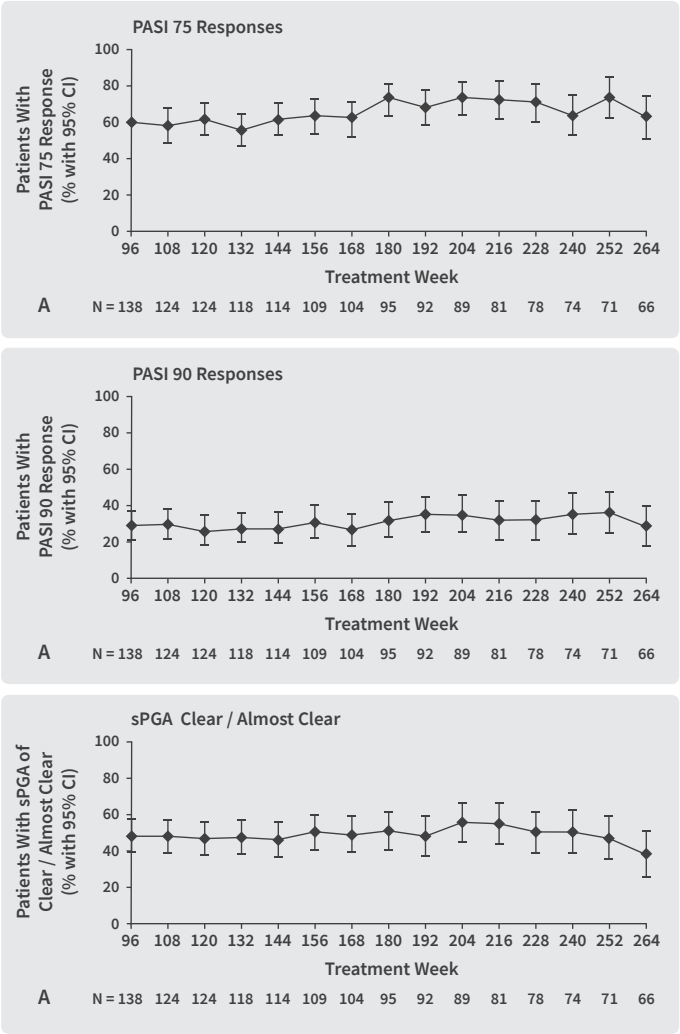
Systemic treatment in severe cases

"Generally, systemic medications should be restricted to children with moderate to severe disease that are not responding or tolerant of topical medication," said Prof. Paller, North-Western University, Feinberg School of Medicine, Chicago (IL/USA) [5].

Systemic therapy is also warranted if the disease has an impact on quality of life, e.g. because it is highly visible. Most of the children and adolescents with plaque psoriasis are treated with methotrexate (MTX), followed by retinoids. There is decades of experience in children with MTX. The dosage is between 0.2 and 0.5 mg/kg/wk, the lowest effective level should be maintained. "MTX may take many months for best effect," said Prof. Paller. The concomitant daily intake of folic acid lowers the risk of gastrointestinal side effects compared to weekly folate. For all immune suppressants, baseline and annual tuberculosis testing and pregnancy counselling is recommended. Since November last year, etanercept the first biologic got approved by the FDA. Trials with etanercept in children and adolescents with moderate to severe plaque psoriasis have shown that the biologic shows a comparable efficacy and safety as seen in adult patients. Recently, the 5-year open-label extension trial was published and showed that etanercept was generally well tolerated and efficacy was maintained over the whole study period (Figure 1) [6].

During the study period, no malignancy or deaths occurred. Only 1 patient had a serious infectious event (cellulitits) related to treatment. A trial, were therapy with adalimumab was compared to MTX, demonstrated that the dose of 0.8 mg/kg adalimumab was significantly superior to MTX regarding PASI response and the percentage of patients with clear or almost clear skin in the PGA. Generally, when using TNF blockers, older, obese children may require higher dosing. According to Prof. Pallers experience, most common side effects are injection site reactions.

Figure 1 PASI Responses are maintained over 5 years in children treated with etanercept [6]



Plaque psoriasis, efficacy outcomes in children and adolescents treated with etanercept. Percentage of patients with 75% improvement in Psoriasis Area and Sensitivity Index score (PASI 75) A, 90% improvement in Psoriasis Area and Sensitivity Index score (PASI 90) B, and static physician and global assessment (sPGA) status of clear/ almost clear (score 0/1) C, from week 96 through week 264 is shown. The number of patients with available data shown below each graph. Data are reported as observed, without imputation for missing data. Error bars represents 95% confidence interval (CI).

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Skin Cancer Prevention and Treatment

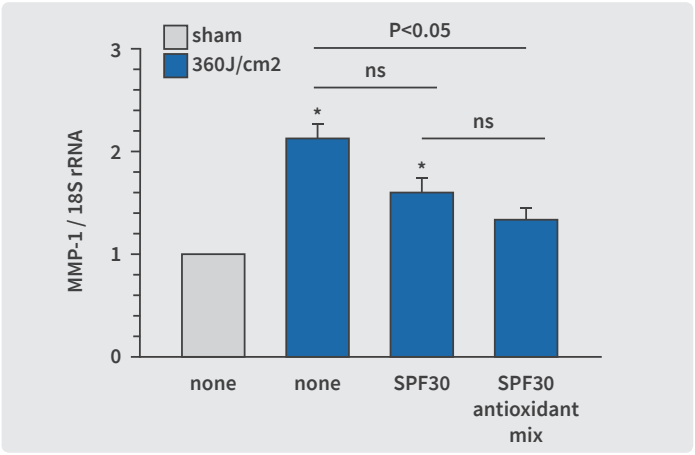
Photoprotection remains a key preventive measure not only with respect to non-melanoma skin cancer (NMSC) but also to melanoma prevention. Lectures on new data regarding melanoma development, diagnostic pitfalls and new therapeutic options attracted the interest of many attendants.

Photoprotection

"Photoprotection is of key importance, whether we want to prevent skin aging or development of skin cancer," said Prof. Henry Lim, chairman of the department of dermatology at Henry Ford Hospital in Detroit (MI/US), and incoming president of the AAD [1]. Unfortunately, the use of topical preparations is limited by the fact that they are applied not generously enough; as Prof. Lim pointed out, a family of four experiencing heavy sun exposure should use one bottle of sunscreen in two days, but studies show families only use 1-1/2 bottles of sunscreen a year. Despite these limitations, wearing protective clothing and applying a broad-spectrum, water-resistant sunscreen with an SPF of at least 30 are still the most reliable methods of sun protection.

A trial showed that the addition of topical antioxidants to sunscreen can diminish the photoaging induced by Infrared A radiation (IRA). IRA upregulates metalloproteinase-1(MMP1)-expression in dermal fibroblasts that leads to breakdown of collagen and photoaging (Figure 1).

Figure 1 The addition of antioxidants to a sunscreen significantly protects human skin against IRA-radiation-induced MMP-1 mRNA expression. MMP-1 = Metalloproteinase 1 [2]



In this double-blind prospective study in 30 healthy volunteers, the capacity of a SPF 30 sunscreen vs. the same sunscreen supplemented with an antioxidant cocktail containing grape seed extract, vitamin E, ubiquinone and vitamin C was assessed [2]. As expected, exposure to IRA radiation significantly upregulated MMP-1 expression, as compared to unirradiated skin. This response was significantly reduced, if the SPF30 sunscreen plus the antioxidant cocktail had been applied prior to IRA radiation. In contrast, treatment of human skin with the SPF30 sunscreen alone did not provide significant protection. "The addition of antioxidants may be beneficial in other conditions aggravated by sun exposure, such as post inflammatory hyperpigmentation and melasma," concluded Prof. Lim.

The most promising results regarding oral sun protection comes from polypodium leucotomos, an extract of a Central American fern plant. Studies have shown photoprotective, immunomodulatory and antioxidative properties of the fern extract [3]. The mode of action needs to be further evaluated, but polypodium leucotomos acts most likely as an antioxidant. In addition, the fern extract can reduce sun sensitivity in people with polymorphous light eruption. Studies comparing the level of protection of the fern extract with that of a traditional sunscreen show the fern extract provides the equivalent to an SPF of 3 to 5. Therefore, non-topical photoprotection is promising as an adjunctive measure, but cannot replace current regimen of photoprotection.

Lower level education: a risk factor of childhood sunburns

Despite health campaigns to minimize UV exposure in Australia, NMSC increased by 86% between 1997 and 2010. Dr. Victoria Harris, Discipline of Dermatology at the University of Sidney, Sydney (Australia) examined the association between parent's knowledge and attitude to sun protection and their child's UV exposure [4]. In the cross-sectional study, parents attending dermatology clinics in Sydney and Gosford completed surveys regarding their behaviours and attitudes toward sun protection of their kids.

Parents with a lower level education were strongly correlated with higher rates of experiencing serious sunburn ($P<0.0001$). In addition, there was strong evidence that the child is more likely to have been seriously burnt when the parent didn't apply sunscreen to the child ($P<0.01$). A weaker but still significant association could be seen between parent burning in the past 12 months and whether their child had also been burnt in that time ($P<0.05$). The older the children were, the more sunburns they had ($P<0.001$).

"Our study shows that older generations of Australians with high incidence of melanoma and NMSC may be transferring negative messages to younger generations in regard to UV exposure behaviours," concluded Dr. Harris.

Keep moles out of the sun

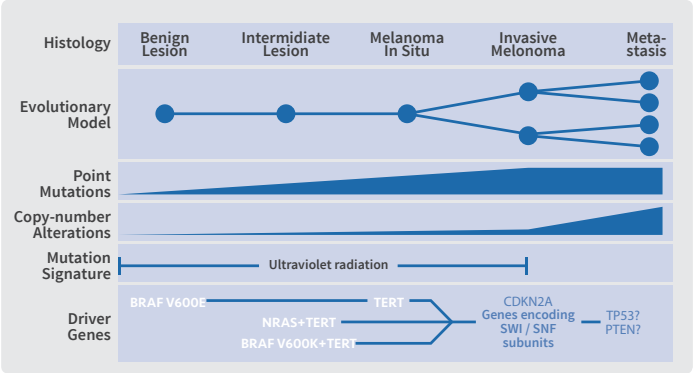
Development of melanoma requires a complex series of genetic mutations — often driven by exposing moles to sunlight — occurring in the right order to overwhelm the immune system to stop the mutated cells. This mutational process was explained in Sunday's Lila and Murray Gruber Memorial Cancer Research Award and Lectureship by Prof. Boris C. Bastian, executive director of the Clinical Cancer Genomics Laboratory at the University of California in San Francisco. (CA/USA), who co-authored a landmark study in the field of melanoma pathogenesis [5]. In this trial, the authors performed a genetic analysis of 37 primary melanomas and their adjacent non-malignant melanocytic neoplasms [6].

In the trial, a succession of genetic alterations during melanoma progression could be defined, showing distinct evolutionary trajectories for different melanoma subtypes. An intermediate category of melanocytic neoplasia could be identified, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. Ultraviolet radiation is a major driver in this stepwise model of melanocytic transformation into melanoma. Therefore, patients with increased numbers of nevi are at increased risk for melanoma. "We found in lesions in which a melanoma arose from an adjacent precursor, that there were shared mutations between the precursor and melanoma areas. The shared mutations presumably were acquired early during the evolution. In the melanoma portions, there were invariably more mutations than in the respective nevus portions, including mutations that led to the transformation of the nevus to become malignant," Dr. Bastian said. "That allowed us to establish a sequential order in which mutations accumulate during the evolution of melanoma from these precursor lesions."
Nevi, which pathologists unanimously graded as benign, only showed a single mutation, whereas melanomas had multiple mutations and chromosomal aberrations. The study identified a set of lesions that showed an intermediate number of mutations, which pathologists graded as borderline lesions.

"To generate a melanoma, you should get the right combination of putting the gas pedal down with BRAF and BRAS mutations, disabling the brakes, and changing some of the cellular differentiation programs by inactivating epigenetic regulators to fully transform those cells.

That insight also should be used to develop a game plan to prevent the development of melanomas," Prof. Bastian said. Although development of melanoma from nevi is complex, it leads to a simple conclusion: "the prevention message should be expanded to include the statement, 'Keep your moles out of the sun,' and that will significantly reduce the probability of having your mole cells turn cancerous," said Prof. Bastian. Models for progression of melanomas developing on sun-exposed-sites (Figure 2). The insights gained from the research could also be used to develop algorithms to better prevent melanomas by identifying high-risk lesions and removing them before they become cancerous. However, one has to keep in mind that the majority of melanomas arise de novo, and only 20 to 30% of all melanomas are associated with a melanocytic nevus [7].

Figure 2 Proposed models for progression of melanomas developing on sun-exposed sites [6]



A lot of room for improvement in diagnosis of subungual melanoma

Subungual melanoma represents 0.7-3.5% of melanoma cases, but often carries a worse prognosis as similarly staged cutaneous melanoma. The most frequent manifestation of subungual melanoma (2/3 of all cases) is longitudinal melanonychia, a brown-black band of the nail plate. However, it is not specific for subungual melanoma and can also have benign etiologies such as subungual hematoma, nail matrix nevus, trauma, lentigo and melanocytic activation. But how good are dermatologists in daily practice in recognizing subungual melanoma? This was assessed in an US-wide survey-based "study of management of longitudinal melanonychia among attending and resident dermatologists" [8].
"Our data reinforce the need for increased efforts in educating dermatologists, particularly residents, about nail examinations, longitudinal melanonychia, and warning signs for subungual melanoma," said Prof. Shari Lipner, New York-Presbyterian Hospital/Weill Cornell Medical Center during the presentation.

Physicians were categorized into three groups based on experience (residents, junior attending <5 years' post-residency, and senior attending >5 years' post-residency. Only 8% of dermatologists ask their patients to remove nail polish at every visit. More senior attending (14%) than junior attending (5%) or residents (1%) request that patients remove nail polish at all examinations (P<0.0001). Only 18% of dermatologists perform nail examination at each visit. More frequent nail examinations were higher amongst junior and senior attending's as compared to residents (P<0.0001). Overall, 54% of respondents stated that they were "confident" in assessing melanonychia, but 28% were "not confident".

Vast majority not aware of ABC mnemonic

In contrast to this finding, only 25% of respondents heard of the ABC mnemonic for subungual melanoma (Table 1.), which comprised more junior (29.3%) and senior attending (32%) than residents (12%; P<0.0001). As Prof. Lipner pointed out, this is the first study to assess nail examination and knowledge of the ABC mnemonic for subungual melanoma amongst dermatologist. The study shows, that there is an unmet need in education dermatologists, particularly residents, about nail examination, longitudinal melanonychia, and warning signs for subungual melanoma.

Table 1 Mnemonic for subungual Melanoma

Letter	Meaning
A	Age: Peak 5th-7th decades Race: African-American, Native American, Asian
B	Band (nail band): Brown-Black Breath (≥3mm) Border (irregular/blurred)
C	Change: Rapid increase in size
D	Digit involved: Thumb > hallux Single digit > multiple digits
E	Extension: extension of pigment to involve nail folds
F	Family or personal history: Of previous melanoma or dysplastic nevus syndrome

Superficial radiation – new treatment option of NMSC

NMSC is rising at a rate of 4-8% annually. The most common forms, basal cell carcinoma and squamous cell carcinoma, both have an overall 5-year survival rate of 95%. Also, Mohs surgery does better than any other therapy, e.g. cryotherapy or curettage, an ever-increasing number of patients, particularly elderly patients, want to avoid surgery. "Superficial radiation (SRT) has evolved as a new treatment option, because it has advanced with the development of better equipment," explained Dr. David J. Goldberg, dermatologic surgeon at Skin Laser and Surgery Specialists of New York/New Jersey (NY/USA) [9].

According to Dr. Goldberg, SRT uses low-energy photon X-rays operating at variable peak voltages of 50, 70, and 100 kVp. It is easy to administer, and it easily targets and treats lesions while delivering gentle, indirect radiation that does not penetrate and impact underlying healthy tissue.

The cure rate for 1,715 primary nonaggressive NMSCs treated with the SRT-100 machine approved by the FDA was 98% according to a study [10]. A benefit of SRT is that it eradicates the tumour while maintaining or improving the quality of life, he said.

Patients best suited to treatment with SRT are those that are elderly and poor surgical candidates, or have contraindications for anaesthesia. It can also be recommended in patients, where surgical intervention is potentially associated with significant cosmetic or functional limitations.

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Hair Loss - Many causes for lot of Distress

Losing one`s hair, for no matter what reason, will likely mean some grade of psychological suffering for women and men alike.

The quest for a reason

"Especially women have great concern about hair loss, as a sign for "something being wrong" with them," explained Dr. Melissa Piliang, Dermatologist, Cleveland Clinic at the beginning of her presentation. Despite of about 50% menopausal women suffering from hair loss, most of them are not aware of their risk increasing with age [1]. Hair loss often adds up to a great amount of stress, anxiety and a negative body image. 55% of patients with female pattern hair loss eventually even have symptoms of depression. The up-side is that 89% of hair loss in these women can be improved by treatment [2].

Where to start?

When it comes to clinical evaluation of hair loss, there are many important questions to ask your patient. Finding out about their reproductive health, recent changes of weight and exercise habits, history of illness, as well as ongoing medication, family anamnesis and moreover, psychological stress is most important. Also, habits of hair grooming like blow-drying and colouring can play a role. The physical exam should include the general habitus, mood and energy status and an impression of hair density. The scalp has to be inspected for erythema, scale, part width, follicular and regular pustules, as well as scars and bald patches. The physician should look for hair breakage and its location. "Have the patients report about hair shedding, or not growing and chronic use of perms," advised Dr. Piliang. There are special nail appearances that are linked to certain diagnoses like hypothyroidism or alopecia areata (AA).

What to test?

Scalp biopsies can be done in vertical and horizontal sections. When performing the biopsy one should first look for an area of the scalp that could best represent the condition suspected. Cultures for bacteria and fungus can be necessary when pustules, scale, drainage and pain are present. The laboratory evaluation should always comprise values for general health (complete blood count, comprehensive metabolic panel), nutritional factors such as ferritin, zinc, vitamin D and hormones (TSH). Furthermore, there can be indications for measuring androgen excess, iron studies and autoimmune diseases.

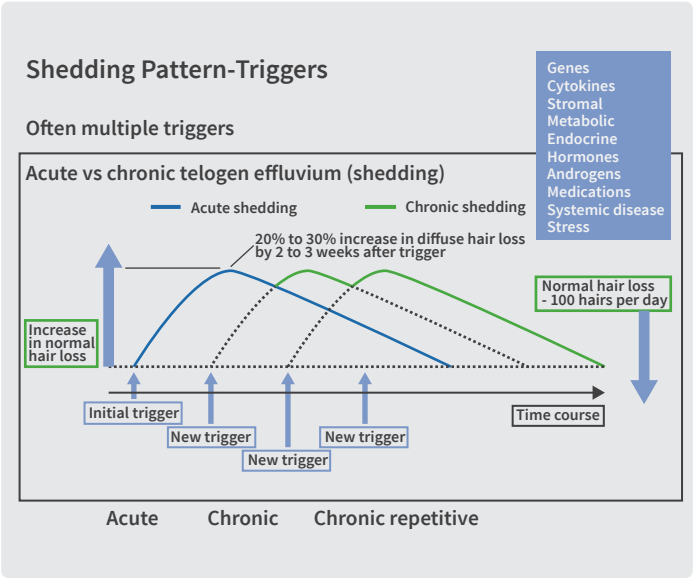
How to classify?

Alopecias are divided into a non-scarring and a scarring or cicatricial group. Within the group of scarring alopecis, Lichen planopilaris(LPP) e.g. accounts for 2-8% of all visits to hair clinics, but 40% of scarring alopecias, LPP. This lymphocytic form is marked by a bright red erythema, together with a sense of burning, pruritus and pain. Central centrifugal cicatricial alopecia (CCCA) will also induce scars. CCCA starts at the top of the scalp and is relatively often found in black women. More diagnoses including scars are folliculitis decalvans, dissecting folliculitis and lupus erythematosus.

The non-scarring alopecias

Telogen effluvium is characterised by excessive daily shedding of 200-500 hairs [1]. Normal daily loss lies between 50 and 100 hairs per day [3]. The triggers for telogen effluvium can normally be found 3-6 month before the start of hair loss [1]. Triggers can be stress, nutritional deficits, recent surgery, child birth, febrile illnesses, extensive weight loss and of course almost any kind of medication. In many cases, multiple triggers can be identified (Figure 1). The occurrence of telogen effluvium can also unmask androgenic alopecia (AGA). A hair collection is helpful to quantify the shedding, as patients often misjudge its extent.

Figure 1 Telogen effluvium: Multiple triggers can be responsible for shedding [1]



In AGA the typical development of follicular miniaturisation is driven by genetics, age and testosterone. The follicles shrink progressively, anagen (hair growth) phases are shorter and concomitantly, the percentage of hairs in telogen augments up to 20%.
"When doing a work-up in females one shouldn't forget to think of the polycystic ovary syndrome that can affect 5-10% of women," indicated Dr. Piliang. She also pointed to the fact that rapid onset of AGA is not common and therefore suspicious for underlying systemic illnesse.

Alopecia Areata: a frequent cause of disability-adjusted life years

The lifetime risk for Alopecia Areata(AA) is around 2.1%. The incidence of this non-scarring disease is found in 0.7 to 4% of dermatologic patients [4]. Although AA can appear at any age, men and women were found to have a mean age of 33.6 when it starts [5]. The pathogenesis of AA is not completely clarified, but it is thought to be an autoimmune-mediated process with mostly patchy loss of hair of the scalp. Supposedly, the disorder is caused by the loss of immune privilege of the growing hair follicle [6].

According to the World Health Organisation, in 2010 AA accounted for more disability-adjusted life years than psoriasis. Furthermore, it entails a reduction of health-related quality of life like AD or psoriasis [7]. Thyroid disorders especially in adults, atopies and psychiatric illnesses alongside with autoimmune diseases like systemic lupus are known co-morbidities associated to AA [4].

Dr. Carolyn Goh, Ronald Reagan UCLA Medical Center, Santa Monica (CA/USA) suggested to consider screening for these other disorders, as well as vitamin D deficiency, when AA is diagnosed. Contradicting results have been found for a positive or negative association of AA with cardiovascular risk, but having AA seems to reduce the risk of skin cancer [8] [9] [10].

Various treatment options for AA

The Janus kinase inhibitors, like ruxolitinib and tofacitinib, appear to be the most promising treatment choices, especially for patients with extensive disease, according to Dr. Goh. But few questions e.g. high oral doses with unknown safety in long-term use or effectiveness in combination therapy remain to be answered [4].
In less extensive and localised cases, triamcinolone acetonide injections and topical immunotherapy are options. In very rapid progressing AA systemic steroids are used but canentail serious adverse events. Treatment choice in AA will normally also involve patient's wishes. There is only limited data on AA therapy with other biologics like ustekinumab, apremilast and abatacept. A combination of simvastatin and ezetimibe resulted in mixed outcomes. Hydroxychloroquine has not been effective. "Traditional therapies are still reliable but may take more than 3 months," remarked Dr. Goh. According to Dr. Goh, the future should involve more research with randomised control trials, as well as a focus on patient-centred outcome. Last but not least, camouflage can be of help until treatment works or in case of its failure.

Why a physician should also know about camouflage?

When it comes to alopecia, medical treatment is hardly ever successful [11]. Among notable exceptions are male pattern hair baldness and cutaneous upus erythematodes. Camouflage does not change the disease, but can assist to provide support in coping. "Prepare a box full of camouflage products to show to your patients and formulate a list of reputable and helpful hair prosthesis and micro tattoo specialists in your area," Dr Adriana N. Schmidt, dermatologist in Santa Monica, CA/USA, recommended. Discussing camouflage can become increasingly more comfortable that way.

There are 3 categories of camouflage of hair loss on scalp or eyebrows: hair fibres/concealers, hair prosthesis, tattoos. In case off eyebrow loss, their recreation can boost the facial expression. Normal-appearing eyebrows can be created by make-up, use of extensions or artificial brows or micro- tattoos using special designed tattooing machines and pigments for natural looks. Hair building fibres for the scalp mostly consist of natural keratin. They are positively charged and thus attach to negative charged hair, resulting in an instantaneous thicker and fuller look of it. Scalp powder (Figure 2) can be sprinkled over the desired area and fixed with spray. They are not water or sweat resistant. If topical treatment is being used, this should be applied beforehand. To use fibres, sprays and lotions the patient must have some hair left. It is important to acquaint the patient with different existing form of prosthesis too. Not all of them are wigs. Clip-on extension toppers, bangs or toupees can provide partial coverage anywhere on the scalp. At the beginning of hair loss, sometimes even changes in hairstyling can be a helpful first step e.g. colouring grey hair, cutting hair shorter to add volume or a zig-zag part to mask thin areas.

Figure 2 scalp camouflage by us of a powder cake (a) before and (b) after in a man and a woman. Powder cake colours the scalp and binds to existing hair fibres. By reducing the contrast between the scalp and hair it gives the appearance of increased hair density (images from phot archives of Dr. R Shapiro. Source: Donovan JCH, Shapiro RL, Shapiro P et al. A review of scalp camouflaging agents and prostheses for individuals with hair loss. Dermatology Online Journal. 2012; 18(8).
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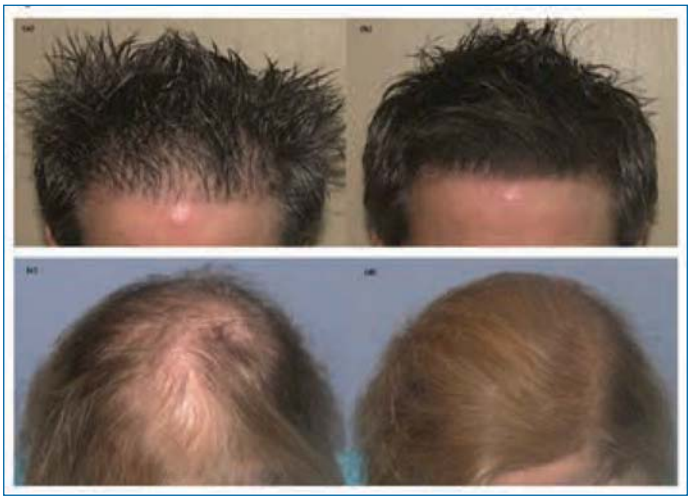
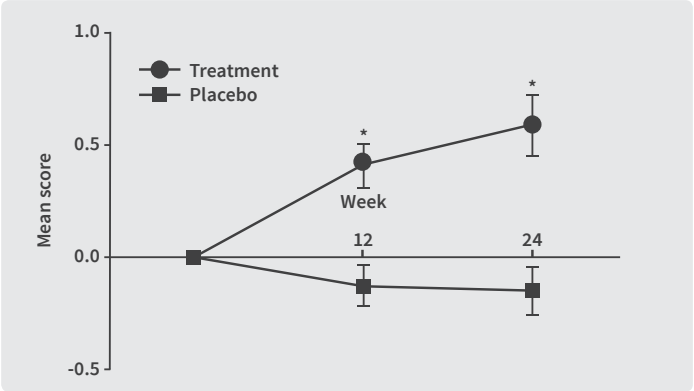


Natural treatment alternatives for alopecia

Patients may ask for more natural options and some botanical ingredients have been studies for their ability to increase hair growth [12]. Plant-based 5-Alpha-reductase (5-AR) inhibitors can be found in pumpkin seed oil, saw palmetto, sophora flavescens and green tea. 5-AR inhibitors can block the transformation of testosterone to dihydrotestosterone. Treatment with 400mg pumpkin seed oil has been tested in a RCT that enrolled 76 men with AGA. It found a 30% and 40% increased hair count at week 12 and 24 respectively, with pumpkin seed oil vs 5% and 10% under placebo [13]. In addition, hair growth during treatment with pumpkin seed oil increased according to investigator assessment of clinical response in a standardized 7-point rating scale (Figure 3). Among the limitations of the study were hair analysis by phototrichography and unclear dosing guidelines [12]. Saw palmetto or serenoa repens (SP) has been investigated in an open-label study with 100 male patients diagnosed having mild to moderate AGA.

One group received 320 mg of serenoa repens (SP) a second group 1mg of finasteride for 24 months. Hair growth under finasteride improved in 68% of patients vs. 38% taking SP. While finasteride worked in front and vertex, SP did so prevalently in the vertex [14]. Whether the observers were independent or blinded remained unclear in this study [12].

Figure 3 Investigator assessment of clinical response using a standardized 7-point rating (-3 = greatly decrease, -2 = decrease, -2 = moderately decrease, -1 = slightly decrease, 0 = no change, +1 = slightly increased, +2 = moderately increased, and +3 = greatly increased).
scale during 24 weeks after study start. Data are expressed as mean with SE. * P<0.001 [13]



Also, Sophora flavescens is given as 5-AR inhibitor. It has shown to improve induction of earlier anagen cycle when applied on the back of C57BL/6 mice [15]. Animal studies with some success in hair growth also exist for gingko biloba and ginseng [12]. No clinical data was found for benefit of above normal level intake of biotin, nor supplementing with green tea, but there are case reports of liver toxicity under green tea.

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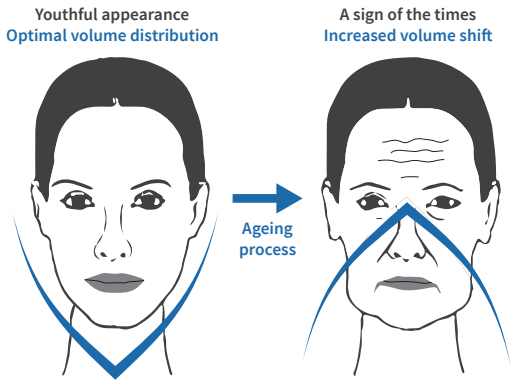
Aesthetic Medicine

The three R's of rejuvenation relaxation, revolumizing, resurfacing and repositioning by a combination of minimal-invasive procedures enable natural treatment results. New devices and lifting sutures have enriched the spectrum of injectable.

Graceful aging- thanks to minimal invasive procedures

"We age three dimensionally. By weakening of muscle and bones we lose the structural support of the overlying tissues," explained Dr. Sabine Zenker, aesthetic expert from Munich, Germany [1]. During aging, the overall hyaluronic acid content is reducing, and its water retention capacity diminishes. Fragmented collagen accumulates, and the skin gets thinner in the course of time. The facial fat, the primary determinant of volume loss, redistributes. All these changes lead to the typical features of aged skin and to the deflation and displacement (fuelled by gravity) seen in the aging face. This volume shift finally leads to the change in the facial form, from the triangle of youth to the inverse triangle of the aged face (Figure 1).
The best way to reverse these three-dimensional processes and give back the lost definition is to follow the four R's of rejuvenation, relaxation, revolumizing, resurfacing and repositioning/redraping. This can only be done by the combination of different non-invasive methods like a volume filler, botulinum-toxin A and a filler with low viscosity to address remaining wrinkles.

Figure 1 In the course of time, the shape of the face changes from the upward triangle of youth to the inverse triangle of the aged face



In her lecture, Dr. Zenker evaluated customized alternatives to standard injectables and devices for facial rejuvenation, such as absorbable lifting sutures or injection lipolysis. Absorbable lifting sutures are used to create zones of traction to lift and reposition tissue. They can be used in the midface, jawline, and eyebrows. Dr. Zenker uses injection lipolysis to reposition jowling or the submental fat pad. The drug mixture includes polyenyl phosphatidylcholine and deoxycholic acid. "In every case, you should tailor the treatment to patient's needs," concluded Dr. Zenker.

Treatment plan

In light of the many possibilities in aesthetic dermatology, treatments should be used as part of a plan. "A major part of that plan should be to not change the overall look of patients, but to make them look like younger versions of themselves," suggested the Session director, Dr. Heidi A. Waldorf, MD, associate clinical professor at Mount Sinai Health and a dermatologist in Nanuet, New York [2].
Once a plan is developed, the dermatologist should outline which procedures will be used, their cost, and the time involved. Finally, it should all be documented, and include photographs and a discussion. In addition, life-style issues like smoking or sun bathing should be addressed.

New devices extend the therapeutic spectrum

During the previous year's new devices, such as IPL´s, radiofrequency fractional lasers and ultrasound skin tightening have enriched the aesthetic field. "Micro needling in combination with radiofrequency is one of the most exciting topics in aesthetic medicine. In our study, it offered a significant lift after 3 month of treatment," said Dr. Michael H. Gold, Gold skin Care Center, Tennessee Clinical Research Center, Nashville (TN/USA) [3]. The tiny needles create micro-channels in the skin, which stimulate the endogen production of collagen and elastin, thus resulting in an increased elasticity of the skin. In a study including 49 patients, therapy with a non-insulated fractional radiofrequency micro-needling system led to a significant wrinkle reduction (evaluated in the „Global Aesthetic Improvement Scale (GAIS), skin tightening, and lifting of the mid and lower face: this effect was evident after 3- months treatments [4]. After treatment, there is a mild to moderate erythema up to 12 hours. Fractional ultrasound is another exciting possibility, which allows stimulation of neocollagenesis in the deep dermis.
Combinations of these devices with skin care and injectables can be considered and may, in many instances, give enhanced results.

Start early

"There is not a lot out there to show us when it's appropriate to start treating these patients. We usually start treating them

when they are already noticing the actual lines, the wrinkles, and the folds," said Dr. Sabrina Fabi, assistant clinical professor at the University of California, San Diego (CA/USA) [5]. The aging process begins already by 25, by 35, the bones have significant reductions in osteons and osteocytes, leading to decreased support of muscles. Dr. Fabi took up the cudgels for an earlier treatment, e.g. in the third decade, to prevent the aging process. Botulinum toxin (BTX) type A is the gold standard for the temporary treatment of dynamic wrinkle reduction. It upregulates collagen expression, increases skin pliability and elastic recoil, prevents etched lines, and improves skin quality.

But it´s never too late for an effective treatment

Dr. Susan H. Weinkle, MD, an affiliate clinical professor of dermatology at the University of South Florida, focused on the treatment of mature patients [6].

"Women on the average would prefer to look about 13 years younger than their actual age," she said. Realistic expectations are important in this age group. "The needle is trumping the knife nowadays," said Dr. Weinkle, patients prefer treatment with dermal injectables over surgery independent of age.

The demands of these patients vary in each decade of life, so treatments need to be adjusted for each age and face style.

In the fifties, subsurface changes begin, that lead to contour changes, which makes a volumizing necessary. "Do not forget to treat the hands in these patients, my favourite is clearly calcium hydroxyapatite in this indication," said Dr. Weinkle.

"With our present treatment opportunity, we can treat people on either end of the age spectrum," concluded Dr. Weinkle.

Concomitant use of cosmeceuticals

Dr. Qian Zheng, of L'Oréal Research & Innovation, examined the evidence of anti-aging treatments. Hyaluronic acid not only improves skin hydration, but also the quality of elastic fibres and the collagen architecture [7]. Studies have shown that topical retinol/vitamin A reduces wrinkles, provides higher density to the dermis, and homogenizes the complexion. The agent LR2412 is a derivative of jasmonic acid that shows significant improvements in wrinkles, skin texture, and pores. Vitamin C/ascorbic acid offers significant protection again photodamage and reduced sunburn cells. The vehicle and packaging of the cosmeceutical ultimately determines efficacy of these active ingredients. Every antiaging cosmetic used during the day should be supplemented by sunscreens with broad-spectrum high ultraviolet protection. They can help prevent hyperpigmented lesions, global skin darkening, and uneven coloration.

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Specific subcision system effective against cellulite

Cellulite may affect up to 85% of all post-pubertal women. Many treatment options are on the market, however, in most cases they provide only minimal and often transient benefits. In 2015, the US FDA approved the device Cellfina for improvement in the appearance of cellulite on the buttocks and thighs, with no loss of benefit for up to 2 years. This novel tissue-stabilized-guided subcision system allows precise infiltration of anaesthesia and minimally invasive subcision. Thereby, the fibrous cords that pull the skin down and are responsible for cellulite dimples are cut. The success of this device confirms the thesis that fibrous septae are the source of most types of cellulite, and that it does not arise from fat underneath the skin pushing up on the dermis – the second theory regarding the ugly bumps that can be emotionally impairing for many women. About 20 to 30 individual cellulite dimples are treated during an average session.

The device was tested in a multicentre prospective study of 55 patients and led to statistically significant improvements at one year after one treatment, with great patient great satisfaction. 2 and 3 year updates demonstrated continued improvement [8] [9].

At the meeting, the treatment results of an observational study in 16 women were presented as an e-Poster.

Treatment results were assessed by a GAIS- evaluation on day 180 post-treatment by the investigator and the patient, by blinded assessment of 2D photography that were judged by 3 physicians and by analysis of 3D Vectra imaging.

In all 16 subjects (average age 44.1), the dimples improved according to the GAIS scale. This result was confirmed by the blinded assessment and the objective analysis of three dimensional images (Table 1).

Table 1 Treatment results of the subcision system Cellfina

Global Assessment Improvement Scale At 180 days (n=13)	Physician	Subject
1: Very much improved	1 (7.7%)	2 (15.4%)
2: Much improved	8 (61.5%)	3 (23.1%)
3: Improved	4 (30.8%)	7 (53.8%)
4: No change	-	1 (7.7%)
5: Worse	-	
	2.23	3.0

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