26th EADV Congress

European Academy of Dermatology and Venereology

13-17 SEPTEMBER 2017 • GENEVA • SWITZERLAND

PEER-REVIEWED CONFERENCE REPORT

Late Breaker

The late breaker session was certainly one of the highlight´s of this year´s meeting. In the CAFÉ trial, dupilumab demonstrated its efficacy in patients with moderate to severe atopic dermatitis even with previous exposure to cyclosporine.

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Skin Cancer

Detection of early melanoma can be lifesaving. The dermoscope plays a key role in early diagnosis. In the future, artificial intelligence might further improve diagnostic skills.

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Psoriasis

IL17-Blockers show sustained efficacy over a treatment period of more than 5 years. The IL-23 pathway is another new fascinating target in treatment of moderate to severe psoriasis.

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MEDICOM
MEDICAL PUBLISHERS

Postal address
Medicom Medical Publishers
PO Box 90
Zipcode 3740 AB
City Baarn
Country The Netherlands

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Telephone +31 85 4012 560
Fax +31 85 4012 569
E-mail publishers@medicom.nl

ISSN 2468-8762 17:17

Letter from the Editor

Prof. dr. Peter van de Kerkhof

Dear Reader,

It is my great pleasure to present the report on 2017 -EADV Annual meeting held in Geneva on September 13-17. The Meeting was a huge success and the programme covered all aspects of dermatology and venereology, incorporating both explorative research and clinical studies. For this report we have selected the presentations that may be most interest to the practicing clinicians. We have focused on the late breaker session, STIs, psoriasis management, skin cancer and aesthetic medicines.

We hope that you enjoy our selections.

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 breaker session attracted numerous visitors. In this session, new trials from different dermatologic indications are presented. Enclosed is a selection of most fascinating or possibly practice changing studies.

Dupilumab: highly effective in patients intolerant to cyclosporine

In the Café study, dupilumab with topical corticosteroids (TCS) significantly improved measures of overall disease severity, skin clearing, itching, and patient reported quality of life measures [1]. All patients included in the Café trial had an inadequate response to TCS and an Eczema Area and Severity Index (EASI) score of over 20. "Two thirds of our patients had been previously treated with cyclosporine, but could not continue due to side effects and/or inefficacy, so our participants were really difficult to treat patients", said Dr. Marjolein De Bruin-Weller, Dermatologist, National Expertise Center for Atopic Dermatitis, University Medical Center Utrecht, Utrecht (Netherlands).

The primary endpoint of the study was the proportion of patients that achieved a 75% or greater improvement in the EASI score at 16 weeks from baseline. A total of 325 patients in Europe were randomised into three treatment groups. 59% of patients who received dupilumab weekly with TCS, and 63% of patients who received dupilumab every two weeks with TCS achieved the primary endpoint, compared to 30% of patients who received placebo with TCS (P< 0.0001) in the overall population. In the patients with prior cyclosporine (CsA) use, 58% of patients who received dupilumab weekly with TCS, and 57% of patients who received dupilumab every two weeks with TCS achieved the primary endpoint, compared to 26% of patients who received placebo with TCS (P= 0.0001 for the high dose and P= 0.0002 for the lower dose). "Not only the CsA naïve, but also the patients with prior CsA therapy fared better with dupilumab: the curves diverged early, already after two weeks of treatment", said Dr. De Bruin-Weller. Primary outcome (EASI 75) was comparable to those at week 52 for a CAFÉ-like subgroup of patients in the CHRONOS trial (Figure 1). "As we have 50 weeks treatment data from the CHRONOS trial, we can superimpose that the efficacy remains long-term", said Dr. De Bruin-Weller. The mean change improvement in EASI from baseline at 16 weeks (a secondary endpoint) was 78% and 80% in the dupilumab/TCS group, compared to 47% for those who received placebo plus TCS (P< 0.0001).

Other secondary endpoints of the study included measures of the impact of dupilumab on the persistent itch caused by the disease, quality of life measures, and symptoms of anxiety and depression. Itch, measured by the mean percent improvement of baseline in the pruritus Numerical Rating Scale (NRS), was 52% and 54% in the two dupilumab groups, compared to 25% for those who received placebo plus TCS (P< 0.0001).

Significant better quality of life

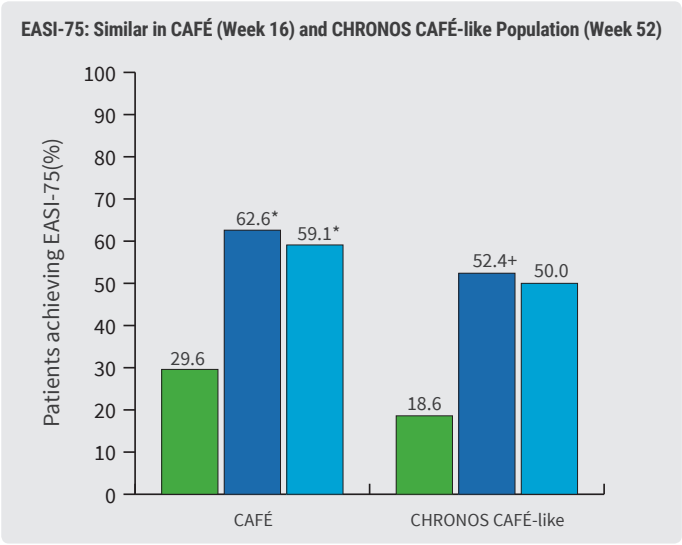
In the dupilumab groups, 78% and 88% of patients in the dupilumab groups were able to gain a greater than or equal to four-point improvement from baseline in a quality of life questionnaire (Dermatology Life Quality Index), compared to 44% of those who received placebo plus TCS (P< 0.0001).

No new adverse events were reported in the study. The proportion of patients reporting an adverse event was similar among the treatment arms. Conjunctivitis was more frequent in patients who received dupilumab with TCS, with 16% and 28%, compared to 11% for patients who received placebo with TCS. Injection site reactions were reported in 11% and 4% among patients who received dupilumab with TCS weekly or every two weeks, respectively, compared to 5% for patients who received placebo with TCS. "The CAFÉ trial shows us that dupilumab can be used in patients who have previously used CsA and stopped it due to intolerance or lack of efficacy and who are not candidates for CsA because of medical conditions or use of contraindicated concomitant medications "concluded Dr. de Bruin-Weller. The results in this study are similar to earlier phase 3 studies (16- and 52-week studies) of dupilumab with or without concomitant TCS.

Omiganan – a topical treatment acting on the microbiome in AD

A phase II trial shows promising results for omiganan, an antimicrobial peptide for the topical treatment of atopic dermatitis (AD) [2]. Omiganan has anti-inflammatory and immune modulatory properties that could be beneficial in AD. In addition, it is active against gram-positive pathogens

Figure 1: EASI-75 Response in the CAFÉ trial (week 16) and CHRONOS CAFÉ like population (week 52). Source: Lecture Dr. De Bruin-Weller.



such as staphylococcus that are abundant on the skin of AD patients. The mode of action (MOA) of omiganan is to shift the microbiome of AD patients towards the microbiome seen in healthy skin. In the dose finding trial, 36 young patients with mild to moderate AD were included. A target lesion was treated either with vehicle or with omiganan in two doses (2.5% and 1%). Patients had to rate their itch by an app. In addition, the app reminded to apply the ointment. Primary endpoint of this trial was the effect in the Scoring Atopic Dermatitis (SCORAD) Index. Prof. Robert Rissmann, Centre for Human Drug Research, Leiden (The Netherlands) pointed out, omiganan 2.5% was more effective than placebo: In addition, the microbiome in the target lesion was assessed. In the high omiganan dosing group, staphylococcus species were significantly reduced compared to baseline. "Therefore, we could proof that omiganan is really acting by a shift in the microbiome from lesional to a non-lesional profile", said Dr. Rissmann. As this was the first study with omiganan, it was tested on a single lesion. Now a trial with a whole-body application is planned. In vitro, omiganan shows efficacy against staphylococcus aureus, which hints to a direct effect of the agent.

"Adherence in this trial was extraordinarily high (98.3% of participants). Also, this trial shows that an app can be a helpful tool to ensure compliance, at least in young patients, said Prof. Rissmann.

Femtomolar: a novel way to block IL-17?

Femtomolar may still be a long way off clinical application, but the molecule is strikingly effective according to a phase I trial presented by Prof. Fredrik Frejd, Affibody AB, Uppsala University, Stockholm (Sweden) [3]. So-called Affibody technology was utilised to generate a novel non-antibody affinity protein based trap with high affinity and selectivity to IL-17A, a proinflammatory cytokine that plays a key role in pathogenesis of psoriasis. The molecule with a crystal structure is 25times smaller than an antibody, which allows to give a higher dose in a given injection volume. "Our molecule binds to both sides of IL-17, whereas secukinumab and ixekizumab only bind to one"; explains Prof. Frejd (Figure 2). The molecule has a very good stability and shows basically no degradation. Single and multiple injections in 46 healthy volunteers were well tolerated. Physiologically, IL-17 helps to fight fungal infections. "For us it was important do demonstrate that we did not find candidiasis in patients treated with this highly effective molecule", said Prof. Frejd. In addition, efficacy was assessed in 13 patients with moderate to severe plaque psoriasis. In patients with psoriasis, a dose-dependent response was demonstrated. Femtomolar has a half-life of 12 days. Upon subcutaneous injection, the bioavailability was 75-80%. A dose of 40mg resulted in an early onset of effect within days after administration, and in a mean PASI reduction of 40% at one week and 60% at three weeks after administration. Initial results of repeated dosing resulted in a higher reduction of absolute PASI compared to a single administration.

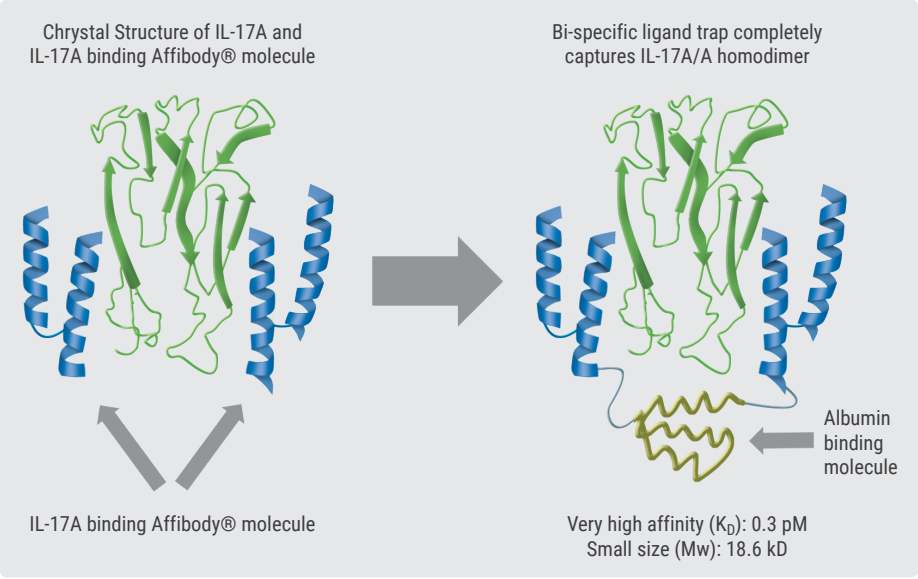
A phase II trial will be initiated in the next weeks.

Serlopitant: an effective central acting itch blocker

Chronic pruritus is a disorder with multiple aetiologies. It can lead to sleep impairment, depression, and anxiety. It has a major impact on quality of life [4].

"Patients would like to forfeit on average 13% of their lifespan to live without this condition", said Dr. Paul, Kwon, Menlo Therapeutics Inc, Menlo Park, California (CA/USA). Therefore, medication that offers a rapid resolve of pruritus is required in different indications in dermatology. 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. Disrupting the itch signal by NK1-R antagonism has been shown to reduce the intensity of itch in chronic pruritus [5]. Serlopitant has demonstrated to affect the central nervous system and manifests a binding of more than 90% of the NK1-R. Signaling on the nerve axis is an important part

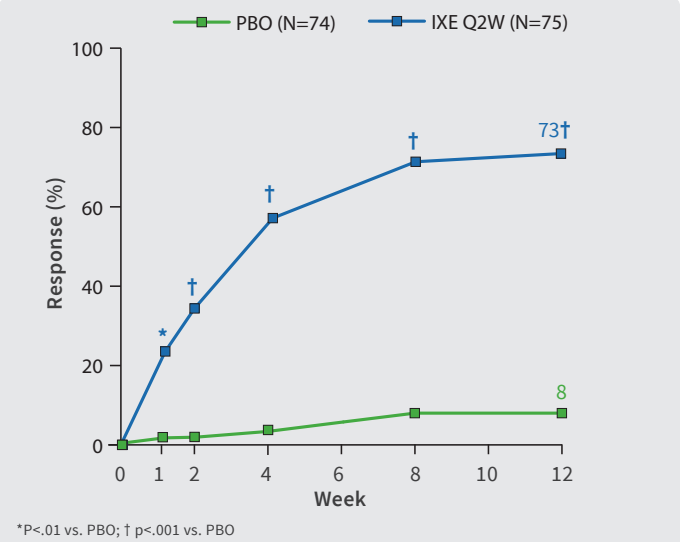
Figure 2: Femtomolar has a crystal structure and is able to completely capture the IL-17A/A homodimer. Source: Lecture Dr. Frejd.



of the itch process. "You feel no itch before this feeling is not processed to the neuron", explained Dr. Kwon.

In the Phase II TCP-101 study 3 doses of serlopitant were tested against placebo in 257 patients that suffered from pruritus that lasted at least 6 weeks and was nonresponsive or inadequately responsive to topical steroids or antihistamines. Patients were treated for six weeks. Serlopitant provided a statistically significant improvement in chronic pruritus, beginning as early as day 2 with the 1 mg dose and day 3 with the 5-mg dose, compared with placebo. The initial improvement in pruritus was sustained to week 6 in both dosing groups. Almost all side effects were mild or moderate although they occurred more frequently with serlopitant. The percentage change from baseline Visual Analogue Scale itch score was significantly greater with serlopitant 1mg (-41,4; P= 0,022) and 5 mg (-42,5; P= 0,013) at week 6 compared with placebo (-28,3).

Figure 3: Primary endpoint of the trial: sPGA of genitalia (0,1) response rate. Source: Lecture Prof. Ryan.



*P<.01 vs. PBO; † p<.001 vs. PBO
ITT= Intent-to-treat; IXE Q2W=80mg ixekizumab every 2 weeks; NRI=non-responder imputation; PBO=placebo; sPGA=static Physician's Global assessment

Ixekizumab: also effective in genital psoriasis

Although genital psoriasis is common (up to 60%) in patients with plaque psoriasis, there exists only limited data from clinical trials [6]. "We have so many trials with systemic biologics, but no trial has addressed genital psoriasis up to know, so we hope that this trial will create more awareness of this problem", said Prof. Caytriona Ryan, St. Vincent´s Hospital, Dublin (Ireland), at the presentation of the trial [7].

All included patients failed to respond or were intolerant of at least one topical therapy for genital psoriasis. In addition, they had to have plaque psoriasis in a non-genital area.

Patients needed only to have a Body Surface Area (BSA) ≥ 1% in this trial, although usually psoriasis patients do not qualify for systemic treatment, if they have less than 10% BSA. "I think to include these patients was very important, because quality of life is so much more impaired if plaques are located in this region", said Prof. Ryan.

The primary endpoint was a Physician Global Assessment (PGA) of 0 or 1 in the genital area, which means clear or almost clear skin. After 12 weeks of treatment, 73% of the treatment group reached this primary endpoint (P< 0.001 vs. placebo), an effect could already be seen after one week (Figure 3). In addition, ixekizumab was effective in a couple of secondary endpoints. Genital itch, that was assessed in patients that had at least an itch of 3 and more at baseline in a numerical rating scale (NRS), improved also by 60%. "For me the most important result is that 78% of patients, whose genital disease affected sex life in the beginning were not disturbed anymore at week 12, and a significant improvement was evident as early as one week after baseline", said Prof. Ryan.

Safety outcomes were consistent with the overall safety profile of ixekizumab.

Tildrakizumab: a novel anti-IL-23 agent for treatment of psoriasis

The investigational highly selective IL-23 inhibitor tildrakizumab appears to be effective for the treatment of psoriasis over a treatment period of two years: These encouraging results showed long-term extensions of two phase 3 trials: reSURFACE1 and reSURFACE2 [8]. All participants in the extension studies had achieved at least PASI 50 in the original studies and the treatment that was given at the end of the study was continued open label. 474 patients completed the extension study reSURFACE1 and 688 patients completed the extension study of reSURFACE 2. More than 80% of patients treated with tildrakizumab 200 mg for 2 years achieved a 75% reduction in Psoriasis Area Severity Index score (PASI 75), and adverse event rates were low.

"Over two years, we have a minimal decline in PASI levels in both study populations," said investigator Prof. Kim Papp, Probity Medical Research in Waterloo (Canada).

After 2 years, 30% of patients had clear skin (PASI 100). "There was a slight decline, but again, it was only minimal over two years", said Prof. Papp.

Adverse events, including severe infections and malignancies, will be monitored for about 5 years, but rates were low for both doses at 2 years, and there were no deaths.

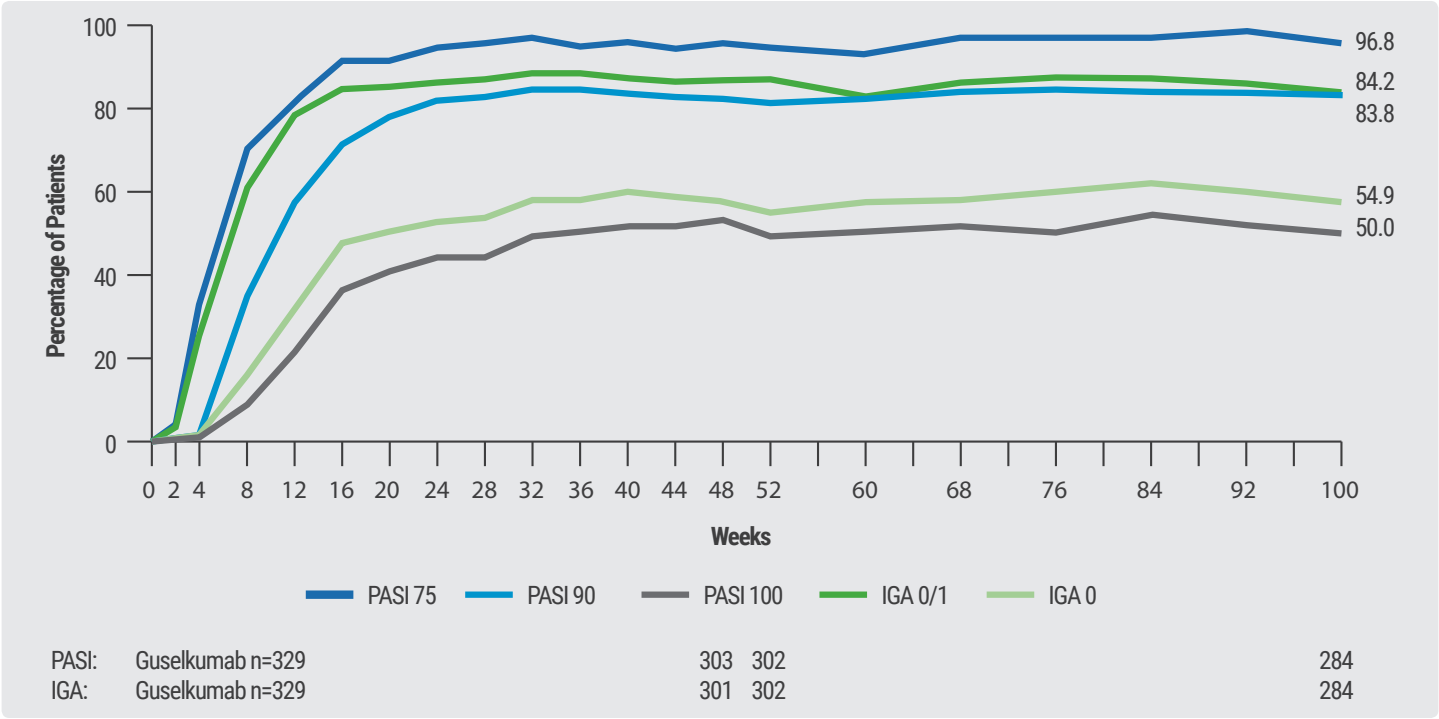
IL-23 blockers have the clinical advantage that they have to be dosed less frequently. After guselkumab, tildrakizumab is likely to become the second IL-23 inhibitor to be approved by the FDA.

Guselkumab safe and effective over two years

The phase III VOYAGE-1-trial was designed to evaluate the efficacy and safety of the IL-23 inhibitor guselkumab compared with placebo and adalimumab in adults with moderate to severe plaque psoriasis. Patients received 100 mg guselkumab at weeks 0 and 4, then every 8 weeks. Participants that completed the randomised, double-blind VOYAGE-1-trial were able to enter the extension trial. "Today I can present you the two-year data from the open label extension of the VOYAGE 1 trial", said Dr. Andrew Blauvelt, Oregon Medical Research Center, Portland (OR/USA) [9].

"We see very high PASI responses regardless of whether patients have been on guselkumab from the beginning, or started with placebo or adalimumab in the first year and were then switched to guselkumab – those patients did just as well", said Dr. Blauvelt. PASI 75 response at 100 weeks were between 94.8% and 97.5%. There was a remarkable low drop-out rate of only 2-6% in the second year. After 100 weeks, 96.8% of patients reached a PASI 75 response, 83.8%

Figure 4: Proportion of patients who achieved PASI 75, PASI 90, PASI 100, IGA Score of 0/1, IGA Score of 0 (week 0-100), as observed. Source: Lecture Dr. Blauvelt.



a PASI 90 response and 50% a PASI 100 response, which means completely clear skin (Figure 4).
Investigator´s Global Assessment (IGA) scores correlates well with PASI 90 – again there was no difference between groups. 54.9. % of patients gained an IGA score of 0/1, which means clear or almost clear skin, 50% of 0 (clear skin). Quality of life, assessed in the DLQI, improved continously from week 48 to week 100.

In conclusion, the extension of the VOYAGE 1 trial shows that efficacy among guselkumab-treated patients was maintained through 2 years of continuous treatment. Efficacy among adalimumab-treated patients who crossed-over to guselkumab improved from week 52 through week 100. The IL-23 inhibitor was well tolerated in the extension study with a similar safety profile as reported in the VOYAGE 1 trial.
In the US, guselkumab was approved earlier this year for the treatment of adult patients with moderate to severe plaque psoriasis.

Ustekinumab: superior drug survival according to a Danish registry

Real-life data on newer biologic and biosimilar agents are lacking, but the DERMBIO registry contains data on all patients with moderate-to-severe psoriasis treated with biologics in Denmark. To shed light on the performance of different biologics in daily practice, Dr. Alexander Egeberg, department of dermato-allergology at Herlev and Gentofte Hospital, Copenhagen (Denmark) presented an analysis of patients treated between January 1st 2007 and March 31st 2017 [10]. A total of 3495 treatment series in 2161 patients could be evaluated. There were 1332 treatment series with adalimumab, 579 with etanercept, 333 with infliximab, 196 with secukinumab and 1055 with ustekinumab. The highest incidence rates for adverse events were seen with secukinumab, adalimumab and infliximab, the lowest with ustekinumab. Discontinuation of treatment was mostly due to loss of efficacy.
There was no difference in drug survival due to the switch from an originator to a biosimilar. Ustekinumab had the lowest risk of discontinuation. "The most evident result of our analysis was that we see an impressive drug survival for ustekinumab", explained Dr. Egeberg. The shortest drug survival was noted with secukinumab. Compared to randomised clinical trials, PASI responses and DLQI scores were generally lower.
Adverse events were most frequent for secukinumab, predominantly infections. In this real-life setting, cardiovascular events were overall rare, but occurred slightly more frequent with secukinumab compared to the other biologics.

Tyrosine kinase inhibitor effective in pemphigus vulgaris

"This is the first time that a Bruton´s tyrosine kinase inhibitor is tested. If you block Bruton's tyrosine kinase, you can impair B-cell function without reducing B cells directly", explained Prof. Dedee Murrell, St. George and Sutherland Clinical School, Sydney (Australia), the mode of action of the drug PRN 1008. An interim analysis of the phase II trial BELIEVE-PV in naïve or relapsing patients with mild to moderate pemphigus vulgaris showed that 42% of patients in the intent-to-treat analysis treated with this tyrosine kinase inhibitor met the primary endpoint of control of disease activity at 4 weeks using ≤ 0,5 mg/kg of prednisolone or equivalent corticosteroid [11]. 44% of patients (4/9) that completed 12 weeks of treatment gained complete clinical remission, with this low dose of a tyrosine kinase inhibitor. Patients showed a 43% improvement in quality of life at 12 weeks.
Pemphigus disease activity index scores fell substantially over the first few weeks in the majority of patients consistent with the early anti-inflammatory effect of the drug. "We managed to get the same efficacy with the new agent together with low dose corticosteroids than that we get usually with a high corticosteroid dose", said Prof. Murrell. No clinically significant safety signals have been observed.
According to Prof. Murrell the agent has the potential to eliminate or at least significantly reduce the need of corticosteroid in pemphigus vulgaris patients that have very few treatment options up to now. This data supports continued development of the agent in pemphigus vulgaris and related autoimmune disorders. "I personally hope that you can use it without steroids", concluded Prof. Murrell.

References

1. De Bruin-Weller. Late Breaking Abstract Nr. 4310, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
2. Rissmann R. Late Breaking Abstract Nr. 4336, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
3. Fredrik Frejd. Late Breaking Abstract Nr. 4355, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
4. Yosipovitch G et al. N Engl J Med 2013;368:1625-34.
5. Lots T et al. J Dtsch Dermatol Ges 2014;12:556-9.
6. Ryan C Et al. J Am Acad Dermatol 2015;72:978-83.
7. Ryan C. Late Breaking Abstract Nr. 2413, 26th EADV, 13-17th September 2017, Geneva, (Switzerland).
8. Papp K. Late Breaking Abstract Nr. 4378, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
9. Blauvelt A. Late Breaking Abstract Nr. 4314, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
10. Egeberg A. Late Breaking Abstract Nr. 4216, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
11. Murrell D. Late Breaking Abstract Nr. 4315, 26th EADV, 13-17th September 2017, Geneva (Switzerland).

Sexually Transmitted Infections

More than one million Sexually Transmitted Infections (STIs) are acquired every day worldwide. How this problem can be adequately managed was one of the main topics of this year´s EADV press conference [1].

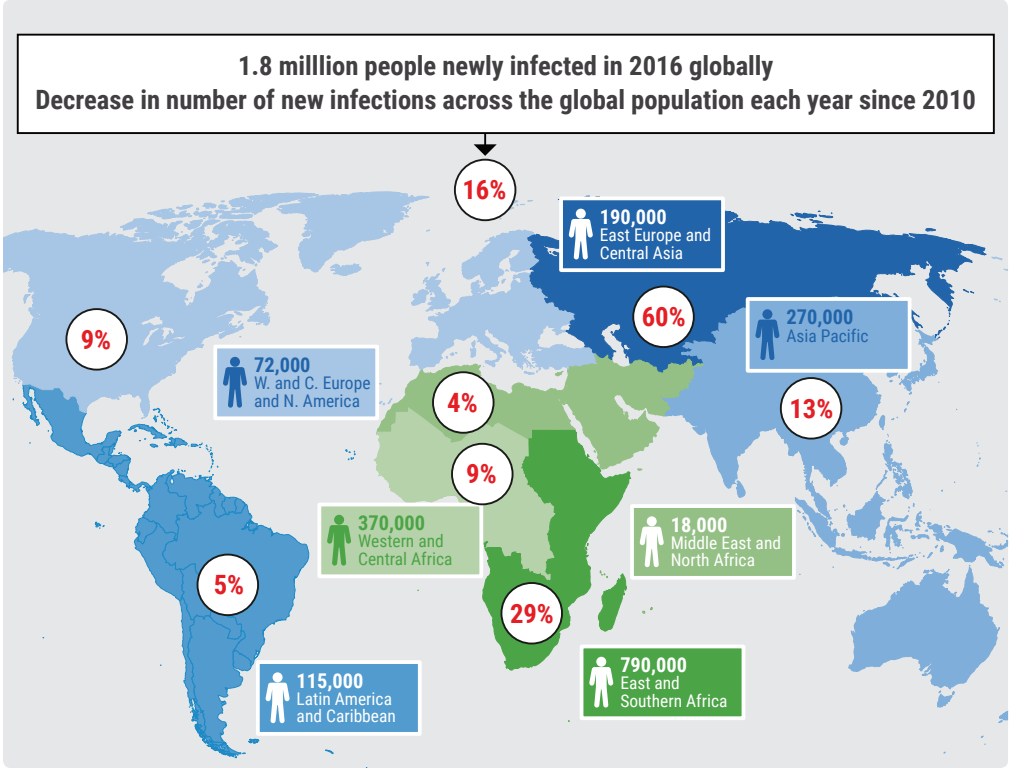
A global health challenge

The HIV numbers published by the WHO last autumn were dramatic: For the first time, the cumulative number of HIV cases in the European Region increased to over 2 million. More than 153 000 new HIV cases contributed to this figure in 2015 – a 7% increase compared to the previous year and the highest annual number since reporting began in the 1980s [2]. Globally, 1.8 million people were newly infected in 2016 (Figure 5). "The appliance of science has resulted in HIV becoming a chronic long-term condition, no longer feared as it was in the 1980s. Some even believe, wrongly, that it can be cured", explained Prof. Colm O'Mahony, Countess of Chester Hospital, Chester (Great Britain). Therefore, people become lax on safer sex nowadays. Back in the 80s, fear was a major factor in changing behaviour. Prevention campaigns were based on it and had a marked effect on STD rates. "Unfortunately, that is history now", said O´Mahony.

An effective mean to prevent new infections is pre-exposure prophylaxis (PrEP), which is available for persons at risk (sex workers, gay men, or partners of HIV-infected patients), but acceptability seems to be rather low and is strongly correlated with education level and monthly income [3]. An anonymous survey showed that more than 70% of high-risk men in Scotland would be unwilling or simply unable to self-fund PrEP [4].

For Prof. O´Mahony, the only efficient way to reduce HIV infection rates is to invest in education." Sex and relationship education should be a major tool in STD prevention, but many countries traditionally have difficulty implementing such programmes." To educate everybody is important because for a long time now it is no longer just gay men, drug addicts and sex workers who are at high risk.

Figure 5: Number of new HIV infections in 2016 and change since 2010. Source: [UNAIDS, data 2017]



Safer sex: better control of other STDs

Not only HIV, but also prevalence of other STIs is increasing dramatically. According to the WHO, more than 1 million STIs are acquired every day [5]. Moreover, STDs are becoming more difficult to treat due to increasing resistance against medications. "This will make some infections almost untreatable in years to come", explained Prof. O'Mahony. Syphilis has re-emerged in several high-income countries. According to WHO estimates, there are 6 million new cases of syphilis annually among people aged 15-49 years [5], mainly due to high-risk sexual activity. The disease can still be treated with penicillin, but this needs to be injected. Azithromycin 2g was initially effective, but syphilis is now resistant to this in most countries. So, the worrying question now is, how long will penicillin work?

Each year, 78 million people are infected with N. gonorrhoea, including nearly 10 million in Europe. Treatment has become a problem, as N. gonorrhoea has developed resistance to all the antibiotics ever used against it. Third-generation cephalosporins have previously been used in the treatment of N. gonorrhoea, but it was only a matter of time until the bacteria acquired resistance. A strain of N. gonorrhoea (H041 strain) resistant to this antibiotic was first identified in a female sexual worker in Japan in 2011 [6]. Remarkably, gonorrhoea retains its resistance to previously used antibiotics, even though they may not have been used for years. It is thought that pharyngeal gonorrhoea plays a major role in development of transmission and resistance [7].

Quadrivalent vaccines offers 100% protection against genital warts

The arrival of imiquimod was big step forward in the science and practical management of even the most difficult cases of genital warts (HPV) [8]. The quadrivalent HPV vaccine (and the nanovalent vaccine) is 100% protective and will eventually eradicate this condition [8]. It is inconceivable that some countries are still choosing the bivalent HPV vaccine, which offers no protection against genital warts. Another problem is vaccine coverage. While it is quite high in the UK (about 89.4%) [9] because HPV vaccination is offered through schools, it is much lower in other countries, e.g. in Germany at around 30% [10]. "To effectively stop the spread of disease we have to make sure that vaccination is not only offered in a few counties, but worldwide.", concluded Prof. Mahoney.

References:

1. EADV official press conference, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
2. World Health Organizaton (WHO), www.euro.who.int/en/media-centre/sections/press-releases/2016/11/hiv-cases-reach-over-2-million-for-the-first-time-in-europe , last accessed 28th of September 2017.
3. Wang Z et al. AIDS Behav 2017. Jul 27. doi: 10.1007/s10461-017-1869-4. [Epub ahead of print].
4. Gilson RI et al. Int J STD AIDS. 2017 Jan 1:956462417723817. doi: 10.1177/0956462417723817. [Epub ahead of print]
5. World Health Organizaton (WHO), www.who.int/mediacentre/factsheets/fs110/en/, last accessed 28th of September 2017.
6. UnemoM et al. Antimicrob Agents and Chemother 2012; 56:1273-80.
7. Fairley CK et al. Emerg Infect Dis 2017; 23:102-4.
8. O'Mahony C. Int J STD AIDS 2001;12:400-3.
9. Barton S et al. BMJ 2013;346:f2184.doi: 10.1136/bmj.f2184 (Published 19 April 2013)
10. www.gov.uk/government/uploads/system/uploads/attachment_data/file/487514/HPV_2014_15_ReportFinal181215_v1.1.pdf , , last accessed 28th of September 2017.

Skin Cancer

The focus on prevention and early diagnosis is of key importance to improve the management of skin cancer. Immunotherapy improved treatment of patients with malignant melanoma. Dermatologists play a key role as a partner for oncologists not only about the therapy but also in management of side effects of these novel drugs.

An Update

There is an impressive body of evidence that most skin cancers (except basal cell carcinomas) are preventable by regular sunscreen use. "The Nambour trial showed that sunscreen use can prevent squameous cell carcinoma (SCC) as well as melanoma", said Prof. Hans Peter Soyer, Dermatology Research Centre, University of Queensland, Woolloongabba (QL/Australia) [1]. In this trial 50% of 1600 randomly selected residents of Nambour, a township in Queensland, applied factor 15+ sunscreen every day for 4 years or they applied sunscreen as they would normally (including no application) [2]. After 15 years, those allocated to daily sunscreen use showed a 50% reduction of all primary melanoma. Invasive melanoma was even reduced by 73%. In addition, SCC were reduced by 40%. Another trial showed that regular sunscreen uses in children (school grade 1-4) reduces nevi compared to a control group [3]. In this trial, sunscreen use was much more important for children with freckles than for children without. If everybody used sunscreen 1,730 melanoma and 14,190 SCCs could be prevented in Australia [4]. Based on this data, sunscreen use over the lifetime is likely cost-effective in preventing melanomas and SCCs.

Despite this data, there are many people who do not use sunscreen at all, e.g. because they "want to tan". "Even in Australia only one third of patients use sunscreen, when they go to the beach, so there is still a lot of room for improvement",

concluded Prof. Soyer. Another drawback is that sunscreen products often are not applied correctly. In addition, people who are using sunscreen tend to stay longer in the sun.

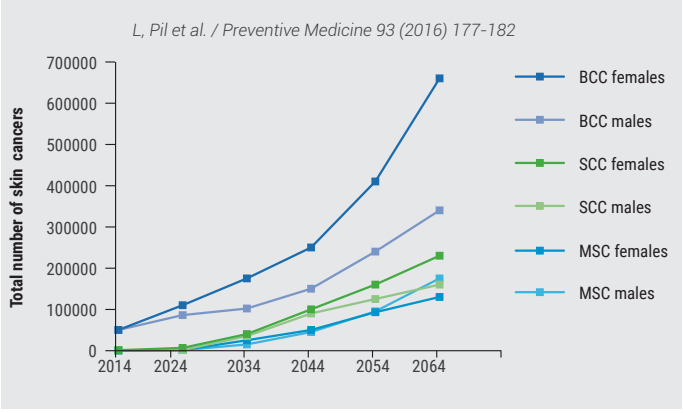
Sunbed use: responsible for over 3,400 cases of melanoma in Europe per year

Although there are numerous awareness campaigns regarding the potential risk of UV radiation, sunbed use is still responsible for more than 450,000 non-melanoma skin cancer cases and more than 10,000 melanomas in the United States, Europe and Australia [5]. In Europe, 3,400 melanoma cases annually are attributable to sunbed use, especially those occurring before the age of 30 [6]. According to the WHO the risk is highest in those exposed to artificial tanning in early life. In 2012, there were over 230,000 new cases of melanoma worldwide, causing an estimated 55,500 deaths [5]. One of the reasons for this strong correlation between sunbed use and melanoma might be the impact of cumulative risk factors among sunbed users: a French study published in the EADV journal this March showed that most of them are females with fair hair and fair, freckled skin [7].

As Dr. Emilie van Deventer, team leader of the radiation programme at WHO, Geneva (Switzerland), pointed out, "Many Euros were invested to inform the public about the risk of sunbeds – but so far with meagre success [8]."

A study published in July analysed why sunbed tanning remains popular in many Western countries, despite the publicised health risks associated with its usage [9]. They found out that sunbed users were concerned with beauty and – surprisingly! – health. They emphasised possible health benefits (e.g. increasing vitamin D levels) while downplaying the real risk. One study investigating the attitudes of UK university students to ultraviolet radiation exposure showed that body image appeared to be a key motivator [10]. The authors argue that public health strategies may benefit from prevention campaigns targeting appearance-related skin cancer. According to a Belgian analysis, further campaigning would be cost-effective [11]: For every euro invested in the campaign, € 3.6 would be saved in the long-term for the healthcare payer. In Belgium alone, the total economic burden of skin cancer in 2014 totaled € 106 million. Figure 6 shows the estimated skin cancer incidence in Belgium according to cancer type and gender (Figure 6).

Figure 6: Estimated trend in skin cancer prevalence in Belgium, separated for gender and skin cancer type: BCC basal cell carcinoma, SCC squameous cell carcinoma, MSC melanoma skin cancer. Source: [11



Melanoma still on the rise

According to an analysis of cancer registry data over three decades from six populations with moderate to high melanoma incidence (US whites, populations of the United Kingdom, Sweden, Norway Australia, New Zealand), melanoma rates between 1982 and 2011 increased at more than 3% annual and are projected to continue rising until at least 2022 [12]. Although the incidence is increasing, there are no more death, probably due to new screening tools that enable early diagnosis. "The melanoma we detect in high risk groups are thin melanoma. Our tragedy is that the killers' thick melanoma develops in persons without nevi. High nevus counts confer a favorable prognosis", said Prof. Myrto-Georgia Trakatelli, Papageorgiou Hospital, Aristotle University, Antolia (Greece) [13]. Histologically, there are clues that hint toward a melanoma or a nevus (Table 1).

Dermoscope – the stethoscope of the dermatologist

Dermatoscopy plays a fundamental role in the early diagnosis of melanoma, because it allows an earlier diagnosis of melanoma, before it becomes clinically suspicious. It is also a valuable tool to identify benign lesions and save patients unnecessary excision. As Prof. Rana Anadolu, Dermatology Clinic, Ankara (Turkey) pointed out, detection of an early melanoma among numerous pigmented lesions in a patient is lifesaving [14]. Nevi are common benign neoplasms that share a common pattern in a single individual. Mostly they are symmetrical, bland with one color and one structure. In contrast, a melanoma stands out from the rest of the pigmented lesions in a patient. Her recommendation to less experienced dermatologists is. "Expose yourself to as much pigmented/non-pigmented skin lesions as possible". The dermoscope is the stethoscope of the dermatologist and a patient´s skin is an atlas of itself. "Melanomas show an asymmetrical increase/change in size, shape, structure and pigment. "Look for chaos: asymmetry of color and structure

Table 1: Histological differentiation of nevi from melanomas. [14]

Some clues…	Nevus	Melanoma
Symmetry, nest uniformity	+	-
Cytologic atypia	-	±/++
Nuclear pleomorphism/mitosis	-	±/++
Dermal inflammation (lymphocytes)	-	+/++
Epidermal ulceration	-	-/++
Epidermal migration of single cells	-/±	+
Maturation of cells with depth	+	-
Sharp lateral circumscription	+	-/±

are hallmarks of melanoma", said Prof. Anadolu. Likewise, chaos in nail lesions are also clue to a melanoma. When in doubt, get a second opinion or excise", recommended Prof. Anadolu.

Artificial intelligence: as good as dermatologists in diagnosis of skin cancer?

Regarding early diagnosis of skin cancer, there is much more to come, Prof. H. Peter Soyer, Dermatology Research Center, The University of Queensland, Woolloongabba (QLD/Australia) [15]. "Nowadays, new high-tech imaging, combined with artificial intelligence and decision support systems will surely redefine the early diagnosis of melanoma and skin cancer!"

A landmark paper was published this February in the internationally renowned journal "Nature" [16]. The authors tested a machine learning, convolutional neural network (CNN) for the classification of skin cancer. CNNs are feed-forward artificial neural networks and learn the filters that in traditional algorithms were hand-engineered. This makes them independent of prior knowledge and human effort. The working group at Stanford University in California used only pixels and disease labels as inputs, the system being "fed", or trained, with a dataset of 129,450 clinical images consisting of 2,032 different diseases (two orders of magnitude larger than previous datasets). The CNN was then tested against 21 board-certified dermatologists on biopsy-proven clinical images, who firstly had to identify the most common skin cancers, and secondly the deadliest skin cancer. The result was astonishing: the CNN achieved a performance on par with all tested experts across both tasks, demonstrating an artificial intelligence capable of classifying skin cancer/melanoma with a level of competence comparable to dermatologists. It could classify skin cancers/melanomas as "biopsy/treatment is needed" or "reassure the patient/everything is fine" as reliably as the experts. According to the authors of the study, deep neural networks deployed on mobile devices can potentially extend the reach of dermatologists outside the clinic. They believe that this technique "can potentially provide low-cost universal access to vital diagnostic care" [16]. The question is, can this really become true – or is it just a "Silicon Valley dream"?

As Prof. Soyer explained, this development of artificial intelligence (AI) and its adoption in dermatology is proceeding rapidly, indeed, and the market for AI technologies is flourishing. One area of focus is on automated analysis of features in dermoscopic images of skin lesions (shape, colour, size), another on identifying potential characteristics of melanoma (i.e. border irregularity, multiple colours within lesions), and AI is being integrated into software for different types of imaging platforms (3D imaging systems, digital dermoscopic images and smartphone dermoscopic images). He also believes that smartphone dermoscopic imaging with built-in AI is likely to be the most accessible method for skin lesion analysis in future.

Limited evidence of many apps

There are pitfalls, however, and dermatologists should seek to ensure minimum quality standards for such devices. One study of current smartphone apps for diagnosing melanoma showed that the app market is a fast-moving one, with almost half of 2014 apps no longer existing in 2017 [17]. At present, 10 melanoma apps have integrated image analysis functions, but their accuracy varies considerably. When three apps with AI were tested on skin lesions in the clinical setting in 2016, sensitivity was found to range from 21 to 72% and specificity from 27 to 100% [17]. "As technology becomes more commonplace in dermatological practice, it is essential to review continuously the accuracy of these devices", explained Prof. Soyer. "The evidence base of many of these apps is improving, but it remains limited due to the vast majority of apps not being peer-reviewed." According to Prof. Soyer, all available apps should be certificated by dermatologists. "We have to ensure a minimum rate of false-positive and false-negative diagnoses. In the end, we are talking about melanoma, a fatal disease that people die of."

Prof. Soyer emphasised that these techniques have definite advantages. One study has shown that they consistently reduced waiting times to assessment and diagnosis, and that patient satisfaction levels were high [18]. "These devices will change the day-to-day practice of dermatologists. We will more or less exclusively see patients with cancer and suspicious lesions that have to be removed. As a

consequence, we will have more time for counselling on treatment, etc., because we will not have to see all the patients who have harmless skin lesions."
In spite of progress in AI, Prof. Soyer is quite optimistic that human dermatologists will always be needed! "Technically, AI systems can be fed with more images than an experienced real-life dermatologist can see in his or her lifetime. But it cannot process contextual information, like family anamnesis or other symptoms. It doesn't see the whole patient", concluded Prof. Soyer.

Dermatologists: key player in the care of patients with metastatic melanoma

As Dr. Simone Ribero, University of Turin (Italy) pointed out, the last seven years of research have changed the therapeutic landscape of metastatic melanoma, and the role of dermatology in managing this condition [19].

"According to their different expertise, many dermatologists are now in the first line facing the metastatic setting of melanoma," said Dr. Ribero. In addition, they are the right specialist to be able to recognise and treat skin adverse events, which are very frequent in immunotherapy and targeted therapy."

The options for advanced melanoma are likely to improve even further in the near future. Talimogene laherparepvec is the first oncolytic immunotherapy, which is indicated for injection directly into unresectable lesions in patients who have recurrent melanoma after an initial surgery. Talimogene laherparepvec is a genetically modified herpes simplex virus type I that preferentially replicates in and lyses cancer cells [20].

Another approach under investigation is inhibition of lymphocyte-activation gene 3 (LAG-3), an immune checkpoint receptor protein found on the cell surface of certain T cells. Simultaneous blockade of LAG-3 + programmed death 1 may synergistically restore T-cell activation and enhance antitumor immunity. Indeed, a molecular antibody targeting LAG-3 showed initial efficacy when given in combination with nivolumab in patients with melanoma previously treated with immune checkpoint inhibitor therapy.
In addition, the combination or sequencing of established targeted and immune therapies in melanoma is providing further benefit. "New evidence is appearing on this topic almost daily, with survival rates that only a few years ago were totally unbelievable," Dr. Ribero said.

The pigment pathway: a strategy to enhance the efficacy of immunotherapy?

New insights into the pigment pathway may one day further improve the efficacy of immunotherapy in melanoma. Checkpoint inhibitors like ipilumab, pembrolizumab and nivolumab have demonstrated a considerable efficacy but only in a minority of patients. "Only about one-third of metastatic melanoma patients have a profound benefit", said Prof. David E Fisher, Director of the Melanoma Program at Massachusetts General Hospital Cancer Center in Boston [21]. Recent investigations suggest that insights into the pigment pathway may lead to new strategies that potentiate the efficacy of checkpoint inhibitors in melanoma. Data have suggested, that patients who have any mutations in the genomes of their tumors respond best to checkpoint inhibitors. To test this hypothesis. Dr. Fisher and his coworkers conducted mouse model experiments using melanoma with a high number of UV-induced mutations. Indeed, checkpoint inhibitor therapy triggered a more intensive response in melanomas with many UV-induced mutations vs melanomas with low numbers of mutations. 75% of mice with UV-mutated melanoma that were treated, cured, and then re-challenged several months later with non-UV-mutated melanoma, rejected the non-UV-mutated melanoma. The initial immune response amplified due to the UV mutations, then spread beyond UV mutations and was able to recognise normal melanocyte proteins. This phenomenon is known in immunotherapy and called epitope spreading. "The T-cells in our mice were able to recognise normal melanocyte proteins", explained Dr. Fisher. This experiment could have tremendous impact on the way, melanoma patients are treated in the future. Many patients who do not respond adequately to checkpoint inhibitors might not have enough mutations. There may be opportunities to exploit the recognition by the immune system of non-mutated protein epitopes against melanocytes as a way of successfully targeting melanoma cells. "We think mutations are important, but only for triggering the initial inflammatory response. After that, the response snowballs, and it really doesn't need those mutations anymore," he said.

Be aware of dermal side effects

While novel therapies for melanoma are very beneficial to patients, dermatologists need to be mindful of the range of adverse effects that can occur, and should learn how to manage them through hands-on experience. "We should not be afraid to use these drugs," said Dr. Effie Soura, dermatologist-venereologist with Andreas Syggros Hospital in Athens (Greece) [22].

Being vigilant is particularly important for hospital-based dermatologists, since cancer patients with adverse events related to melanoma therapy may require a multidisciplinary approach. Dermatological adverse events are not always very well depicted in clinical studies, because they are conducted by oncologists. Their description of dermatologic side effects can sometimes be misleading.

A resource developed to aid dermatologists in the grading of dermatology adverse events of cancer treatments is TOXICAN: this tool was presented as a poster at the 13th Congress of the European Association of Dermato-Oncology (EADO) in May 2017.

Each novel immunotherapeutic agent has a characteristic and sometimes unique safety profile. One example Dr. Soura shared is the BRAF inhibitor vemurafenib, which is associated with UVA-induced phototoxicity that can lead to painful blistering and sunburn. Combinations of novel drugs are not necessarily causing more side effects: For example, the combination of BRAF inhibitor and MEK inhibitor can actually reduce toxic effects compared with BRAF inhibition alone, according to several studies, including a randomised phase II study of dabrafenib and trametinib vs. dabrafenib alone.

Most grade I/II dermatologic adverse events can be managed with standard treatments such as topical corticosteroids. Grade III/IV events might typically require more aggressive therapy and withholding of the melanoma treatment. To care best for patients with metastatic melanoma, Dr. Soura emphasised the importance to work in a network of clinicians.

References:

1. Soyer HP. Presentation D3T02.3A, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
2. Green AC et al. J Clin Oncol 2011 Jan 20;29(3):257-63. doi: 10.1200/JCO.2010.28.7078. Epub 2010 Dec 6.
3. Gallagher RP et al. JAMA 2000 Jun 14;283(22):2955-60.
4. Olsen CM et al. Aust N Z J Public Health 2015 Oct;39(5):471-6. doi: 10.1111/1753-6405.12470.
5. www.apps.who.int/iris/bitstream/10665/255695/1/9789241512596-eng.pdf, last accessed 29th of September 2017.
6. Boniol M, Autier P, Boyle P et al. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012; 345: e4757.
7. Grange F, Mortier L, Crine A et al. Prevalence of sunbed use, and characteristics and knowledge of sunbed users: results from the French population-based Edifice Melanoma survey. J Eur Acad Dermatol Venereol 2015; 29 Suppl 2: 23-30.
8. Van Deventer E. Official EADV press conference, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
9. Taylor J, Murray M, Lamont A. Talking about sunbed tanning: Social representations and identity-work. Soc Sci Med 2017 Jul; 184: 161-168
10. Kirk L, Greenfield S. Knowledge and attitudes of UK university students in relation to ultraviolet radiation (UVR) exposure and their sun-related behaviours: a qualitative study. BMJ Open 2017 Mar 13; 7(3): e014388.
11. Pil L, Hoorens I, Vossaert K Burden of skin cancer in Belgium and cost-effectiveness of primary prevention by reducing ultraviolet exposure. Prev Med 2016 Dec; 93: 177-182.
12. Whiteman DC et al. J Invest Dermatol 2016 Jun;136(6):1161-71. doi: 10.1016/j.jid.2016.01.035. Epub 2016 Feb 20.
13. Trakatelli MG. Presentation D1T10.3D, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
14. Anadolu R. Presentation D1T10.3B, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
15. Soyer HP. Official EADV press conference, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
16. Esteva A et al. Nature. 2017 Feb 2; 542(7639):115-18. . doi: 10.1038/nature21056. Epub 2017 Jan 25.
17. Ngoo A et al. Austral J Dermatol. 2017 Feb 27. doi: 10.1111/ajd.12599. [Epub ahead of print].
18. Finnane A et al. Teledermatology for the Diagnosis and Management of Skin Cancer: A Systematic Review. JAMA Dermatol 2017 Mar 1; 153(3): 319-327. . doi: 10.1001/jamadermatol.2016.4361.
19. Ribero S. Presentation D1T10.4C, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
20. Kohlhapp FJ, Kaufman HL. Clin Cancer Res 2016 Mar 1;22(5):1048-54. doi: 10.1158/1078-0432.CCR-15-2667. Epub 2015 Dec 30.
21. Fisher DE. Presentation PLA-03, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
22. Soura E. Presentation D1T10.4D, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
22. Soura E. Presentation D1T10.4D, 26th EADV, 13-17th September 2017, Geneva (Switzerland).

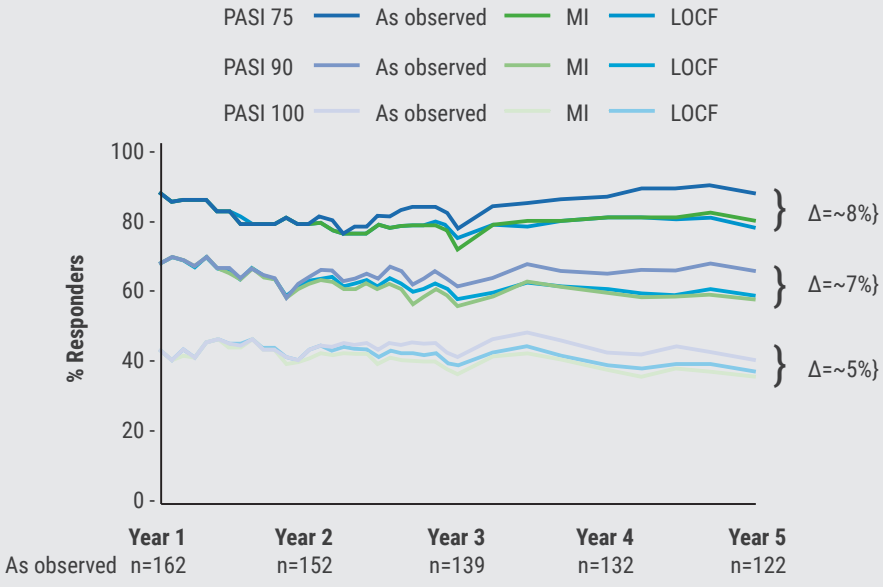
Management of Psoriasis

New therapeutic agents, such as blockers of proinflammatory cytokines, and small molecules have improved treatment modalities in psoriasis. In addition, new data regarding comorbidities and possible mechanisms to influence them were presented.

Many New Agents in the Pipeline

An increasing number of biologics and small molecules are broadening the therapeutic landscape of psoriasis. Today, clear or almost clear skin is a target that can be reached by the majority of patients. IL-17 is a key molecule in the pathogenesis of psoriasis. Whereas secukinumab and ixekizumab are direct blockers of the cytokine IL-17A, brodulamab is a IL-17 receptor blocker that does not only inhibit IL-17A, instead all the members of the IL-17 family (IL-17A to F). As Prof. Kristian Reich, Dermatologikum Hamburg, Hamburg (Germany) pointed out, brodalumab has a broader mode of action. New data presented during the meeting emphasise the efficacy of inhibition of this pathway as a major treatment modality for psoriasis.

Figure 7: SCULPTURE extension: Clinical responses in psoriasis over 5 years, Source [1]



LOCF, last observation carried forward; MI, multiple imputation; n, number of evaluable patients in the as observed analysis (the number of evaluable patients in the MI and LOCF analyses was 168 at each time Point); PASI, Psoriasis Aera and Severity Index score

Secukinumab maintains efficacy over more than 5 years

Secukinumab shows sustained skin clearance rates after a treatment period of 5 years. This data comes from a multicentre, double-blind and open-label, 5-year extension to the pivotal Phase III SCULPTURE study [1]. All patients who completed 52 weeks of the SCULPTURE study were eligible to continue the same dose and regimen in the extension study (N=642). The primary objective of this extension study was to assess the long-term safety and tolerability of secukinumab in patients with moderate-to-severe plaque psoriasis.

Over the extended treatment period from year 1 (week 52) to the end of year 5 (week 260), PASI 75/90/100 response rates remained consistent. PASI 75 and PASI 90 response rates were achieved by 89% and 69% of psoriasis patients at year 1 ('as observed' analysis) and this high rate was maintained to year 5 (89% and 66%, respectively; Figure 7). In addition, 44% of psoriasis patients achieved completely clear skin (PASI 100) at year 1 and 41 % had still clear skin after 5 years [1].

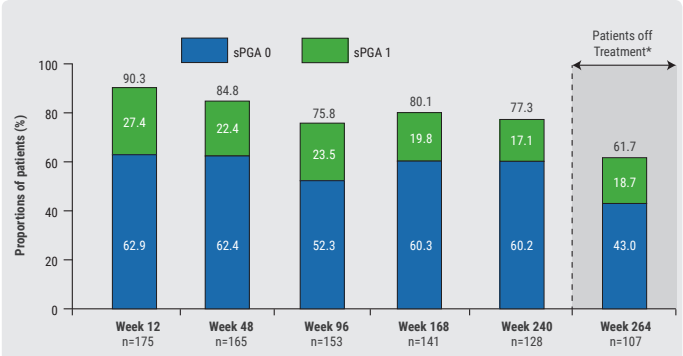
Two thirds of patients reported no impact of skin disease on their lives through 5 years of treatment: DLQI 0/1 responses were 72.1% at year 1 and 65.5% at year 5.

"These final data are meaningful for dermatologists as they show that the high efficacy and safety of secukinumab was sustained over the 5-year treatment period.", said Dr. Robert Bissonnette, Innovaderm Research, Montreal (Canada). This analysis is the first phase 3 study of an IL-17A inhibitor evaluating efficacy and safety up to 5 years of treatment at the approved dose. Secukinumab continued to have a favorable and consistent safety profile, and low immunogenicity.

Complete clearance is sustained during long term treatment with brodalumab

Long term data of the IL-17 receptor antagonist brodalumab showed that efficacy is maintained over a treatment period of 5 years: this showed the open-label extension of the phase II study NCTO1101100 [2]. Eligible patients had moderate to severe psoriasis and initially received brodalumab or placebo for 12 weeks. Of the 1818 patients that entered the trial 107 (59.1%) remained on study at week 264. The most common reasons for discontinuation were consent withdrawal (n = 19) and adverse events (n = 16). 90.3% of patients were "clear" or "almost clear" of psoriasis (sPGA score 0 or 1) at week 12: More than 75% of patients maintained this response through to week 240. The proportion decreased to 61.7% at the final study visit (Figure 8). A similar pattern was observed for PASI 75, PASI 90 and PASI 100 with response rates of 90%, 80% and 60% through to week 240, respectively, with a decrease at week 264. The safety profile was consistent with that observed in shorter studies with brodalumab, with no new safety signals being identified [2].

Figure 8: Proportion of patients with sPGA 0 or 1 during treatment with brodalumab: Source: [2]



* At week 264, patients had been off treatment for ≥ 6 weeks

The authors conclude that the high level of efficacy observed in the initial 12-week study was sustained in most patients up to week 240. At the final study analysis (week 264), when patients had been off treatment for at least 6 weeks, there was a general decrease in response across all efficacy parameters. These data are in line with the long-term extension results of the phase III study AMAGINE II: Robust and high levels of complete clearance were sustained for up to 120 weeks in patients with moderate to severe psoriasis [3].

Ixekizumab versus ustekinumab in nail psoriasis

Up to 82% of patients with psoriasis have disease that affects the fingernails, a more difficult to treat manifestation of psoriasis, and associated with a relatively longer time to resolution due to the slow nail growth [4]. A phase 2 clinical trial previously demonstrated improvement in fingernail psoriasis following treatment with ixekizumab [5]. During the EADV meeting, a subanalysis of the IXORA-S trial was presented [6]. In this Phase 3b trial, ixekizumab demonstrated superior efficacy to ustekinumab up to week 24, with regard to skin clearance [7]. In the new interim analysis, data on patients that had nail involvement at baseline were evaluated, and improvement of nail psoriasis after 24 weeks was assessed with "The Nail Psoriasis Severity Index", a standardized tool to assess nail involvement (6]. At baseline, 84 ixekizumab-treated (61.8%) and 105 ustekinumab treated patients (63.3%) presented with fingernail psoriasis. By week 24, almost half of ixekizumab treated patients (48.8%) reached complete clearance of fingernail psoriasis compared to 22.9% of patients treated with ustekinumab (P< 0.001). Significant differences between the two groups were seen as early as week 16. The authors conclude that long term data are needed for full evaluation of the effect of both therapies on fingernail psoriasis. The total study period is 52 weeks.

Biosimilar infliximab effective in real-world setting

Patients with plaque psoriasis, psoriatic arthritis, or both showed a good response to the biosimilar infliximab (CT-P13), irrespective of whether patients were naive to infliximab or were receiving prior treatment with infliximab originator and switched to infliximab biosimilar. This was the result of an analysis of practice records presented during the meeting [8]. "Mean PASI scores did not show a significant difference in the values recorded before, during, or after the switch from infliximab to biosimilar CT-P13," noted Dr. Alessandro Giunta, University of Rome Tor Vergata, Rome (Italy). Dr. Giunta and colleagues conducted this single-centre observational study to evaluate the efficacy and safety of the biosimilar in patients treated with infliximab originator who were switched to the biosimilar (cohort A) and in a second population of patients who were naive to infliximab and received the biosimilar for treatment of psoriatic arthritis and plaque psoriasis (cohort B). They performed this analysis, because up to now, there are few data on patients switched from the originator to the biosimilar in daily clinical practice. All patients in cohort A received infliximab at 5 mg/kg at weeks 0, 2, 6, and every 8 weeks thereafter with PASI and pain Visual Analogue Scale (VAS) recorded every 8 weeks during the 40 weeks before starting the biosimilar, and every 8 weeks for 48 weeks after the biosimilar was started. No differences in PASI or pain VAS scores between patients previously treated with the infliximab originator versus naive patients were observed.
"Biosimilars represent a great opportunity to reduce healthcare cost and to increase the number of patients treated with biologics," concluded Dr. Giunta.

Extension of UNVEIL study shows effect over 52 weeks

Not only biologics, but also small molecule offer further options to treat patients with psoriasis. During the meeting, the results of the extension of the UNVEIL study was presented that demonstrated the short and long-term effect of apremilast. As Dr. Bruce Strober, Chair of Dermatology at University of Connecticut, Mannsfield (CT/USA) pointed out, patients included in this trial had no prior exposure to systemic treatments or biologics. The safety and efficacy of apremilast was compared to placebo during a 16-week controlled phase. The second objective was to assess long-term efficacy and safety of apremilast up to one year [9]. All included patients had moderate plaque psoriasis at baseline, defined as affected BSA between 5 and 10% and a score of 3 (moderate) in the PGA based on a scale ranging from 0 (clear) to 5 (very severe). At week 16, significantly greater improvements in PGA x BSA occurred in patients receiving apremilast compared to placebo. During the extension phase, improvement was maintained in the group that was initially treated with apremilast and emerging in the group that received placebo up to week 16 before they were switched to apremilast: After 52 weeks, mean percentage change from baseline in PGA x BSA Score was -42.2 in the placebo/apremilast group and -49 in the group that received apremilast from the beginning. In addition, significantly more patients treated with apremilast achieved an PGA score of 0 or 1 at week 16 (clear or almost clear skin) compared to placebo. Long term PGA response was maintained in the

open-label treatment phase and was 35.9 in the placebo/apremilast group compared to 29.1 in the apremilast/apremilast group. The incidence of adverse events did not increase with longer exposure to apremilast. In addition, safety and tolerability were consistent with previous studies a no new safety issues were observed up to 52 weeks

Patients are highly satisfied with apremilast treatment

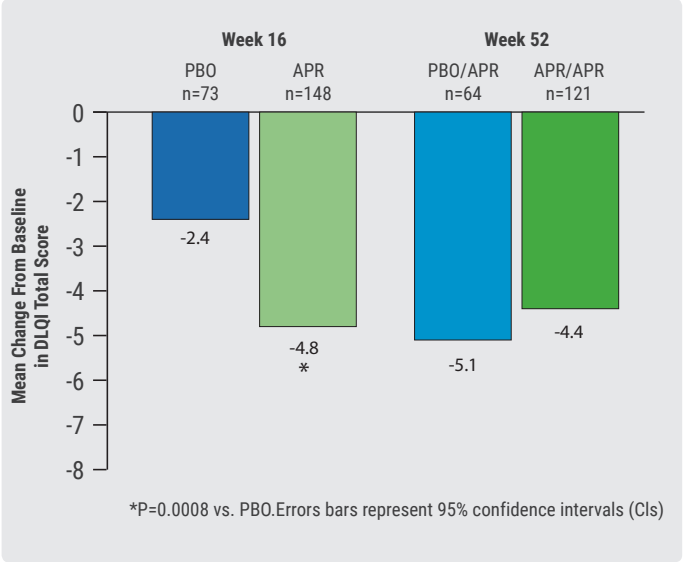
Another analysis of the UNVEIL trial showed that patients treated with apremilast gained an improved quality of life and high satisfaction with the treatment [10]. Patients were administered the 10-question DLQI (range 1 to 20), pruritus VAS (0 to 100 mm) and the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM, range 1 to 100).

At baseline, patients in the UNVEIL study had a mean DLQI score of 11.0 and a mean VAS score of 56.6 at baseline. As early as week 16, patients saw significant improvement and experienced a reduction of -4.8 in DLQI score with apremilast compared with -2 with placebo (Figure 9; P< 0.001). The majority of patients reported improved quality of life; the difference between apremilast and placebo was significant for the proportion of patients achieving a minimal clinically important difference representing an at least 5-point improvement in DLQI score (P< 0.001).

At week 16, patients also demonstrated improvement in the pruritus VAS, and both TSQM global satisfaction and effectiveness ratings were also significantly improved with apremilast compared to placebo. All improvements were sustained through week 52 in patients receiving apremilast initially, and patients who switched from placebo to apremilast also saw significant improvements.

At week 52, patients receiving apremilast demonstrated mean DLQI improvements from baseline of -4.4, and patients switched to apremilast showed a reduction of mean -5.1, with 59.4% of patients on apremilast/apremilast and 55.6% of patients receiving placebo/apremilast achieving the MCID on the DLQI. By week 52, apremilast and placebo/apremilast patients showed reduced pruritus VAS scores of -20.8 mm and -25.3 mm from baseline, respectively.

Figure 9: Improvements in DLQI total score in patients treated with apremilast compared to placebo in the UNVEIL trial. PBO placebo. APR apremilast. Source: [10]



Distinct antipruritic effect

Pruritus is a common symptom in psoriasis, which has a detrimental effect on quality of life. A study from Austria analysed the reduction of pruritus in a NRS, ranging from 0 = not itch to 10 = worst imaginable itch [11]. In chronic plaque psoriasis patients who received apremilast in the standard dose for at least three months, apremilast led to a significant decrease in the NRS from 5.6±0.6 at baseline to 2.4±0.8. In 50% of patient's pruritus resolved completely. Concomitantly, quality of life assessed in the DLQI showed a significant reduction from 11 ±1.7 to 5.3±1.1.

With regard to costs of treatment, apremilast is superior to biological therapy. This showed a small cost analysis of patients treated with different biologics and apremilast in in a dermatology clinic in Italy: In this trial, apremilast reduced cost compared to secukinumab by 77.8%, compared to ustekinumab by 53% and compared to secukinumab by 47% [12].

New data on psoriasis comorbidity

Increased release of pro-inflammatory cytokines from immune–related cells and chronic activation of the innate and adaptive immune system cause long-term damage to multiple tissues and organs in patients with psoriasis. Therefore, life expectancy of patients with moderate to severe psoriasis is 10 years less compared to healthy persons [13]. Patients with moderate to severe psoriasis have an increased risk of conditions such as cardiovascular disease, obesity, diabetes mellitus, and metabolic syndrome. The precise mechanisms underlying the observed increase in cardiovascular disease in psoriasis remain to be defined but inflammatory pathways mutual to both conditions are probably involved [14]. In addition, patients with moderate to severe psoriasis have a significantly higher prevalence of psychiatric disorders, namely depression, anxiety, and bipolar disorders compared to controls [15]. But does this drive patients to more suicidal behavior? This question was

addressed by an epidemiologic study from Great Britain that investigated the association between psoriasis and risks of suicide and nonfatal harm [16].

Data were derived from a primary care database that included 398 clinical practices from England. In a cohort of 56,961 patients with psoriasis and 876,919 comparison patients the risk of suicide was investigated, the cohort investigated the risk of self-harm constitutes of 54,709 patients with psoriasis and 813,699 comparison patients. In the latter, people with a history of self-harm at baseline were excluded. A higher percentage of psoriasis patients compared to controls suffered from psychiatric comorbidity, and alcohol misuse. In addition, the psoriatic patients had a higher rate of prescription of psychotropic medication. Despite these differences, there was evidence of a lower risk of suicide in people with psoriasis. However, there was a distinct influence of age at time of diagnosis. The risk of suicide was significantly below 1 for people with psoriasis who were diagnosed with the disease at 40 years or older, whereas there was no association if the diagnosis occurred prior to age 40 years. No evidence of an association between psoriasis and nonfatal self-harm risk was found.

An e-poster by the same author showed that patients with psoriasis have also a higher risk to die from alcohol-related death compared to the general population [17]. Psoriasis patients died not only more often from alcohol abuse compared to the general population, but also at a younger age. Psoriasis patients died on average three years younger, women even about 5 years earlier due to their alcohole problem than those without psoriasis that died of alcohol related death. Results were consistent after sensitivity analysis. The authors conclude that alcohol misuse often remains unidentified and undertreated in primary care. Healthcare practitioners should be aware of the psychological difficulties in people with psoriasis.

Effective treatment – a way to influence comorbidities

Effective therapy can reduce the cardiovascular mortality of psoriatic patients: This could be shown for different treatments such as TNF blockers and methotrexate [18]. The role of IL-17 blockers with regard to cardiovascular comorbidity is discussed controversially [19].

The CARIMA trial presented during the meeting hints towards an cardioprotective effect of the IL-17 blocker secukinumab [20]. According to Prof. Kristian Reich, Dermatologikum Hamburg, Hamburg (Germany) and coauthor of the trial, CARIMA is a milestone in explaining a possible cardioprotective effect of psoriasis therapy: In this prospective trial, influence of therapy with secukinumab on flow-mediated dilation (FMD), a marker of endothelial function, was evaluated in patients with moderate to severe plaque type psoriasis that showed inadequate response, intolerance or contraindication to first-line conventional systemic psoriasis treatments. According to a metaanalysis, an elevation of only 1% in FMD results in a risk reduction of cardiovascular events of 13% [21]. The primary endpoint of the trial was the baseline-adjusted FMD in patients treated with 300mg secukinumab versus placebo after 12 weeks: After this time, all patients received secukinumab until week 52. A numerical, but clinically meaningful improvement of FMD (>1%) was already observed after 12 weeks in patients treated with 300 mg secukinumab. The difference reached statistical significance after 52 weeks for both patients treated with 150 mg and with 300 mg secukinumab. In addition, comparison of baseline FMDs of the psoriasis patients with healthy volunteers showed that psoriasis patients had lower FMD values compared to volunteers, although patients included in the CARIMA trial were no classical cardiovascular high-risk group. This indicates a higher incidence of endothelial dysfunction associated with subclinical atherosclerosis in all psoriasis subjects. The authors conclude that secukinumab may improve endothelial function, thereby reducing cardiovascular disease progression in psoriatic patients [20].

References:

1. Bissonnette R et al. Poster P2223, 26th EADV, 13-17th September 2017, Geneva. (Switzerland).
2. Menter A et al. Poster P944, 26th EADV, 13-17th September 2017, Geneva.
3. Lebwohl M et al. Poster P945, br26th EADV, 13-17th September 2017, Geneva (Switzerland).
4. Klaassen K et al. J Eur Acad Dermatol Venereol. 2014;28(12):1690-1695.
5. Langley RG et al. J Eur Acad Dermatol Venereol 2015;29:1763-1770.
6. Ghislain PD et al. Poster P1274, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
7. Reich K et al. Br J Dermatol 2017:doi:10.1111/bjd.1566.
8. Giunta A et al. Poster P1959, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
9. Strober B Et al. Presentation FC02.08, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
10. Gold L. et al. Poster P1954, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
11. Sadoghi B et al. Poster P3070, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
12. Palmiotti G et al. Poster P2521, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
13. Greb JE et al. Nat Rev Dis Primers 2016 Nov 24;2:16082. Doi: 10.1038/nrdp.2016-82.
14. Ryan C, Kirby B. Dermatol Clin 2015Jan;33(1):41-55. doi: 10.1016/j.det.2014.09.004.
15. Han C et al. J Drugs Dermatol 2011 Aug;10(8):843-50.
16. Parisi R et al. Poster P1009, 26th EADV, 13-17th September 2017, Geneva (Switzerland)
17. Parisi R et al. Poster P1003, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
18. Churton S et al. Drugs 2014 Feb;74(2):169-82. doi: 10.1007/s40265-013-0173-5.
19. Torres T et al. Am J Clin Dermatol 2016 Apr;17(2):107-12. doi: 10.1007/s40257-015-0166-0.
20. von Stebut-Borschitz E et al. Poster P1818, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
21. Inaba Y et al. Int J Cardiovasc Imaging 2010 Aug; 26(6), 631-40. doi: 10.1007/s10554-010-9616-1. Epub 2010 Mar 26.

Atopic Dermatitis

There is a high medical need for AD drugs that are safe and effective, and can be given for a long time. The advent of biologics and small molecules will enable a better management, particularly of patients with moderate to severe AD.

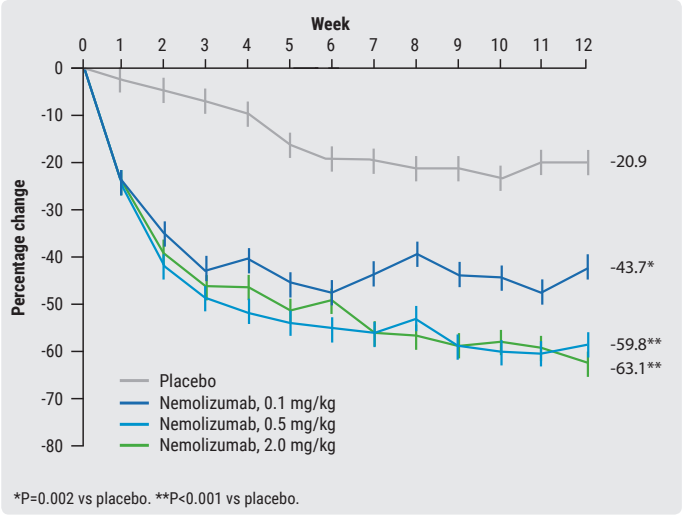
The beginning of a new era

Patients with AD experience debilitating effects that impact day-to-day functioning and have long-term consequences. The symptoms that bothers patients most is the frequent and intense itch, which can lead to sleep disturbances such as difficulties falling asleep and frequent awakenings [1]. Studies have shown that patients with AD have an impaired quality of life [1,2]. In AD, the underlying inflammation drives a chronic itch-scratch cycle, and thus perpetuates skin signs and symptoms [3].

Topical therapy is not sufficient to control more severe AD and can be associated with side effects if used inappropriately. In clinical trials, only 12% of patients with moderate to severe AD reach clear or almost clear skin when treated with topical steroids only [4].

As Prof. Julien Seneschal, department of dermatology and paediatric dermatology, University Hospital Bordeaux, Bordeaux (France) pointed out, systemic immunosuppressants, namely Ciclosporin A are more effective than topical agents, but they are associated with potential risks and require extensive laboratory monitoring.

Figure 10: Nemolizumab is able to lower the pruritus (% change in an VAS) in patients with AD. Source: [9].



*P=0.002 vs placebo. **P<0.001 vs placebo.

"Systemic steroids are rapidly effective, but have an unfavourable risk/benefit ratio and should therefore be limited to a short treatment period", said Prof. Seneschal [5]. Therefore, there is a high need for effective and safe targeted therapies, particularly for patients with moderate to severe AD.

"Antibodies are very specific and therefore have much less side effects than we thought ten years ago" said Prof. Tilo Biedermann, Department of Dermatology and Allergology, Technical University Munich (Germany [6]). At the moment, different antibodies are tested in this indication. Targeting the type 2 helper T cell (Th2) pathway is most promising treatment for atopic dermatitis.

Nemolizumab: an effective itch treatment

Pruritus elicited by Th2-inflammation is well drugable, as showed the development of nemolizumab, an antibody that blocks the receptor of IL-31. The expression of IL-31 is increased in AD lesions and correlates with disease severity [7,8]. By interrupting the vicious cycle of itch and scratching, lesions might improve. Indeed, this could be shown in a phase II trial, where treatment with different doses of nemolizumab led not only to a reduction of itch of up to 63.1% in a pruritus VAS in the highest dose, but also to a reduction of EASI-score from baseline to 12 weeks of up to 42.3% in patients with moderate to severe AD [9] (Figure 10). "I think, you block only the side effect, but not the cause, because the pruritus is the consequence of inflammation, but maybe there is a niche for this product", said Prof. Biedermann. In addition, nemolizumab could be used together with a topical anti-inflammatory agent like topical corticosteroids TCS or in other dermatologic indications, where itch is the predominant symptom.

Another interesting target is IL-13. This Th2 cytokine plays a role in the pathophysiology of AD and is upregulated in acute and chronic AD lesions [10].

In a phase 2 study, the IL-13 antibody tralokinumab improved symptoms of AD in patients with moderate to severe symptoms: With the highest dose, 75.1% of patients achieved an improvement of EASI of more than 50% [11]. In this trial, tralokinumab demonstrated also significant improvement in quality of life and pruritus compared to placebo.

A new kid on the block is tezepelumab, a blocker of the pro-inflammatory cytokine thymic stromal lymphopoietin. This

cytokine is pivotal to the pathophysiology of widespread allergic diseases mediated by Th2 responses, including asthma and atopic dermatitis. Therapy with tezepelumab proved to be highly effective in patients with uncontrolled allergic asthma, and will probably also be assessed in AD [12].

IL-4/IL-13: most successful in clinical trials

Dupilumab is a human monoclonal antibody against interleukin-4 receptor alpha, that inhibits signaling of IL-4 and IL-13. Therefore, it is probably more effective compared to the sole blockade of IL-13. Both IL-4 and IL-13 are type 2 cytokines that are important drivers of atopic and allergic disease. Their expression is increased in AD lesions, and show a correlation with disease activity and severity. 671 and 708 patients with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment were included in the two randomised, placebo-controlled, phase 3 trials SOLO 1 and SOLO 2, [13]. In the SOLO I trial, in the dupilumab group 38% of patients (every week) or 37% 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% in the placebo group at Week 16 (primary endpoint), results of the SOLO 2 trial were similar. Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. "I think dupilumab is really the great improvement: In the trials we see the kind of effect we see with CsA, but without the side effects", said Prof. Biedermann. We have some conjunctivitis but DLQI is very good in these patients.

Dupilumab: sustained efficacy over a year

In the randomised, double-blind placebo-controlled phase 3 trial CHRONOS 740 adults with moderate to very severe AD was assigned to mid-potency topical corticosteroids along with topical calcineurin inhibitors as needed in steroid-sensitive locations, then randomised 3:1:3 to either subcutaneous dupilumab (Dupixent) at 300 mg once weekly, placebo injections, or dupilumab at 300 mg every 2 weeks on top of the topical therapy. CHRONOS participants were severely ill: Their median BSA of involvement was 55%, 60% were men, the median baseline EASI score was 30, and 50% of patients had an IGA score of 4, indicative of severe disease. Half of subjects had a history of asthma, nearly half had a history of allergic rhinitis, and one-third had a history of food allergies.

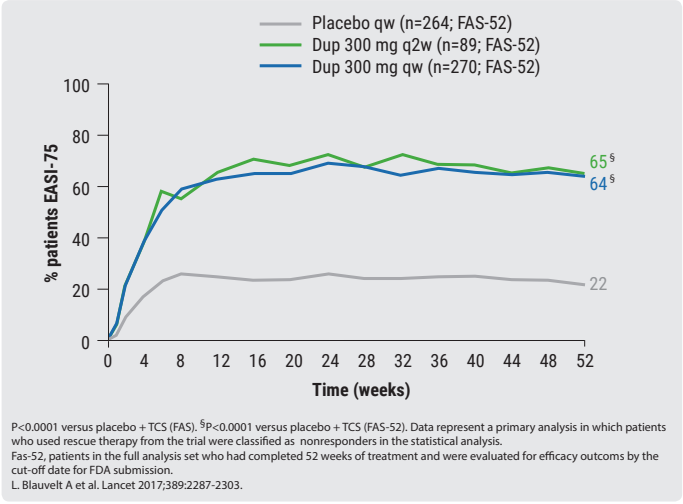
The main results of the CHRONOS trial were presented at the annual meeting of the American Academy of Dermatology this spring and published recently [4]. In this trial, dupilumab was strikingly effective: At 16 weeks, 39% of both dupilumab dosing groups compared to 12% of the placebo group achieved the primary endpoint of CHRONOS, an Investigators Global Assessment (IGA) of 0/1, which means clear or almost clear skin coupled with 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 ($P< 0.0001$; Figure 11). In addition, both dupilumab arms were significantly superior to placebo in several secondary endpoints, e.g. regarding the reduction on the EASI-by 75%. The agent also had a positive impact on pruritus, the symptom that bothers AD patients most. In the CHRONOS trial, dupilumab showed a good safety profile: Mild injection site reactions were twice as common in patients who got dupilumab than in those who received placebo injections. Also, conjunctivitis occurred in 14% of patients on weekly dupilumab and 19% with biweekly dupilumab, compared with 8% of controls. The mechanism of conjunctivitis is unknown, but it may be AD specific, because dupilumab was not associated with a higher rate of conjunctivitis compared with placebo in other indications (e.g. asthma).

Subgroup analysis shows: all patients benefit of dupilumab

A new subgroup analysis of the CHRONOS trial presented during the meeting shows that the novel IL-4 and IL-13 signaling blocker dupilumab was effective in all assessed subgroups [14]."Dupilumab with concomitant topical corticosteroids improved signs and symptoms of atopic dermatitis, compared with placebo injections regardless of age, sex, BMI, or prior history of asthma, allergic rhinitis, or food allergies," said Dr. Andrew Blauvelt, president of the Oregon Medical Research Center, Portland (OR/USA) who presented the new analysis. "The new subgroup analysis is a good thing for us. It means we don't have to look for the type of AD patient that may respond to this drug. We can say pretty much all comers, at least in this trial, did well despite their baseline characteristics," said Dr. Blauvelt.

Referring to this data, Prof. Biederman said that dupilumab seems to be an "One fits them all agent": However, he believes that the future of AD treatment is the personalised and targeted therapy of deeply phenotypted AD. An example is the anti-IL-5 blocker mepolizumab. Eosinophils play an important role in the pathogenesis of AD. As IL-5 is essential for eosinophil growth, differentiation and migration, the Anti-IL5 agent mepolizumab was assessed in a small trial in AD

Figure 11: Percentage of patients gaining an EASI-75 response in the CHRONOS trial: Source [4].



P<0.0001 versus placebo + TCS (FAS). §P<0.0001 versus placebo + TCS (FAS-52). Data represent a primary analysis in which patients who used rescue therapy from the trial were classified as nonresponders in the statistical analysis.
Fas-52, patients in the full analysis set who had completed 52 weeks of treatment and were evaluated for efficacy outcoms by the cut-off date for FDA submission.
L. Blauvelt A et al. Lancet 2017;389:2287-2303.

patients [15]. In this trial, therapy with mepolizumab did not result in clinical success, but this could have been due to the wrong patient selection. According to Prof. Biedermann, mepolizumab is likely effective in the subgroups of patients with a high eosinophil count. Likewise, patients with highly pruritic AD could benefit from the anti-IL-31R antibody nemolizumab, that might be applied with a topical anti-inflammatory agent.

JAK inhibitors –new oral treatment options in AD

"Not everybody with AD wants an injection. We are also in desperate need for safe oral medications for atopic dermatitis for long term use", said Prof. Emma Guttman-Yassky, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York (NY/USA). This gap could be filled by the once-daily oral inhibitor of Janus kinase (JAK) 1 and 2, baricitinib, according to preliminary data of a 16-week phase II randomised, placebo-controlled study including a total of 124 patients with moderate to severe AD [16].

Patients were randomised 4:3:3 to placebo, baricitinib 2 mg once daily, or baricitinib 4 mg once daily. All participants received background treatment with 0.1% triamcinolone cream starting four weeks before randomisation. The primary objective of the study was percent of the patients that achieved a reduction in disease severity of at least 50% as measured by the EASI. After 16 weeks of treatment with 4 mg baricitinib daily in combination with a topical steroid, 61 percent of patients (n = 38) achieved EASI-50, compared with 37% of patients (n = 49) treated with topical corticosteroid alone (P< 0.05). In addition, 57% of patients in the baricitinib 2 mg group (n = 37) achieved EASI-50, though the result only approached statistical significance vs corticosteroid alone (P= 0.065). However, the sample size was small and patients already received topical steroids for four weeks prior to randomisation, which reduced the baseline EASI and may have minimised differences between treatment arms and placebo.

According to Prof. Guttman-Yasski, the effect of baricitinib was noted early: at four weeks, EASI-50 was achieved in 68% of patients in the baricitinib 4 mg group and 62% of the 2mg group, compared with 16% of patients in the topical corticosteroid only group (P< 0.001). Baricitinib was tested in combination with topical steroids, "because we wanted to simulate the real-life situation, in which often patients use topical steroids together with a systemic treatment.

49% of patients treated with topical corticosteroid only, 46% of patients in the baricitinib 2mg group, and 71% of the 4mg group experienced side effects. The overall tolerability of baricitinib was good. The most common events in the 4mg group were nasopharyngitis, headache, upper respiratory tract infections and asymptomatic increases in creatine phosphokinase. After these encouraging results, a phase III investigation of baricitinib for atopic dermatitis is under way.

As Prof. Guttman-Yasski emphasised during her presentation, topical JAK inhibitors could play a role in the management of less severe AD. A phase II trial published last year tested a 2% topical tofacitinib preparation [17]. This JAK inhibitor is orally already approved for rheumatoid arthritis. Compared to a vehicle ointment, it improved Eczema Area and Severity Index (EASI) score at week 4 in 69 patients with mild to moderate AD. In addition, it had a distinct antipruritic effect. The authors conclude that the topical JAK inhibitor treatment could be the first novel topical option for 15 years in AD treatment.

References:

1. Simpson EL et al. J Am Acad Dermatol 2016;74:491– 8. doi: 10.1016/j.jaad.2015.10.043. Epub 2016 Jan 14.
2. Drucker AM et al. J Invest Dermatol 2017 Jan;137(1):26-30. doi: 10.1016/j.jid.2016.07.012. Epub 2016 Sep 8.
3. Yosipovitch G et al. Curr Allergy Asthma Rep 2008;8:306–311. 6
4. Blauvelt A et al. Lancet 2017 Jun 10;389(10086):2287-2303. doi: 10.1016/S0140-6736(17)31191-1. Epub 2017 May 4.
5. Seneschal L. Presentation D2T10.2D, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
6. Biedermann T. Presentation D2T10.2C, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
7. Nemoto O et al. Br J Dermatol 2016;174:296–304. . doi: 10.1111/bjd.14207. Epub 2015 Dec 19.
8. Bieber T, D'Erme AM, Akdis CA et al. J Allergy Clin Immunol 2017;139:S58–S64.
9. Ruzicka T et al. N Engl J Med 2017 Mar 2;376(9):826-835. doi: 10.1056/NEJMoa1606490.
10. Gittler JK, et al. J Allergy Clin Immunol 2012;130:1344–1354.
11. Wollenberg A et al. Poster P4496, 75th AAD, 3-7th March 2017, Orlando (FL/USA).
12. Corren J et al. N Engl J Med 2017 Sep 7;377(10):936-946. doi: 10.1056/NEJMoa1704064.
13. Simpson EL et al. N Engl J Med 2016 Dec 15;375(24):2335-2348. Epub 2016 Sep 30.
14. Blauvelt A. Presentation FC03.09, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
15. Oldhoff JM et al. Allergy 2005 May;60(5):693-6.
16. Guttman-Yassky E. Abstract 156, 26th EADV, 13-17th September 2017, Geneva (Switzerland).
17. Bissonnette R et al. Br J Dermatol 2016 Nov;175(5):902-911. doi: 10.1111/bjd.14871. Epub 2016 Sep 24.

Management of Acne: A Disease with Many Facets

Clinical appearance is of key importance in the selection of the most successful acne therapy. New insights into risk factors and frequent comorbidities were presented during the meeting and should be considered. Acne has a major impact of patient´s quality of life [1]. This is underlined by studies that found the emotional stress caused by this disease is comparable to that of chronic conditions like e.g. diabetes [2,3]. Acne is characterised by a chronic inflammatory process of the pilosebaceous duct, involving ductal obstruction due to altered proliferation and desquamation of the keratinocyte, increased sebum and Propionibacterium (P.) acnes [1]. New data show that stress and impaired thyroid function are associated to acne in adult women [4]. Another study presented at the congress confirmed a relation between intake of sugar or milk and worsening of acne. Especially sugar increases insulin growth factor 1, activating receptors in sebaceous glands and keratinocytes. The signalling endorses e.g. comedonogenesis and follicular inflammation [5].

The right approach for every patient

Acne has its highest prevalence in teenagers, but still 1% of men and 5% of women suffer from lesions at the age of 40 [1]. The disease can span over decades and therefore needs ongoing treatment that should be started as soon as possible [6]. In order to find the suitable treatment strategy, patients are generally classified according to clinical appearance and severity of the disease in to 4 groups of acne: comedonal, mild to moderate papulopustular, severe papulopustular/ moderate nodular, severe nodular/conglobate [7]. The morphology of present lesions has a large impact on the optimal choice of drugs [7]. Prof. Dr. Zrinka Bukvic Mokos, Dermatology, University Hospital Center Zagreb School of Medicine, Zagreb (Croatia), referred to topical retinoids (TR) as first line treatment for comedonal acne [6]. TR tackle acne from various angels. They act anti-comedogenic and comedolytic by reducing formation, maturing and number of comedones [6]. The anti-inflammatory mode of action of TR results from targeting cyclooxygenase-2 as well as down-regulating the expression of toll-like receptor 2 thereby inhibiting inflammatory mediators [8]. Furthermore, second generation TR like adapalene, regulate retinoid-dependent gene expression by hindering activity of other transcription factors [8]. The appearance of a potential adverse irritant contact dermatitis depends on amount, frequency and site of application as well as co-medication, type of skin and irritant washing [6]. According to Prof. Dr Mokos, all TR show similar efficacy against inflammatory lesions, but adapalene has the best profile when it comes to safety and tolerability and is furthermore preferred by the patients over tretinoin [6]. Second line options for comedonal acne are azelaic acid and benzoyl peroxide. Azelaic acid decreases the free fatty acid level, exerts mild anti-inflammatory action and has a comedolytic as well as antimicrobial effect [6]. Benzoyl peroxide (BPO) acts bacteriostatic without creating resistance, besides reducing free fatty acids and lowering reactive oxygen species (ROS), but shows little comedolytic effect [6].

The armamentarium for mild to moderate papulopustular acne consist of fixed dose combinations (FDC) of BPO, with either adapalene or clindamycin as first line. For second line there is the choice of BPO, azelaic acid, TR, FDC of clindamycin with tretinoin, or combination of systemic antibiotics with adapalene. "With fixed dose combinations you can address many different features of moderate papulopustular acne", said Prof. dr Mokos and continued that "in addition, the FDC of topical tretinoin and topical antibiotic will lead to better adherence". She also stressed that topical antibiotics must not be used in monotherapy as this can cause antimicrobial resistance in P. acnes and its global resistance has already been at 62% in 1996. With regard to the profile of side effects, among the systemic antibiotics doxycycline should be preferred over minocycline [6]. Prof. Dr. Mokos further advised to prevent antimicrobial resistance by not to combining topical with systemic antibiotics, never use antibiotics in maintenance therapy and generally not longer than 3 months.

"After achieving excellent results in initiation therapy, the biggest mistake is to stop treatment, as every patient needs a maintenance treatment", Prof. Dr Mokos emphasised. She suggested topical retinoid or azelaic acid for comedonal or mild to moderate papulopustular cases.

References:
1. Dawson AL, Dellavalle RP. BMJ. 2013 May 8;346: f2634.
2. Knutsen-Larson S et al. Dermatol Clin. 2012 Jan;30(1):99-106.
3. Saitta P, Grekin SK. J Clin Aesthet Dermatol. 2012 Mar;5(3):51-7.
4. Vergou T et al. Poster P2476, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
5. Dréno B. Poster 3280, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
6. Mokos ZB. Presentation D2T11.2A, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
7. Nast A et al. J Eur Acad Dermatol Venereol. 2016 Aug;30(8):1261-8.
8. Leccia MT. J Eur Acad Dermatol Venereol. 2015 Aug;29(8):1485-92.

Rosacea: New Perspectives on the Horizon

Diagnosing and treating rosacea is a currently evolving field, turning towards a feature and patient centered approach. New topical combination therapies show promise. Rosacea is a chronic inflammatory skin disease that is characterised by a recurrent centrofacial erythema [1,2]. Data on prevalence of disease vary geographically between 0.09 and 22% [1,3]. A presented Brazilian cross-sectional study found the strongest risk factors for rosacea in fair skin (phototype I or II), caucasian ethnicity and positive family history, whereas smoking is seen controversially [4]. The pathophysiology of rosacea is still not cleary understood, but it is known that alterations of the innate and the adaptive immune systems are involved [2]. Furthermore, triggering factors like e.g. UV exposure, extreme temperatures, alcohol, spicy food and Demodex mites are known [1,2].

Focusing on the phenotype rather than the subtype

The diagnosis of rosacea is based on the presence of transient erythema, teleangiectasia and inflammatory papules or pustules [2]. For management of treatment a classification by subtype exsists, dividing patients into erymathematoteleangietatic, inflammatory papulopustular, phymatous and ocular [2]. But there is a wide variety of overlap of the rosacea features between these types that may lead to difficulties in determining the clinical presentation, and confound severity assessment [2,5]. Therefore the novel "Gobal Rosacea Consensus Panel" recommends a phenotype based approach to diagnose and classify rosacea by its clinical characteristics: persistent centrofacial erythema associated with periodic intensification by potential trigger factors or phymatous changes are considered diagnostic; flushing, telangiectasia, inflammatory papules/pustules or ocular manifestation are looked upon as major, whereas burning, stinging, dry sensation of the skin and oedema as minor features [1,2]. Accordingly, treatment should focus on the clinical presentation.

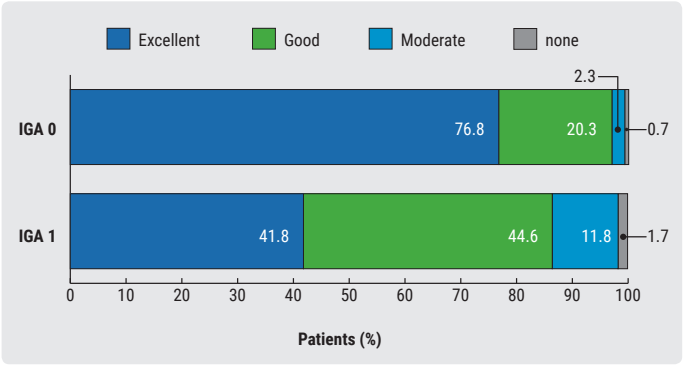
The wide choice of therapies

In her talk, Dr. Eva Remenyik, director of dermatology, University of Debrecen (Hungary), pointed to the necessity of trigger avoidance, photoprotection and barrier improving skin care besides specific treatment for all patients with rosacea [1]. For the management of erythema she recommended especially the use of topical α-adrenergic agonists such as brimonidine and oral beta blockers (e.g. carvedilol). "Brimonidine is 80% effective in decrease of flushing over 8-12 hours", Dr. Remenyik said. In case of paradox flushing she suggested to improve the skin barrier after exclusion of allergy [1]. "If you see papules you have to use anti-inflammatory medications like azealic acid, ivermectin and metronidazole", she proposed. The just published Swiss S1 guideline for rosacea also names topical and systemic antibiotics as well as topical and systemic retinoids for papuopustular rosacea [3].

A study of topical treatments presented by Dr. Linda Stein Gold, dermatologist, Henry Ford Medical Center, Westboomfield (USA) and her collegues on the EADV investigated the combination of brimonidine 0.33% gel with ivermectin 1% cream for mild to moderate rosacea [6,7] They found that the simultanoues therapy with both drugs demonstrated superior efficacy in comparison to vehicle. Furthermore it appeared that adding brimonidine to therapy from day 1 may lead to additional benefit and acceleration of treatment without loss of tolerability.

In case of the presence of pronounced phyma, topical or

Figure 12: Even for rosacea patients there is a notable difference between IGA 0 and IGA 1 results Source. [8]



systemic anti-inflammatory therapy might not be sufficient and interventional reduction can be necessary [1]. For those interventions the use of ablative laser is now more common than classical abrasive tools [3].

Setting the right treatment target

A pooled analysis of 4 different trials treating 1366 rosacea patients with either topical ivermectin 1% once daily, metronidazole 0.75% twice daily or placebo was done, in order to look for a potential difference between the goal 'clear' equalling an IGA of 0 and 'almost clear' describing IGA 1 [8,9]. Benefits of treatment were measured by DLQI, patient reported success and time to relapse. Significantly more 'clear' than 'almost clear' subjects had a clinically meaningful difference in DLQI (59% vs. 44%; $p < 0.001$). Within the group of 'clear' subjects 35% more reported 'excellent' treatment success than did the 'almost clear' patients (77% vs 42%; Figure 12) and the time to relapse was about 5 months longer when patients had reached the IGA 0 [9]. These results underline the importance of setting the treatment goal of rosacea patients to 'clear' [8].

References:

1. Remenyik E. Presentation D2T11.2B, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
2. Tan J et al, Br J Dermatol. 2017 Feb;176(2):431-438.
3. Anzengruber F et al. J Eur Acad Dermatol Venereol. 2017 Aug 21[Epub ahead of print]
4. Rocha R, Brenner FM. Poster P1023, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
5. Tan J et al. Br J Dermatol. 2017 Jan;176(1):197-199.
6. Gold LS et al. Poster P1695, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
7. Gold LS et al. J Drugs Dermatol. 2017 Sep 1;16(9):909-916.
8. Del Rosso et al. Poster P0062, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
9. Webster G et al. J Dermatolog Treat. 2017 Aug;28(5):469-474.

Hair Loss in Women

Female pattern hair loss (FPHL) is the most common cause of hair-loss in women and its prevalence increases with advancing age. Women who do not respond to minoxidil might benefit from additional therapies such as Platelet Rich Plasma or micro needling.

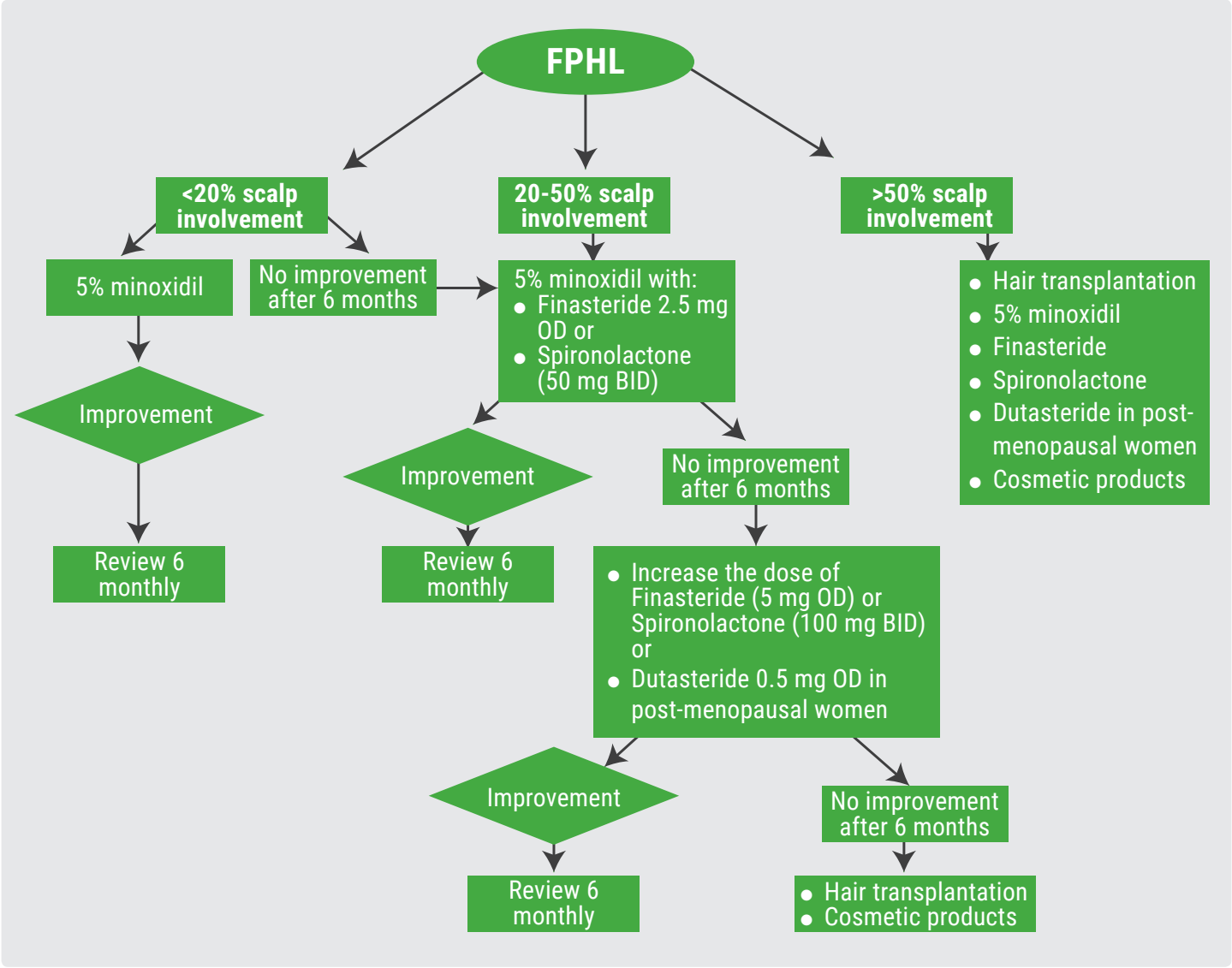
New and adjuvant treatment options

Female pattern hair loss (FPHL) has emerged as the preferred term for androgenetic alopecia (AGA) in females owing to the uncertain relationship between androgens and this entity [1].

Patients with FPHL often experience psychological distress and impaired social functioning. They typically present with thinning over the frontal, parietal, and central scalp with retention of the frontal hairline. It is characterised by a widened midline part toward the front of the scalp. According to Prof. Jerry Shapiro, New York University School of Medicine, New York (NY/USA) the diagnosis of a female pattern hair loss is usually straightforward from the history and examination of the hair and scalp [2]. Trichoscopy show hair shaft thickness heterogeneity. A scalp biopsy is rarely required to diagnose FPHL. It is only necessary to perform it to exclude other causes of hair loss. "Our data show that a very high percentage (38.6%) of patients with FPHL have histories of concomitant telogen effluvium (TE). AGA can be unmasked and made worse by episodes of TE, which are often triggered by many physiologic, medical factors including medication and extreme stress. Many medications can be responsible for hair loss: Acitretin, heparin, interferon alfa, lithium, valproic acid and warfarin can cause a telogen effluvium after a lag time of 2-3 months. Bleomycin, busulfan, cisplatin and other chemotherapeutics lead to an anagen effluvium 7 to 14 days after start of treatment.

"In my practise, the most frequent psychosocial stressor that can initiate a TE are the three B´s bereavement, breakup (divorce), bankruptcy", said Shapiro. In women, psychosocial stressors are often responsible for hair loss: In a twin study,

Figure 13: Treatment algorithm for female pattern hair loss. Source [4]



factors associated with increased frontal hair loss and thinning of hair included higher severity of stress [3].

According to a data analysis of 210 patients with a diagnosis of FPHL performed by Prof. Shapiro, only 38% of patients had normal vitamin D levels [4]. A history of hypothyreoidism, and hypertension were also common in these patients. "Therefore, in every patient with AGA, serum ferritin, vitamin D, and zinc levels should be routinely assessed", recommended Prof. Shapiro. Low serum ferritin, Vitamin D, and zinc levels have also been shown to be possible contributory factors in hair loss in another study [5]. In his practice, 5% minoxidil solution/foam is the first-line treatment of AGA. If patients fail to demonstrate improvement while on monotherapy, a combination of minoxidil with spironolactone or finasteride is given, as shown in his treatment algorithm of FPHL (Figure 13).

PRP : a valuable adjuvant therapy for nonscarring alopecia

During the PRP procedure, autologous plasma and platelets are first separated out and then injected into selected areas. 55% of the total blood volume is plasma and contains blood proteins, nutrients, vitamins, hormones, electrolytes and growth factors like IGF the latter is probably most responsible of the effect of Platelet Rich Plasma (PRP). "In our practice, we recommend 2 PRP sessions at 1-month intervals. Then we assess the effect with a hair count. If patients respond to treatment, we continue monthly PRP for another 4 months and evaluate. If there is no successful response, PRP has to be stopped", explained Prof. Shapiro. A randomised, placebo-controlled, double-blind study in 25 patients with AGA showed a significant effect after 3 PRP treatments,

1 month apart: Compared with baseline, PRP led to an increase in mean anagen hairs, telogen hairs and hair density (P< 005[6]). But not every patient responds to PRP, therefore it should not be performed as a monotherapy for FPHL.

Prof. Shapiro also uses microneedling in selected patients. In a pilot trial, weekly microneedling treatment together with minoxidil lotion was compared to a monotherapy with minoxidil in 100 men with androgenetic alopecia [7]. The combination therapy was significantly more effective regarding mean change in hair count at week 12, investigator evaluation according to a visual analogue scale and in patient´s evaluation. The authors conclude that microneedling is a safe and promising tool in hair stimulation to treat hair loss refractory to minoxidil monotherapy.

References:
1. Olsen EA. J Am Acad Dermatol. 2001 Sep; 45(3 Suppl): S70-80.
2. Shapiro J. Presentation D2T01.4D, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
3. Gatherwright J et al. Plast Reconstr Surg 2012 Dec;130(6):1219-26. doi: 10.1097/PRS.0b013e31826d104f.
4. Siah T et al. Trichology 2016 Apr-Jun;8(2):57-61. doi: 10.4103/0974-7753.188033.
5. Kantor J et al. J Invest Dermatol 2003 Nov; 121(5):985-8.
6. Alves R et al. Dermatol Surg 2016; Apr;42(4):491-7. doi: 10.1097/DSS.0000000000000665.
7. Dhurat R et al. Int J Trichology 2013 Jan;5(1):6-11. doi: 10.4103/0974-7753.114700.

Treatment of the Aging Face

Filler injections and Botulinum toxin (BTX) A are the most frequent non-surgical procedures of the aging face: New techniques and unusual indications were discussed during the EADV meeting.

Current trends in skin rejuvenation

Nonsurgical cosmetic procedures, including therapy with energy-based devices, neurotoxins, and dermal fillers, are increasingly utilised in combination approaches to improve outcomes. BTX treatment should be planned 2 weeks prior to filler. Using BTX first can help in assessment of the need for treatment of residual issues such as static lines and deep folds that can be treated with hyaluronic acid fillers. There are also new ways to use filler. "If we put a filler under a muscle, the muscle is stretched and the filler acts as a blocking point. This is a myomodulation principle, which is new in filler use", explained Dr. Koenraad De Boulle, Aalst Dermatology Clinic, Aalst (Belgium) [1]. An example for this procedure is lifting the lateral brow. According to his experience, this is a perfect indication, because if a brow lift is done with BTX A, there is always the danger of a brow ptosis.

Only by stretching and reframing with volume fillers, the effect of ample filler use can even be similar to that of a facelift. In this case, 8 to 12 injections points are necessary. Another novel indication is a shriveled earlobe. The aging process leads to a laxity and sagging skin, also at the earlobe. Likewise, an earhole that became too big in the course of time can be treated with 2 ml of a hyaluronic acid (HA) filler,

Dermal fillers can not only be used to fight signs of aging: Another new and rewarding indication for their use are atrophic acne scars. 2ml HA filler lead to a dramatic improvement of this condition.

Fillers: extremely safe, if used correctly

The recent concerns regarding the toxicity of the cross-linking agents of HA fillers are not founded. Butanediol diglycidyl ether is the most commonly used agent and indeed was found to be mutagenic. "But the extra cancer risk is infinitesimally small", said Dr. De Boulle. A review confirmed the fact that after degradation of crosslinked HA filler, they break down into harmless byproducts or into byproducts that are identical to substances already found in the skin [2]. Usually, dermal filler is very well tolerated. Complications are rare, and late complications such as late occurring nodules nearly always are the result of an infection [3]. Infections need to be avoided at all costs. Patients selection is critical, and dermal infections or an exacerbation of AD are a contraindication for the use of a filler. "If you have a late occurring nodule, do not start with steroids but with antibiotics and give a high dose long term", recommended Dr. De Boulle. Any excess HA can be dissolved with a hyaluronidase injection.

BTX in the lower face: an expert indication

Only glabellar folds and crow´s feet are approved indications of BTX A. However, according to the experience of Dr. Anthony Benedetto, dermatologist at Crozer-Chester Medical Center, Philadelphia (PA/USA) there are a lot more

rewarding indication for the use of BTX, such as perioral rhytides, chin puckering, and in general the lower face [1]. However, only experienced dermatologist should treat the lower face, because due to the midface interplay of muscles, there is always the chance of a functional impairment, e.g. mouth movements. BTX A injection in the depressor anguli oris can result in complications such as speech difficulties or an asymmetric smile. To treat perioral rhytides, 1 to 2 IU of BTX A per quadrant at or above the vermillion border should be injected. "It is really important to inject very superficially. The injection of the midline should be avoided not to flatten the cupids bow. This treatment leads to a nice eversion of the vermillion, even patients over 65 years can benefit of this treatment", said Dr. Benedetto. Another indication is the marionette lines, the downward corners of the mouth that gives the face a look of sadness or even disapproval. These "sad lines" at the corners of the mouth result from an imbalance between the action of the M. zygomaticus major, the M. risorius, the M. levator anguli oris and the M. depressor anguli oris together with the gravity.

In the lower face, minimal amounts of BTX are necessary to create an effect. "There is a narrow margin of success: 1 or 2 IU to much can cause mouth dysfunction", concluded Dr. Benedetto.

References:

1. De Boulle K. Presentation D3T02.4A, 26th EADV congress 13-17th September 2017, Geneva, Switzerland.
2. De Boulle K et al. Dermatol Surg 2013 Dec;39(12):1758-66. doi: 10.1111/dsu.12301. Epub 2013 Aug 13.
3. De Boulle K, Heydenrych I. Clin Cosmet Investig Dermatol 2015 Apr 15;8:205-14. doi: 10.2147/CCID.S80446. eCollection 2015.