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24th World Congress of Dermatology

International League of Dermatological Societies

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PEER-REVIEWED CONFERENCE REPORT

Treating Psoriasis in 2019
Although there has been tremendous progress in drug development during the last decade, there is still an unmet need in the care for psoriasis patients, for example in access to care.

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Dermal Reactions to Systemic Drugs
Immunotherapy and targeted therapy have both enabled a huge progress in oncology. On the other side of the coin are the prominent cutaneous toxicities that every dermatologist should recognise.

read more on PAGE 8

Optimising the Management of Keloids
Keloids are often very distressing and painful for the patient. As there is no one-size-fits-all when it comes to treatment, different options have to be weighed and advice from experienced experts can be very useful.

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

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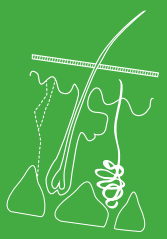

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Letter from the Editor

Prof. dr Peter CM van de Kerkhof

Dear Colleagues,

The 24th World Congress of Dermatology is the worldwide congress with participation of more than 14,000 delegates. Over 150 sessions were organised covering 43 topic areas. Delegates attended from more than 140 countries.

In this Medicom Conference Report you can find a selection of information across Dermatology. Perhaps the most important development in Dermatology is translational research, with impact on patient care. Also important are new drug developments and selection of treatments based on stratification of patient groups with clinical characteristics and biomarkers.

In psoriasis, there is a knowledge revolution on treatment selection based on clinical aspects and endotype and therapeutic revolution with the availability of targeted therapies. Availability of biosimilars with price reductions of TNF-alpha inhibitors has opened opportunities for prescribing biologics in underserved areas of the world. In particular in atopic dermatitis and hidradenitis chronica suppurativa, similar developments in innovation in personalised treatment and targeted therapies in inflammatory dermatoses can be seen. An important area is lupus erythematosus: Insights in the lupus complex are developing rapidly and new therapeutic approaches are available. It is important for dermatologists to follow these developments.

Not only in inflammatory dermatoses but also in oncology important innovations in targeted therapies and treatment selection based on molecular characteristics of the malignancies are developing rapidly, with clear advances in the management of melanoma. Current medications used in oncology may have cutaneous side effect and prevention of such side effects by EGFR inhibitors. What to do in case of cutaneous side effects to checkpoint inhibitors can be found in this review.

In daily practice, the management of keloids is a frequent problem. In this review some new aspects will be highlighted.

Biologics have opened the door for drug development of small molecules, which can be given as oral drugs and in the future as topicals if the molecular weight is sufficiently low. For diseases such as vitiligo and alopecia areata these developments have resulted in new therapeutic leads.

What is a congress without posters? A wealth of innovation was presented by presenters from all over the world. In this review you find some interesting communications.

Best Regards,
Prof. dr Peter CM van de Kerkhof
Senior professor of dermatology
Radboud University Nijmegen Medical Centre, the Netherlands

Biography

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

Conflict of Interest Statement

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

Treating Psoriasis in 2019

Biologics: biosimilars and lifestyle

Although therapeutic care of psoriasis has improved tremendously in the past decade, unequal access to medicine and specialist care still persists. Despite pharmaceutical progress, lifestyle management is also still of crucial importance because patient characteristics influence response to treatment.

Biologics have revolutionised psoriasis care and made total skin clearance an achievable goal [1]. A retrospective cohort study has shown a significant reduction for all hospital resources in the year following initiation of biologic therapy in 76 patients with severe psoriasis; and inpatient admissions was lowered by more than 80% [2]. Thus, at least some of the higher drug costs are offset by substantial reductions in the number and length of hospital admissions. "However, significant unmet needs remain with the use of biologics," said Prof. Jonathan Barker (King´s College London, United Kingdom). They are expensive, most patients have localised disease, and they are not 100% effective in all patients. In addition, the effect diminishes with time, and there are concerns of adverse events.

Biosimilars will improve access to treatment

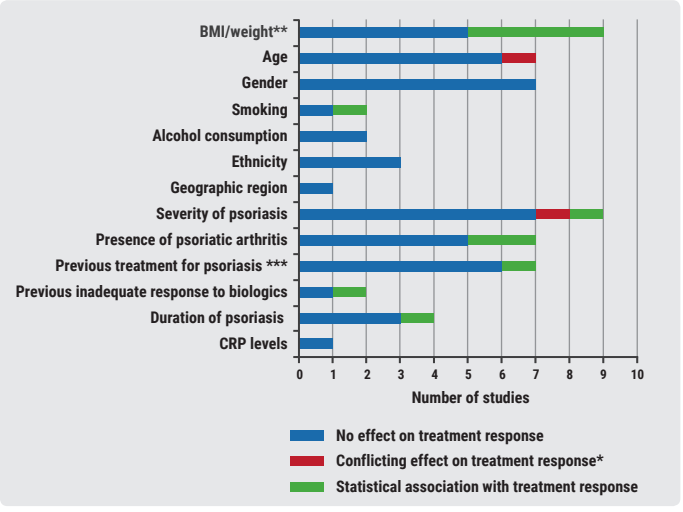
A huge step forward to a more cost-effective therapy is the introduction of biosimilars. They have the potential to improve access to treatment by reducing the financial burden on healthcare systems. In addition, the branded products have reduced their prices by about 20% in the United Kingdom in response to the availability of less expensive biosimilars and competition between the biosimilars themselves [3]. As Prof. Barker pointed out, a biosimilar is the same as the reference medicine with respect to the amino acid sequence and dose and route of administration. It is also highly similar to the reference with respect to structure, biological activity, efficacy, safety, and immunogenicity profile. Previous comparisons have shown no clinically meaningful differences to the reference medicine.

Access to psoriasis care is still unequal and shows a close relationship to the socioeconomic status of a country. According to the World Bank nomenclature, psoriasis is not on a list of diseases requiring public health programmes in low to middle income countries. In these countries, resource allocation for dermatology is very low, and they deal with a shortage of dermatologists. "Access to specialist care and therapy will probably remain a privilege. However, if therapy was less costly, it would be easier to fight for funding," said Prof. Barker.

Why lifestyle still matters

Psoriasis is associated with obesity, but the direction of this causal relationship remained unclear. A recently published study investigated this relationship using genetic variants as instrumental variables for Body Mass Index (BMI) and provides evidence that a higher BMI leads to a higher risk of psoriasis [4]. Another reason for improving patient's lifestyle is that response to biologic treatment is influenced by certain clinical factors (see Figure) [5]. Factors that do not influence treatment include alcohol consumption, CRP levels at baseline, gender, ethnicity, and geographic region. Other factors gave conflicting evidence, e.g. age and psoriasis severity. The one factor that consistently adversely affected response was an increased BMI. In contrast, there was no evidence of a causal effect of psoriasis on BMI. This highlights the importance of weight management for improvement of therapeutic outcome but also for prevention of psoriasis.

Figure: Potential factors associated with response to biologic agents in patients with psoriasis [4]



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Choosing the right biologic in psoriasis

Biologic therapies for psoriasis are currently prescribed in a neither efficient nor cost-effective way. Disease endotypes, genotypes, cytokines, or patient baseline characteristics could allow for a better guidance in treatment choice.

Therapeutic challenges in psoriasis management include disease clearance and maintaining remission effectively. New and developing insights into the aetiology of the condition, including the key genomic, immune, and environmental factors, have led to the development of precision therapies according to disease and drug endotype. Today, numerous biologics are approved with different targets. "However, it is critical to understand the real-world efficacy and safety profile of these agents," said Prof. Nick Reynolds (Newcastle University, United Kingdom) [1]. In an analysis of the 3,523 biologically-naïve patients in the BADBIR registry, drug survival of ustekinumab was shown to be superior to etanercept, infliximab, and adalimumab –even after accounting for relevant covariates [2]. As Prof. Reynolds pointed out, studies like this will aid clinical decision making when choosing biologic therapy for psoriasis patients.

Therapy according to disease endotype

Another way to choose the "right therapy" is to stratify response according to endotype analysis. An example of a successful therapy according to disease endotype is the inhibition of the interleukin(IL)-36 pathway for the treatment of generalised pustular psoriasis (GPP). Current genetic knowledge strongly links GPP to IL-36 signalling, and IL-36 is also highly expressed in GPP skin lesions [3]. In a first proof-of-concept study with 7 adults with moderate-to-severe GPP between 22 and 58 years of age, therapy with the monoclonal anti-IL-36 receptor antibody BI 655130 was remarkably successful. After a single dose of the antibody, all patients achieved a GPP Area and Severity Index Score of 0/1 (i.e. almost clear or clear skin) by week 4; 71% of patients already achieved this in week 1 or 2. Over 40% of patients were free of pustules within 2 days of treatment.

Another example of an endotype-driven selection of a biologic is the HLA-C*06:02 genotype, which is associated with a distinct psoriasis endotype. In an analysis of a psoriasis registry, with genome-wide genotype data of 1,326 patients, the HLA-C*06:02-negative patients were more likely to respond to adalimumab, whereas HLA-C*06:02-positive patients responded better to ustekinumab treatment [4].

Even certain cytokines can predict response to a biologic. In a trial published earlier this year, serum IL-19 levels at week 2 were predictive of outcome to ixekizumab at 16 weeks [5]. The lower the IL-19 levels were at 2 weeks, the better was the improvement in the Psoriasis Area and Severity Index (PASI) after 16 weeks.

Another analysis of the BADBIR registry showed that certain baseline characteristics are predicative of biologic treatment response [6]. The researchers investigated associations between 31 putative predictors and achievement of PASI 90 response at 6 months. In this analysis, white ethnicity was associated with a nearly 50% improved response, whereas obesity (>110 kg) and palmoplantar psoriasis were associated with significantly worse response. As Prof. Reynolds pointed out, the British Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium was founded to better understand determinants of response to biologic therapies and deliver, in close collaboration with commercial partners, a clinical test to predict response to biologic treatment in a cost-effective manner.

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Registries – an important research tool in biologics

Registry data on the use of biologics give important additional information on how the drug is behaving in daily practice.

As Prof. Bruce E. Strober (UConn Health, USA) pointed out, randomised controlled clinical trials (RCT) lasting up to 1 year now exist for all biologics and present the "gold standard" of evidence-based medicine [1]. However, they have several important limitations: they allow no long-term (>1 year) comparative efficacy assessments; milder patients are often excluded as only more severe patients are enrolled; and due to strict inclusion criteria, patients are generally healthier than in daily practice and have less comorbidities. No combination therapy is evaluated in these trials, even though combinations are very common in daily practice.

"To get a thorough picture of a drug, registries are required to establish comparative long-term effectiveness," said Prof.

Strober. They allow longer term cross comparisons, often beyond 1 year, and are a valuable tool to assess efficacy and safety in daily practice [1]. Questions that can be uniquely addressed with registries are real-world durability of response, effectiveness and safety in patients with major comorbidities, and the important question of whether treat-to-target is being practiced.

An example of a real-life assessment of systemic treatment and durability of response comes from the BIOBADADERM registry [2]. In this registry, the durability of response was compared between classic systemic therapies and biologics (i.e. TNF inhibitors and ustekinumab) prescribed from 2008-2013 in hospitals in Spain in 1,956 patients with moderate-to-severe psoriasis. Median follow up time was 3.3 years. In this analysis, biologics showed a higher drug survival than classics. The main reason for discontinuation was lack of efficacy (36.4%) and remission (27.2%).

Despite the large amount of data available on biologics, analyses from registries and RCTs that incorporate analyses of the newer therapies, such as selective IL-23 inhibitors, IL-17 inhibitors, and apremilast, are still lacking. One study published this year that tried to fill this gap is an analysis of the Danish DERMBIO registry, which compared the drug survival of the IL-17 blockers secukinumab and ixekizumab over 12 months [3]. Drug survival of ixekizumab was significantly higher compared with secukinumab. After a year 23.5% vs 0.0% of bio-naïve secukinumab and ixekizumab treated patients with moderate-to-severe psoriasis discontinued therapy. Surprisingly, drug survival was higher for ixekizumab even though secukinumab-treated patients had been treated with significantly fewer biologics before starting this drug.

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Atopic Dermatitis – What is New

Insights into pathogenesis of AD define novel therapeutic targets

Novel insights into the pathogenesis of atopic dermatitis (AD) are leading to many new treatment options–both systemically and locally. Prof. Graham Ogg (Oxford University, United Kingdom) pointed out that AD pathogenesis is complex, encompassing both genetic and environmental risk factors [1]. In addition, different therapeutic targets might be required for different types of AD, e.g. acute vs chronic or Western vs Asian.

In 2007, a null inactivating mutation in the filaggrin gene was recognised as an important predisposition factor for childhood eczema and eczema-associated asthma. Filaggrin null alleles are also an indicator of poor prognosis in AD, predisposing to a form of eczema that starts in early infancy and persists into adulthood [2]. In addition, dysregulation of innate and adaptive immunity plays a key role [3]. A transcriptome study of nonlesional skin and acute and chronic lesions has shown that acute disease was associated with significant increases in gene expression levels of major T(H)22 and T(H)2 cytokines, whereas T(H)1 activation can be found in the chronic lesional stage [4]. Therefore, different cytokines are involved in different AD stages (see Figure) [5-7]. Type-2 cytokines also inhibit filaggrin expression [8]. The interplay between type-2 inflammation and microbiome leads to further skin barrier degradation and inflammation, and *S. aureus* binding and colonisation [9]. Clinical studies with broad and targeted therapeutics have helped to elucidate the contribution of various immune axes to the disease phenotype. Immune activation extends well beyond lesional AD because non-lesional skin and the blood component harbour AD-specific inflammatory changes [9]. This emphasises the necessity of systemic therapy in moderate to severe disease.

All AD subtypes share Th2 activation

Th2 activation is common in all AD subtypes. Yet, stratification

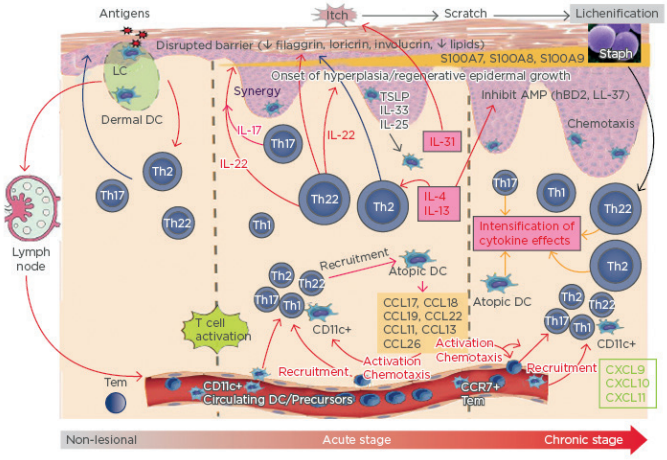
of biomarkers specific to different AD phenotypes may be important for developing a personalised medicine approach for AD [10]. The importance of the type-2 immune response with the cytokines IL-4 and IL-13 explain the efficacy of the IL-4/IL-13 blocker dupilumab, which impacts both the inflammation and the barrier dysfunction of AD [10]. In the phase 3 SOLO1 and SOLO2 trials, 48% of patients reached the primary endpoint of improvement of the Eczema Area and Severity Index (EASI) by 75% [11]. "This research cements AD as a reversible, immune-driven disease, like psoriasis", said As Prof. Emma Guttman-Yassky (Icahn School of Medicine at Mount Sinai Medical Center, USA). Results of a phase 2b study with the human IL-13 antibody tralokinumab showed that IL-13 inhibition is enough for controlling AD [12]. In this trial, tralokinumab significantly improved change from baseline in EASI score vs placebo (adjusted mean difference, -4.94) [12]. In another study with the IL-13 inhibitor lebrikizumab, 56.1% of patients treated with lebrikizumab every 4 weeks and 60.6% of patients treated with lebrikizumab every 2 weeks gained an EASI 75 response at week 16 [10].

Another interesting target is IL-31, commonly referred to as the "itch-cytokine", which is highly expressed in AD lesions and correlates with disease severity. In a phase 2b trial, the combination of topical corticosteroids and the anti-IL-31 agent nemolizumab was assessed in adults with moderate to severe AD and severe pruritus. Nemolizumab showed good efficacy for pruritus, but only modest efficacy on AD severity [13].

OX40 pathway: A first step towards disease modification?

An interesting novel target is the OX40 pathway. Inhibition of this costimulatory OX40 molecule appears to have improvements on lesional skin pathology and clinical disease activity parameters in patients with moderate-to-severe AD, suggesting its therapeutic potential in AD. In a first proof-of-concept study [14], administration of 2 intravenous doses of the anti-OX40 antibody GBR 830 administered 4 weeks apart induced significant and progressive improvements in clinical severity scores and in the cutaneous molecular AD signature lasting until day 71. "OX40 antagonism may help not only suppress the atopic Th2 inflammation, but also increase T-regulatory cells and achieve tolerance, which could enable us to influence disease modification," concluded Prof. Guttman-Yassky. Thus, GBR 830 may provide a novel therapeutic paradigm for patients with moderate-to-severe AD.

Figure: Pathogenesis of AD in different disease stages. Data derived from [5-7]



AMP, antimicrobial peptide; CCL, chemokine ligand; CXCL, CXC chemokine ligand; DC, dendritic cell; hBD2, human β-defensin-2; LC, Langerhans cell; TSLP, thymic stromal lymphopoietin. Figure kindly provided by Dr Guttman-Yassky.

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Combinations are hot in AD treatment

In her lecture, Dr Magdalena Trzeciak (Medical University of Gdansk, Poland) advocated combination therapy in AD [1]. Not only can topicals be combined, even novel targeted therapies work better with additional topical treatments. There are many good reasons for using combinations: they provide additive or synergistic efficacy compared to monotherapy, and as the required dose of individual agents can be reduced, combinations are often more tolerable compared with monotherapy.

Emollients are the cornerstone of AD treatment: they prolong time to flare, reduce the number of flares and the amount of topical corticosteroids (TCS) needed to achieve similar reductions in eczema severity [2]. Their use is also recommended in current guidelines for all AD patients [3]. Emollients restore the impaired barrier function of the epidermis, prevent microbes and irritants from entering the skin, reduce pruritus, and prevent water loss. Even petrolatum

has shown not only to be an "inert" moisturiser, but to significantly upregulate antimicrobial peptides and innate immune markers, and improve epidermal differentiation [4]. Emollient use in newborns at high risk for AD even lowers the relative risk for developing AD by about 50% [5].

Moisturiser: the base of every AD therapy

Moisturisers combined with active treatment gave better results than active treatment alone [2]. "Therefore, emollients and any other therapy are the most important combination in AD treatment", said Dr Trzeciak. Another useful combination is TCS and topical calcineurin inhibitors (TCI). "One should be aware of the fact that more than 40% of our patients have a TCS phobia," emphasised Dr Trzeciak. Due to their efficacy, TCS are still the first-line treatment in the acute phase. TCIs are indicated in problem areas such as the face, intertriginous sites, or anogenital area. They have the advantage that their use does not lead to atrophy, glaucoma, or cataracts. However, side effects are burning and irritation of the skin, and UV protection should be recommended to all patients.

Several trials have shown that the (sequential) combination of TCS and TCIs is more effective than monotherapy. During flares, the sole use of TCS is recommended, whereas treatment with TCIs should be performed between flares. "Between flares, TCIs should be applied to previously affected areas of skin, whereas emollients are indicated on the entire body," recommended Dr Trzeciak. A study on intermittent topical betamethasone butyrate propionate/tacrolimus sequential therapy showed that it improved lichenification and chronic papules of patients with AD more efficiently than the so-called proactive therapy, consisting of an intermittent topical betamethasone butyrate propionate/emollient sequential therapy after 4 weeks of treatment [6]. Another study showed that simultaneous application of a TCS and TCI is superior to monotherapy with TCI with regard to the scores for erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting [7]. Interestingly, the combination was also better tolerated. Also, the short-term combination of (diluted) TCS and/or emollients and wet wrap therapy was shown to be effective in patients with severe AD (defined as result in the Severity Scoring of Atopic Dermatitis [SCORAD] of >50) [8].

Combinations are also possible with novel targeted therapies, e.g. the IL-4/IL-13 inhibitor dupilumab. This was shown in the LIBERTY AD CHRONOS trial [9]. In this trial, all patients were treated with TCS with or without TCIs, and additionally received dupilumab (every week or every 2 weeks). Dupilumab added to standard TCS therapy improved AD signs and symptoms with acceptable safety [9]. The efficacy of a combination therapy of TCS and targeted treatment was also shown in a phase 2b study in which a combination of TCS with the anti-IL-13 agent tralokinumab was associated with early and sustained improvement in AD symptoms compared with TCS and placebo [10].

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Dermal Reactions to Systemic Drugs

Cutaneous adverse events due to EGFR inhibitors

Due to the key role the epidermal growth factor receptor (EGFR) receptor plays in skin physiology, cutaneous toxicities are extremely frequent during therapy with these agents. In his presentation, Dr Pietro Sollena (University of the Sacred Heart in Rome, Italy) pointed out that prophylactic strategies are most successful in lowering these side effects [1].

Single and multiple kinase inhibitors are now targeted therapeutic strategies for the treatment of human malignancies, producing variable outcomes compared with conventional cytotoxic therapy. However, 45-100% of patients treated with an EFGR inhibitor present with cutaneous toxicities [2]. This is due to the key role of EGFR signalling in skin [2]. As Dr Salena described, EGFR is centrally involved in the maintenance of normal skin architecture, in growth and repair processes, and in the regulation of the inflammatory response of the epithelia. EGFR is most prominently expressed in proliferating basal keratinocytes.

EGFR inhibition results in numerous adverse effects on the skin, such as apoptosis, atrophy, telangiectasia, and a reduced photoprotection. Skin toxicities are due to damage of the epithelial barrier, loss of antimicrobial mechanisms (especially protective mechanisms against *Staphylococcus aureus*), and the extensive release of inflammatory chemokines and cytokines [2]. Adverse events after therapy with an EGFR inhibitor follow a typical time course: acneiform rash is common in the first 4 weeks of therapy, followed by post-inflammatory effects. Xerosis starts after more than 5 weeks, and fissures typically emerge after 7 weeks. The last manifestation is paronychia. Cutaneous rash caused by EGFR inhibitors is characterised by follicular and perifollicular papules and pustules, pruritus and/or burning sensations. It typically occurs in a seborrhoeic distribution, primarily on the face, scalp, neck, and upper torso.

In a trial, a pre-emptive skin treatment regimen to avoid skin toxicities that included the use of skin moisturisers, sunscreen, topical steroid, and doxycycline was able to reduce the incidence of grade 2 skin toxicities by more than 50% [3]. This skin reaction had an early onset, but the severity of EGFR inhibitor-induced papulopustular eruptions often decreases with continued use of the drug. "Usually, the eruptions are sterile. Therefore, perform systematic bacterial swabs only in case of persistent, atypical, or late form of acneiform eruptions," recommended Dr Sollena. Late papulopustular rash is a distinct clinical entity [4]. It occurs after several months, usually on the limbs, sparing the face, and with pruritus and S. aureus superinfection. Xerosis and pruritus usually start more than 5 weeks after treatment and have a major negative impact on quality of life. Fissures are also complications appearing in later treatment phases [5,6]. Nail changes such as paronychia are less common and generally seen after a longer period of treatment [6]. This disorder is characterised by an inflammatory process involving the soft tissues around the nail. It can lead to infection and the consequent swelling and tenderness often affect daily activities. According to a meta-analysis, the overall incidence of all-grade nail toxicity was 17.2% in patients [7].

When undergoing treatment with EFGR inhibitors it is further important "to avoid skin irritants and soaking of hands and feet for a prolonged time period in soapy water," stated Dr Sollena. Patients are advised to make sure that their feet are dry before putting on shoes. The EGFR is also expressed on eye surfaces as well as in the tear and sebaceous glands. Up to 15% of patients receiving anti-EGFR therapy can experience ocular toxicity [8]. "Treating a skin reaction only once it occurs may not be the most effective management approach. Prophylactic strategies for cleansing, skin care, and sun protection are more successful in reducing the incidence of skin adverse events", concluded Dr Sollena.

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Management strategies for drug-induced mucositis

According to oncodermatologist Dr Vincent Sibaud (University Institute Cancer Toulouse Oncopole, France), drug-induced mucositis requires an early aggressive treatment [1].

Both chemotherapy and radiotherapy can induce mucositis; although with a different phenotype. Chemotherapy leads to a more diffuse mucositis with poorly limited lesions on a non-keratinised mucosa. Mucositis can be found in the buccal mucosa, on the floor of the mouth, the ventral side of the tongue, and the soft palate. The erythematous or ulcerated lesions are covered with a pseudomembrane. In contrast, radiation therapy leads to a severe mucositis localised within the irradiated field [2]. Mucosa can both be keratinised and/or non-keratinised.

mTOR inhibitors, such as everolimus and temsirolimus, are novel anticancer drugs that induce aphthous-like lesions in up to 50% of treated patients [3]. This is a class effect and the most frequent dose-limiting toxicity of these agents. Mostly, they occur within the first cycle (<8 weeks) after a median onset time of 10 days. Single or multiple, painful, well-circumscribed, round superficial ulcers are found on the non-keratinised mucosa. Targeted therapy, such as angiogenesis inhibitors and anti-EGFR agents, can also lead to mucositis/stomatitis. Usually, lesions are well demarcated, self-limiting, and aphthous-like, and sometimes occur with dysgeusia. Opportunistic infections, such as *candidiasis*, are also common.

Immune checkpoint inhibitors lead to specific oral lichenoid reactions [4]. They are either isolated or associated with skin or genital involvement. Lesions look plaque-like, ulcerative, or atrophic/erythematous. Another possible consequence of immune checkpoint inhibitors is sicca syndrome or even autoimmune bullous disorders [5]. Regular oral examinations should be offered to treated patients [6].

"With regard to mucositis management you have to be aggressive," recommended Dr Sibaud. This approach is also recommended in the ESMO Clinical Practice Guidelines, which state that every patient should receive instructions on daily oral supportive care. They should use a soft toothbrush and nonmedicated oral rinses (e.g. normal saline) [7]. Topical steroids, low-level laser therapy, pain management, and morphine mouthwash are also recommended. The SWISH trial demonstrated the efficacy of a prophylactic use of a dexamethasone-base mouthwash in 85 postmenopausal women receiving everolimus and exemestane for hormone-receptor positive metastatic breast cancer [8]. In this trial, prophylactic use of the mouthwash beginning on day 1 of cycle 1 (10 ml for 2 minutes, and spit; 4 times daily for 8 weeks) was advocated. By 8 weeks, the incidence of ≥ grade 2 stomatitis was 2%, without any grade 3; whereas in a historical cohort 33% had ≥ grade 2 stomatitis [8].

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Skin toxicity of immune checkpoint inhibitors

Immune checkpoint inhibitors have revolutionised cancer therapy, for example in the treatment of malignant melanoma. Unfortunately, the use of these agents is associated with many immune-related adverse events (irAEs).

In general, cutaneous toxicity is a predictive biomarker for clinical outcome in patients receiving anticancer therapy [1]. There is a clear association between cutaneous toxicity and efficacy of treatment not only with immunotherapy, but also in targeted therapy and cytotoxic chemotherapeutics.

Anti-programmed cell death receptor-1 (PD-1) antibodies act via blockade of the PD-1 receptor, an inhibitor of the T cell effector mechanisms that limit immune responses against tumours. "IrAEs may involve numerous organ systems, but mainly the skin," said Prof. Jennifer N. Choi (Northwestern Feinberg School of Medicine, USA) [2]. Of irAEs related to checkpoint inhibitors, 30-40% are cutaneous side effects [3]. Approximately 30% of patients suffer from immunotherapy-induced pruritus, which is associated with rash and xerosis. Another anti-PD-1 side effect is an exacerbation of psoriasis [4]. 71% of cases had a history of psoriasis. Mean time of onset between anti-PD1 initiation and psoriasis flare is 50 days. "If there is a known history of psoriasis, make sure patients are followed carefully during immunotherapy," suggested Prof. Choi. In addition, TCS treatment should be initiated early on with a maintenance regimen. The following regimen has

been successfully tested: TCS for 2 weeks, then topical calcipotriene cream during the week and TCS on weekends [2]. If this is not sufficient, phototherapy should be added while on immunotherapy. Vitiligo is another dermal toxicity, which occurs in up to 25% of patients [5]. Even rare cases of PD-1 induced scleroderma, lupus erythematosus, and alopecia areata are described in the literature [6,7].

The management of immunotherapy-related toxicities should follow the National Comprehensive Cancer Network Guideline. In this guideline, recommendations for continuing or halting immunotherapy can also be found [8].

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Lupus Erythematosus Today

New targets and biologics for cutaneous lupus erythematosus

Prof. Victoria P. Werth (University of Pennsylvania, USA) pointed out the need for new therapeutics in cutaneous lupus erythematosus (CLE) for patients resistant to conventional immunosuppressive agents [1].

Most therapeutic trials with novel agents focus on systemic lupus erythematosus (SLE) and exclude CLE patients. However, CLE and SLE share the same pathology. To solve this gap, a lupus community panel proposed to optimise future clinical trials [2]. If skin improvement is strong enough when nested in a SLE study, treatment should be made available for patients with CLE irrespective of whether they meet SLE classification. A couple of biologics have shown activity in CLE, including the IL-12/IL-23 inhibitor ustekinumab. Ustekinumab was shown to result in significant improvement in disease activity, assessed in the responder index 4 in the SLE disease activity index 2000 (SLEDAI-2K) [3].

B cells: an important novel target

The hallmark of lupus is dysregulation of B cells. B-cell-targeted therapies are therefore the focus of recent clinical research. Biologics targeting B cells are belimumab and rituximab. Belimumab is an antibody binding to the B lymphocyte stimulator (BLys), a factor involved in the survival or differentiation of B cells. The agent has shown to improve overall SLE disease activity in the most common musculoskeletal and mucocutaneous organ domains [4]. The chimeric anti-CD20 monoclonal antibody rituximab has been used with success in recalcitrant lupus manifestations [5].

Another approach: JAK inhibitors and IFNAR antibodies

First data from a double-blind, placebo-controlled, phase 2 trial with the Janus Kinase (JAK)1 and JAK2 inhibitor baricitinib showed that the 4 mg dose significantly improved signs and symptoms of active SLE in patients who were not adequately controlled despite standard-of-care therapy [6]. However, patients included in this trial had low skin activity, and showed no improvement in skin symptoms.

The type I interferon (IFN) system plays a key role in SLE pathogenesis: increased expression of type I IFN-regulated proteins can be found in the blood and target tissues of patients with CLE and SLE [7]. Cell signalling by all type I IFNs is mediated by the IFN-alpha receptor (IFNAR) [8]. This is the rationale for developing IFNAR antibodies. In a phase 2b, randomised, double-blind, placebo-controlled study, the efficacy and safety of the IFNAR antagonist anifrolumab was assessed [9]. Therapy with anifrolumab led to an at least 50% improvement in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with CLASI activity score ≥10 at baseline [9]. In this study, therapy had a greater effect size in patients with a high IFN signature at baseline.

Prof. Werth concluded that "SLE patients will probably benefit most from combination therapy – similar to the situation in oncology."

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Novel lupus classification will aid future research

Until 2015, there was no uniform definition of cutaneous lupus erythematosus (CLE), which made it difficult to identify a study population for observational and interventional trials [1].

In 2015, an expert group met for a consensus agreement and agreed that a single international classification scheme is needed to enable communication with patients and physicians [2]. The lack of classification criteria led to heterogeneity in observational and interventional research efforts, stated Prof. Joseph F. Merola (Brigham and Women´s Hospital, Harvard Medical School, USA). Particularly striking was the absence of classification criteria for discoid lupus erythematosus (DLE), the most common type of CLE. Therefore, a list of 12 potential clinical and histopathologic items to serve as classification criteria of DLE was developed in 2017 (see Figure) [3]. "This effort represented a key step towards the development of formal DLE classification criteria," concluded Prof. Merola.

Figure: Potential classification criteria of discoid lupus erythematosus. Modified from [3]

Morphology	Histopathology	Location
Erythematous - violaceous in color	Interface / vacuolar dermatitis	Location in the conchal bowl
Atrophic Scarring	Peri-vascular and/or peri-appendageal lympohistiocytic infiltrate	Preference for head and neck
Dyspigmentation	Follicular keratin plugs	
Follicular hyperkeratosis/ plugging (adherent scale, follicular in origin)	Mucin deposition	
Scaring alopecia	Basement membrane thickening	

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Hidradenitis Suppurativa

Various guidelines with much overlap

Different guidelines for the management of hidradenitis suppurativa have emerged in the recent years. As they are all based on the same data of evidence, a joint venture for consolidation would be desirable, argued Prof. Gregor Jemec (Zealand University Hospital, Denmark).

Hidradenitis suppurativa (HS) is a chronic, systemic condition with recurrent painful deep-seated nodules, sinus tracts, and abscesses that gravely impacts quality of life [1]. Appropriate treatment is often delayed due to under-recognition. "Many different organisations have created guidelines for the treatment of hidradenitis suppurativa independently of each other, and my conclusion is that we should really work together on these guidelines," said Prof. Jemec [2]. The European guidelines were published in 2015. They were followed by the British guidelines in 2018 and North American in 2019 [3,4,5]. These guidelines are based on the same body of evidence that lead them to similar recommendations, including: 1) acknowledgement of patient's morbidity; 2) medical treatment with tetracyclines, in combination with clindamycin and rifampicin, or adalimumab; 3) surgery and supportive care [2]. "So, we are all harvesting the same fruits over and over again and we are wasting immense amounts of work in doing this from scratch," explained Prof. Jemec, and he was happy to announce that during the WCD, the leadership of the various involved organisations have discussed the possibilities of future collaboration on this matter.

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Surgeries in hidradenitis suppurativa

There are many efficacious surgical options for hidradenitis suppurativa (HS), mostly needing long wound care and a committed patient.

Mostly, stage 3 HS is when surgery is discussed, but it can be also an option in solitary lesions [1]. "Surgery should definitely be considered in diffuse or nearly diffuse areas, unresponsive lesions with failed topical or systemic therapy, and in the case of considerable scarring," explained Dr Stanislav Tolkachjov (Mohs Surgery, USA). Possible good choices for HS are deroofing/unroofing, skin tissue-saving excision with electrosurgical peeling (STEEP), and wide surgical excision (WLE) [1]. Before deciding on surgery, the patient needs to understand that the disease can recur and has to be willing to go through long-term wound care and potential multiple procedures. In extensive gluteal disease, a diverting ostomy might facilitate difficult wound care.

Deroofing is a surgical option that can be done by the dermatologist. It can be used in stage 1 and 2 or as adjunct procedure in stage 3. After local and sometimes tumescent anaesthesia, a blunt probe is inserted to follow the sinus tract and the roof is cut and coagulated electrosurgically. Thereafter, the inflammatory material needs to be removed by scraping the floor with dry gauze or curette [1,2]. Especially in deroofing, CO2 laser vaporisation is a good surgical method for small but persisting lesions [3].

STEEP is an intermediate option between deroofing and WLE, removing more fibrous tissue than the first, but maximally sparing the subcutaneous fat [1,4]. STEEP and WLE are done under general anaesthesia. In comparison to WLE, STEEP is likely followed by fewer contractions. In WLE, the surgeon strives to remove the clinically diseased or fibrous tissue until normal fat is visualised. Primary wound closure is mostly avoided. Vacuum-assisted closure, negative pressure wound treatment with instillation, and grafts can be an option [1,5,6]. "About half of the time inflammatory nodules pop up right around the site of the operative field, but that doesn't mean that the patients aren't doing better in terms of their symptoms," Dr Tolkachjov commented. Procedures under local anaesthesia recur more often compared with the ones under general anaesthesia (40.6% vs 28.6%) [7]. Most patients showed relevant long-term benefit from WLE and no sinus tracts, fistulas, nor HS-related scar formation [1]. "Try putting yourself in the place of the patient with severe HS and you forget all about the difficulty of treating HS," Dr Tolkachjov invited his fellow physicians in conclusion.

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Antibiotics in hidradenitis suppurativa

Antibiotics still play an important role in hidradenitis suppurativa (HS). Overuse or arbitrary use should be avoided, stated Dr Dunja Ana Vekic (University of New South Wales, Australia).

Although HS is not primarily an infectious disease, bacteria contribute to the inflammatory drive [1]. The microbiome of healthy skin and HS is different and bacterial biofilms possibly play a role in chronic HS [1-3]. Various guidelines suggest antibiotics in mild-to-moderate HS and also for acute lesions of all stages [1,4, 5]. Currently, clindamycin 1% is the only recommended topical therapy for mild disease as it demonstrated benefit over placebo [1,4,6]. Oral antibiotics should be given for Hurley stages 2 and 3 and non-responders to topical antibiotics [1]. Approved agents for monotherapy are tetracycline, minocycline, and the most commonly prescribed doxycycline [1,5]. Combination therapy is recommended with clindamycin plus rifampicin [1].

Concerns for antibiotic therapy include substantial resistance rates, overuse or arbitrary treatment duration, adverse events influencing compliance, and lack of randomised controlled trials [1,7]. "The future management of HS will probably be moving from antibiotic therapy to a more personalised treatment and immunotherapy," was the opinion of Dr Vekic.

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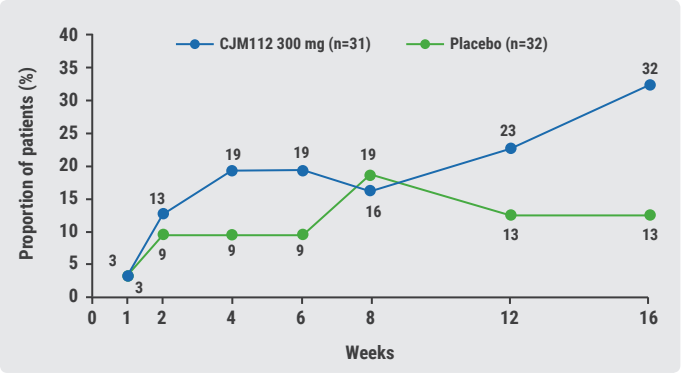
Biologicals beyond TNF blockade

Tumour necrosis factor (TNF) blockers are currently recommended in existing guidelines. Recent trials strive to find other targets for treatment as numerous immunological events are involved in hidradenitis suppurativa (HS).

"Looking at biologics beyond TNF blockade, I will concentrate on IL-1α, ß and the possible role of IL-17 and IL-23," said Prof. Brian Kirby (St. Vincent's University Hospital, Ireland) [1]. He emphasised that unlike in psoriasis, clinical trials will mostly show very high placebo response rates; one of the reasons that HS studies can be more difficult to interpret. In a not yet published phase 2 study without a placebo control group, bermekimab targeting IL-1α led to a positive Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12 in 61% of the TNF-naïve patients [1,2]. A placebo-controlled phase 2 study of anakinra, an IL-1 receptor antagonist showed 78% HiSCR response at week 12 for the anakinra group vs 30% for placebo (P=0.04).

Focusing on the Th17-pathway, a phase 3 study is already planned for secukinumab; although the results of the phase 2 study have not yet been published. A small case series showed improvement with secukinumab and 4 individual case reports stated successful treatment with this agent [1,3-7]. "The first real evidence that we have seen to date that suggested that IL-17 blockade may be useful, comes from an RCT testing the new molecule CMJ112," said Prof. Kirby. 66 patients of Hurley stage 2 or 3 were randomised to receive either CJM112 300 mg subcutaneously or placebo [8]. Primary endpoint was a decrease in HS physician global assessment (PGA) at week 16. It was met by 32% with CMJ112 and 13% with placebo (see Figure). There was a decrease in inflammatory lesions of 56% vs 30%. For IL-23 inhibition with guselkumab a phase 2 study is ongoing. Furthermore, IFX-1, an anti-complement factor C5a antibody, achieved HiSCR in 83% at day 50, but the study only comprised 12 adults and there was a significant number of adverse events [1,9]. "There are multiple potential targets for biological therapy of HS, but RCTs seem to be difficult and this may have to do with the disease itself," told Prof. Kirby. "Until now there is a paucity of good evidence, but several phase 2 trials are still ongoing," he concluded.

Figure: HS-PGA responder rate (primary endpoint) by treatment group up to week 16 [8]



An HS-PGA responder has an initial HS-PGA score of at least 3 at baseline that decreased by at least 2 points to week 16. A missing post-baseline value resulting from a missing assessment was imputed using the LOCF procedure.

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Small Molecules – What to Expect

Novel treatment options for many dermatologic indications

More and more new oral small molecules are entering the dermatologic arena. A relevant advantage over biologics is their oral bioavailability.

Small molecule inhibitors are organic compounds with different chemical structures and molecular weights ranging from 500 to 900 Da. As Prof. Lone Skov (Herlev-Gentofte Hospital, Denmark) pointed out, they have a simple structure and are easy to produce; hence, they are much cheaper than biologics [1,2]. Small molecules can easily diffuse across cell membranes to reach intracellular sites. Once the inhibitor enters the cells, it affects various other molecules and reduces cellular levels of specific proteins [3]. In comparison to larger molecules such as monoclonal antibodies, they have the advantage of possible oral administration and ease of combination with other treatments [3].

TYK2 inhibitor promising in psoriasis

Prof. Lars Iversen (Aarhus University Hospital, Denmark) pointed out that some small molecules have already been used for decades in the treatment of psoriasis [4]. In Germany and the Netherlands, methylfumarate has been the mainstay of treatment for psoriasis. Apremilast is a novel treatment option, approved for the therapy of psoriasis and psoriatic arthritis.

The JAK/STAT signalling pathway is also important in psoriasis. There are 4 Janus kinase (JAK) family members, JAK1, JAK2, JAK3, and TYK2. "A phase 2 study showed that TYK2 inhibition is very promising," said Prof. Iversen. In this double-blind, phase 2, dose-finding trial, the TYK2 inhibitor BMS-986165 was assessed in patients with moderate-to-severe psoriasis. In the highest dose (12 mg daily), 75% of patients reached a Psoriasis Area and Severity Index (PASI) 75 response after 12 weeks (P<0.01 compared with placebo) [5]. Larger and longer-duration trials of this drug are required to determine its safety and durability of effect in patients with psoriasis. "I believe that small molecules will definitely have a future in therapy of psoriasis," concluded Prof. Iversen.

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Long awaited oral therapy for moderate-to-severe AD

There is an urgent need for a non-steroid oral therapy for patients, particularly paediatric patients, with severe atopic dermatitis (AD). Small molecules could be the solution.

A couple of small molecules are in the pipeline for moderate-to-severe AD, such as several Janus kinase (JAK) inhibitors, began Prof. Thomas Bieber (University Medical Center Bonn, Germany) in his presentation [1]. In a phase 2b trial, the selective JAK1 inhibitor upadacitinib showed promising results [2]. Patients inadequately controlled by topical treatment, or for whom topical treatments were not medically advisable were randomised to once-daily upadacitinib monotherapy in 3 doses or placebo. The primary endpoint of this study was the mean percentage improvement in Eczema Area and Severity Index (EASI) score from baseline to week 16. At week 16, all upadacitinib dose groups experienced statistically significant improvements compared with placebo. Mean EASI scores improved 23% for placebo vs 74.4% for the 30 mg dose upadacitinib over the 16-week trial. Upadacitinib was also effective with regard to a couple of key secondary endpoints such as EASI 75 or EASI 90 response, or clear or almost clear skin according to investigator´s global assessment (IGA 0/1). Already after 2 weeks, the agent showed a rapid onset of action with significant differences compared with placebo. It also had a rapid antipruritic effect.

A recent phase 2 study showed a similar efficacy of the JAK1/2 inhibitor baricitinib in patients with moderate-to-severe AD [3]. At week 16, 61% of patients treated with 4 mg baricitinib and topical corticosteroids achieved an EASI 50 response compared with 37% with placebo. The agent showed rapid improvements in EASI, itch, and sleep disturbance with significant improvements seen as early as week 1. Baricitinib is currently approved for rheumatoid

arthritis. "At the moment, most of the experiences with JAK inhibitors are in rheumatoid arthritis patients. We do not know whether we will see the same side-effect profile in a dermatologic population," said Prof. Bieber.

Prof. Bieber concluded that there will be a competition between biologics and JAK inhibitors in the systemic treatment of AD. An advantage of the JAK inhibitors is their rapid onset of action and rapid itch control. Whereas biologics have a very good risk/benefit ratio, JAK inhibitors offer only an acceptable risk/benefit ratio and a narrow therapeutic window. The possibility of the oral intake will lead to a good acceptance, especially in paediatrics.

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Novel treatment options in alopecia areata and vitiligo

Small molecules have demonstrated remarkable efficacy in alopecia areata and vitiligo. In both autoimmune diseases, Janus kinase (JAK) inhibitors are the first specific effective therapy.

Alopecia areata (AA) is a non-scarring alopecia, which affects about 1-2% of the population. As Prof. Brett King (Yale University School of Medicine, USA) emphasised, there is a high medical need for treatment options, especially for advanced disease [1]. Research using human clinical samples and a mouse model demonstrated that cytotoxic T lymphocytes mediate AA in part through JAK signalling [2]. IL-15 and IFNγ are key cytokines in the development of AA and can be blocked by JAK inhibitors.

The first report of the efficacy of a JAK inhibitor was published after a psoriasis patient with concomitant AA was treated with tofacitinib and experienced a complete regrowth of hair [3]. After this experience, a first open-label trial with the JAK inhibitor tofacitinib was performed. In this trial, 32% of patients experienced a 50% or greater improvement in the Severity of Alopecia Tool (SALT) [4]. Another 32% of patients showed a hair growth of 5-50%, and 36% did not respond to treatment.

Since then, several publications have demonstrated efficacy of oral tofacitinib and ruxolitinib [5-9]. In a retrospective study with 90 patients, oral tofacitinib led to a clinic response in 77% of patients, with 58% achieving a greater than 50% change in SALT score over 4-18 months of treatment [6]. JAK inhibitors have also been effective in the treatment of adolescents or preadolescents [7,8]. According to the results of a pilot trial including 10 patients, tofacitinib is also active as a 2% ointment [10].

Prof. King recommended to start tofacitinib in a dose of 5 mg twice daily, or ruxolitinib 10 mg twice daily. All patients have to be screened for HIV, HBV, HCV, and tuberculosis prior to treatment. In addition, a complete blood count and comprehensive metabolic panel should be performed prior to treatment and 1 month after starting treatment, and then 3-4 months thereafter.

"I re-evaluate my patients in week 12, and consider increasing the dose if hair regrowth is inadequate", said Prof. King. A near-complete scalp hair regrowth is usually seen after 6-12 months of treatment. Unfortunately, treatment is likely necessary for maintenance of hair regrowth. The scalp usually responds better than eyebrows and eyelashes.

Vitiligo: a disfiguring autoimmune disease

In the last decade, research has determined the autoimmune pathways responsible for progression of vitiligo. Gene expression profiling in lesional skin of patients and a mouse model of vitiligo indicated an increase in expression of IFNγ and IFNγ-induced genes [11-13]. In this context, vitiligo is more similar to AA than it is to psoriasis [14]. Accordingly, the JAK/STAT pathways also play a key role in the pathogenesis of vitiligo. Both tofacitinib and ruxolitinib have shown efficacy in vitiligo patients [15,16].

In a 20-week, open-label, proof-of concept trial, 9 vitiligo patients were treated with 1.5% ruxolitinib cream twice daily [17]. At week 20, 4 patients with significant facial involvement had a 76% improvement of facial vitiligo. Three out of 8 patients responded on body surfaces, and 1 patient responded on acral surfaces [17]. "Ruxolitinib cream may therefore offer a valuable new treatment option," concluded Prof. King.

Another trial hinted to the fact that repigmentation in vitiligo using tofacitinib may require concomitant light exposure [18]. In this retrospective case series, 5 patients achieved some repigmentation at sites of either sunlight exposure or low-dose narrowband ultraviolet B phototherapy.

Three clinical trials are currently ongoing with JAK inhibitors in vitiligo: 2 studies of topical JAK inhibitors (i.e. a phosphate

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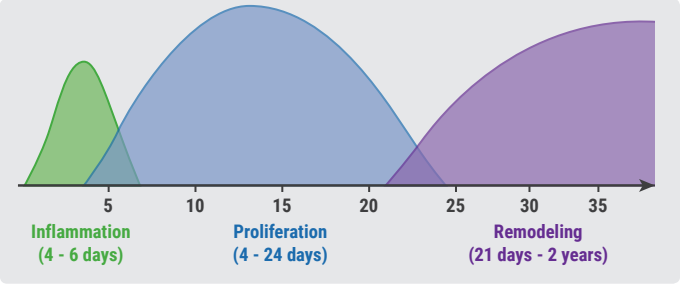
Optimising the Management of Keloids

Keloids: a faulty switch in wound healing?

Keloids emerge when normal wound healing is disturbed. Although much is known about the pathogenesis, the reasons for induction of keloids still remain unclear.

"Normal wound healing is like a good story: there is a beginning, a middle, and an end," Prof. Greg Goodman (Monash University, Australia) began his lecture [1]. Normal wound healing starts with an inflammatory phase (see Figure), with activation of the clotting cascade as well as action of cytokines and the attraction of immune cells. Next is the proliferative phase, which lasts for about 6-7 weeks. The fibrin plug is replaced by granulation tissue, fibroblasts generate collagen 3, extracellular matrix and re-epithelialisation takes place as keratinocytes migrate across the wound surface. Angiogenesis also induces the production of immature leaky blood vessels to allow easy access of nutrients. During the final remodelling phase, the granulation tissue changes from type 3 collagen to type 1, the immature vessels regress, and the now stronger scar tissue contracts.

Figure: The 3 phases of normal wound healing. Modified from [1]



"We need to think of keloids as a faulty switch in the transition from the proliferation to the remodelling phase with a failure of apoptotic control of reticular dermal healing," explained Prof. Goodman. Overexpressed growth factors and increased activity by fibroblasts can be observed in keloids; proinflammatory factors continue to be upregulated; and a gap between extracellular matrix stiffness and cellular stiffness increases the likelihood of keloid progression [2]. Lastly, keloids have a 20-fold increase of collagen levels, the fibroblasts proliferate faster and the balance is lost between pro- and anti-inflammatory mediators [1]. There may be a genetic basis for the inability to turn of the proliferative phase and enter the remodelling phase. "We have a few details of what is abnormal and how it happens, but virtually no knowledge of why it happens," concluded Prof. Goodman.

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Treating keloids with injections

Injecting keloids is one of the common treatment approaches. Outcomes and relapse rates are best if different agents are combined [1].

Three main injectable drug classes are often used in the treatment of keloids and hypertrophic scars: corticosteroids (CS), antimetabolites (e.g. 5-fluorouracil [5-FU]), and anti-tumour agents (e.g. bleomycin) [1,2]. Among other things, steroids suppress the inflammatory process, reduce the synthesis of collagen and glycosaminoglycans, and inhibit fibroblast growth [3].

The most commonly used CS is triamcinolone acetonide (TAC) in a dose of 10-40 mg/mL; but different treatment intervals are reported on in literature [3]. Used as monotherapy, CS are primarily efficacious in 50%-100% but show a substantial recurrence rate of 9%-50% [3]. In a comparison between TAC injections and 5-FU injections over 6 months, no statistical significance was found, but 5-FU had fewer local adverse events such as skin atrophy (TAC 44% vs 5-FU 8%) or telangiectasia (TAC 50% vs 5-FU 21%) [4]. Superior results were achieved by a combination of TAC/5-FU, which showed no recurrence at 6-months follow-up [5]. The combination may also have fewer adverse effects [3]. When tested against 5-FU, bleomycin had better data for efficacy and remission that were irrespective of age, sex, scar site, and duration of disease [6]. Recurrence rates for monotherapy with bleomycin were 0-15% [3]. Besides TAC and 5-FU, botulinum toxin A is currently being investigated and has been shown to modulate activity of keloids and hypertrophic scars by acting on expression of fibroblast and modulating their activity [7-10].

The injections themselves can be painful, but so can the administration of lidocaine [11]. "Benzyl alcohol in bacteriostatic saline is a preservative. It gives you 30 seconds of painless anaesthesia," was the practice tip of Dr David M. Ozog (Henry Ford Hospital, USA). He advised a preload of bacteriostatic saline to be immediately followed by lidocaine into the centre of the saline. "You have to do it quickly," Dr Ozog added. "You cannot inject the bolus of benzyl alcohol and then wait a little with the lidocaine - it has to be right there."

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Treating keloids with lasers

Lasers are rarely indicated as a monotherapy of keloids. However, they are recommended as a means to facilitate delivery of topical drugs, according to Dr Matteo Tretti Clementoni (Laserplast, Italy) [1].

"Lasers play a fundamental role in the treatment of hypertrophic scars," said Dr Tretti Clementoni. Placing this in perspective, he explained that they give unsatisfactory results in most cases as monotherapy [1]. "I think that some distinctions should be made regarding specific anatomical sites, the dimension of the keloid, and the use of lasers in combination with other therapies," Dr Tretti Clementoni continued. For example, CO2-ablation showed a recurrence rate of 100% in 18 weeks [2]. In a review, best results and lowest rates of recurrence were found in ablative laser treatment of small keloids of the earlobe [2]. Vascular lasers showed their best results when pulsed dye laser therapy was combined with triamcinolone acetonide (TAC). The evidence on Nd-YAG laser use is rather contradictory in terms of recurrence rates [1]. Several studies have investigated the impact of a same-session use of ablative fractional laser to assist increased drug delivery deeper into the skin. The rationale being the synergistic action in enabling the agents to penetrate the stratum corneum through laser-created microscopic treatment zones [2].

Combination of topical drug and laser causes less pain

The combination of topicals with laser not only has shown to be effective, but a study assessing the pain of the treatment found a mean pain score of 1.1 (laser+topical drug) vs 6.1 (steroid injection alone) [3-6]. For ear keloids, Dr Tretti Clementi achieved very good results by combining laser cutting of the keloid plus fractional deep treatment of the bed plus laser-assisted drug delivery with TAC, 5-fluorouracil, and botulinum toxin A [1]. Another practical tip from Dr Ozog (Henry Ford Hospital, USA) was the use of laser pre-treatment when addressing truncal or painful keloids by a multi-step regimen [7]. First, one should achieve complete anaesthesia with bacteriostatic saline followed by lidocaine. Then he advised to soften and treat the scar with a pulse dye laser (1.5 milliseconds in a 10 mm spot size at 7 joules). "This does two things," explained Dr Ozog. "It has been shown to downregulate molecular pathways involving keloids, but it also immediately, within 20 to 30 seconds, creates an oedematous plane, which allows us to easily inject the keloid." Another possibility would be to apply cryotherapy for 3-5 seconds that will cause the same

oedema. He stressed that when employing this technique, dermatologists will have to get accustomed to inject more superficially than they are used to as they must visualise the steroid going into the keloid. "We have seen life-changing results in patients with sternal or painful keloids," he reported.

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What the future of keloid treatment could hold

Less explored therapies include procedures with injection-free drug delivery that may gain further importance in the armamentarium for keloid treatment [1].

A new method of treatment application that has recently been investigated is thermomechanical drug delivery into keloid skin [2]. In a retrospective study, 7 patients were given a mix of triamcinolone acetonide (TAC) plus 5-fluorouracil in a ratio of 1:9 after skin treatment with a titanium tip heated to 400°C. After 8 topical thermal ablations (1 ablation performed every 2-3 weeks), mean keloid Vancouver Scar Scale score was significantly reduced from 8.6 ± 1.2 at baseline to 5 ± 2.7 (P=0.001) [2].

"As a principle after surgery of a keloid of the earlobe, the wound should be closed without tension," said Dr Somesh Gupta (All India Institute of Medical Sciences, India) in his lecture on less explored and experimental treatments for keloids. Injections, pressure, or a combination of both are possible options to avoid recurrence after surgery, according to Dr Gupta [1]. "In general, we do not give injections because they are painful. We often prefer to use pressure earrings using neodymium magnetic discs," he continued. This easy and economically available possibility should be applied for about 5-6 hours a day, in order to avoid necrosis.

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Malignant Melanoma – Advances in Management

Will malignant melanoma become a curable disease?

Melanoma therapy has been revolutionised. Five-year survival after metastatic cancer is a marker for highly likely continuous complete remission (CR), whereas 10-year survival after metastatic cancer is a marker for definitive cure [1,2]. In this respect, modern therapeutic options have proven to lead to a continuous CR, said Prof. Claus Garbe (Eberhard Karls University, Germany) [1].

In the COMBI-d and COMBI-v trials, first-line treatment with dabrafenib plus trametinib led to long-term benefit in approximately one third of the patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation [3]. More than a decade ago, the diagnosis of metastatic melanoma was still a death knell: long-term survival was non-existent, only 3% of patients survived for 5 years [4]. "The first glimmers of hope were seen in 2010, with the publication of data on ipilimumab and vemurafenib," said Prof. Garbe. With the arrival of immunotherapy and targeted therapy, long-term survival was still rare in about 10-20% of patients [5,6]. The modern era of melanoma therapy started with combination therapy [3,7]. With the combination of encorafenib and binimetinib, 39% of patients survived 5 years [7]. However, as Prof. Garbe pointed out, this is by no means the end of the story: even more effective combinations are yet to come.

BRAF inhibition is known to increase T cell infiltration, melanoma antigen expression, and PD-1/PD-L1 expression,

which may lead to synergistic activity with anti-PD-1 therapy. This was the rationale to assess therapy with the anti-PD-1 antibody spartalizumab in combination with dabrafenib and trametinib in previously untreated patients with advanced *BRAF* V600-mutant melanoma. [8]. In the COMBI-i trial, the triple therapy showed a promising and durable overall response rate of 75% with a CR in 33% of patients. With more than 15 months of follow-up, median progression-free survival was not reached. The safety profile was manageable. "With these sophisticated multimodal combinations, we will probably reach long-term survival rates of 60 to 79%," concluded Prof. Garbe.

When to stop therapy?

Prof. Caroline Robert (Institute Gustave Roussy, France) discussed the question whether therapy can be halted after patients reach CR [9]. With immunotherapy, this is obviously the case, as was shown by the long-term results of the KEYNOTE-001 study in patients who experienced CR with pembrolizumab [10]. Of 655 treated patients, 105 (16.0%) achieved CR after a median follow-up of 43 months. Therapy with pembrolizumab was discontinued by 91 patients (86.7%). The 24-month disease-free survival rate from time of CR was 90.9% in all 105 patients with CR and 89.9% in the 67 patients who discontinued pembrolizumab after CR. The low incidence of relapse after approximately 2 years from discontinuation provides hope for a cure–at least in some patients.

Unfortunately, this is different with targeted therapy. In a published case series of 12 patients with metastatic melanoma who achieved a CR and then ceased BRAF inhibitor-based therapy, 6 patients subsequently relapsed, and there were no predictors for disease recurrence [11]. However, all patients were suitable for subsequent therapy, including recommencing BRAF/MEK inhibitors with at least 2 out of 3 responding.

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Surgical management of melanoma

Surgical therapy is mainly indicated in stage III disease, whereas systemic medical treatment now plays a key role in stage IV melanoma.

Prof. John Kelly (The Alfred Hospital, Australia) stated that surgery for melanoma has changed [1]. Sentinel lymph node biopsy (SLNB) is still indicated in all melanomas equal to or greater than 1 mm. However, its predictive value is limited given that 62% and 48% of patients with intermediate or thick melanomas, respectively, who have positive results will still be alive at 10 years. On the other hand, 35% of patients with thick tumours will die within 10 years after a negative result [2].

Surgery remains the standard of care for clinically evident stage III disease, also after neoadjuvant treatment. In stage IV, surgery is only indicated in easily resectable or imminently threatening melanoma, because stage IV is now the mainstay of systemic therapy. Surgery is used initially for brain metastases. In addition, it can be a valuable option for patients progressing during immune or targeted therapy.

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Best of the Posters

Statin use elevates risk of eczema and atopic dermatitis

A cohort study showed that patients taking statins are at a significant higher risk to develop eczema/atopic dermatitis compared with individuals not taking these medications [1]. As statins are frequently prescribed in the elderly, dermatologists should be aware of this association.

Statins are widely prescribed to patients with lipid disorders or heart disease due to their proven cardioprotective efficacy. They inhibit hepatic cholesterol synthesis and increase hepatic cholesterol uptake. In addition, they have immune-modulating effects [2]. The latter may interfere with eczema or atopic eczema. Indeed, there are published reports of statin-induced dermatological complications, although the frequency of eczema has not been assessed previously [3,4].

In this retrospective analysis, data was derived from medical records of patients admitted to the University of Iowa hospitals and Clinics. Patients with heart disease who were taking a statin before 2012 were compared with patients with heart disease who had never been prescribed a statin. In both groups, the development of eczema/atopic dermatitis was assessed over a time period of 6 years. The data was stratified by various factors including gender, age, weight, BMI, alcohol consumption, and smoking status.

Patients taking statins had an incidence of eczema of 6.77% compared with 1.68% in those not taking statins (P<0.001). This translates into a >4-fold elevated relative risk of developing eczema in statin users. Male patients had a higher risk for eczema compared with female patients. There was also a higher incidence in eczema in non-Caucasians compared with Caucasians. Patients in the age group >60 years even had a 7 times higher relative risk to develop eczema compared with patients in this age group that did not take statins.

The study authors plan to elucidate this association further in a prospective trial to assess whether there are differences in the intake of different statins with respect to development of eczema.

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Novel selective IL-23 blocker highly effective over 2 years

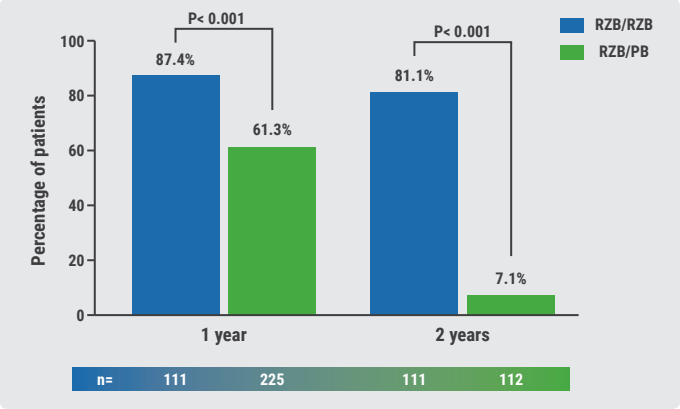
Results of the phase B of the IMMhance study show that more than 80% of patients continuously treated with the IL-23 inhibitor risankizumab reach complete or almost complete clearance of their psoriasis after two years [1].

The IMMhance study consisted of 2 phases: results from the first phase were previously reported, and showed that after 16 weeks of treatment, the selective IL-23 inhibitor risankizumab (n=407) met the co-primary endpoints Psoriasis Area and Severity Index (PASI) improvement by 90% and complete or almost complete clearance of skin lesions according to physicians global assessment (sPGA 0/1) vs placebo (n=100) (P<0.001). The second phase (week 28 through week 104) of this trial evaluated the efficacy and safety of continuous therapy with risankizumab vs randomised withdrawal, as well as re-treatment.

Patients who achieved sPGA 0/1 at week 28 with risankizumab were re-randomised to continue either risankizumab (n=111) every 12 weeks or to withdrawal (n=225). The primary endpoint in the second phase of the study was percentage of patients that reached sPGA 0/1 at 1 year; ranked secondary endpoint was achievement of sPGA 0/1 at week 104 (2 years) among re-randomised patients.

Both the primary and secondary endpoints were achieved for risankizumab compared with placebo (P<0.001; see Figure). Median time to relapse (sPGA >3) was significantly different between patients re-randomised to risankizumab compared with those re-randomised to placebo (placebo 295 days vs risankizumab not determinable due to low number of relapses in this group; P<0.01). In addition, an increasing proportion of patients treated with continuous risankizumab achieved

Figure: Primary and secondary efficacy endpoints of sPGA 0/1 at 1 and 2 years [1]



RZB, risankizumab; PB, placebo; sPGA, physician´s global assessment.

PASI 100 and sPGA 0 over time during the treatment period in part B.

After 2 years, 81.1% of patients achieved sPGA 0/1. Among 153 patients re-randomised to placebo who relapsed, 83.7% regained sPGA 0/1 after re-treatment with risankizumab (re-treatment was started after the sPGA score regressed to ≥3 during withdrawal). Treatment-emergent adverse events were comparable across treatment groups at week 16 and in re-randomised arm from weeks 16-104. Most frequent treatment-emergent adverse events in all groups were infections. No new safety signals emerged over 2 years.

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