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REVIEW ARTICLE

Dermatology today and tomorrow: from symptom control to targeted therapy

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Abstract For many decades and until recently, medical approach to dermatologic diseases has been based on the physician's ability to recognize and treat symptoms. Nowadays, advances in the understanding of the biology of diseases and in technologies for intervening against them have allowed physicians to diagnose and treat underlying disease processes rather than simply addressing the symptoms. This means that rather than addressing 'the disease in humans', physicians can now address the particular pathologic (biologic, molecular) disturbance as it presents in the individual patient, i.e., physicians now can practice something much closer to 'personalized medicine', leading to greater benefits for the patients and the health of society in general. The deeper understanding of ultraviolet radiation, the importance of photoprotection and increased knowledge about signalling pathways of melanoma and carcinoma have led to more complete care for the dermatologic patient. The current popularity for excessive exposure to the sun, without adequate application of the appropriate photoprotection remedies, is the origin of melanoma, but also for the weakening of the structure and functions of the skin. Indeed, fragility of the skin can affect humans around the world. In the senior population, this skin fragility is accompanied by pruritus, whereas atopic dermatitis is an inflammatory disease with highest prevalence in children and adolescents. Acne, the number one reason for dermatologic consultations worldwide, increases its prevalence in adolescents and in females. Senescent alopecia affects humans after menopause and andropause. The articles in this publication present an overview of the current advanced understanding of the diagnosis and therapeutic approaches in 6 fields of dermatology – dermatopaediatry and gerontodermatology, oncodermatology, hair loss, atopic dermatitis, photoprotection and acne – and thereby serve as a useful compendium of updated information and references for all healthcare professionals who see patients with presentations of the symptoms of these diseases.
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From paediatric to geriatric dermatology: focus on populations with fragile skin

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Highlights in fragile skin

Fragile skin is defined as a dysfunction of the epidermal barrier, with consequently decreased protection against invasive pathogens and environmental assaults and loss of regulation of water and electrolytes. Neonates and infants have physiologically fragile skin due to the immaturity of the skin barrier, whereas the elderly have fragile skin due to age-related changes in structure and function. Xerosis in neonates and infants can lead to atopic dermatitis (AD), but studies suggest that the risk of developing AD can be reduced by application of appropriate emollients and moisturizers. In the elderly, conditions such as incontinence-associated dermatitis may be treated with emollients along with first-line topical corticosteroid therapy. Pruritus, which is common in children and the elderly, may require systemic treatment in addition to topical corticosteroids or topical calcineurin inhibitors. New topical agents such as phosphodiesterase-4 (PDE4) inhibitors are becoming available, and new targets for systemic treatment of pruritus are under investigation.

Introduction

The skin of newborns and infants and of elderly adults is characterized by its fragility, i.e., dysfunction of the barrier that protects the human body against external stressors. 'Fragile' skin has decreased resistance to invasive pathogens and environmental insults and decreased capability to regulate loss of water and electrolytes.[1,2] Fragile skin is not a diagnosable disease *per se*, but a subjectively (self-reported) or objectively (clinically) evaluable condition involving the structure and function of the epidermal barrier. It should be distinguished from genetic skin fragility disorders such as epidermolysis bullosa that require medical intervention.[3]

Fragile skin results from a broad spectrum of causal conditions, ranging from perceived skin reactivity to life-threatening diseases. Four categories of fragile skin have been defined, based on their origin: physiological (constitutional), which is related to age and seen in neonates/infants and the elderly; pathological, caused by acute or chronic diseases; environmental (circumstantial), caused by external factors such as climate and pollution, or internal factors such as stress or hormones); and iatrogenic, caused by pharmaceutical interventions such as oral isotretinoin or long-term corticosteroids or aesthetic procedures such as laser peeling.[1] In neonates and infants, skin fragility exists due to the immaturity of the skin barrier, whereas in the elderly, it is due to skin barrier decline (involution). Fragility of the epidermis changes with age due to pathological causes such as dermatological disorders (xerosis and pruritus for example), environmental or iatrogenic causes. Most of fragile skin seen in dermatological practice is pathological, caused by associated diseases such as acne, psoriasis and atopic dermatitis.[1,4]

Epidemiology of fragile skin

A substantial proportion of the general adult population identifies as having fragile skin. Worldwide, fragile skin is reported in all skin types. Among a total of 4913 individuals aged 13–65 years surveyed in France, Spain, Sweden, Japan and the United States, 24.44%, 29.71%, 52.67% and 42.20% with Caucasian North, Caucasian South, Asian and Black skin, respectively, self-reported skin

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fragility.[5] The prevalence of perceived fragile skin varies by geographical location. Responses to online questionnaires from representative groups of national populations have reported rates from 23% in Germany,[6] 41% in the United Arab Emirates (UAE),[7] 45.9% in Russia and 50.0% in Mexico,[8] and up to 56% in Taiwan.[9] Higher rates were significantly associated with environmental and lifestyle factors, such as stress, humidity and pollution, and fragile skin was reported more frequently by women than men in most groups.[5,7–9]

Fragile skin in newborns and infants

The skin of newborns and infants is considered as physiologically fragile. Research over the past decade has shown that newborn skin is structurally and functionally immature compared with adult skin.[10–12] After birth, the skin undergoes a physiological maturation process that continues at least throughout the first year of life. Compared with adults, newborns and infants have reduced thickness of the stratum corneum, smaller corneocytes and higher pH (alkaline) at the skin surface, which all contribute to reduced epidermal barrier function (Fig. 1).

Newborns have a lower capacity for sweating, but newborn skin has reduced water-holding capacity than adult skin. Whereas in adults, skin hydration is preserved by classical moisturizing factors, including intercellular lipids (mainly ceramides), sebum (triglycerides), and natural moisturizing factor (NMF; a molecular complex consisting largely of amino acids, urea, lactate, pyrrolidone carboxylic acid), levels of sebum and NMF concentration are lower in infant skin.[11,12] Consequently, transepidermal (endogenous) water loss (TEWL) is more important in infants.[11] This increased permeability can lead to xerosis, particularly on exposed skin, and a greater risk of irritant or allergic contact dermatitis. Decreased skin hydration associated with impairment of the skin barrier function renders it more susceptible to chemical irritation and infections compared with adult skin. The risk of atopic dermatitis developing from external stimuli is also increased, particularly in infants already at high risk (having a first-degree relative with atopic dermatitis). Skin dryness also leads to the early appearance of fine cracks and fissures.

Protection of newborn and infant skin

Special skin care is needed for all newborns. Several studies have shown that the use of emollients on infant skin can improve epidermal barrier function and that barrier creams protect the skin from irritation.[13] Emollients have been shown to help restore skin elasticity, maintain skin homeostasis, and control TEWL. A randomized controlled trial in 227 healthy Asian newborns aged found that moisturizing skincare (bathing every 2 days and using lotion daily) for the first 3 months of life resulted in lower face TEWL and higher face and body stratum corneum hydration compared with daily bathing without lotion.[14] The moisturizing routine also significantly reduced diaper dermatitis, a common problem in infants caused by prolonged contact with urine and faeces. It also reduced rates of body skin problems between ages 1 and 3 months (42.1% vs. 55.2% in controls). Between birth and 1 month, 6.3% of newborns had diaper dermatitis compared with 15.9% of controls, suggesting that moisturizing care has prophylactic effect on diaper dermatitis. Another recent study of skin care and cleansing oils (Primalba®, A-Derma, Pierre Fabre, Lavaur, France) used over 6 weeks in 60

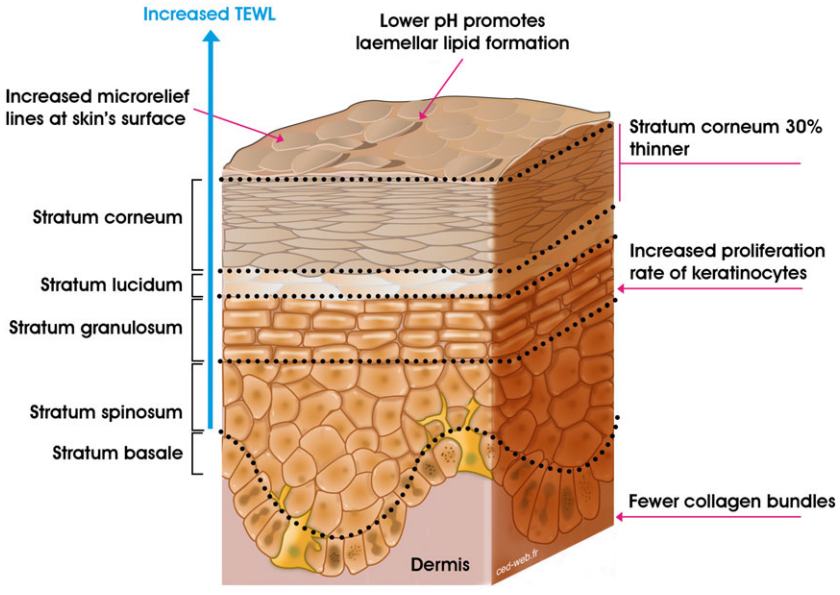

Figure 1 Structure of newborn skin. Copyright belongs to A-DERMA.

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healthy newborns (age < 4 days) significantly reduced skin pH and increased skin hydration and improved xerosis and overall skin condition.[15] There was no adverse effect of the skin care on physiological development of the skin or on skin microflora.

Primary prevention of atopic dermatitis

Since dry skin is the main cause of atopic dermatitis (AD) in infants, restoring impaired skin barrier function starting at birth may reduce the risk of developing AD. Recent studies have demonstrated that early initiation of basic skin therapy has protective effects in infants at risk of developing AD.[16] A small pilot study demonstrated the safety and feasibility of this approach using an oil-in-water emulsion (Cetaphil®, Galderma, Lausanne, Switzerland) that also reduced AD development.[17] A follow-up randomized controlled trial in 124 newborns reported a 50% reduction in risk of AD after 6-month use of daily, full-body emollient therapy compared with no emollient use.[18] In another randomized controlled trial in Japan, daily application of a widely used emulsion-type moisturizer (2e [Douhet] emulsion, Shiseido) to 59 high-risk neonates during the first 23 weeks of life reduced the risk of developing AD by week 32 by 32% compared with 59 control subjects.[19] In addition, the prevalence of food allergy was increased in the infants with AD compared to those without AD, suggesting that skin inflammation plays an important role in development of food allergy.

Other emollients are being investigated for prevention of AD. A recent study demonstrated the safety and tolerability of three formulations of Rhealba Oat plantlet extract-based emollient with Biovect Technology (Exomega Control®, A-Derma, Pierre Fabre, Lavaur, France) administered to the skin of 53 health newborns a risk of developing AD.[20] Rhealba Oat plantlet extracts have been shown to have anti-inflammatory properties.[21] Large-scale studies are currently underway to determine whether the observed effects of emollients in prevention of AD persist over the long term.[16] One of these is the Barrier Enhancement for Eczema Prevention (BEEP) trial, which is following almost 1400 newborns in the United Kingdom.[22]

Fragile skin in the elderly

Ageing is associated with structural and functional changes of the skin that result in increased fragility.[23] Cell replacement declines, and skin barrier function and mechanical protection become compromised. Wound healing and immune responses are delayed, sebum decreases, and at the cellular level, NMF and lipids in the stratum corneum decline. The clinical phenotype of fragile skin in the elderly comprises morphological markers such as senile purpura, stellate pseudo scar, and skin atrophy, along with functional expressions of skin fragility such as frequent skin lacerations, delayed wound healing, non-healing atrophic ulcers and subcutaneous bleeding with the formation of dissecting haematomas, leading to large zones of necrosis.[24]

Age-related skin changes in skin barrier function often result in dermatological disorders and skin injuries. Xerosis (dry skin) is a common diagnosis in the elderly, with a prevalence of around 50% in community-dwelling adults aged ≥ 65 years of around 50%[25,26] and 85% in those who are hospitalized.[27] Xerosis is the primary cause of pruritus (see below), and early treatment of xerosis may prevent scratching and complications. In addition to changes in environment (ensuring optimum humidity and avoiding excess heat) and bathing habits (avoiding hot water and harsh soaps), application of emollients to rehydrate the skin is recommended. The beneficial effect and acceptability of emollients have been demonstrated in several studies,[27] and topical steroids may also be needed for short-term use.

Another skin problem common in the elderly due to skin fragility is incontinence-associated dermatitis (IAD), caused by excessive moisture from urine and/or faeces that leads to overhydration and chemical irritation of the epidermis.[28–30] Clinical signs of IAD range from inflamed erythematous skin to severe partial thickness skin loss (denudation, erosion, abrasion or superficial ulceration). IAD affects up to 50% of all incontinent patients.[23] According to a study in elderly patients aged around 81 years, those whose develop IAD are more often male, have diabetes, a higher body mass index (BMI) and moist perianal skin. They are more likely to be affected by faecal incontinence than by urinary incontinence and show higher degrees of functional and physical impairment.[31] Anti-inflammatory agents such as topical corticosteroids are first-line treatment for rapid relief from eruptions, along with emollients and barrier creams. Rhealba Oat plantlet extract barrier cream (Dermalibour + Barrier®, A-Derma, Pierre Fabre) proved effective for IAD (microbiological, pharmacological and clinical studies) in elderly patients.

Pruritus in the young and elderly

Pruritus (itch) is common in children and the elderly. Chronic pruritus (i.e., pruritus lasting ≥6 weeks) is regarded as a symptom of dermatological diseases such as AD, psoriasis, and urticaria, but it is also associated with systemic, neurological and psychiatric diseases or it may be of mixed or unknown origin.[32,33] Xerosis is considered to be the major cause of chronic pruritus in the elderly, but many older patients have pruritic skin due to immunosenescence or sensory dysfunction as it occurs in diabetes and HIV infection, due to small fibre neuropathy.[34,35] Many drugs can cause pruritus, and polypharmacy is especially common in elderly patients.[32] In children, pruritus is primarily due to dermatoses, but also rarely to inherited cholestatic liver disease, chronic kidney failure, or tumours of the central nervous system that produce localized itching, such as spinal neurofibroma.

Few data exist on the exact prevalence of chronic pruritus, but several studies have reported that it affects up to 17% of the adult population.[36,37] The rate increases with age and is

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especially high in the elderly.[38] In a Mexican geriatric population, the prevalence of pruritus was reported as 25%.[39] In children, data from 2370 outpatients attending a dermatological clinic in Turkey showed that 2.8% were diagnosed with generalized chronic pruritus.[40] Chronic pruritus is associated with similar neurophysiology, clinical signs and effects on quality of life in adults and children, but sensory perception is increased in the elderly compared with younger adults. Patients aged over 65 years rate the itch intensity higher than younger patients,[41] whereas young children are less able to rate itch intensity or localize its source.[42]

Several guidelines and algorithms focused on diagnosis and treatment of pruritus have been published.[33,43,44] During medical workup, it is important to remember that pruritus may be a marker for occult disease such as cancer.[45] Treatment should be individualized, with a stepwise approach. A variety of topical and systemic therapies are available; combination therapy is usually preferred to monotherapy. Emollients are regarded as first-line therapy for mild or localized itch and xerosis.[46] Use of emollients reduces the requirement for topical corticosteroids, which is particularly beneficial in elderly patients, in whom they can cause further thinning of the skin as well as impairment of the immune response.[47] The antipruritic effect of 2-week treatment with a Rhealba Oat extract-based emollient (Xeramega Confort®, A-Derma, Pierre Fabre) was demonstrated in a study involving 30 French outpatients aged ≥60 years with chronic pruritus.[48] At the end of 2 weeks of treatment, more than half of the subjects reported an improvement in pruritus, and 30% reported complete disappearance, whereas pruritus remained stable during a 2-week non-treatment phase.

Topical therapies are important for treatment of pruritus especially in the elderly. (Table 1).

In addition to corticosteroids, topical calcineurin inhibitors act as anti-inflammatory therapies.[49] A topical anti-inflammatory ointment containing crisaborole, a phosphodiesterase 4 (PDE4) inhibitor, available in the United States and under evaluation in Europe, has been shown to produce early relief of pruritus in AD.[50] Janus kinase (JAK) inhibitors may be effective for pruritus, according to clinical studies.[51,52] Topical agents with antipruritic effects include polidocanol, a topical anaesthetic. Capsaicin, which also acts as an anti-inflammatory,[53] and menthol and its derivatives, which have a cooling effect,[54,55] both act via transient receptor potential (TRP) on channels, which are expressed in many skin cell types.[56] A novel drug in development is pegcantratinib, a tropomyosin receptor kinase A (TrKA) antagonist, that has already been shown to be effective in psoriasis.[57]

Systemic treatment of chronic pruritus is usually necessary in addition to topical agents (Table 2).[58]

Non-sedating antihistamines and immunosuppressive drugs are widely used. Oral antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and mirtazapine, have been associated with marked improvement of pruritus.[59] A promising approach is via inhibition of the neurokinin-1 (NK1), the receptor for substance P, which plays a major role in inducing itch.[60] A recently reported study with serlopitant in adults with chronic pruritus reported a significant reduction in pruritus at 3 weeks compared with placebo.[61] Other targets in systemic inflammation and neurologic signalling are currently under investigation for treatment of pruritus.[60]

Table 1 Approaches to topical therapies for pruritus

Topical agents	
Emollients/moisturizers	
Anti-inflammatory agents	
Corticosteroids	
Immunomodulators (calcineurin inhibitors)	Tacrolimus, pimecrolimus
PDE4 inhibitors	Crisaborole
JAK inhibitors	Delgocitinib (JTE-052)*, tofacitinib*
Antipruritic agents	
Local anaesthetic/moisturizer	Polidocanol
TRPV1 agonist	Capsaicin
TRPM8 agonists	Menthol and derivatives
TrkA antagonist	Pegcantratinib (SNA-120/CT327)*

JAK, Janus kinase; PDE4, phosphodiesterase 4; TrkA, tropomyosin receptor kinase A; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1.
*In clinical development for dermatological conditions.

Conclusion

With understanding of skin fragility in the very young and elderly, improved skin care routines including dermocosmetics and new targeted therapies will provide increased protection

Table 2 Systemic therapy recommendations for pruritus in the elderly

Systemic agents	
Non-sedating antihistamines	Cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine
Immunosuppressants	Azathioprine, ciclosporin, methotrexate
Gabapentinoids	Gabapentin, pregabalin
Antidepressants	Paroxetine, sertraline, fluvoxamine, mirtazapine
M-opioid receptor antagonists	Naloxone (iv), naltrexone (oral)
Substance P/neurokinin-1 receptor antagonists	Serlopitant*, tradipitant*, aprepitant*

Adapted from Pereira & Ständer (2018).[58]
*In clinical development for dermatological conditions.

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against changes in the epidermal barrier and the development of dermatological pathologies such as atopic dermatitis in children and IAD (incontinence-associated dermatitis) in seniors.

Update on the pathogenesis and treatment of skin cancers

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Highlights in oncodermatology

The understanding of molecular pathogenesis of cutaneous malignancies has been really improved in the past years, leading to the development of targeted therapies and immunotherapies. However, as some patients are not eligible for these treatments, that's why new treatments and combinations of immunotherapy need to be developed, thanks to an even better knowledge of the signalling pathways in cutaneous cells.

Introduction

The past decade has seen significant advances in the understanding of molecular pathogenesis of cutaneous malignancies. Increased knowledge about specific signalling pathways has led to the development of targeted treatments (Table 3) and immunotherapies that have dramatically improved progression-free survival and even overall survival in melanoma, basal cell carcinoma (BCC) and even some rarer cutaneous carcinomas.

However, large subgroups of patients remain who are not candidates for currently available targeted therapies and who cannot tolerate or are resistant to immunotherapy, and as the incidence of many of the cancers rises with ageing populations, new therapies are needed.

Table 3 Pathways for targeted treatments in skin cancer

Type of cutaneous cancer	Possible target	Active agents
Melanoma	BRAF/MEK/MAPK	Dabrafenib + trametinib vemurafenib + cobimetinib encorafenib + binimetinib
	Immune checkpoints PD-1/PD-L1, CTLA-4	Nivolumab, pembrolizumab
BCC	Hedgehog pathway	Vismodegib, sonidegib
MCC	Immune checkpoints PD-1/PD-L1	Pembrolizumab, avelumab
DFSP	PDGFRB	Imatinib

BCC, basal cell carcinoma; BRAF, B-Raf proto-oncogene serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DFSP, dermatofibrosarcoma protuberans; MAPK, mitogen-activated protein kinase; MCC, Merkel cell carcinoma; MEK, mitogen-activated protein kinase; PD-1, programmed-death receptor 1; PDGFRB, platelet-derived growth factor receptor beta; PD-L1, programmed-death receptor ligand 1.

Advances in treatment of metastatic melanoma

Until 2011, the standard of care for metastatic melanoma was chemotherapy with dacarbazine (DTIC), although in randomized controlled trials, dacarbazine as monotherapy or part of a combination regimen was associated with response rates of only 5–28% and no significant increase in survival duration.[62] At that time, the median survival of patients with non-resectable metastatic melanoma was 6–10 months, with only 4–6% of patients surviving to 5 years.[63,64] More toxic multidrug chemotherapy-based combinations were studied in clinical trials that reported improved response rates compared with single-agent dacarbazine, but no improvement in overall survival (OS).[65] Since 2011, two new distinct approaches to systemic treatment of metastatic melanoma have emerged: targeted therapy with BRAF (B-Raf proto-oncogene serine/threonine kinase) inhibitors and MEK (mitogen-activated protein kinase) inhibitors, and immunotherapy with checkpoint inhibitors against CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitors and PD-1 (programmed cell death protein 1) and its ligand L1 (PD-L1). Each of these groups has demonstrated increased response rates and extended progression-free survival and OS compared with dacarbazine.[66,67]

Targeted therapies

Ultraviolet radiation (UVR), the most important risk factor for cutaneous melanoma, is known to directly induce so many carcinogenic mutations within the melanocytes that the mutagenic burden of melanoma is the highest of all cancers.[68] The Cancer Genome Atlas Network project classified melanomas into four large genomic subtypes: mutant *BRAF*, mutant *NRAS*, mutant *NF1* and triple wild-type (i.e., without mutations in these 3 genes).[69] This classification does not predict outcome, but the mutations specify therapy. Significantly mutated genes in cutaneous melanoma include *BRAF*, *NRAS*, *CDKN2A* and *TP53* (Table 4).[70]

Melanomas from chronically sun-exposed skin have most often *NF1*, *NRAS* mutations and occasionally *BRAF* mutations, whereas melanomas from intermittently sun-exposed skin tend to have *BRAF* mutations (50%) or *NRAS* mutations (15–20%).[71–73] The occurrence of these activated mutants is generally mutually exclusive. In rare melanomas with chronic sun damage, such as acral and mucosal melanomas, *KIT* mutations are more common and *BRAF* mutations fewer.[74]

Oncogenic mutations in *BRAF* and *NRAS* induce overstimulation of the RAS/RAF/MEK/ERK signalling pathway (also known as the MAPK [mitogen-activated protein kinase] pathway), which is central to the pathogenesis of cutaneous melanoma. Most *BRAF* mutations (89%) involve the kinase activation loop at the p.V600 position (*BRAF* V600). The most common *BRAF* V600 mutation (80%) is a valine to glutamic acid mutation at codon 600 (V600E), which is associated with a 500-fold increase in the kinase activity of *BRAF*. This leads to cascade activation of MEK and ERK. The *BRAF* V600E mutation

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Table 4 Common gene alterations in melanoma and clinical implications

Mutation	% of melanomas with mutation	Phenotypic associations and other characteristics	Targeted therapies available or in clinical trials
BRAF *BRAF* V600E *BRAF* V600K	40–50 70–88 of *BRAF* 11–20 of *BRAF*	Young age Intermittent sun-exposed primary site Trunk, limbs primary sites High naevus count Tans easily Superficial spreading histogenetic type	BRAF inhibitors MEK inhibitors
NRAS	15–20	Intermittent sun-exposed sites Low or absent pagetoid epidermal scatter Peripheral circumscription	PD-1 inhibitors MEK inhibitors CDK4/6 inhibitors
NF1	10–15	Sun-exposed skin	Type 2 RAF inhibitors MEK inhibitors P13K/mTOR inhibitors
KIT	1–2	Acral and mucosal sites Acral and mucosal lentiginous histogenetic melanoma types	KIT inhibitors Other tyrosine kinase inhibitors
GNAQ/ GNA11	80–90	Uveal melanoma	MEK inhibitors
TERT promoter	40–50	UVR-mediated mutation (in 86% of cutaneous melanomas)	Not yet in development
CDKN2A	25–35	Familial melanoma	CDK4/6 inhibitors
PTEN	4–8	May correlate with immune resistance	PD-1 inhibitors

Adapted from Scolyer *et al.* (2011)[71] and Davis *et al.* (2018)[75]

is seen most frequently in younger patients (age < 40 years).[72,75,76] It is usually a very early oncogenic event and is frequently the only activating mutation found in benign naevi.[77] Another BRAF V600 mutation (V600K) is found in 10–20% of patients with *BRAF*-mutated melanoma and approximately 100 other, relatively rare *BRAF* mutations have been identified.[76,78] Mutations of *BRAF* V600 have been established as an important target in recently developed molecular targeted therapy for melanoma.

Three BRAF inhibitors are available for treatment of BRAF V600-mutated advanced melanoma: vemurafenib, dabrafenib and encorafenib. Randomized controlled trials showed that in BRAF V600, BRAF inhibitors vemurafenib and dabrafenib were associated with prolonged PFS and/or OS compared with dacarbazine,[79–83] but the most effective treatment in these patients, and the current first-line option in these patients, has been established as a combination of a BRAF inhibitor and MEK inhibitor. Three of these combinations have received regulatory approval: vemurafenib plus cobimetinib, dabrafenib plus trametinib and second-generation BRAF inhibitor encorafenib plus binimetinib. BRAF/MEK combined therapy produces response rates around 20% higher than BRAF inhibitor monotherapy, median PFS exceeds one year and OS reaches approximately 2 years.[83–87] Baseline lactate dehydrogenase (LDH), ECOG performance status, disease burden, and gene signature appear to be key determinants of survival outcomes in patients with *BRAF* V600-mutated metastatic melanoma treated with BRAF and/or MEK inhibitors.[88] High baseline neutrophil-to-lymphocyte ratio predicts worse outcome in these patients.[89]

Immunotherapy

The manipulation of the immune system by blocking ligands and receptors that act as regulators of the T-cell activation, the so-called immune checkpoints, exemplified by the CTLA-4 and PD1, have become important strategies for control of melanoma. The CTLA-4 inhibitor ipilimumab and the anti-PD1 antibodies pembrolizumab and nivolumab are all approved for treatment of unresected or metastatic melanoma based on studies that showed greater efficacy in terms of survival and tumour response compared with chemotherapy.[66,90] Prolonged remission of response after treatment discontinuation was seen in the KEYNOTE-001 study, in which 89.9% of patients who had a complete remission with pembrolizumab were disease-free 2 years after treatment had stopped.[91] Nivolumab is also approved in combination with ipilimumab for treatment of metastatic melanoma, based on the results of the Checkmate-067 study, in which the combination proved more effective than either monotherapy.[93]

Cutaneous toxicities are a class effect of checkpoint inhibitors and are observed in around one-third of treated patients.[92,94–97] Non-specific maculopapular rash and pruritus represent the most common dermatological manifestations, with a calculated all-grade incidence of around 15%. Other characteristic toxicities include lichenoid dermatitis[98] and psoriasis[99,100] may also develop. Vitiligo-like lesions are frequent in melanoma patients,[101,102] but have not been reported in other types of solid tumours. Hair and nail changes, often underestimated by physicians, are also likely. These adverse events are usually mild, self-limiting and readily manageable. However, early recognition and adequate management are critical to prevent exacerbation of the lesions, to limit treatment interruption and to minimize quality-of-life impairment.

New therapeutic approaches

Successful application of the effects of anti-CTLA4 and anti-PD-1/PD-L1 in activating T-cell responses generated interest in finding other receptors to serve as immunotherapeutic targets in melanoma.[103,104] One of these targets is LAG-3 (lymphocyte activation gene-3), which is similar to CTL4.[105] Relatlimab

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(BMS-986016), a humanized monoclonal antibody (MAb) directed against LAG-3, has potential immune checkpoint inhibitory and antineoplastic activities and shows evidence of synergy when combined with PD-1 blockade. Relatlimab is being studied in combination with nivolumab and in Phase 1/2a study, heavily pretreated melanoma patients resistant to anti–PD-1/PD-L1 were observed to regain responses to treatment with the combination regimen[106] targeting co-stimulatory receptors with agonist antibodies, and a growing number of these agents are making their way through various stages of development.

A potential therapeutic option for treatment of *BRAF* V600 mutant advanced melanoma is a combination of targeted therapy and immunotherapy. *BRAF* V600 mutation in melanoma increases production of immunosuppressive factors, leading to an immune-suppressive phenotype.[107,108] Mutated *BRAF* may induce T-cell suppression via secretion of inhibitory cytokines or by membrane suppression of co-inhibitory molecules such as PD-1 and PD-L1, suggesting that a combination strategy targeting BRAF, MEK and PD-1 signalling could be effective. It was suggested that in combination, these agents could provide a durable response and prolonged survival. Combinations in clinical trials include pembrolizumab with dabrafenib and trametinib; atezolizumab (anti-PD-L1) with vemurafenib and cobimetinib; and nivolumab with dabrafenib and trametinib. Phase 1/2 results have reported promising antitumour activity in *BRAF*-mutant melanoma.[109–111] Preliminary results of Phase 3 trial with another triplet combination, PDR001 (anti-PD-1) with dabrafenib and trametinib, recently reported manageable safety profile and demonstrate promising activity in patients with *BRAF* V600 mutant melanoma.[112] Phase 3 study with atezolizumab plus cobimetinib and vemurafenib versus placebo plus cobimetinib and vemurafenib is ongoing in previously untreated *BRAF* V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (IMspire150 TRILOGY).[113]

Over 100 doublet combination treatments are being explored in melanoma, many within clinical trials. Tilsotolimod (IMO-2125), a Toll-like receptor (TLR) 9 agonist, is being evaluated in combination with ipilimumab in Phase 3 clinical trial for the treatment of metastatic melanoma patients whose disease progressed after anti-PD-1 therapy.[114] In Phase 2 study, 71.4% of patients experienced disease control (CR, PR or SD).[115] A number of co-stimulatory agents of immune checkpoints, like monoclonal antibodies that target CD40 receptor that is essential for activating both innate and adaptive immune systems, are being developed in combination therapy in advanced/metastatic melanoma.[116,117]

Another combination immunotherapy using PD-1/L1 checkpoint inhibitors utilizes talimogene laherparepvec (T-VEC), a first-in-class oncolytic herpes simplex virus genetically engineered to selectively replicate and lyse tumour cells and overexpress granulocyte macrophage colony-stimulating factor (GM-CSF), resulting in induction of tumour-specific T-cell response.[118] Already approved for clinical use in Europe and the United States, in Phase 3 trial, the durable response rate (DRR) with T-VEC was 16% vs. 2% with GM-CSF.[119] T-VEC is now being studied in combination with pembrolizumab in stage IIIB-IV metastatic melanoma in Phase 1b/3 trial. The results of Phase 1b showed confirmed/not-yet-confirmed objective ORR per immune-related response rate (irRC) 48%/57% and CR rate 14%/24%.[120]

Keratinocyte carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer worldwide.[121] Most cases of BCC result from mutations in key receptors in the Hedgehog (HH) signalling pathway, which controls cell proliferation, cell fate specification, tissue patterning and tissue homeostasis in developing and adult organisms. Aberrant HH pathway activation in BCC involves inactivation mutations in the PTCH1 (Patched 1) transmembrane receptor in about 85–90% and activating mutations in SMO (smoothened) transmembrane receptor, a cell-associated signal transmitting component, in about 10%.[121,122] Ultraviolet radiation (UVR) is the primary aetiologic agent for BCC, with skin type, age, history of BCC, genetic disorders (e.g., Gorlin syndrome, xeroderma pigmentosum) and immunosuppression. Two agents that inhibit SMO in the HH pathway, vismodegib and sonidegib, showed efficacy in clinical trials and received regulatory approval in Europe and the United States for treatment of locally advanced BCC and, for vismodegib only, metastatic BCC.[123,124] Approval for once-daily vismodegib, the first in class, was based on the findings of Phase 2, non-placebo-controlled, prospective cohort study (ERIVANCE) that showed overall response rates (ORR) of 43% for locally advanced BCC and 30% for metastatic BCC.[125] Approval of sonidegib was based on Phase 2 non-placebo-based randomized, controlled study (BOLT) that showed objective responses of 57% and 65% in locally advanced BCC and 23% and 37% in metastatic BCC, respectively, for 200 mg and 800 mg doses.[126] A 30-month follow-up study confirmed long-term efficacy and safety of the recommended 200 mg.dose.[127] Other HH pathway inhibitors are in development.[121]

Rare cutaneous malignancies

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine tumour of the skin. Over the past 10 years, the incidence of MCC has been increasing worldwide.[128] For advanced MCC, cytotoxic chemotherapy only infrequently (<10% of cases) offers durable clinical responses (>1 year). The Merkel cell polyomavirus (MCPyV) is clonally integrated in approximately 80% of MCC tumours, and the remaining 20% of MCC tumours have large numbers of UVR-associated mutations.[129] Merkel cell carcinoma is characterized by high expression of PD-L1 in the tumours, which led to recent clinical trials involving PD-1 pathway blockade in advanced MCC. Trials showed a high

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frequency of durable responses in patients treated with PD-1 inhibitors, but prior chemotherapy was associated with decreased responses.[130] Recently, the PD-1 blocker avelumab, the first agent for metastatic, relapsed/refractory MCC was approved after it showed efficacy in advanced cases in the international Phase 2 Javelin Merkel 200 trial.[131,132] However, approximately 50% of patients with MCC do not benefit long-term from PD-1 pathway blockade and new strategies are needed to broaden antitumour immune responses in these patients.

Dermatofibrosarcoma protuberans (DFSP) is a relatively uncommon soft tissue neoplasm of intermediate- to low-grade malignancy that rarely metastasizes. Activating mutations in the genes for PDGF or PDGF receptors have been recorded in DFSP, which led to the approval of molecularly targeted therapy with imatinib, which inhibits tyrosine kinases as well as PDGF receptors, in unresectable cases and as neoadjuvant therapy.[133] Potential new therapies for advanced or metastatic DFSP include multikinase inhibitors pazopanib[134] and regorafenib.[135]

Precancer lesions

Actinic keratoses (AK) derive from neoplastic epidermal keratinocytes and are the most common cutaneous neoplasms. The predominant risk factor for AK is ultraviolet radiation (UVR), so that the prevalence is greatest in countries with high levels of UVR exposure such as Australia, where the prevalence has been estimated at 40–50% of the population aged 40 years and older.[136] The prevalence in Northern Hemisphere countries ranges from 11% to 25%.[137] Additional risk factors include older age, male sex, fair skin, and immunodeficiency, particularly after organ transplantation. Compared with immunocompetent patients, immunocompromised individuals are at a 65- to 250-fold higher risk of developing AKs and invasive squamous cell carcinoma (SCC).[138] It has been suggested that human papillomavirus (HPV) skin infection may be associated with an increased risk for AK and SCC, since the E6 protein of cutaneous HPV is believed to contribute to reduced levels of Bak protein, a key component of the protective response of keratinocytes to UVR.[139–141]

Actinic keratoses is a precursor lesion of SCC, and analyses of gene expression profiles of AK and SCC indicate that they are closely related genetically.[142] Most AKs do not progress to invasive SCC. Rates of progression of individual AK lesions to SCC vary. According to one calculation, the rate of progression to SCC ranges from 0.075% to 14% per year over 5 years.[143] Another group reported that the risk of progression of AK to primary SCC is 0.60% at 1 year and 2.57% at 4 years.[144] However, although the risk of progression to SCC is low, the majority of SCCs arise from AKs. AK progresses to SCC via two pathways, most frequently by direct invasion from proliferating basaloid atypical keratinocytes limited to the epidermal basal layer (AK I) (differentiated pathway), and by stepwise progression from AK I to AK II and AK III (classic pathway).[145] All AK lesions, irrespective of intraepidermal neoplasia thickness, are potentially invasive. To date, there are no reliable clinical predictors that can distinguish between an AK lesion that will regress and an AK that will become malignant and transform into SCC,[146] reinforcing the need to treat all AK lesions as well as field cancerization.

Lesion-directed therapy of AK involves removal of single lesions by excision or curettage or by physically destructive methods such as cryotherapy. However, multiple AK on actinically damaged skin (field cancerization) require treatment modalities that can be applied on large surfaces, such as photodynamic therapy (PDT) using a topical photosensitizer such as aminolevulinic acid (ALA) or methylaminolevulinate (MAL) followed by high-intensity red light. In response, reactive oxygen species are formed, which lead to destruction of atypical keratinocytes. Other approved topical treatments include 5-fluorouracil cream or solution, imiquimod cream, diclofenac gel and ingenol mebutate. Imiquimod is a topical immune response modifier through antagonizing TLR-7 and thus stimulating the immune response against atypical keratinocytes. Diclofenac is a cyclooxygenase (COX) inhibitor that showed antiproliferative and proapoptotic effects in SCC cell lines. In a recent study comparing ingenol mebutate gel with diclofenac gel applied to discrete AK lesions on the face and scalp, AKCLEAR 100, patient treatment satisfaction and efficacy were significantly higher with ingenol mebutate.[147] 5-Fluorouracil (5-FU) is a chemotherapeutic agent that destroys tumour cells via interference with DNA and RNA synthesis. A Cochrane review concluded that the choice of therapy should be based on factors such as tolerability, cost or cosmetic results.[148,149] New formulations with lower concentrations of 5-FU (4%) have comparable efficacy but improved local tolerability.

Conclusion

Advances in immunotherapy and targeted therapies and other treatments have revolutionized the treatment of metastatic melanoma and other skin cancers. The clinical benefit induced by such therapies has dramatically improved progression-free survival, and even overall survival, but not all patients benefit from these treatments and new treatments and combinations of immunotherapy are needed to improve outcomes in these patients. A better knowledge of the signalling pathways in cutaneous cells and of the role of mutations in the genesis of cutaneous malignancies will lead to new generations of therapies. At the same time, the demand for preserved quality of life is increasing and every healthcare professional is concerned by providing support and adequate responses. A multidisciplinary management of the frequent and sometimes new skin, but also hair and nail disorders, requires more information and patient education programmes about protection against solar radiation, the main risk factor in most of these cancers. Simple tools such as dermoscopy allow a more accurate detection of skin cancers at early stages. Secondary prevention should not be neglected.

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Key issues in hair loss: from physiology to treatment

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Highlights in trichology

Many aspects of the pathophysiology of androgenetic alopecia (AGA) and senescent alopecia, which may be a separate disorder, have yet to be determined. To date, only two medications, topical minoxidil and oral finasteride, have been approved for treatment of AGA in Europe and the United States. Another 5α-reductase inhibitor, dutasteride, is frequently used off-label. New topical formulations of finasteride and minoxidil are under development to improve the safety and convenience of application of these agents. A number of promising new therapeutic targets are also under investigation including the Wnt signalling pathway, which may be involved in the failure of hair follicle stem cell differentiation, and prostaglandins that have been discovered to inhibit hair growth. Other treatment options currently available include physical therapies such as low-level laser therapy, regenerative therapies such as platelet-rich plasma and stem cell therapy and hair transplant procedures. To date, approved therapies have been lacking for alopecia areata, but oral formulations of mechanism-targeted drugs such as Janus kinase (JAK) inhibitor appear promising.

Introduction

Androgenetic alopecia (AGA), also known as pattern hair loss, an androgen-induced progressive disorder, is the most common type of hair loss in men and women. The hallmark of AGA is a progressive miniaturization of the hair follicle which leads to fine and short vellus transformation of thick and long terminal hairs. Only 2 medications are approved in the United States and Europe for treatment of AGA: topical minoxidil and oral finasteride, although others are used off-label.[150] Currently available medical treatments are not curative, and it is an important aspect of AGA management to ensure that patients understand the limitations of these treatments. Much still remains to be determined about the pathophysiology of AGA and the most appropriate treatments. Some of the current key issues are outlined below.

Senescent alopecia – myth or reality?

Senescent alopecia (SA) is considered to be a hair loss disorder that affects people older than 50 years with no family history or prior evidence of pattern balding. It is characterized by reduction of hair density, hair greying and weakening of hair shaft resistance and barrier while maintaining the anagen/telogen ratio.[151] It has been suggested that SA and AGA represent two independent hair disorders and that non-androgen pathways may contribute to hair loss. This is supported by the phenotype of hair loss seen in patients with Hutchinson–Gilford progeria syndrome patients.[152] However, the concept of SA is still controversial and considered by many to be a continuum of AGA. A review of 2149 scalp biopsies from elderly men and women with or without pattern or diffuse alopecia concluded that most cases of significant hair loss in the elderly were androgen driven and that old age alone should not be regarded as a cause of hair loss.[153] The results of a small histological study suggested that the hormonal differences might exist between these two conditions.[154] Microarray analyses of gene expression patterns between AGA and SA scalp biopsies showed difference in gene expression profiles, suggesting that they might be independent hair disorders and that non-androgenic pathways can also contribute to hair loss.[155] SA is not currently a primary diagnosis in clinical practice and is mainly diagnosed and treated as AGA or diffuse alopecia in the elderly. However, if it is a real condition, novel therapeutic targets may be identified for prevention or treatment of hair disorders.

New treatment targets: the Wnt/β-catenin pathway

Androgenetic alopecia is characterized by a progressive miniaturization of the hair follicle that leads to fine and short vellus transformation of thick and long terminal hairs. The wingless-related integration site (Wnt) signalling pathway through β-catenin is an essential component in the maintenance of hair-inducing activity of the dermal papilla and growth of hair papilla cells.[156] In AGA, androgens impair dermal papilla-induced hair follicle stem cell differentiation, inhibiting Wnt signalling.[157] Recent data suggested that Wnt agonist/antagonist expression imbalance in dermal papilla cells by androgens is responsible for the failure of hair follicle stem cell differentiation into hair lineage, thus contributing to AGA development.[158] Activation of the Wnt/β-catenin pathway may be inhibited by CXXC-type zinc finger protein 5 (CXXC5), which is present in human hair follicle dermal papilla cells. In a recent study, CXXC5-null mice showed accelerated hair regrowth and additional regrowth after activation of the Wnt/β-catenin pathway with valproic acid.[159] Previous studies show increased human hair growth with valproic acid[160,161] and, another Wnt/β-catenin activator, methyl vanillate.[162] Low-level laser therapy also has been shown to stimulate hair growth by activating Wnt/β-catenin signalling.[163,164] Thus, activation of the WNT/β-catenin pathway appears a promising potential therapeutic target in AGA.

Prostaglandins and hair growth

Prostaglandin metabolism has recently received attention as a therapeutic target for AGA since prostaglandin (PG) E2 and PGF2α are known to induce hair growth. Minoxidil, the first topical agent approved for treatment of AGA, is believed to act by increasing production of PGE2.[165] Studies with PGF2α

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analogues latanoprost and bimatoprost have reported significant increases in hair density and pigmentation.[166] A placebo-controlled trial in men with mild AGA showed significantly increased hair density and pigmentation after daily application of 0.1% latanoprost for 24 weeks.[167] More recently, it has become apparent that prostaglandins, specifically PGD2, can also inhibit hair growth.[168] PGD2 appears to act by enhancing testosterone formation through crosstalk between the PGD2-reactive oxygen species (ROS) axis and testosterone metabolism in keratinocytes, suggesting that AGA patients might benefit from the use of an ROS scavenger like N-acetyl-cysteine or other antioxidants in addition to other AGA therapies.[169]

Safety of 5α-reductase inhibitors Finasteride, which is approved for benign prostatic hyperplasia (BPH) (5 mg dose) as well as male pattern baldness (1 mg), has recently been implicated in 'postfinasteride syndrome' (PFS), a loosely defined spectrum of sexual, physical and psychological symptoms, particularly associated with the 1 mg dose, that apparently did not resolve after stopping finasteride.[170] Based on reports of persistent sexual symptoms, low mood, anxiety and cognitive complaints in some men who had used finasteride for hair loss, the FDA and other regulatory authorities mandated safety label changes for finasteride (both doses) adding warnings about these potential side-effects. Although some reports suggested the possibility of persistent side-effects,[171–173] research has so far failed to identify a pathogenic mechanism underlying PFS.[170,174] Many believe there is insufficient evidence for PFS as a true syndrome (symptom complex) rather than side-effects typically reported in studies of a drug.

Dutasteride is approved in the United States and Europe for BPH but is also used off-label to treat male pattern baldness. As a newer drug, the long-term effects of dutasteride have been studied less extensively than finasteride, although in parallel, single-arm studies, only mild adverse events, particularly erectile dysfunction and decreased libido, were recorded over follow-up periods up to 6 years.[175–177] Well-designed, randomized, double-blind, long-term follow-up studies are needed to evaluate the true effectiveness and safety of dutasteride.

Optimizing topical treatments Emerging evidence suggests that topical finasteride may be a promising treatment modality with a less severe side-effect profile than systemic therapy. A number of topical drug delivery formulations have been proposed for finasteride, including topical microneedles, aerosol foams, nanoemulsions, microsponges, emulsifier-free formulations, fullerenes, ointments, pastes, creams, gels and lotions.[178] The effect of a topical solution of 0.25% finasteride on scalp dihydrotestosterone (DHT) in men with AGA suggested that sexual side-effects would be minimized compared with oral finasteride.[179] A topical solution of 0.25% finasteride admixed with 3% minoxidil tested in 40 men with AGA was reported to be significantly superior to minoxidil alone in improving hair density, hair diameter and global photographic assessment.[180] About 90% of patients treated with the combined solution experienced moderate to marked improvement with minimal effect on plasma DHT levels and no systemic adverse events. To date, research on topical application of finasteride has been limited to a small number of randomized controlled trials and retrospective studies.[181]

Efforts are also continuing to improve the efficacy, without compromising safety, of topical minoxidil. Investigations are ongoing into nanoemulsion formulations, which may improve absorption of minoxidil through the stratum corneum.[182] Use of a high-concentration (15%) topical minoxidil solution resulted in 60% of subjects achieving a clinically significant response based on target area hair counts.[183] Scalp hydration was also reported to improve the drug permeation rate.[184] A 5% minoxidil topical foam used once daily has been reported to be safe and effective in improving hair regrowth, scalp coverage and hair density in women with female pattern hair loss.[185] This formulation may prove more convenient and cosmetically acceptable to women.

Low-level laser therapy

Interest in the application of lasers to stimulate hair growth was originally generated by anecdotal evidence of paradoxical hypertrichosis during laser epilation.[186] Low-level laser therapy (LLLT) now appears to be a promising non-invasive treatment for AGA that is safe for self-administration,[187] with a pooled increase in hair count comparable with finasteride or minoxidil use.[188] A double-blind, randomized, multicentre study showed statistically significant improvement in hair density in all LLLT-treated patients compared with sham device treatment.[189] Another study reported a significant difference between LLLT and sham device treatment in investigator global assessment, but not in patient satisfaction.[190] The optimal regimen for LLLT treatment of AGA remains unclear and is reflected by the different treatment parameters of the studies. The exact mechanism of how LLLT promotes hair growth remains poorly understood. Most studies are sponsored by device manufacturers, which could be a potential source of publication bias.[187] In order for LLLT to be predictable and reproducible, therapeutic parameters, including wavelength, irradiance and exposure time, must be established.[191,192]

Platelet-rich plasma

Platelet-rich plasma (PRP) injections have become popular in practice as a minimally invasive and cost-effective treatment. Local injections of PRP may be an appealing treatment modality because they can easily be administered at outpatient clinic settings.[193–195] In a few studies, PRP treatment was associated with a statistically significant increase in hair count and hair diameter[196] and mean hair density on the anterior crown.[197] In a

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double-blind, placebo-controlled pilot study in women with female AGA, statistically significant differences in hair count and hair mass were not observed, although 13.3% of the women who received PRP claimed to have experienced substantial improvement in hair loss, rate of hair loss, hair thickness compared to treatment compared with none of the placebo group.[198] There are no sustained results on overall efficacy, and none of the studies performed to date have been sufficiently powered to assess the risk–benefit of this modality.[193] The lack of a standardized method for preparation of platelet-derived products makes it difficult to correlate clinical results between studies.[199] It is evident that a standardized treatment protocol is lacking for the application of PRP[196] and larger studies with long-term follow-up are warranted to validate or disapprove this treatment modality.[195]

Stem cell therapy

Stem cell therapy has been applied in several types of alopecia, but most research has focused on its application in AGA. Three modalities have been developed with the aim of rejuvenating follicular stem cells. Follicular stem cell isolation and injection without culture is a straightforward mode of treatment, but more scientific evidence is needed to support its use. Adipose tissue-derived stem cells (ADSC) appear effective,[200–202] but a surgical procedure is needed to obtain the adipose tissue (liposuction). Cultured follicular stem cells (follicular regeneration) may be more widely adopted in future.[203] Compared with studies in animals, human trials have produced mainly disappointing results and further research is needed.

Latest advances in hair transplantation

Hair transplantation has seen recent technological advances in recovering and placing grafts.[204] New automated and robotic technologies may increase speed of follicular unit extraction[205] and longitudinal partial follicular unit transplantation may be an option for preserving the partial follicular units that remain in the dermis in the donor area so that they can regenerate to produce an intact follicular unit.[206] Continuing controversies in hair transplant surgery include optimal donor harvesting techniques, elliptical donor harvesting versus follicular unit extraction and the role of low-level light surgery and platelet-rich plasma therapy in the procedure.[207]

Janus kinase inhibitors in alopecia areata

Currently, there are no approved therapies for alopecia areata (AA) in Europe or the United States and treatment is challenging. Among the most exciting developments in AA treatment are Janus kinase (JAK) inhibitors, a class of drugs that specifically target the enzymes inside hair follicles that maintain their dormant state in AA.[208] JAK kinase inhibitors are believed to directly stimulate follicle regeneration, promoting anagen progression follicles out of the telogen phase back into active growth.[162] Numerous studies have recently been reported with oral tofacitinib, oral baricitinib and oral ruxolitinib in AA.[209–212] Hair regrowth of 40–60% has been reported with these drugs, which have already been approved for other indications. Topical formulations of JAK inhibitors have been under investigation in AA to avoid the AEs reported with systemic JAK inhibitors such as infections, viral reactivation, bone marrow disruption, transaminase and lipid changes.[213–215] However, a programme to develop topical ruxolitinib in AA was recently terminated after data from a 24-week Phase 2 clinical trial '[did] not justify progression of the program into pivotal studies'.[216] Two major problems of treatment with JAK inhibitors are costs and the likelihood of relapse after stopping treatment.[212] Other classes of targeted therapies are in development for treatment of AA.[217]

Conclusion

While oral finasteride and topical minoxidil continue to be the treatment standards in AGA, oral dutasteride is also a promising modality. Topical formulations of 5α-reductase inhibitors under investigation and new topical formulations of minoxidil may prove safer than those the formulations currently available. Both LLLT and PRP may be useful as monotherapy or adjunctive therapy to established therapies, but long-term large-scale follow-up studies need to be done to establish standard protocols. Before use of regenerative therapies can be approved for hair loss, more studies of efficacy and safety are needed. In AA, oral or topical JAK inhibitors may be the first treatment to receive regulatory approval if concerns about long-term use can be resolved.

Advances in the understanding of atopic dermatitis leading to therapeutic innovation

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Highlights in atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disease often associated with asthma, allergic rhinitis and immunoglobulin E (IgE)-mediated food reactions. A large variety of treatments have already been described for atopic dermatitis: emollient therapy, anti-inflammatory therapy and antimicrobial therapy which seems optimal in a majority of patients.

Disease-modifying strategies, such as subcutaneous immunotherapy, or targeted therapy with AD-targeting biologics are just emerging. New European Guidelines JEADV 2018, as well as the current European Dermatology Forum (EDF) guideline on AD management, provide excellent sources of information for the clinicians.

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Introduction

Atopic dermatitis (AD), one of the most common inflammatory skin disease, affects children and adults and is associated with significant social, financial and public health burdens.[218,219] Many patients with AD, especially the moderate-to-severe forms, have other atopic comorbidities as well as other chronic health conditions.[220] Until recently, there have been limited treatment options beyond topical agents, but recognition of AD as a multifactorial, heterogeneous disease based on interactions of susceptibility genes, environmental factors, impaired skin barrier integrity and immune dysregulation has led to a greater understanding of the disease and the identification of new therapeutic targets (Fig. 2).

The interactions between epidermal barrier (skin barrier dysfunction), immunologic factors (e.g., changes in cell-mediated immune responses and IgE-mediated hypersensitivity) and environment form the basis of AD pathophysiology.[218,221]

Skin barrier defects in AD

Barrier impairment and immune dysregulation are known to play major roles in AD pathogenesis. According to the 'inside-out' hypothesis, immune dysregulation drives the disease and barrier dysfunction is an epiphenomenon, whereas according to the 'outside-in' hypothesis, epidermal barrier dysfunction incites the disease, leading to secondary immunological changes.[222,223] Over the past decade, experimental and clinical data have highlighted the primary pathogenic role of skin barrier deficiency in patients with AD, with a positive feedback loop between the skin epithelium and the immune system. Understanding the mechanisms of skin barrier maintenance is essential for improving management of AD and limiting downstream atopic manifestations.

Loss-of-function mutations in the gene encoding the epidermal barrier protein filaggrin (*FLG*) have been shown to be a strong predisposing factor for AD development.[224] Filaggrin contributes to the mechanical strength and integrity of the stratum corneum and its component amino acids form the natural moisturizing factor, which plays an important role in the maintenance of epidermal hydration and homeostasis.[225,226] Impairment of the stratum corneum results in increased transepidermal water loss (TEWL) and an influx of allergens. A 50% decrease in filaggrin expression is associated with an eight-fold increase in risk of AD, and a complete lack of *FLG* expression increases the risk up to 150-fold. Only 10–40% of AD patients have an *FLG* mutation; however, yet decreased filaggrin expression is found in almost all AD patients, suggesting that additional factors are needed for AD development. Filaggrin expression in keratinocytes has been shown to be decreased in the presence of T helper 2 (T_H2) immunity cytokines IL-4 and IL-13,[227] IL-25[228] and IL-33,[229] suggesting that the atopic immune response contributes to skin barrier dysfunction in AD. In addition, thymic stromal lymphopoietin (TSLP), an interleukin (IL) 7-like cytokine, is also produced by the impaired skin barrier in AD. TSLP has been shown to stimulate dendritic cell-mediated T_H2 inflammatory responses.[230,231] These cytokines

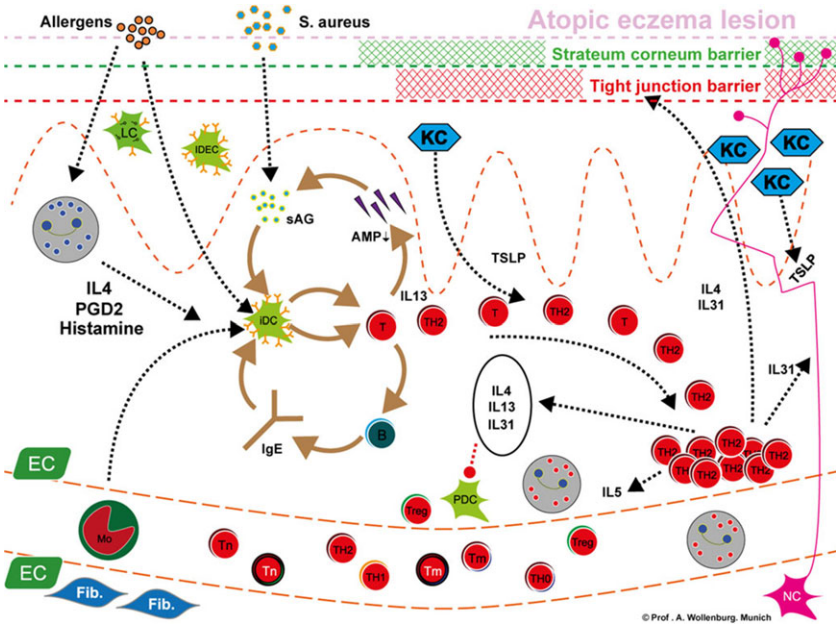

Figure 2 Pathophysiology of atopic dermatitis.Reprinted from Wollenberg A *et al. J Eur Acad Dermatol Venereol* 2018; **32 (Suppl 1)**: 1–15.

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inhibit the keratinocyte terminal differentiation, contributing to a further decrease in epidermal barrier function and setting up a vicious cycle that exacerbates the disease and maintains skin inflammation.

Topical therapy for AD

Children born to families with a history of AD are at high risk of developing the disease, and it is now known that proactive use of emollient can prevent skin barrier damage. The preventative effects of daily application of emollients from birth on development of AD have been shown in 2 short-term studies[18,19] and are now being tested in a large, long-term trial[22] (see paper by Tennstedt and Saint Aroman in this issue). In adults and children with AD, emollients are the mainstay of management.[232] Overall, moisturizers show beneficial effects, prolong time to flare, and reduce the number of flares, as well as having a steroid-sparing effect.[233] Moisturizers combined with active treatment ('proactive' therapy) appear more effective than active treatment alone. These effects have been demonstrated in infants and adults with AD using daily treatment with Rhealba® Oat plantlet extract (Pierre Fabre).[234] Duration and number of flares were significantly reduced in a study of infants with moderate AD, and disease severity improved significantly in these patients and in adults and children with mild AD.

Early treatment with topical anti-inflammatory agents such as topical corticosteroids and calcineurin inhibitors in infants can provide long-term control and may prevent sensitization to allergens through the skin. It is not known if such treatment may have a positive effect on the development of asthma and other atopic comorbidities. Maintaining skin barrier function and reducing levels of immunoglobulin E (IgE) and type 2 cytokines may prevent the so-called 'atopic march'.[235] If treatment is administered within the first month of life, it has been suggested that the disease will become quiescent. In a 5-year randomized study originally intended to compare efficacy of topical calcineurin inhibitors and topical corticosteroids in 2439 infants aged 3–13 months, both treatments were effective in over 50% of infants within the first month of life.[236] In the majority, the disease became totally quiescent, demonstrating the possibility of obtaining early control of AD in infants and preventing further evolution of the disease. Several studies have shown that many AD patients with apparently healthy skin have subclinical inflammation, high skin barrier damage, and production of type 2 cytokines (IL-4 and IL-13), which promote inflammation and block transcription of skin barrier-related genes.

Almost 10 years since the development of topical calcineurin inhibitors, novel topical agents are now becoming available[219,232,237] (Table 5).

A topical phosphodiesterase 4 (PDE4) inhibitor, crisaborole, became available in the United States for use mild-to-moderate AD in patients age ≥ years in 2017 and is under regulatory review in Europe.[237] PDE4 activity is increased in inflammatory cells of patients with AD, leading to degradation of intracellular cAMP and subsequently increased production of proinflammatory cytokines. In clinical trials, crisaborole 2% ointment was associated with early and sustained improvement in disease severity, pruritus and other AD symptoms.[238] Other topical PDE4 inhibitors in clinical trials for AD include difamilast (RVT-501) and lotamilast (OPA 15406). Agents that target Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway have the potential to block downstream signalling of T_H2 cytokines involved in AD.[239] Topical formulations of JAK inhibitors are being developed for use in AD.[240] Delgocitinib (JTE 052) and ruxolitinib (approved in oral formulation for myelofibrosis in the United States and other countries) are in clinical trials. A topical cream formulation of an aryl hydrocarbon receptor (AhR) agonist is in late-stage clinical trials. It has been shown to block inflammatory mediators, including IL-6 and IL-17A, and enhance skin barrier function.[241] Along with the new agents, topical treatment is likely to remain the keystone of treatment for mile-to-moderate AD.

Adherence to current topical treatments

Despite the favourable benefit–risk profile of topical treatments for AD, few patients achieve good control of the disease. In the Spanish DATOP survey, 58% of adults and 50% of children with moderate-to-severe AD failed to achieve control despite their prescribed treatment regimens, mainly due to low adherence.[242] Between 15% and 25% of patients did not use drug therapy even though they had active lesions and only one-third of patients used treatment after the first day of flare-up even though they knew they needed it. It is known that in chronic conditions, that around 50% of prescribed medicines are not taken as recommended, this value is probably lower for topical agents.[243–245]

Over 700 drivers of poor adherence have been identified in dermatology to date.[246] Poor doctor–patient relationship is a primary factor, along with lack of patient knowledge about the disease, conflicting/incorrect information about the treatment and application, and lack of belief in the treatment. A key factor in AD is the concern about the adverse effects of topical corticosteroids, so-called 'corticophobia'. Up to 80% of patients being treated with topical medications are concerned over their use, resulting in 29–49% failing to adhere to a prescribed steroid cream.[247] Many patients (62%) say they would prefer to apply a non-steroid treatment as early as possible to prevent a flare occurring or worsening, and many (47%) are willing to tolerate AD symptoms without initiating treatment.[248] Patients often express fear and anxiety about the safety and efficacy of topical corticosteroid treatment, confusing it with oral or systemic steroids.[243] Other misunderstandings include how topical corticosteroids act: 30-60% patients believe that hydrocortisone is the most potent corticosteroid, and some contend that

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Table 5 New agents under development for atopic dermatitis (Phase 2 and higher only; as of 5 September 2018 upon the information in the manuscript. Authors are the authors of this manuscript)

Agent	Developer(s)	Mechanism of action	Administration	AD indication	Clinical phase
Crisaborole	Pfizer	PDE4 inhibitor	Topical	Mild to moderate	Approved USA 2016; Registration EU
Dupilumab	Regeneron/Sanofi	Anti-IL-4Rα mAb	sc injection	Moderate to severe	Approved USA & EU 2017, Japan 2018
Baricitinib	Eli Lilly/Incyte	JAK1/2 inhibitor	Oral	Moderate to severe	Phase 3
Upadacitinib	AbbVie	JAK1 inhibitor	Oral	Moderate to severe	Phase 3 (FDA-designated breakthrough therapy)
PF-04965842	Pfizer	JAK1 inhibitor	Oral	Moderate to severe	Phase 3 (FDA-designated breakthrough therapy)
Tralokinumab	AstraZeneca/LEO	Anti-IL-13 mAb	sc injection	moderate to severe	Phase 3
Nemolizumab	Maruho/Galderma	Anti-IL-31RA mAb	sc injection	Moderate to severe	Phase 3
Tradipitant	Vanda	NK-1R antagonist	Oral	Moderate to severe	Phase 3
Delgocitinib	Japan Tobacco/Tori/Leo	JAK1 inhibitor	Topical	Mild to moderate	Phase 3 Japan, Phase 2 Europe
Tapinarof	Dermavant	AhR agonist	Topical	Mild, moderate, severe	Phase 3
Etokimab	AnaptysBio	Anti-IL-33 mAb	sc injection	Moderate to severe	Phase 2b
Lebrikizumab	Roche	Anti-IL-13 mAb	sc injection	Moderate to severe	Phase 2b
Ruxolitinib	Incyte/Novartis (ex-US)	JAK1/2 inhibitor	Topical	Mild to moderate	Phase 2b
GBR-830	Glenmark	Anti-OX40 mAb	iv infusion	Moderate to severe	Phase 2b
ASN002	Asana	JAK/SYK inhibitor	Oral	Moderate to severe	Phase 2b
Difamilast	Otsuka/Medimetriks	PDE4 inhibitor	Topical	Mild to moderate	Phase 2
Lotamilast	Roivant/Dermavant	PDE4 inhibitor	Topical	Mild to moderate	Phase 2
Tezepelumab	AstraZeneca	Anti-TSLP mAb	sc injection	Moderate to severe	Phase 2
MOR106	Novartis	Anti-IL-17c mAb	iv infusion	Moderate to severe	Phase 2
ZPL-389	Novartis	H4R antagonist	Oral	Moderate to severe	Phase 2

AhR, aryl hydrocarbon receptor; H4R, histamine 4 receptor; IL-31R, IL-31 receptor; IL-4Rα, interleukin-4 receptor subunit-α; JAK, Janus kinase; mAb, monoclonal antibody; NK1R, neurokinin-1 receptor; PDE4, phosphodiesterase 4; SYK, spleen tyrosine kinase; TSLP, thymic stromal lymphopoietin.

corticosteroids kill bacteria.[243] Patients' erroneous beliefs are often sustained and amplified by media, pharmacists, primary care physicians and even dermatologists and paediatricians.[249,250] The consequences of corticophobia are insufficient frequency of application, inadequate amount and early withdrawal of topical treatment which result in lack of disease control.[251]

Improving adherence to AD therapy is a big challenge. Therapeutic education for patients and increased training for caring physicians are the main tools for increasing patient adherence to effective topical therapies in AD.[243] A supportive physician–patient relationship must be established, with an established schedule of frequent visits; electronic messaging and phone calls can be useful. It is important to raise patient awareness; therapeutic education programmes are important because they reassure the patients that the treatment they are using is correct and safe.

Patients, or the parents in case of children, should be provided with knowledge about the pathophysiology of AD and why it will never resolve without treatment. Patients should be given clear and simple instructions focusing on the correct application of topical TC therapy. Fast and effective therapy will create trust and confidence, which will lead to increased patient adherence.

New systemic therapy approaches

Accumulating evidence indicates that moderate-to-severe AD should be considered a systemic disease that should be treated with a systemic agent. Nonetheless, treatment guidelines currently in use consider systemic treatment to be last-resort therapy in AD patients[252,253] and even recent guidelines recommend systemic treatment only in patients with severe AD (SCORAD >50 or persistent eczema).[232,254] Many adult patients with severe AD are maintained on topical therapy because of potential side-effects of systemic therapy and because of lack of long-term control with currently available systemic agents.[255]

Until recently, systemic treatment for AD consisted of immunosuppression with oral corticosteroids (for short-term use only) and ciclosporin (approved in Europe and Japan for short-term treatment of severe, refractory AD in adults and used off-label in the United States in children and adults).[219,256] Oral corticosteroids have an unfavourable risk–benefit profile, and

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ciclosporin is associated with nephrotoxicity. Methotrexate, azathioprine and mycophenolate mofetil (MMF) are all also used off-label in children and adults.[219,256]

A pipeline of targeted systemic therapies currently in development is based on increased understanding of the mechanism of AD and is particularly focused on suppressing the skewed immune activation (Table 5).[219,257] Many of these agents are in Phase 2 or 3 clinical trials for use in AD. The first to become available in Europe and the United States, in 2017, was dupilumab, a monoclonal antibody (mAb) that targets the α subunit of the IL-4 receptor, which is part of the IL-4/IL-13 complex.[258,259] By modifying IL-4/IL-13 signalling, dupilumab reduces AD pathogenetic mechanisms such as T_H2 cell responses and IgE class switching. When given at the approved dose of 300 mg sc, the full effect of dupilumab is seen at around 1 month. In large clinical trials, about one-third of AD patients had complete resolution of signs and symptoms.[260,261] Dupilumab was approved for moderate-to-severe AD in adults. It is not yet licensed in children, although it has been reported to be effective.[258] Non-infectious conjunctivitis has been reported more frequently in patients taking dupilumab in clinical studies.[260–264] In practice, reported rates of dupilumab-associated conjunctivitis range from 8.5% to 50%.[264,265] Many cases appear manageable with commercially available fluorometholone 0.1% eye drops or off-label tacrolimus 0.03% eye ointment.[265]

Other biological agents in development similarly inhibit T_H2 cytokines (e.g., IL-4, IL-5, IL-13, IL-31 and their receptors) or T_H22/T_H17 cytokines, levels of which are increased in lesional skin. MAbs in late clinical development that have attracted interest include nemolizumab (anti-IL-31 receptor A), which was associated with improvements in pruritus and in sleep disturbance in a randomized clinical trial,[266,267] tralokinumab[268] and lebrikizumab[269] (anti-IL-13), along with ANB020 (anti-IL-33),[270] MOR-106 (anti-IL-17C),[271] and GBR-830,[272] which blocks OX40, a co-stimulatory receptor on activated T cells. Orally administered selective JAK inhibitors are also in late-stage trials for AD[273] including JAK1/2 inhibitor baricitinib[274] (already approved in rheumatoid arthritis) and JAK1 inhibitors upadacitinib,[275] PF-04965842,[276] and delgocitinib (JTE-052).[51] Upadacitinib and PF-04965842 were designated breakthrough therapies in AD by the US Food and Drug Administration (FDA) in 2018.

ASN002 inhibits both JAK and spleen tyrosine kinase (SYK), so in addition to inhibiting cytokine signalling through IL-4, IL-13, IL-23 and TSP, it also targets IL-17.[277]

Neurokinin 1 (NK1) inhibitors such as tradipitant[278] are a new class of agents aimed at blocking the release of substance P which is induced by stressful stimuli and is associated with increased pruritus.[279] Histamine antagonists have been evaluated in patients with AD, and since in addition to its role as a mediator of pruritus, histamine has also been reported to be involved in AD pathogenesis.[280] Histamine 4 receptors (H4R) are expressed on human T_H2 cells, and their activation leads to IL-31 synthesis. H4R antagonists are being investigated in AD, although the most recent study, with ZPL-389, showed an improvement in AD severity but not in pruritus.[281]

It is envisaged that a number of these agents in development will be approved in Europe and the United States by 2020.

Conclusion

After a decade of little progress in the treatment of AD, increasing understanding about the mechanism of the disease is leading to the emergence of new topical and systemic agents for treatment of mild, moderate and severe AD.[282] Biologicals targeting key mechanisms of the atopic immune response will change treatment options as long-term disease-modifying drugs. Promising biological agents will be safer, but probably expensive. Comparing biomarkers with individual responses to experimental agents will help to determine subphenotypes within AD that predict prognosis and treatment responses of the new agents. New biologics will be combined with topical therapy. Flare prevention will become more important, and proactive therapy will be used to target subclinical inflammation of AD. Emollients will remain the basis of AD treatment.

Photoprotection: update on current issues

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Highlights in photoprotection

Ultraviolet radiation (UVR), especially UVB, is well known as a major risk factor for melanoma, keratinocyte carcinomas and photoageing. UVR-induced effects are now known to continue even after UVR exposure. The practice of photoprotection implies wearing appropriate clothing outdoors and applying sunscreen to uncovered areas of skin. The clinical benefits of sunscreen have been demonstrated in randomized controlled trials that established their role in the prevention of actinic keratosis, squamous cell carcinomas, naevi and even melanomas. Some sunscreens contain known allergens or leave an acceptable film in the skin, and some ingredients appear to have harmful effects on the environment since they are not eliminated in wastewater, so new, safer sunscreen ingredients are under investigation. In addition to UVR, other wavelengths of the solar spectrum including visible and infrared ranges produce biological effects. New topical antioxidants and oral agents could potentially provide additional protection. Continued public education, especially for especially for young people, is needed about the risks associated with sun exposure and artificial tanning and the practice of photoprotection.

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Introduction

Many studies have demonstrated that ultraviolet radiation (UVR) is an important risk factor for melanoma[283–285] and the most important risk factor for keratinocyte cancers (basal cell carcinoma and squamous cell carcinoma).[286–288] It has been estimated that UVR exposure is associated with 65% of melanoma cases and 90% of keratinocyte cancers.[289] The precise pattern and timing of UVR exposure and its relation to skin cancer risk, however, differ among these three main skin cancer types. An individual's response to UVR is linked to multiple inherited and environmental factors, such as skin phototype, hair and eye colour, presence of naevi, outdoor exposure to UVR (occupational or recreational) and childhood sunburn.[290] Indoor tanning (sunbed use) is also associated with an increased risk in melanoma.[291]

Ultraviolet B (UVB) and, to a lesser extent, UVA, are known to cause cellular DNA damage, including cyclobutane pyrimidine dimers (CPDs) that are responsible for a variety of signature UV mutations associated with skin carcinogenesis.[292,293] High rates of UVR-induced mutations have been reported in melanoma[122] and squamous cell carcinoma[294] and are associated with aggressive behaviour or metastatic potential. Recently, advances in the development of targeted therapies for melanoma and basal cell carcinoma have occurred.[284,295] Photoprotection practice involves staying in the shade when outdoors, wearing appropriate protective clothing including a wide-brimmed hat and sunglasses, and applying sunscreen only in the areas that cannot be covered by clothing. The effects of sunscreen in minimizing the development of skin cancer have been demonstrated for keratinocyte carcinomas[296,297] and melanoma[298,299] and do not differ according to sex, age, skin type, occupation, history of burns, history of skin cancer and presence of naevi.

Despite increasing knowledge about preventing skin cancers, challenges remain in photoprotection, as reviewed below. Data are emerging that radiation from other parts of the solar spectrum may have carcinogenic effects similar to those of UVR and that the effects of UVR itself persist beyond direct exposure. Current sunscreens are inadequate to protect against these types of radiation and innovation in topical and oral photoprotective agents are needed. Behavioural interventions are also necessary, especially for younger people in whom tanning is commonly practised.

Effects of non-UV solar radiation

Ultraviolet radiation accounts for only 2–5% of the solar spectrum, and other wavelengths are implicated in skin damage, although they have been studied less extensively than UVR. Infrared (IR) radiation (760 nm–1 mm) is widely considered to cause skin damage, as demonstrated in animal and human skin with IR-A (760–1400 nm) that reported upregulation of matrix metalloproteinases (MMPs) 1 and 9 and reduced collagen production.[300–302] Some of these studies were criticized for using irradiation doses higher than the usual dose experienced by humans.[303] It has been suggested that the effects of IR radiation on the skin are due to the heat it generates[303,304] and that under certain conditions, e.g., cool weather, IR-A radiation from sunlight can have beneficial effects on the skin.[303] Nonetheless, topical products have been developed to protect against the effects of IR-A radiation, including formulations reported to inhibit IR-A-induced generation of free radicals[305] and others containing antioxidants to counter upregulation of MMP-1.[306]

Visible light (400–760 nm), especially the shorter wavelengths, has been linked with skin hyperpigmentation and melasma[307–309] and has been shown to activate MMPs and reduce collagen production by inducing oxidative stress.[310] In one study, artificial UVA1 (340–400 nm) induced immediate pigment darkening, some of which resolved within one week.[308] In contrast, visible light produced significantly more intense immediate pigment darkening that persisted longer.[308] Only darker skin types (IV–VI according to the Fitzpatrick scale) were affected. A synergistic effect between UVA1 radiation and visible light was suggested by data showing that pigment intensity induced by pure visible light plus UVA1 radiation was greater than the pigment produced by pure visible light alone.[309] Currently available organic (chemical) UV filters do not protect the skin from the effect of visible light,[311] and new photoprotection agents are needed.

Delayed photodamage

Recent research suggests that skin damage continues even after direct exposure to UVR, further emphasizing the need for proper photoprotection. In an *in vitro* study, murine and human melanocytes were found to generate CPDs for 3 h after the exposure to UVB and UVA was stopped.[293] However, when albino mouse melanocytes (without melanin) were used, peak CPD formation was detected immediately after UVA exposure, indicating that melanin is involved in the so-called 'dark CPD formation'. *In vivo*, black mice with melanocytes containing eumelanin showed dark CPD formation after UVA exposure. In mice with melanocytes that synthesized red-yellow pheomelanin, both initial and dark CPD formations were twice as frequent as in black mice, suggesting that pheomelanin is a more potent dark CPD generator than eumelanin. Of note, fair-skinned people have a higher ratio of pheomelanin vs. eumelanin and 2–4 times greater risk for melanoma than dark-haired individuals, but whether pheomelanin contributes to skin cancer formation in humans is as yet unknown, since there no data in humans. α-Tocopherol (vitamin E) has attracted attention since it was shown to prevent the formation of UVB-induced CPD in human keratinocytes.[312] Incubation of keratinocytes with α-tocopherol (vitamin E) added before or

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after UVA1 exposure blocked the formation of light and dark CPDs, suggesting that similar agents might be beneficial if incorporated to topical sunscreen products.[313]

Safety of sunscreen ingredients

Concerns about several components of sunscreens have led to their use being restricted in some geographical areas, leading to a shortage of alternative products, or they have been modified to improve safety.

Allergens Two ingredients found in a wide range of currently available sunscreens have been proclaimed 'Allergen of the Year' by the American Contact Dermatitis Society: benzophenones in 2014[314] and alkyl glucosides in 2017.[315] The recognition for benzophenones was based mainly on the properties of benzophenone-3 (known in the United States as oxybenzone). Benzophenone-3 can cause contact allergic and photoallergic response[316] and in laboratory studies has shown weak oestrogenic and potent anti-androgenic effects.[317,318] Benzophenone-3 is widely used in the United States, where it is found in almost 65% of non-mineral sunscreens,[319] and the Centers for Disease Control and Prevention (CDC) has estimated that up to 96.8% of the US population is exposed to benzophenone-3 through different sources.[320] In Europe, where there is a mandatory labelling requirement stating 'contains benzophenone-3',[321,322] benzophenone-3 has been replaced with other UVA filters in most sunscreens. Environmental effects of benzophenones have raised concerns, as they are not easily removed by common wastewater treatment plant techniques, and consequently, they have been found in water resources worldwide.[323] They have also been linked to coral reef bleaching. In 2018, Hawaii became the first US state to pass a bill banning the sale and distribution of sunscreens containing benzophenone-3 or octinoxate (ethylhexyl methoxycinnamate) without a doctor's prescription.[324]

Alkyl glucosides are non-ionic surfactants found in leave-on cosmetics, including sunscreens, as well as rinse-off cosmetics. Since they are biodegradable, use of alkyl glucosides is increasing. Originally considered to have lower irritancy and allergenicity than harsher anionic surfactants, reports of allergic contact dermatitis associated with these products have recently increased.[325] Around 15% of the 20 best-selling sunscreens available online contain alkyl glucosides.[326]

Nanoparticles Sunscreens containing zinc oxide (ZnO) and titanium oxide (TiO_2) inorganic filters offer broadband UVR protection, and as nanoparticles, they produce reduced whitening on the skin compared with older generation inorganic sunscreens. ZnO nanoparticles are able to absorb over the entire UVA-UVB spectrum, whereas TiO_2 nanoparticles absorb more efficiently in the UVB range (350–290 nm).[327] Size reduction of nanoparticle TiO_2 to <100 nm increases UVB absorption at the expense of UVA-1.[328] Concerns were raised related to the development of reactive oxygen species (ROS) in the presence of UVR shown *in vitro*, resulting in damage to the viable cells, and whether the nanoparticles were small enough to penetrate the epidermis and enter the bloodstream.[329] However, it should be noted that nanoparticle coatings (such as silicon dioxide) are commonly used, which prevent the ROS from affecting the surrounding microenvironment. In addition, the skin itself has an antioxidant mechanism that neutralizes the effects ROS.[328] Current evidence suggests that the nanoparticles may lodge in hair follicles[330] but do not penetrate into the dermis in an significant amount.[326,328] At present, there is no evidence that there are any consequences on human health, although there are insufficient data on inflamed skin where the epidermal barrier function has been compromised. Environmental effects of nanoparticles have been reported.[331,332]

New concepts in photoprotection

Antioxidants in sunscreens Sunscreens containing antioxidant have been shown to reduce the reactive oxygen species (ROS), cytokines and MMP production induced by visible light.[310] It has now been demonstrated that sunscreen containing stabilized antioxidant is more effective than sunscreen alone in suppressing UVR-induced pigmentation, depletion of Langerhans cells and induction of MMP-9 and in suppressing IR-A induction of MMP-1.[306,333] However, antioxidants are inherently unstable, and to be beneficial in sunscreen, they must be formulated in a stabilized and biologically active composition.

Photolyases Photolyases, naturally occurring enzymes that are absent in placental mammals but present in other animals, plants and bacteria, have been incorporated into sunscreen due to their ability to repair UVR-induced DNA damage by reducing formation of CPDs and UVR-induced apoptosis in the presence of visible (violet-blue) light.[334,335] Photolyases were first isolated from a cyanobacterium, *Anacystis nidulans*, in marine plants. A photolyase-containing emulsion (Eryfotona® AK-NMSC, ISDN) with a SPF 50 was shown to be more effective than sunscreen alone in down-regulating many of the side-effects associated with UVR, such as expression of p53 (linked to apoptosis) and Ki67 (cell proliferation).[336] The same photolyase liposome-encapsulated emulsion was reported to suppress development of actinic keratoses after successful photodynamic therapy.[337]

Oral vitamin D A new concept in photoprotection is the application of the anti-inflammatory effects of high-dose oral vitamin D. In a pilot, proof-of-principle interventional study, 20 subjects who took a single dose 200 000 IU of vitamin D_3 one hour after receiving three minimal erythema dose of solar-simulated radiation showed attenuated local inflammatory response to the

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radiation, resulting in reduced skin redness, decreased epidermal structural damage, reduced expression of proinflammatory markers in the skin and upregulated skin barrier repair gene expression.[338] This effect is believed to be brought about by inhibition of inducible nitric oxide synthase (iNOS; or *NOS2* gene) and TNF-α (or *TNFA* gene) by activated macrophages.[339] However, the investigators cautioned that supplementation with high-dose oral vitamin D_3 should not replace photoprotective behaviour, including the regular use of sunscreen.[340] In addition, since vitamin D_3 was administered in the study after sunburn had already occurred, it is not known whether it would act as an anti-inflammatory agent if given before the development of sunburn. As the commonly recommended daily dose of vitamin D is in the range of 600–2000 IU, the high dose used in this study is not recommended for daily intake.

Protection of adolescent skin

Children and teenagers are a particularly susceptible population for long-term harmful effects of UVR. Data suggest that up to 50% of total UVR up to age 60 occurs before age 20.[341] Regular sunscreen use in this age group could significantly reduce lifetime incidence of skin cancer, but adolescents and young adults have the lowest skin protection rates of all age groups.[342] Tanning behaviours, both outdoor sunbathing and indoor sunbed use, are prevalent in young adult populations and are strongly associated with increased risk of both melanoma and keratinocyte cancer.[343–345] Optimizing the use of sunscreens and altering tanning behaviours in the young remain a challenge, in part because some adolescents exhibit difficulties in planning and thinking long term, a need for immediate results, difficulties in resisting temptation, lower risk perception and being more receptive to rewards than punishment. This behaviour is due to immaturity of the prefrontal cortex of the brain, which does not complete development until around the age of 25 years.[346] Another reason for the failure of efforts to date may be the addictive nature of UVR. Recent research has suggested a biological addiction to UVR.[347–349] Some findings support a causative pathway mediated by UVR-induced release of β-endorphin, an endogenous opioid.[350]

A number of studies have confirmed the existence of tanning addiction ('tanorexia') and related comorbidities in adolescents. Although not yet referenced as an addiction by the American Psychiatric Association's *Diagnostic and statistical manual of mental disorders* (DSM-V), tanning addiction is usually diagnosed on the basis of an obsessive desire to acquire and maintain a suntan, by natural or artificial methods. A recent study identified 7% of 16-year-olds as meeting the criteria for tanning addiction, often associated with problems of substance abuse and psychological factors.[351]

Parents play a very important role in the tanning habits of their adolescent children. Adolescents who have parents who tan and/or have a favourable attitude towards tanning are more likely to seek a tan.[352–354] A US study showed that 45% of those who began tanning younger than age 16 often started with a family member.[355] Preventive interventions should target parents about their own behaviour and on their views of the social and cultural impact of a tanned skin rather than on the risk of cancer.[356]

Targeting children in paediatric offices regarding UV exposure may be a practical approach.[356,357] Education and outreach including counselling by paediatric healthcare providers may be needed to make the parents more aware of the harms associated with indoor tanning for adolescents, to engage them as partners in skin cancer prevention for youth, to control the degree of sunlight exposure and to serve as an example for adolescents.[350] Regulatory action on tanning salons may be an additional approach. To date, Brazil and Australia have banned indoor tanning, while Austria, Belgium, Finland, France, Germany, Iceland, Italy, Norway, Portugal, Spain, the UK and several US states have banned indoor tanning for people younger than age 18.[358]

Conclusion

The understanding of the prevention of skin cancers with adequate photoprotection help reduce the incidence of cancers, that's why innovations in topical and photoprotective agents need to be developed, and public education need to be improved.

Acne: what is the best approach to management?

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Highlights in acne

Treatment of acne should always begin as early as possible, with the goal of preventing scarring. Topical retinoids such as adapalene or isotretinoin are considered the basis of treatment for all grades of acne and for mild-to-moderate acne. Adapalene plus benzoyl peroxide (BPO) is now the preferred first-line therapy for most patients because of its synergistic effect on inflammation. Systemic antibiotics are recommended for additional use in patients with moderate-to-severe acne, but long-term therapy with either topical or systemic antibiotics is discouraged because of the likelihood that resistance will develop. Both topical and oral therapies are associated with high levels of non-adherence, and new strategies are needed to manage patients' unrealistic expectations of treatment. Interventional approaches such as chemical peels, laser and light-based therapies can be used for treating acne and acne scarring, a source of distress in most cases. Effective cosmetic management alongside pharmaceutical treatment can reduce inflammation and

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reduce the drying effects of some acne treatments and increase adherence.

Introduction

Acne, a chronic inflammatory disease of the pilosebaceous follicles, is one of the most common dermatologic conditions, especially among adolescents.[359] The greatest burden of the disease worldwide is in Western Europe, high-income North America and southern Latin America.[360] Acne is frequently characterized by elevated sebum production related to androgen stimulation of sebaceous glands, altered keratinization (hyperkeratinization), hypercolonization of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), innate immunity activation and inflammation.

Acne varies in severity and presentation from mild comedonal formation to more severe papules, pustules and nodules. The most appropriate treatment depends on the patient and the severity of the disease, but there is currently no standardized acne grading system for acne severity,[361–363] so that although current guidelines categorize acne as mild, moderate or severe, these definitions can vary.[364,365] The Investigator's Global Assessment (IGA) severity scale allows a clinician to establish the patient's general clinical condition, taking into account the quality and the quantity of the lesions.[366,367] However objective assessments of clinical severity of acne as measured by clinicians do not always correlate with the patient's perception of its severity.[368] Acne can be treated with many topical and systemic therapeutic agents or non-pharmaceutical interventions, nowadays following a strategy consisting of an induction phase followed by a maintenance phase. Treatment should be started as early as possible to minimize scarring, the most severe sequela of acne.

Topical treatment

Topical retinoids should be considered the basis for treatment of all acne patients, as they are likely to produce faster remissions and prevent development of postinflammatory acne lesions.[363–365,369] Topical retinoids have been shown to normalize the abnormal differentiation and hyperproliferation of follicular epithelium, which, in turn, prevents the formation of microcomedones and subsequent development of inflammatory and non-inflammatory acne lesions. Current European guidelines for the treatment of acne recommend topical retinoids (adapalene, alitretinoin, isotretinoin, tazarotene or tretinoin) as monotherapy for mild/comedonal acne.[364] Adapalene, isotretinoin and tretinoin have demonstrated no significant difference in efficacy, but adapalene has lower irritant potential. Strong evidence indicates that topical retinoids have anti-inflammatory properties as a class effect[370] and that early treatment can inhibit expression of proinflammatory cytokines such as Toll-like receptor 2 (TLR-2).

For mild-to-moderate papulopustular acne, retinoids and a range of additional topical treatments are supported by high strength recommendations, including benzoyl peroxide (BPO), retinoids (adapalene in preference), azelaic acid and topical antibiotics (erythromycin or clindamycin). Adapalene, azelaic acid and BPO show comparable efficacy.[364] In a fixed-dose combination, adapalene and BPO have been shown to act synergistically on inflammatory patterns through regulation of innate immunity.[371] The combination of adapalene and BPO is now preferred first-line therapy for almost all patients with acne[372] because of its synergistic effect on inflammation and because it can minimize the impact of resistance to antibiotics that can develop over the long term (>3 months), and produce clinical improvement in facial scars and skin texture. Fixed-dose combinations are available in two adapalene concentrations (0.1% and 0.3%) combined with BPO 2.5%.[372] The combination has been shown to be extremely effective in mild-to-moderate acne.[364] In addition to targeting multiple pathogenic factors, by blocking *C. acnes*, early activation of the inflammatory response, reduction of microorganisms and keratolytic effects, adapalene/BPO also produces clinical improvement in facial scars and skin texture (Fig. 1).[373,374] Other fixed-dose combinations recommended include BPO/clindamycin which showed superiority over each as monotherapy and comparable efficacy with adapalene/BPO and clindamycin/tretinoin. The recommendations for these combinations of topical treatments have important implications since they are comparable to systemic treatments, suggesting that moderate and even severe acne may sometimes be managed only by topical treatments.[375]

Systemic antibiotics

Systemic treatments target the induction phase of acne treatment. They are guideline-recommended for use in combination with a topical retinoid and BPO in moderate-to-severe acne, but a recommendation for systemic antibiotics has been upgraded in recent guidelines to medium strength for the combination with adapalene in mild-to-moderate acne.[364] Evidence supports the use only of tetracycline or macrolide antibiotics. The tetracyclines are considered first-line therapy in moderate-to-severe acne (except where contraindicated). Doxycycline or lymecycline should be selected in preference to minocycline (increased side-effects) and tetracycline (poorer efficacy). All 4 cyclines have comparable efficacy against inflammatory lesions. There is evidence for superior efficacy for tetracycline compared with systemic macrolides.

Although oral erythromycin and azithromycin can be effective for acne, their use should be limited to patients who cannot use tetracyclines, e.g., pregnant women or children ≤8 years of age. Erythromycin is associated with increased risk of bacterial resistance (see below). Use of systemic antibiotics other than the tetracyclines and macrolides is discouraged, because they are limited data supporting their use in acne. Trimethoprim–sulfamethoxazole may be used in patients who are unable to tolerate tetracycline or in treatment-resistant patients. Guidelines recommend that use of systemic antibiotics should be limited to

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the shortest possible duration and they should be re-evaluated after 3–4 months of use because of possible development of resistance. In real-world clinical practice, antibiotics should be avoided when effective alternatives are available, except in cases where inflammatory acne is not responding well to topical treatments or acne located on the trunk or multiple body areas.

Antibiotic resistance Current guidelines strongly discourage long-term therapy with either topical or systemic antibiotics because of the likelihood of bacterial resistance.[364,365,376,377] Both correct and incorrect use of antibiotics may induce antibiotic resistance. Many countries have reported that over 50% of *C. acnes* strains are resistant to antibiotics, particularly topical macrolides.[377] Cyclines may be associated with significantly less resistance because they act mainly modulating innate immunity (inhibition of granuloma, inflammatory cytokines, chemotaxis of granulocytes and monocytes, and metalloproteinases).[378] When a topical retinoid is applied with a topical antibiotic, the retinoid increases permeability of the skin to other topical agent and improves bioavailability, and minimum inhibitory concentration (MIC) is achieved in a shorter time.[379] Oral antibiotics have a role in the treatment of moderate-to-severe acne but only with a topical retinoid, BPO or their combination, and they should only be used for up to 3 months.[364] In future, improved understanding about the role of *C. acnes* and the innate immune system in acne should help clinicians devise effective treatment strategies without reliance on antibiotics.[370]

Systemic retinoids

Isotretinoin remains the most effective systemic treatment for moderate-to-severe acne at a dose of 0.3–0.5 mg/kg or ≥0.5 mg/kg for conglobate acne.[364] Treatment should continue for at least 6 months and can be prolonged if response is inadequate. Isotretinoin is the only systemic treatment that can prevent scarring. It is also effective in controlling seborrhoea though a dose-linked mechanism that appears to start with induction of apoptosis and cell cycle arrest within the sebaceous gland.[380,381] Systemic isotretinoin also has a similar effect on TLR-2 to that of the topical formulation.[382] Isotretinoin may not be effective in familial acne, in young or older patients, or in certain groups of women, such as women with persistent or late-onset acne.[383] Positive predictive markers of increased risk of relapse to isotretinoin have been identified as severe seborrhoea and a high score of inflammatory lesions at the end of treatment, early age, family history of acne, prepubertal acne and acne extended to the trunk.[384] In female acne, a significant correlation was observed between facial response and low body mass index, low glycaemic load diet, no tobacco use and absence of early acne onset and of lesions on the neck.[385]

Among the side-effects of retinoids is acne fulminans, which may be prevented or minimized by reintroducing isotretinoin at a low dose.[386,387] Isotretinoin has also been linked with depression,[388–390] and care should be taken in prescribing it for patients with a history of psychiatric disorders.[391] Evidence for an association with inflammatory bowel disease has also been contradictory.[392–394] Clinical studies have suggested that intermittent, low-dose isotretinoin could be safer and as effective, but this has only been demonstrated in one clinical trial in mild-to-moderate acne[395] and is not recommended in current guidelines.

In adult women with acne, spironolactone, an anti-androgen, may be used at low doses (50–150 mg/day), off-label, as an alternative to isotretinoin or as second-line treatment after relapse.[383,396–398] Combination oral contraceptives are also effective in reducing acne in women.[364,383,399] There is evidence that third- and fourth-generation combinations may be more effective than first- and second-generation drugs.[400] Neither oral nor topical retinoids should be prescribed to female patients who are or may become pregnant, due to the well-known high risks of teratogenicity.[364,365,391] Zinc gluconate, which has been shown benefit in inflammatory acne,[401] may be appropriate in pregnant women. A prescription survey in around 10 000 pregnant women and 2000 breastfeeding women treated for acne with zinc gluconate identified only 4 serious adverse events not proven to be related to zinc.[402] Topical and oral zinc have been shown to have antibacterial and anti-inflammatory effects and may decrease sebum production.[403]

Problem of non-adherence

The main limiting factor of topical and oral therapy is non-adherence.[404] Some of the features in acne treatment that discourage the patient and lead to non-adherence include the latency period before the appearance of clinical improvement, slow progress in improvement, the frequency of relapses and side-effects related to therapy. Non-adherence is a worldwide problem. A worldwide survey of oral and/or systemic treatment, using a validated assessment tool,[405] found that poor adherence risk was greatest in Europe (58%) compared with Asia (48%) and the Americas (43%).[406] Poor adherence was independently correlated with younger age (<15 years), the occurrence of side-effects, lack of improvement as evaluated by dermatologist, previous systemic therapy, lack of knowledge about acne treatment, consultation with a primary care physician and lack of patient satisfaction with treatment. Factors that had a positive effect on adherence were more severe acne, use of cosmetics (moisturizers, cleansers), use of either topical therapy alone or isotretinoin, good clinical improvement as evaluated by the dermatologist, patient satisfaction with therapy and knowledge about acne treatment. A review of studies published between 1978 and 2013 reported similar adherence topical and oral medications (76%).[407] The occurrence of side-effects and young age were cited as the top reasons for poor adherence, followed by forgetfulness. Adherence may be improved by simplifying treatment regimens (medications requiring less frequent dosing) and by

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avoiding long periods between visits to physician.[363] New strategies are needed to increase adherence through understanding the needs of the patient, and additional tools are needed to measure adherence, since rates reported by patients are often overestimates.[408]

Interventional approaches to acne and acne scarring

Acne Chemical peels are used in the management of acne and acne scars.[409,410] Peeling agents such as glycolic acid and salicylic acid may be used to reduce inflammatory and non-inflammatory lesions. However, multiple treatments are needed, and the results are not long-lasting.[365] No placebo-controlled trials have been carried out with chemical peels. Laser- and light-based therapies administered are widely used in the treatment of acne and acne scarring[411] and may provide additional benefit, although high-quality evidence for their use is lacking.[412] Light-emitting diode (LED)-based devices use blue light (407–420 nm) and red light (620–700 nm), which are absorbed by endogenous coproporphyrins produced by *C. acnes, which* generate singlet oxygen species that destroy the bacteria.[412] Red light penetrates deeper into the skin where it modulates cytokine release from macrophages, reducing the inflammation.[413] Combined blue and red light appears more effective than either alone,[414–416] with a 77% reduction in inflammatory lesions reported in a recent clinical trial.[416] Laser-based therapies, including pulsed dye laser (PDL), potassium titanyl phosphate (KTP) laser, Nd:YAG and laser-based photodynamic therapy (PDT), have been shown to be effective in the treatment of active acne,[410,417] but many studies were limited by small patient numbers, and lack of control populations and comparison with standard therapies. PDT uses photosensitizers, often 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), with red light and intense pulsed light the most frequently used light sources.[418] A 77% reduction in inflammatory lesions was reported with ALA-PDT activation by long-pulsed PDL (595 nm).[419] PDT may be a good adjunctive treatment for mild-to-severe acne, especially in patients who have not responded to topical therapy and oral antibacterials, and are not good candidates for isotretinoin.[418] Other interventional options that can be used: for inflammatory acne include intralesional injection of a corticosteroid (triamcinolone) that can produce improvement in large nodular lesions and keloid scars within 48–72 h.[420]

Acne scars Facial scarring affects both sexes equally and occurs to some degree in 95% of cases.[421] Postacne scarring is associated with significant psychosocial distress.[422] The degree of scarring has a genetic basis, and scarring can worsen with age. Many grading scales have been proposed for acne scars,[423,424] but none of them has been adopted universally and photographic standards are often applied. Treatment of acne scars is often based on whether the scarring is atrophic (boxcar, ice pick or rolling) or hypertrophic. Multiple procedures are usually involved, including surgery, chemical peeling, injectables, lasers and other energy-based devices.[425–427] Outcomes remain unpredictable, so it is important to establish realistic expectations with patients before treatment. Patients' goals and expectations regarding treatment timeline, number of treatment sessions, length of recovery and projected outcomes should be discussed in order to optimize treatment experience and patient satisfaction.[425] Dermatologists can optimize outcomes by starting treatment as soon as possible and by taking good-quality high-resolution pre-treatment photographs (or video).

Ablative and non-ablative lasers are used with the aim of producing neocollagenesis. The appropriate choice of laser treatment should take into account the extent of scarring, the type and morphology of acne scars, as well as the patient's skin type. Fractional ablative lasers may offer the best compromise between efficacy and adverse effects, but non-ablative lasers, such as the 1550 nm and the 1540 nm, may be appropriate in patients with milder scars or who prefer to defer ablative treatment. Microneedling and microneedling fractional radiofrequency have recently emerged for treatment of acne scars with good results reported. Studies have confirmed improvement of scars with these procedures[426,428,429] but with few participants. Dermabrasion may be a good option to soften superficial atrophic scar edges, but it is associated with scarring, pigment alterations and milia formation.[430]

Skin fragility

Another factor that can limit the success of acne therapy is skin fragility.[1,4] Acne skin is fragile due to alteration in sebum composition, functional alteration of filaggrin, persistent inflammation of the skin and some aggressive therapies.[4] Many topical anti-acne treatments, including BPO and topical retinoids, can alter skin barrier function, causing an increase in transepidermal water loss, decreased skin hydration, and skin sensitivity/irritation, and reducing stratum corneum thickness.[4,431] Thus, acne sufferers often experience a double cause of fragile skin, both from the disease itself (pathological) and the treatment (iatrogenic).[1,4]

Dermocosmetics contribute to the success of anti-acne treatments, by providing optimal hygiene, compensating the irritation and dryness induced by medications, and allowing use of adapted cosmetics and sun protection.

Effective acne treatment strategies should combine pharmacological and cosmetic therapies.[432–434] Non-aggressive skin cleansing and moisturizing should be carried out during therapy.[435] Moisturizers can counteract the drying effects of some acne medications and help maintain the skin barrier through mild surfactant and lipid/moisturizing components, enhancing stratum corneum barrier function and thus reducing inflammation.[436–438] In adult female patients treated over 4 weeks with a weakly acidic foaming facial skin cleanser based on a mild

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detergent and an aqueous lotion with eucalyptus extract and a moisturizing gel containing pseudo-ceramide and eucalyptus extract, acne was significantly reduced and endogenous ceramide level in the stratum corneum significantly increased.[437] In a study in patients with mild-to-severe acne who used adapalene concomitantly with a moisturizer (heparinoid), adherence was increased and the treatment period with initial therapy significantly extended compared with use of adapalene alone.[439] No adverse effect of the moisturizer was observed on the number of comedones and inflammatory eruptions. Cosmetic products containing Rhealba® Oat plantlet extract (Pierre Fabre) have been shown to be effective adjunctive agents when combined with standard acne treatment regimens, restoring skin barrier integrity and reducing inflammatory properties, by inhibiting the inflammasome pathway.[440,441] New roles of dermocosmetics in modulation of the skin microbiome.[442–444] Recently, Myrtacine® (*Myrtus communis* extract)-based cream was shown to significantly reduce the level of erythromycin-resistant strains of *Cutibacterium* in acne patients, which was associated with a decrease in acne lesions.[445,446]

New frontiers in the evaluation of acne

The activities of Pierre Fabre's Clinical Skin Research Center located at the Hôtel-Dieu St-Jacques in Toulouse focus on four areas: - understanding the physiology of the skin and the pathophysiology of dermatologic and hair conditions; - development of new methods for skin evaluation; - assessment of tolerability, efficacy and consumer acceptability of dermocosmetics and medical devices; - and cosmetovigilance. Specific processes have been developed to assess the tolerability and efficacy of Pierre Fabre dermocosmetic products for acne-prone skins. Microcomedones should be considered a key target in acne management as they represent the early 'invisible' stage preceding inflammatory and retentional skin lesions that are clinically apparent. Non-invasive biophysics and imaging approaches provide robust key tools for innovative and robust spectroscopic and imaging techniques for research into acne-prone skin, and also evaluation of Pierre Fabre's dermocosmetic products and medical devices. The aim is to retrieve precise structural and functional information about the skin. This dedicated approach is used from the experimental model development through final clinical studies. Some new technologies have recently been introduced including 3D imaging of inflammatory lesions with a new high-magnification camera. *In vivo* confocal imaging helps to obtain information on skin cell morphology and organization, and infrared and Raman spectroscopy are used to analyse the physical chemistry of skin. Digital technology such as image processing and biostatistical data processing reinforces this analysis. Finally, these data are globally analysed and compared with other types of evaluation involving clinical scoring, image analysis and pharmacological methods to achieve robust design for clinical development studies at Pierre Fabre Dermo-Cosmétique.

Conclusion

Acne treatment should be started as soon as possible and include topical treatment and systemic antibiotics or retinoids. In some cases, interventional approaches can be used to treat acne and acne scarring. In any case, the main limiting factor of treatments is non-adherence, that's why new strategies are needed.

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