Therapeutic Management of Atopic Eczema

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Abstract: The present review aims at giving a condensed view on the current status of therapy of atopic eczema - a common chronically relapsing inflammatory skin disease. Atopic eczema is a multifactorial disease with a tendency for chronification. Owing to the associated genetic factors, therapeutic amelioration of skin symptoms is often only transient. Therefore, treatment basically focuses on symptomatic relief. Atopic eczema treatment should more than any other disease be guided by an individualized approach taking not only the phenotype and genotype of the disease but also psychosocial and gender aspects into account. Significant gains have been made in our understanding of atopic eczema, especially recent insights into genetic and immunologic mechanisms, but still, there is no single treatment to date that has proven to be the quantum leap for atopic patients. Novel treatments have been developed and trialled, however, more studies on novel therapies such as biologicals addressing efficacy, optimum dose and duration of treatment and the target phenotype are urgently needed. Hopefully, the tremendous progress in basic research in the last years will provide new targets for prevention and treatment in the future.

Keywords: Atopic eczema, pernonalized therapy.

INTRODUCTION

Atopic eczema (AE) is a chronic eczematous skin disease with a relapsing remitting course [1]. It is responsible for a serious burden on the affected individuals, the society and the society. AE worldwide prevalence is increasing [2], being highest in the pediatric population with values of up to 20% [3]. Early onset of AE has been associated with an increased risk of asthma and many authors have indicated AE as the first step of the atopic march.

AE is characterized by pruritus and inflammation of the skin [4]. The diagnosis of atopic eczema (AE) is made using evaluated clinical criteria [5]. According to current knowledge, the underlying pathomechanism is a combination of a dysfunction of the physical and immunological barrier of the skin and a TH2-dominated deviation of the immune system. Recently, a strong association with loss-of-function mutations in the gene filaggrin was reported, which results in an epidermal barrier impairment [6, 7]. Two major elements in the dysfunction of the immunological barrier are hypersensitivity responses to environmental allergens and innate immune reactions triggered by microorganisms.

Atopic eczema (AE) is a disease that occurs frequently in daily medical management. A first step in efficient AE management constitutes sufficient information of patients to achieve compliance/ adherence for medical treatments. A second step is a personalized therapeutic management depending on e.g. the phenotype of the disease, age, gender and skin type [8,9]. This review aims at giving an overview about the current status of modern AE-management which implies a holistic approach including not only modern, innovative therapy but also 'Eczema school' educational programs and psychosomatic counselling.

PATIENT EDUCATION IN THE MANAGEMENT OF ATOPIC ECZEMA

Patient education programs have been proven to be effective in chronic diseases such as diabetes or asthma. In view of the burden of the disease in families with children affected by atopic eczema, a multidisciplinary approach has been developed in Germany and studied in a multicenter randomised controlled trial. The program was scheduled to weekly sessions of two hours each over a total of six weeks. In affected children up to 7 years of age the program deals with the parents only, in children from 8-12 years children and parents take part in the program, adolescents from 13-18 are trained on their own.

Children and parents are trained how to identify and avoid individual provocation factors, adequate skin care and specific treatment options as well as complementary therapeutic modalities are discussed. A special part deals with diagnosis and treatment of food allergies in childhood atopic eczema and preventive strategies. Behaviour-oriented psychological intervention is focused on interrupting the itch-scratch cycle by improving perception of critical situations, training of alternative habits to scratching, discrimination and control of scratch stimuli and relaxation techniques. Furthermore the training aims at reduction of negative effects on social life by development of behavioural competence for an improved coping with stress and illness-specific problems

The results of the multicentre trial evaluating the program have been published in 2006 [10] showing that the intervention group showed better values in multiple psycho-social scales such as ability to deal with the disease, confidence in medical treatment or aggression against scratching, but also concerning severity of skin disease (objective SCORAD).

EMOLLIENTS/BASIC THERAPY

Most AE is moderate and patients can be treated with emollients and topical anti-inflammatory agents. Emollients are used to restore disrupted epidermal barrier function in AE. The choice of an oil-in-water or water-in-oil emulsion depends on the actual skin condition. Highly inflammatory lesions (erythema, oozing) should be treated with emollients with low fat content. For chronic eczematous lesions (lichenification, prurigoform) emollients with higher fat content are in general preferable. Ointments with very high fat content or hydrophilic gels containing (almost) no fat should be avoided [11]. With flare-ups the choice of the emollient has to be adapted.

Glycerol and urea are often added as moisturizers to emollients. *In-vivo*-studies in healthy volunteers have shown that 10% glycerol is more effective than 5% glycerol, whereas 10% urea did not show an advantages compared to 5% urea [12, 13].

Although the importance of regular use of emollients in AE is agreed upon in most guidelines and expert statements [8, 14, 15], few studies have proven this effect [16]. Some other studies have shown that regular basic therapy reduces signs and symptoms of

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AE with less or equal consumption or topical steroids [17, 18]. A new epidermal barrier repair (EpiCeram® Skin Barrier Cream) specifically composed to correct lipid-biochemical abnormalities in AE has been shown non-inferior to fluticason propionate cream regarding pruritus and sleep loss as well as SCORAD (SCORing Atopic Dermatitis) reduction [19]. Experimental data suggests that regular use of topical glucocorticosteroids can add to the disruption of epidermal barrier function by inhibiting epidermal synthesis of fatty acids [20]. This effect can be alleviated by application of a mixture of ceramids, free fatty acids and cholesterol [21], further supporting regular use of appropriate emollients.

As effectiveness of basic therapy is directly linked to regular application, acceptance is a crucial issue. Doctors should ask their patients if they are happy with texture, dispersion, permeation and flavor of their emollient and assist in choosing individually adapted products.

ANTI-MICROBIALS

The high degree of skin colonization with Staphylococcus (S.) *aureus* on affected as on clinically unaffected skin is the most characteristic microbiological feature in AE. Several studies have determined a colonization rate with *S. aureus* as high as 90 % of all analyzed patients [22-24]. When analyzing the role of *S. aureus* in AE, several factors have to be taken into account. First, there seem to be crucial factors for a preferential adherence and a continuous colonization on atopic skin [25], second, defense factors are impaired in atopic individuals including diminished defensin expression and polymorphisms in pattern recognition receptors [26, 27], third, there is a preferential induction of IgE antibodies against staphylococcal components in atopic patients leading to aggravation of clinical symptoms [28], and fourth, many of the strains isolated from atopic eczema are producers of superantigens which continuously stimulate the host immune system and thereby contribute as a distinct risk factor for the chronification and exacerbation of skin symptoms [29, 30] .

Ever since the description of the crucial role of *S. aureus* in AE, there has been an ongoing debate as to whether an antimicrobial therapy is of benefit for the patients.

Significant *S. aureus* infection is the most common complication of AE, associated with more severe eczema, excessive scratching and special subtypes ("weepy eczema") [31]. There is no data why some individuals seem to be more at risk than others, nor if colonization with specific *S. aureus* strains predisposes to relevant impetiginization. Diagnosis of impetiginized eczema is based on the typical clinical picture with oozing and formation of yellowish crusts. In these cases, *S. aureus* density is usually >103 CFU/cm^2.

As up to 100% of AE patients are colonized and exact quantitative analyses are not routinely performed, detection of *S. aureus* is not diagnostic. Bacterial culture prior to therapy is however important to be able to adjust primary antibiotic treatment if necessary and detect *Streptococcus pyogenes* or other bacteria which might be involved.

The handling of *S. aureus* loaded eczema has to include two different strategies, treatment of infected skin and prevention from colonization/ infection in patients at risk. While for obvious reasons, antibiotics are exclusively used in treatment interventions, the management of atopic eczema patients often includes the use of antiseptics to prevent colonization or reduce bacterial counts.

Owing to that, most of the studies in AE patients have looked at *S. aureus* count reduction and at the same time at improvement of clinical scores. While the latter is a suitable endpoint for study approaches, bacterial reduction can not be unambiguously contributed to the antibacterial treatment as amelioration of the inflammation through steroid or calcineurin inhibitors also results in reduced bacterial numbers [32, 33].

Topical Antibiotics

Besides the systemic application of antibiotics, topical formulations either alone or in combination with anti-inflammatory drugs have been used to treat *S. aureus*-superinfected or colonized eczema. Of note, the studies performed with diverse local antibiotics such as mupirocin ointment (2%) [34], fusidic acid [35] or prednicarbate cream in combination with didecyldimethylammonium-chloride [36] did not show an advantage of the combination of antibiotic with steroid as compared to the steroid alone. However, there seem to be no reports of major side effects which are usually restricted to irritations and lead to withdrawal from treatment only in very few cases. Weather new classes of antibiotics such as the pleuromutilins [37] will add new clues to our understanding of local antibiotic treatment remains to be investigated.

Antiseptic Treatment

Antiseptics are the treatment of choice to reduce bacterial load in atopic eczema patients. The main advantages of antiseptics compared to topically applied antibiotics are: their potential to induce resistance in *S. aureus* strains even with repeated and widespread use seems to be very low, different preparations are available to suit individual needs according to disease activity, area and concomitant treatment and they rarely cause delayed-type hypersensitivity.

In severe widespread bacterial infection antiseptic baths can be of great value to get rid of the crusts and therewith a substantial part of bacterial load. Antiseptics used for baths include potassium permanganate, sodium hypochlorite, triclosan and chlorhexidine gluconate. Prophylactic antiseptic treatment is often recommended to patients with frequent bacterial infection, although there is no data to prove this effective. An antiseptic ointment (1-2% triclosan or 0.5-1% chlorhexidine digluconate added to the emollient) can be used on a daily basis for the whole body or for selected body areas in patients with heavy colonization or recurring staphylococcal superinfection.

A randomized study from Singapore evaluated efficacy and safety of an emollient containing 1% triclosan over a 27-day treatment period in mild to moderate atopic eczema showing that the triclosan group was slightly better regarding SCORAD change from baseline. Of note, topical glucocorticoid use in the triclosan group was half compared to the placebo group with 22g and 44.2g, respectively ($p<0.05$) pointing towards a steroid-sparing potential of a triclosan-containing emollient [38].

Silver Textiles

Silver coated textiles are an alternative to antiseptic or antibiotic treatment in order to reduce staphylococcal load in AE patients. Most of the available silver-coated textiles are made from smooth materials minimizing irritation by clothing. Two studies showed that silver coated texiles can reduce effectively *S. aureus* colonization which was paralleled by a substantial reduction in clinical severity scores [39,40]. Recently research has focused on silver nanoparticles as possible alternative in the treatment of multidrug resistant bacteria [41].

In conclusion, although many of the antibiotic and antiseptic approaches indeed reduce the amount of staphylococcal colonization, this seems not sufficient to induce sustained improvement of eczema scores. The degree of inflammation seems to be a crucial parameter and by its own strongly impacts on the bacterial load. Thus, a general recommendation for addition of antibacterial measures to AE anti-inflammatory therapy can not be given with the published data. Approaches to diminish bacterial counts to prevent spreading and multiplication in a prophylactic way should focus on patients at risk.

LOCAL ANTI-INFLAMMATORY TREATMENT

At present, the drugs that can sedate the inflammation of AE sufficiently and with proven effectiveness and safety topical corti-

costeroids and topical calcineurin inhibitors such as tacrolimus and pimecrolimus. In general, local anti inflammatory drugs do not cure eczema, but are highly effective in controlling or suppressing symptoms in most cases. Sufficient strength, dosage, adaequate galenic and correct application are essential for effective topical therapy. Gender differences in atopic diseases have been described [42]. In the same line also gender differences in topical treatment of eczematous reactions have to be taken in to account as described for acute pastes contact dermatitis by Noiesen *et al.* [9].

Bases such as ointment, cream, lotion, and pastes must be selected according to the condition and site of skin lesion. Patients with acute, oozing and erosive lesions may first be treated with "wet wraps" until oozing stops. According to former guidelines, anti inflammatory local treatment should be administered to lesional skin only. However, actual studies support a proactive treatment concept which is defined as a combination of long-term (twice or once a week), low dose, anti-inflammatory treatment (topical steroids or calcineurin inhibitors) applied to previously affected areas of skin [43, 44]. This should be combined with liberal use of emollients on the entire body (Fig. (**1**)).

The effectiveness of topical corticosteroids and the occurrence rate of topical side effects parallel each other - even though the therapeutic index improved with the newer corticosteroids. However, it is important to select drugs at ranks appropriate for the ''severity of eruption'' without selecting too strong topical corticosteroids. Due to the increased potential for systemic absorption of topical agents in infants, lower potency agents are recommended.

In general, for mild-moderate eczema a weak steroid may be used (e.g. Hydrocortisone or Prednisolonacetat), whilst more severe cases require a higher-potency steroid (e.g. Fluocinonide, Mometasone furoat). Medium-potency corticosteroids such as Clobetasone butyrate, Prednicarbat are also available. Generally modern glucocorticosteroids (such as Prednicarbate, Hydrocortisone butyrate or Methylprednisolone aceponat, Fluticasone propionate or Mometasone furoate) with a favourable risk-benefit ratio should be preferred for long term treatment in AE. When topical corticosteroids are discontinued after inflammation hase been settled, it is important to discontinue them gradually while observing the symptoms, for example to reapply them intermittently or to switch to a lower-potency steroid. However, this principle does not apply when side-effects such as contact sensitivity to topical corticosteroids develop.

The introduction of topical calcineurin inhibitors (TCIs) more than 10 years ago represented the first new class of anti-inflammatory medication approved for the treatment of AE since topical corticosteroids. Topical calcineurin inhibitors provide targeted anti-inflammatory activity without the local or systemic side effects seen with topical corticosteroids. The most common side effects encountered with the use of TCIs are pruritus, stinging, and warmth sensation at the application site. These are usually mild and resolve within the first few days of use. Generalized viral infections such as eczema herpeticum or eczema molluscatum have been observed during TCI treatment [45], however, several clinical trials failed to demonstrate an increased frequency [46, 47]. In January 2006, the US Food and Drug Administration (FDA) revised the product label for tacrolimus ointment and pimecrolimus cream based on rare reports of cancer in patients using TCIs and a theoretical risk of malignancy based on the mechanism of action of TCIs. However, recent safety reviews strengthen approval of Tacrolimus ointment and pimecrolimus cream as therapy for the treatment of AE. According to the PRACTALL Consensus Report TCI are also recommended as first line therapy [48]. Of note, patients should be advised to restrain from extensive sun and UV-exposure while being treated with TCI.

PHOTO(CHEMO)THERAPY

The general observation that patients with AE improve during summertime [49] in parallel with scientific immunological details [50] suggest UV radiation as a potent tool in atopic eczema management [51]. It has been repeatedly shown that phototherapy can improve AE via different mechanisms including reduction of bacterial colonization and improvement of barrier function. Specific ultraviolet (UV) modalities, such as medium-dose or high-dose UVA1 [52] and narrowband (NB) UVB, with a high output and a narrow emission spectrum are considered as very efficient regimens for treating chronic AE. In general, phototherapy should not be applied in patients younger than 12 years. In acute AE only UVA1 has been shown to be effective. Of note, all UV treatments and especially photochemotherapy pose a long term risk for the development of skin cancer.

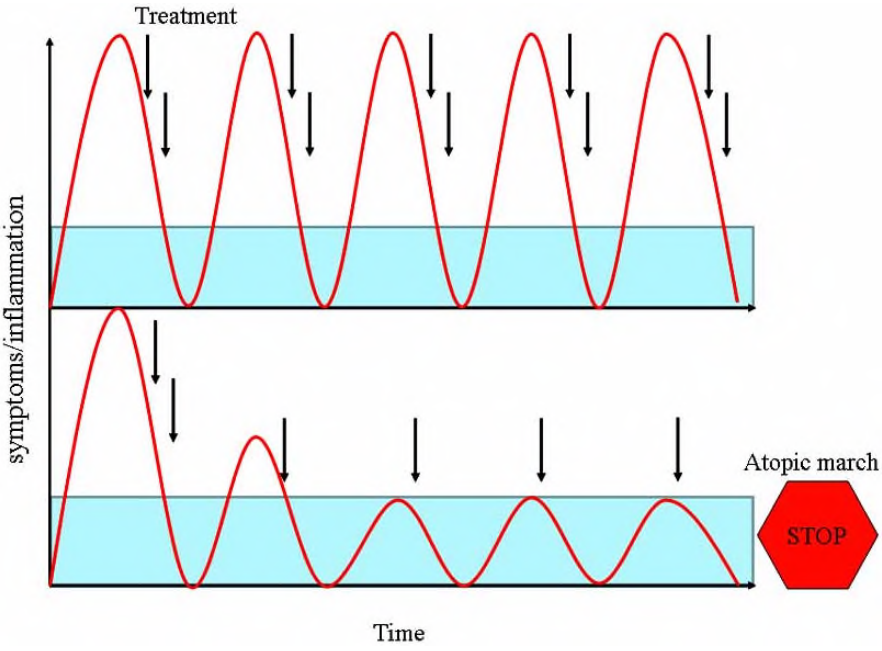

Fig. (1). Traditional (top) and modern proactive therapy (bottom) of atopic eczema. Effectiveness of proactive local therapy has been described for steroids and TCIs.

SYSYTEMIC ANTI-INFLAMMATORY THERAPY

Patients with severe atopic eczema often remain refractory to pure topical treatment. It is for these patients, that we strive to develop new promising systemic treatment options. Up to now, systemic glucocorticosteroids, cyclosporine A, azathioprine and mycophenolate mofetil are the most commonly applied systemic anti inflammatory drugs in AE with their well known limitations and side effects [53].

Corticosteroids are sometimes administered p.o. to severe AE patients as induction therapy and are known to be effective from experience. Considering the systemic side-effects, short-term administration is recommended [8].

At present, the drug showing the most convincing evidence for its use in the systemic treatment of severe, recalcitrant AE is cyclosporine A. Cyclosporine A significantly decreases symptom scores, disease extent, pruritus and sleep deprivation, and has also been shown to improve quality of life [54, 55]. Of note, there is a large body of information on the use in pediatric patients, providing a therapeutic option in difficult to treat children with AE [56].

Everolimus a rapamycine-derived macrolide with immunosuppressive and antiproliferative effects demonstrated efficacy both, in the prophylaxis of organ rejection in kidney transplant patients and in decreasing disease activity in psoriasis patients. On the contrary, everolimus does not seem to be an effective treatment in AE patients, either in combination with prednisone or with CsA [57]. However, this report describes only 2 patients. Thus further investigations on the clinical efficacy should be awaited.

Azathioprine is a long-known systemic immunosuppressive agent affecting purine nucleotide synthesis and metabolism, which has been shown to be effective for many dermatological conditions and can be used, in a non-licensed indication, for AE [58, 59]. It has several adverse effects, including myelosuppression, hepatotoxicity and susceptibility for infection, and the recommended dosage (1–3mg/kg/day) should be determined on the basis of individual thiopurine methyl-transferase (TPMT) levels.

Leflunomide is a pyrimidine de novo synthesis-inhibiting immunosuppressant drug with extremely long *in vivo* half-life. It has been shown to inhibit autoimmune T-cell proliferation and production of autoantibodies. Additionally, it decreases eotaxin release by IL-4/TNFα-stimulated keratinocytes [60]. As T-cells and eosinophils play an important role in the pathophysiology of atopic eczema, leflunomide represents a promising drug for patients with severe atopic eczema. Interestingly, to date, only two published clinical investigation evaluated the efficacy of leflunomide as treatment for atopic eczema [61, 62]. In these studies in recalcitrant atopic eczema leflunomide monotherapy induced a long-lasting remission or at least acceptable skin response within a steroid sparing regimen. Taken together, compared with most conventional systemic immunosuppressive agents, leflunomide seems to have an acceptable risk-benefit ratio, qualifying for alternative use in patients with contraindication to common immunosuppressants, if confirmed by larger proof-of-principle studies.

Cysteinyl leukotrienes (Cys-LTs) are potent proinflammatory mediators derived from arachidonic acid through the 5-lypoxigenase pathway. Antagonist drugs to the Cys-LT-receptors, such as montelukast, zafirlukast and pranlukast, block the effect of Cys-LTs including changes in vascular permeability, inflammatory cell influx, smooth muscle contraction and increased mucus production in the airways. Two published randomized, double-blind, placebo-controlled trials investigated the effect of montelukast in children with moderately to severe atopic eczema and adults with moderate atopic eczema and show inconsistent results [63, 64]. While montelukast reduced symptom scores in children, no effect was seen in adults – compared to placebo.

Reports of successful treatment of atopic eczema with mycophenolate mofetil (MMF) exist both for adults and children [65, 66]. MMF doses of range 40-50 mg kg(-1) daily in younger children and 30-40 mg kg(-1) daily in adolescents. The medication is in general well tolerated, with rare cases of infectious complications or induction of leucopenia, anaemia, thrombocytopenia or elevated aminotransferases. MMF represents another promising therapeutic alternative to traditional systemic immunosuppressive agents with less favourable side-effect profiles, and prospective controlled studies are warranted, to further assess its benefit in AE.

BIOLOGICALS – TARGETED THERAPY

Traditional systemic agents used for the treatment of atopic eczema are associated with significant potential toxicities and sometimes do not provide adequate therapeutic responses. Biologic agents hold promise for a more targeted and less toxic approach to AE systemic therapy. A number of case reports and pilot studies suggest effectiveness of selected biologicals. However, representative, randomized, placebo controlled studies are still lacking. Biologicals target specific steps in the cascade of an inflammatory response. Approaches resulting in reduced T cell activation and T cell recruitment block the cascade in a very early step. Indeed, agents such as alefacept (fusion protein of lymphoyte function and antigen (LFA- (CD58)) [67, 68] and efalizumab [69] (anti CD11α antibody, no more available) have been shown to be effective – both in significant reduction of the symptoms and the reduction in steroid use.

The role of B-cells in the course of atopic eczema is still a matter of debate [70, 71]. Notably, strongly elevated levels of serum IgE are a hallmark of adult patients with generalized extrinsic atopic eczema. Thus, it has been postulated for a long time that B-cells, having undergone the immunoglobulin switch to IgE and plasma cells producing IgE, play a central role in the pathogenesis of atopic eczema. Interestingly, depletion of B-cells by rituximab resulted in rapid and sustained reduction in skin inflammation [72], suggesting a further option for systemic AE treatment and supporting the view of an important role of B cells in the immunopathogenesis of atopic eczema. Since serum IgE has a relatively short half-life of about 48 hours, one would expect a substantial decrease in serum IgE after depletion of B-cells. Interestingly, patients treated with rituximab showed only a minor reduction in total IgE concentrations and no alteration of allergen-specific IgE levels in blood [72]. Whereas blood B-cells were below detectable levels after treatment, the observed reduction in skin-resident B-cells was only approximately 50%. Although skin B-cells were not completely depleted, the reduction seemed to reduce inflammation, probably by decreasing the B-cell functions as antigen-presenting cells and activators of T-cells. Hypotheses on the nature of the constant serum immunoglobulin levels include long-living plasma cells in the bone marrow and autonomous IG production within mucosal sites. However, these convincing initial results have not been confirmed in a czech pilot study in which two patients had been treated with rituximab showing no amelioration after treatment [73]. These controversies could be due to the fact at different subtypes and phenotypes of atopic eczema exist – which is evident - and that these different types respond disparately to targeted therapy.

TNFα is a proinflammatory cytokine released by macrophages, monocytes, T cells, keratinocytes and dendritic cells. It is critically involved in Th1, Th17 and Th22 mediated immune reactions. These T helper cell subsets are also thought to play a major role in acute exacerbated atopic eczema and the chronic form of AE [29, 74-76]. Thus, expectedly, anti-TNF alpha monoclonal antibodies significantly improved clinical parameters (decreased EASI and pruritus) in some reports. However, efficacy was not sustained throughout maintenance therapy [77, 78]. Of note, also induction or exacerbation of atopic eczema by anti-TNF-alpha therapy has been described [79, 80].

IgE is high in a subgroup of atopic eczema patients – the so called extrinsic type going along with significant sensitization to

environmental allergens [81]. Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It represents a unique biologic therapeutic drug approved for treating atopic patients with moderate to severe persistent allergic asthma with a serum IgE ranging from 30 to 700 kU/L. It has to be administered subcutaneously according to the patient's weight and baseline IgE titers (0.016 mg/kg/IU). Its efficacy in asthma, allergic rhinitis, food allergy and latex allergy has been demonstrated, but its concrete role in the treatment of AE has not yet been established. Its efficacy in reducing serum IgE levels had led to preliminary applications in selected patients suffering from atopic eczema in combination with allergic asthma or from atopic eczema alone [82].

In addition to these selected cases, there are reports, including studies from our own group, of efficacy of omalizumab in patients with refractory atopic eczema and IgE levels far exceeding 700 kU/L. During low-dose anti-IgE-therapy with 150 mg omalizumab administered subcutaneously every two weeks for 10 cycles, we observed in 6 of 11 patients a good to very good clinical response (measured by SCORAD), 3 patients with clinically no relevant changes and 2 patients with flare-ups of their disease during treatment. This observed clinical improvement supports other above mentioned case reports concerning good efficacy of omalizumab in selected patients.

Since our severely affected atopic patients had serum levels of IgE up to 30.000 IU/ml and more, thus exceeding the approved limit by far, omalizumab was used in much lower dosage than required for the complete removal of IgE from the circulation. It seems that this antibody does not have to completely remove IgE from serum in order to achieve good clinical response. Interestingly, molecular changes such as an observed switch to reduced IgE/IgG mRNA production appear to identify clinical responders. The effect of omalizumab in these patients seems to be of more regulatory mechanism than simply IgE-blocking [83]. However, this marker as well as the clinical amelioration will have to be confirmed in larger cohorts including adequate control groups. In view of the good safety data for omalizumab and even when considering the reported risk of anaphylactic reactions, current data suggest this biological as an alternative for treating patients with severe, recalcitrant atopic eczema.

Taken together, targeted therapy is a promising therapeutic option in moderate to severe atopic eczema. The obvious, in part very contradictory results described in the different case reports and pilot studies concerning the effectiveness of the specific drug reveal the demand of exact phenotyping and perhaps genotyping of each the patient in order to established a personalized therapy.

EXPERIMENTAL APPROACHES

Allergic diseases such as asthma, allergic rhinitis, allergic conjunctivitis, and atopic eczema are clinically challenging. Although current treatments as discussed in this review are effective at reducing symptoms, they do not address the underlying cause of the allergic response. Therefore, novel therapies that target upstream causative events in allergic diseases are desirable. The induction of RNA interference (RNAi) by small interfering RNA (siRNA) is a potent method for specifically knocking down molecular targets [84]. Skin appears to be a favourable target for small interfering RNA (siRNA) therapy. However, it is difficult to introduce hydrophilic macromolecules, including siRNA, into the skin by conventional methods. A further hurdle for therapeutic application is the limited stability of double-strand RNA (dsRNA). Azuma et al have shown a successful treatment using CD86 siRNA targeting cutaneous DCs [85] after a topical application of cream-emulsified CD86 siRNA. Notably, this treatment ameliorated the clinical manifestations in murine contact hypersensitivity (CH) and atopic eczema (AE)-like disease. In order to optimise the penetration also a iontophoretic technique was successfully used [86].

A further experimental approach consists in the use of aliamides [87]. Endogenous aliamides are known to down-regulate mastocyte reactivity by their action through the vanilloid (VR1) receptors, and keratinocytes, and through the CB1 and CB2 cannabinoid receptors linked to G-protein. Thus, aliamide action is most probably a multifaceted mechanism interfering with the inflammatory process occurring in AE further beyond the known and controversial anti-histamine pharmacologic effect. A pilot study performed by Pulvirenti assessed the efficacy and safety of twice daily application of a topical emulsion containing adelmidrol 2% in a series of 20 patients affected by mild AE. Complete resolution with no side effects was observed in 16 (80%) patients after 4 weeks of treatment, with no relapses at 8-week follow up. Controlled clinical studies in larger series are warranted to confirm the efficacy of aliamide in the management of AE.

Bacteria found in thermal spring water were proven to cure eczema when applied directly to the skin. Gueniche *et al.* performed a prospective, double-blind, placebo-controlled clinical study with a cream containing a 5% lysate of the nonpathogenic bacteria Vitreoscilla filiformis. Of note, compared with placebo, V. filiformis lysate significantly decreased SCORAD levels and pruritus. Furthermore, qualitative and quantitative assessment of cutaneous microbial colonization revealed that V. filiformis lysate reduced Staphylococcus aureus colonization of the skin. Also the skin barrier improved significantly with the cream alone. The authors hypothesize that the significant improvement via V. filiformis lysate may be in part due to reduction of S. aureus, but may also relate in most parts to a direct immunomodulatory effect on skin-associated immune responses [88].

CONCLUSION

Therapy of atopic eczema remains despite the development of innovative, new therapeutic approaches with low side-effects a demanding challenge and is the domain of the expert dermatologist or at least physician with sufficient dermatological skills. Anti-inflammatory topical treatment is used for exacerbation management, however more recent data clearly points to the effectiveness of a proactive therapy. Topical steroids remain the first choice of therapy. The topical calcineurin inhibitors tacrolimus and pimecrolimus expand the available choices of topical anti-inflammatory treatment and are preferred in the anti-inflammatory treatment in certain locations such as the face. First line therapy is possible and recommended by several authors [48]. Systemic anti-inflammatory treatment should be persevered for severe AE. Clinical and experimental data suggest that microbial colonization and superinfection with germs such as *Staphylococcus aureus* may induce disease exacerbation. Thus, additional antimicrobial/antiseptic treatment is justified. Adjuvant therapy includes UV irradiation (UVA1 wavelength or UVB 311 nm). Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programmes have been proven to be helpful.

In summary, atopic eczema treatment should more than any other disease guided by an individualized approach taking not only the phenotype and genotype of the disease but also psychosocial aspects into account. Novel treatments have been developed and trialled, however, more studies on biologicals addressing efficacy, should be performed. There is enormous need to discover key immune pathways that characterise different phenotypes of atopic eczema which will in turn provide new targets for prevention and treatment in the future.

FUNDING

This work was in part supported by grants from the Bayerische Forschungsstiftung, Deutsche Forschungsgemeinschaft and the KKF University Hospital "Rechts der Isar", Technical University Munich.

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