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REVIEW ARTICLE

Long Term Treatment Concepts and Proactive Therapy for Atopic Eczema

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Atopic eczema, also known as atopic dermatitis, is a frequent, highly pruritic, chronic skin disease, which is typically running in flares. The traditional treatment mainly consists of the reactive application of topical anti-inflammatory agents such as topical corticosteroids and topical calcineurin inhibitors. The short term benefit of this approach is well known, but long term remission between flares is difficult to achieve. Therefore, innovative long-term treatment strategies targeting flare prevention and skin barrier stabilization are needed. We and others have shown that normal looking, non-lesional skin of atopic dermatitis patients is immunobiologially not normal but characterized by an invisible inflammation and barrier defect. This has led to the novel concept of proactive therapy, which is defined as long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin. This review article describes the most important long-term treatment options for atopic dermatitis, which includes emollient therapy, the novel concept of proactive treatment, the different ultraviolet light modalities and a selection of systemic immunosuppressive drugs and biologics. Current trial data, licensed indications, off-label use and relevant side effects of the different treatment modalities are summarized.
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-Keywords-
Atopic eczema, Emollients, Flare prevention, Proactive treatment, Topical calcineurin inhibitors, Topical corticosteroids

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INTRODUCTION

Atopic eczema, also known as atopic dermatitis (AD), is a very common, clinically defined, chronic relapsing skin disease with a high socioeconomic burden. The prevalence in German children is estimated at 15%, whereas about 2～5% of the adults are affected[1]. The treatment options for visible lesions and acute flares are numerous, mostly anti-inflammatory and well described in the literature. This includes a current position paper of the European Task Force on Atopic Dermatitis (ETFAD) of the European Academy of Dermatology and Venerology (EADV)[1] and a current guideline of the European Dermatology Forum[2]. In contrast, long term treatment of AD is aimed at targeting the barrier dysfunction and immunodeviation with best efficacy and minimal side effects. This is extremely important, as many patients are children and the disease is running a benign course. Several systemic treatment options for AD are described, but chosen rarely and in severe AD only, because of their side effects.

The traditional approach of so called "reactive" AD therapy has recently been questioned by us and others, leading to the new concept of "proactive" AD therapy. This contribution reviews the long term treatment options for AD and focuses on the novel concept of "proactive" therapy for AD.

TOPICAL ANTI-INFLAMMATORY THERAPY

Traditional textbook chapters and position papers on AD called for a manifestation-adapted, topical anti-inflammatory treatment of visible skin lesions[3,4]. The optimal therapy of severe lesions was a stronger steroid preparation than the

optimal therapy for mild lesions. Once there were no skin lesions visible any more, the anti-inflammatory therapy had to be tapered down and stopped completely and was substituted by barrier-stabilizing emollients. As the anti-inflammatory treatment followed the area and severity of the visible skin lesions, this treatment concept is nowadays referred to as "reactive therapy".

Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are well established agents for a reactive therapy of AD[1,5,6].

The treating physician can select from numerous TCS preparations depending on the skin lesions to be treated, and the majority of acute eczema flares may be cleared successfully with this strategy[1]. However, recurrences are the rule with this strategy, and a long term control of the recurrent flares seems nowadays a more important goal than the treatment of acute flares.

Proactive therapy - immunological basis

Based on this background, an alternative, immunologically based treatment approach has emerged in recent years, which has shown great success in several clinical trials. This "proactive" approach is based on the fact, that normal looking, non-lesional skin of AD patients is not normal, but has a barrier defect and shows signs of a minimal inflammation: First, the skin barrier function of non-lesional AD skin is damaged, which is witnessed by the increased transepidermal water loss through the stratum corneum[7-10]. Filaggrin mutations have been identified as the genetic background of a subgroup of AD patients[11]. Second, the fraction of long chain fatty acids in the lipid bilayer of the stratum corneum is reduced by 60% in non lesional AD skin compared to healthy skin[12]. Third, histological examination showed an activation of the venules, as well as a low-grade lymphocytic infiltration in non-lesional AD skin[13]. Finally, the density of high-affinity immunoglobulin E (IgE) receptors on the surface of the epidermal Langerhans cells, which is an important receptor for the IgE-mediated allergen presentation, is significantly upregulated in non-lesional AD skin[14,15]. In summary, the non-lesional AD skin may look normal to the naked eye, but shows many independent signs of subclinical inflammation.

Proactive therapy - definition and history

Proactive therapy also starts with an intensive topical anti-inflammatory therapy until all lesions have mostly cleared, but the relevant aspect is per definition the following, long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin together with daily application of emollients to unaffected areas[16]. This "minimal therapy for minimal eczema" therapy will not be stopped after clearance of the visible eczema, but will be continued at low-frequency, usually twice weekly[16]. Data from different trials with TCI and TCS have confirmed a significant improvement of skin lesions, a significant reduction of flares and improved quality of life for the patients.

From a patient perspective, the disease no longer controls the patient's actions, but the patient himself is actively controlling the disease[10]. Another important aspect is the scheduling of the control visits: In proactive therapy, these are planed beforehand and time contingent, whereas control visits in a reactive treatment concept are taking place symptom contingent following acute relapses[10].

The first clinical trial of intermittent anti-inflammatory therapy has been published in 1999[17]. The general concept of an immunobiologically based, time contingent, low-dose anti-inflammatory therapy with behavioral therapeutic background was presented by us in 2007 at the biannual meeting of the German Dermatological Society (DDG) in Dresden[18] and has been published in detail as "proactive treatment" in 2009[10]. We have deliberately chosen the term "proactive treatment" in accordance with the writings of Frankl[19] and the existing nomenclature of a physician-initiated scheduling of patient contacts in the behavioral therapeutic context[10]. As of today, the concept of proactive therapy is recommended in the European guidelines for the treatment of atopic eczema[1,2].

The scientific background of this clinical recommendation is largely based on clinical trial data from 9 randomized, placebo-controlled trials, which have assessed the efficacy of TCS and TCI. Useful outcome parameters for comparison of these clinical trials are the median time to first flare or the percentage of flared patients after a fixed time period (e.g. 3 months), but only if these are compared for both active drug and placebo control group. The sole percentage of flare-free patients at the end of study visit is not a useful parameter for study drug efficacy, as it is highly influenced by the duration of the trial and the severity of the patient group than of the efficacy of the study drug.

Proactive clinical trials with trials with topical corticosteroids (TCS)

Five clinical trials investigating the intermittent use of two TCS for AD have been published so far. These trials allow some conclusions about their suitability for proactive therapy.

Van der Meer et al.[17] tested fluticasone propionate 0.005% ointment in a 16-week proactive phase in 90 moderately and severely affected AD patients for the first

time. The proactively treated patients showed significantly less eczema flares.

Hanifin et al.[20] evaluated the optimal frequency of application of fluticasone propionate 0.05% cream in 348 patients with mild to severe atopic eczema. In this regime the drug was initially administered four times, and then twice weekly for 20 weeks. The risk for flare development under proactive treatment was 7.7-fold lower than under placebo therapy.

Berth-Jones et al.[21] compared the efficacy of different fluticasone galenics in the proactive treatment regimen with 295 patients suffering from moderate to severe atopic eczema over a study period of 16 weeks. After healing of skin lesions the treatment consisted either of fluticasone propionate 0.05% cream, with fluticasone propionate 0.005% ointment or of placebo twice a week. The recurrence-free period under proactive therapy was more than twice as long as under reactive treatment. The number of recurrences was 5.8 times lower in the cream group and 1.9 times lower in the ointment group compared to the placebo therapy

Glazenburg et al.[22] studied the biweekly application of fluticasone propionate 0.005% cream in a 16-week, placebo- controlled, randomized study of 75 moderately to severely affected children with a similar result: the risk of an AD flare in the reactive treatment group was more than twice as high as in the proactive treatment group.

Peserico et al.[23] tested methylprednisolone aceponate 0.1% cream in a proactive approach over 16 weeks in adult AD patients. The percentage of placebo-treated patients who have developed no flare during the entire study period is unusually high (66%). It could be possible that an unusually mild patient group has been studied by the authors.

All these 5 studies with TCS followed a double blinded, randomized and placebo-controlled design. However, none of them covered a time-span exceeding 20 weeks. The suitability of TCS for long-term flare prevention is widely accepted based on this data material[2], even if one-year studies have not been performed with TCS.

Proactive clinical trials with topical calcineurin inhibitors (TCI)

Four double-blinded, randomized, placebo-controlled studies with proactive TCI application have been published so far, which allow a statement about their suitability for proactive therapy. All studies have been performed with tacrolimus ointment, and none with pimecrolimus cream. The two European tacrolimus studies differ from the US-American studies in the overall study duration and frequency of drug application.

Wollenberg et al.[24] studied the proactive use of tacrolimus 0.1% ointment on 257 adult patients with mild, moderate and severe AD in European long-term multicenter trial over 12 months. The open-label induction phase was performed with tacrolimus 0.1% ointment twice daily for up to 6 weeks. A double blinded, randomized, placebo controlled one-year maintenance treatment phase followed with twice weekly application of tacrolimus 0.1% ointment or placebo ointment and liberal use of emollients. The proactive tacrolimus 0.1% ointment-treated patients showed significantly fewer flares (56.9% vs. 29.6% of all patients, $p<0.001$) with a significantly reduced duration of flares (12.4% vs. 31.5% treatment days, $p<0.001$). The median flare-free time was also significantly longer under proactive treatment with tacrolimus ointment (142 days vs. 15 days; $p<0.001$)[24].

Thaçi et al.[25] conducted a European children study with tacrolimus 0.03% ointment in an analogue study design over 12 months on mild to severely affected children. Again, the pro-active therapy reduced the number of flares and prolonged the flare-free time significantly compared to placebo application. During the 12 months treatment time, 63 patients (50.4%) of the proactive group but only 37 patients (29.6%) of the placebo group remained flare-free[25].

A retrospective subgroup analysis of the moderate to severe AD patients, which is the currently licensed indication for tacrolimus ointment, was made from the combined data set of the Wollenberg and Thaci trials[24,25] and published by Reitamo and Allsopp[26] in 2010.

Paller et al.[27] tested the thrice weekly proactive use of tacrolimus 0.03% ointment in a 40 weeks trial against placebo in moderate to severely affected children. A total of 206 children entered the preceding open label induction phase with tacrolimus 0.03% ointment. The median time to the first flare was significantly longer (116 days vs. 31 days) in the proactively treated patients (n=68) than in the control group (n=37).

Breneman et al.[28] tested the thrice weekly proactive application of tacrolimus 0.03% ointment (children) and tacrolimus 0.1% ointment (adults) in 383 moderate to severely affected AD patients. The median flare-free time in the proactive treatment group was significantly prolonged (169 days vs. 43 days) compared to the control group. It is noteworthy, that only half of the patients entering the induction phase (197 of 383) were randomized into the 40 weeks maintenance phase.

Proactive therapy - comparing TCS and TCI

Clinical experience and published trial data both indicate the general suitability of TCS and TCI for proactive

therapy. The profile of side effects does not depend on the proactive or reactive use of the substances, but on the respective substance class effects of TCS and TCI as such. None of the drugs tested showed an increased risk for cutaneous infection if applied proactively. Though skin atrophy is a known side effect of improper reactive TCS application, this has not been observed during proactive application of fluticasone propionate[20]. The twice weekly application of tacrolimus 0.1% ointment is sufficient to keep patients in a tolerant, non-burning state.

Mild, moderate and severe AD patients will profit from proactive therapy especially with tacrolimus ointment, as they have less skin lesions, less flares, longer flare free intervals and a better quality of life[24,29]. A head to head comparison between proactive use of TCS and TCI has not been published, and differences in disease severity of the study population, application schedule and duration of the published trials make a direct comparison difficult.

As most of the mild AD patients in our own institution are well controlled with a traditional, reactive treatment regimen, we recommend them continuing this approach. Most moderate and severe AD patients treated in our institution are treated in a proactive way with either TCS or TCI. A recent label change of tacrolimus ointment has explicitely included the proactive, long-term intermittent use for AD in children and adults.

Topical antiseptics

Most AD patients are colonized with *Staphylococcus aureus*, and several studies have determined the colonization rate with *S. aureus* as high as 90% of all AD patients analyzed[30,31]. A defective innate immune system permits the colonization, which may give rise to AD exacerbation and severe impetiginization[32]. Reducing the density of *S. aureus* colonization is an important treatment aim in all AD patients, and treatment options have been reviewed in a recent publication[31].

The topical application of antibiotics is generally not recommended in AD because of the high risk for resistance development[4,33,34]. Topical antiseptics are favored in AD patients, as resistance is generally not an issue and contact allergy is rare[1,31]. Triclosan, chlorhexidine gluconate or micro silver are suitable agents for traditional compounding or are available as ingredients in ready to use emollients[31]. Potassium permanganate ($KMnO_4$) and sodium hypochlorie may be used for antiseptic baths[35]. Textiles with antiseptic properties such as silver-coated textiles or AEGIS-coated silk fabric may also be helpful, as they are easy to use on a daily basis[31,32,36].

Phototherapy

Most AD patients report an improvement of their disease from natural sun exposure during the summer months. Standardized treatment with different ultraviolet (UV)-bands is well established for AD treatment[1]. The best results have been achieved with UVA1 (340～400 nm), broadband UV (UVA＋UVB 290～400 nm) and narrow band UVB (311 nm)[1]. Narrow-band UVB has been shown to reduce microbial colonization[37]. UV therapy is usually combined with TCS and emollients. A combination of UV light with TCI or ciclosporin is critically discussed and not recommended[1]. The clinically most relevant side effects of UV light are photocarcinogenesis for the UVB and skin ageing for the UVA spectrum. In our institution, the recommendation and use of UV-therapy is largely restricted to adult patients.

SYSTEMIC ANTI-INFLAMMATORY THERAPY

Most AD patients are well controlled with topical therapy. We consider the use of systemic treatment only in severe AD patients not responding to topical therapy[38,39]. Ciclosporin A (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate (MTX) are established treatment options for these patients[1].

CyA

CyA is a calcineurin inhibitor and licensed throughout Europe for therapy of severely affected AD patients[2]. CyA treatment is well tolerated in children also[40]. The efficacy and safety of CyA for AD is well documented, and treatment recommendations, as well as formal guidelines have been published[1,41]. Published side effects include acute and chronic nephrotoxicity, hypertension, infections, gingival hyperplasia, elevated blood lipids, liver enzymes and bilirubine, are dose dependent and observed more frequently in adults than in children[40]. A close monitoring of serum creatinine, blood pressure and protein in the urine is obligatory[42]. Treatment is usually started with 3 mg/kg/day and may be raised up to 5 mg/kg/day or tapered down to the lowest effective dose according to clinical response[42]. Concomitant topical treatment with TCI or TCS is recommended by us and others[1,43]. Treatment with CyA is our first choice for systemic AD treatment, as it is the only drug licensed for this indication in our home country.

AZA

AZA is frequently used off label for severe AD treatment, but mostly in the United Kingdom and the United States. It

affects the purine nucleotide synthesis and metabolism and has anti-proliferative and anti-inflammatory effects[43,44]. A dose-dependent immunosuppressive and cytotoxic effect on Langerhans cells has been reported in vitro[44]. Only a few controlled studies with long-term use of AZA in AD patients are published[1,19]. A significant improvement of the AD lesions, a reduction of total serum IgE levels and moderate side effects have been reported in a recent pediatric study running over three months[45]. Infections, skin cancer, gastrointestinal disturbances, hepatotoxicity and rare but severe bone marrow suppression are typical side effects of AZA. As patients with low activity of thiopurine methyl transferase are particularly vulnerable for AZA toxicity, a blood test should be performed before the first administration of AZA[43].

MMF

MMF is another purine antagonist and inhibits selectively and reversibly the enzyme inosine monophosphate dehydrogenase[46]. MMF has antiproliferative effects, and is better tolerated than AZA by most patients[19,46]. A number of smaller case series are published, which showed good efficacy and relatively low side effects[46-48]. Treatment with MMF is considered in our institution if CyA treatment is not feasible.

MTX

MTX is a folic acid antagonist inhibiting purine and pyrimidine synthesis, thus leading to an antiproliferative effect on T-cells, and increasing adenosine levels, thus exhibiting anti-inflammatoy effects[49]. On a cellular level, MTX inhibits leukocyte chemotaxis, Langerhans cell function and the release of various cytokines including tumor necrosis factor (TNF)-alpha, interleukin (IL)-10 and IL-12[44]. MTX is an inexpensive drug and used since many years for many indications including AD. Typical side effects of MTX include hepatotoxicity, nephrotoxicity, susceptibility to infection and teratogenicity. Regular blood tests and folic acid supplementation must be performed during treatment MTX treatment. A recent controlled study confirmed the efficacy of MTX in AD[50] in addition to several case reports indicating a good therapeutic response and acceptable tolerability[51,52]. Treatment with MTX is inexpensive and considered in our institution if CyA treatment is not feasible.

Biologics

Targeted therapy with highly selective biologics has successfully entered clinical reality of psoriasis treatment in the last decade. Many biologics have been tested for treatment of severe AD in small case series, but the published results are not convincing. None of these agents is licensed for AD, and none of them is recommended in the current guidelines[1,2].

Neither the TNF-α blockers etanercept and infliximab[53,54], nor the IL-5 antagonist Mepolizumab[55] showed convincing results in smaller case series. The monoclonal antibody Omalizumab binds free IgE and inhibits IgE binding to the high-affinity IgE-receptor. As Omalizumab is licensed for severe bronchial asthma, there is clinical experience from co-treatment of concomitant AD in addition to some smaller case series[56,57]. The Omalizumab dosing regimen of the published AD cases is highly variable, the results are incoherent, and the overall efficacy appears low. Rituximab is an anti-CD20 antibody, which leads to an almost complete B-cell depletion[58]. A recent case series showed some improvement of AD lesions, as well as a reduced number of T cells[58].

In view of the high costs and limited efficacy, none of the currently available biologics seems promising for AD treatment.

Allergen-specific immunotherapy

Allergen-specific immunotherapy is the only known causal, long-term treatment option for Type-I sensitization to allergens. Hence, patients with extrinsic AD should profit from immunotherapy with their relevant allergens, e.g. house dust mite. On the other hand, uncontrolled AD has been regarded a relative contraindication for immunotherapy for many years. Recent studies have shown that immunotherapy may actually improve the course of AD, as witnessed by a lower consumption of TCS[59]. Immunotherapy is clearly not contraindicated because of AD, and immunotherapy for AD can be regarded a "small step in the right direction", but currently, AD is clearly not an indication to start immunotherapy[1,2].

Education

The psychosociological profile of the mostly young, internet legible, mobile AD patients suffering from a from a greatly reduced quality of life makes this patient group quite susceptible for quackery. Many university hospitals are running eczema schools delivering high quality, evidence based information to AD patients. This includes medical education about the disease and its treatment options, but also support for problems of daily life. In our institution, parents of AD children, as well as adult patients are receiving information on medical, psychological and nutritional aspects of AD management from an interdisciplinary team during a 6×2 hours evening course period. The benefit of this training for children and parents has been demonstrated[60]. Outcome research on an age-

adapted analogous training for adults is under investigation.

CONCLUSION

AD is a chronic skin disease, which requires permanent treatment. In mild cases, a regular application of barrier-stabilizing emollients and a reactive anti-inflammatory therapy may sufficient. In moderate to severe AD, proactive therapy with TCI or TCS is the long-term treatment concept of choice. Systemic immunosuppressive drugs are needed in refractory cases only. Oral alitretinoin is an option for chronic atopic hand eczema, as this drug is approved for all subtypes of severe hand eczema and extrapalmar AD lesions are shown to improve also[61]. Eczema schools with a structured education program increase the medical knowledge and self-management abilities of AD patients, and are highly encouraged. All AD patients should, in the sense of Frankl[19], become proactive with regard to their disease - which means becoming active before a minor problem becomes a situation.

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