

Novel immunological approaches in the treatment of atopic eczema

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Purpose of review

Atopic eczema is a common inflammatory skin disease showing chronically relapsing eczema and high association with elevated serum IgE levels. A subgroup of atopic eczema patients requires systemic immunomodulatory treatment for long time periods. However, beyond cyclosporine A and azathioprine, only limited consent exists on systemic treatment options.

Recent findings

Timely published systemic treatment modalities include studies on efalizumab (anti-CD11a antibody), infliximab, adalimumab, and etanercept (anti-TNF- α treatment), omalizumab (an anti-IgE antibody), rituximab (an anti-CD20 antibody), specific immunotherapy, leflunomide, and leukotriene receptor antagonists with varying clinical results and with particular safety profiles.

Summary

Although there is not yet a treatment modality reaching clinical efficacy of cyclosporine A as gold standard of systemic therapy, limitation in its application duration as in its side effect profile as well as the search for alternatives has set a focus on the new alternatives of which especially B-cell-directed therapies might be promising candidates.

Keywords

atopic eczema, efalizumab, leflunomide, leukotriene receptor antagonists, omalizumab, rituximab, sublingual immunotherapy, tumor necrosis factor- α antagonists

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Introduction

Atopic eczema (atopic dermatitis) is a chronic inflammatory skin disorder usually presenting with severe pruritus and flaring eczematous lesions in varying localizations depending on the age of the patient. The disease is based on both, a disturbance of the epidermal barrier and increased tendency to IgE production, partly on a genetic disposition, and can be triggered by several environmental factors including commonly encountered allergens, accounting for its high association with elevated serum IgE levels [1,2[•],3].

Skin lesions are assumed to result from complex interactions between IgE-bearing antigen-presenting cells, T-cell activation, mast-cell degranulation, keratinocytes, eosinophils, and the combination of immediate and cellular immune responses [4–6] fostered by defects of the physical barrier, such as stratum corneum lipid-protein disturbances resulting, among others, from filaggrin gene mutations [7[•],8].

Apart from topical treatment with emollients, topical glucocorticosteroids and calcineurin inhibitors, promising effects of topical treatment with novel aliamides [9] and ceramides [10], have been described. Nevertheless, patients with severe atopic eczema often remain refractory to purely topical treatment. It is for these patients, that researchers strive to develop new promising systemic treatment options apart from systemic glucocorticosteroids, cyclosporine A, azathioprine, and mycophenolate mofetil with their well known limitations and side effects.

CD11a blockade

Efalizumab, a humanized monoclonal antibody against the CD11a molecule, acts as inhibitor of T-cell activation and thereby impairing recruitment of T-cells into the skin. This antibody has been initially studied in psoriasis [11,12]. The role of T-cell-mediated inflammation in atopic eczema and the well established mode of action of this drug were the rationale for a few pilot studies using

weekly subcutaneous injections of efalizumab for severely affected patients. The treatment was initiated with a 0.7 mg/kg loading dose followed by 1 mg/kg weekly doses [13[•],14,15].

Even though these studies lacked control groups and involved only small numbers of patients, promising results such as improvement of Eczema Area and Severity Index (EASI) scores by up to 50% and significant reduction of pruritus were described. A common clinical observation was the rather gradual than abrupt improvement of skin lesions. Information on possible side effects has been obtained from large study groups of psoriasis patients. Adverse events of efalizumab treatment include reversible thrombocytopenia (0.3% of patients, also observed in one atopic patient), worsening of disease beyond baseline levels after drug discontinuation (up to 14%, also observed in two atopic patients), and potentially increased risk of infection and malignancy (not clearly demonstrated in phase 3 trials) [16–19]. Considering the lower end-organ-toxicity and apparently lower risk of immunosuppression, efalizumab could become an appealing treatment option for patients not qualifying for cyclosporine A.

Anti-TNF- α treatment

Infliximab is an anti-TNF- α chimeric monoclonal antibody that is effective in chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis, all associated with a Th1 response [20–22]. The better understanding of TNF- α as proinflammatory cytokine produced by inflammatory dendritic epidermal cells in the acute phase of atopic eczema [2[•]] led among other reasons to the experimental use of infliximab in this usually Th-2-associated disease. Sporadic cases were reported as well as an open, prospective pilot study with intravenous infliximab (5 mg/kg) administered in nine patients with atopic dermatitis refractory to conventional therapy [23,24]. The induction therapy significantly improved clinical parameters (decreased EASI and pruritus), but efficacy was not sustained throughout maintenance therapy. Only few patients achieved excellent response during long-term use. Although not formerly proven, as for autoimmune diseases, the development of neutralizing antibodies to infliximab may at least partially account for nonresponders.

Side effects of infliximab include infection, especially reactivation of tuberculosis, infusion reactions, and induction of lupus erythematosus-related autoantibodies as well as clinical features [20–22]. There have also been reports of atopic dermatitis induced or precipitated by anti-TNF- α therapy, possibly due to downregulation of Th1 cytokines, resulting in manifestation of Th2-associated disease [25,26]. Overall, considering the limited efficacy of infliximab in maintenance therapy for

atopic dermatitis, long-term use of this drug without addition of other immunosuppressive agents in severely affected patients seems rather improbable and remains restricted to particular cases.

Anti-IgE antibody

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody recognizing human IgE at the same position as the high-affinity receptor Fc ϵ RI, has been effective in reducing asthma exacerbations and allergic rhinitis. It is approved to treat severe asthma in patients with serum IgE levels lower than 700 IU/ml.

Efficacy of omalizumab 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 [27,28]. These reports, however, gave controversial opinions.

In addition to these selected cases, there are reports, including studies from our own group, on effects of omalizumab in patients with refractory atopic eczema and IgE levels far exceeding 700 IU/ml [29[•],30[•],31]. During low-dose anti-IgE-therapy with 150 mg omalizumab administered subcutaneously every two weeks for 10 cycles, we observed in six of 11 patients a good to very good clinical response [as measured by drop in score of atopic dermatitis (SCORAD)], in three patients clinically no relevant changes, and in two patients 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.

As 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 [29[•]]. 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 [32], we think it may provide an alternative for treating patients with severe, recalcitrant atopic eczema.

Anti-CD20 antibody

Rituximab is a chimeric monoclonal anti-CD20 antibody that eliminates B-cells from the circulation, thus a highly

effective therapy for various forms of B-cell lymphomas and autoimmune diseases such as pemphigus vulgaris and systemic lupus erythematosus [33,34]. As strongly elevated levels of serum IgE are a hallmark of adult patients with generalized extrinsic atopic eczema, 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 dermatitis.

Under this assumption, a pilot study with six patients was conducted in Switzerland [35^{••}], administering two intravenous applications of rituximab, each 1000 mg, 2 weeks apart. All six patients showed an improvement of their skin symptoms within 4–8 weeks with significant diminution of EASI scores of up to 70%. As serum IgE has a relatively short half-life of about 48 h, one would expect a substantial decrease in serum IgE after depletion of B-cells. Interestingly, this group observed only a minor reduction in total IgE concentrations and no alteration of allergen-specific IgE levels in blood. 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 immunoglobulin production within mucosal sites. Side effects of rituximab include fever attacks, which can be prevented by administration of paracetamol prior to antibody infusion, infusion reactions, and infections. Evaluating the data of this study, rituximab appears to be a very promising treatment option for patients with severe recalcitrant atopic dermatitis.

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 [36].

Allergen-specific immunotherapy

As the allergic or extrinsic form of atopic dermatitis can be elicited or aggravated by aeroallergens or food allergens, it was hypothesized for a long time that specific immunotherapy would be of clinical benefit [37]. Two recent clinical studies conducted with sublingual immunotherapy (SLIT) in mite-sensitized children and adults with a duration of 12 and 18 months, respectively, showed improvement of mild-to-moderate atopic eczema with significant reduction of SCORAD and concomitant therapies such as topical corticosteroids [38[•],39[•]]. Treatment was very well tolerated apart from

minor adverse events. Nevertheless, severely affected patients experienced only marginal benefit. SLIT was reported to induce a relevant worsening of atopic dermatitis in some patients, which might mirror the well known observation of eczema exacerbation after skin or mucosal contact with allergen if tolerance is not achieved through the applied SLIT. This risk, as well as the moderate results observed in the group of severely affected patients, represents possible limits of this treatment. Interestingly, subcutaneous specific immunotherapy (SCIT) using an allergoid extract showed good results in an open-labeled pilot study using also house dust mite extracts leading to clinical improvement as well as to changes in chemokine concentrations together with specific IgG4 induction [40[•]]. These results were in accordance with a previously conducted German multicentre, randomized, double-blind dose-response SCIT trial with house dust mite extracts that led to an impressive dose-dependent SCORAD decline and reduction of topical corticosteroids [41]. The discrepancy between the different studies might be explained by the route of application, but further studies with ameliorated desensitization extracts including adequate control groups are warranted by the preliminary results.

Leflunomide

Leflunomide is a pyrimidine de-novo synthesis-inhibiting immunosuppressant drug exhibiting an extremely long in-vivo half-life that has been shown to inhibit autoimmune T-cell proliferation and production of auto-antibodies. Additionally, it decreases eotaxin release by IL-4/TNF- α -stimulated fibroblasts [42]. As T-cells and eosinophils play an important role in the pathophysiology of atopic eczema, in theory, leflunomide represents a promising drug for patients with severe atopic eczema. Interestingly, to date, only one clinical investigation evaluated the efficacy of leflunomide as long-term treatment for atopic eczema [43]. In two patients with recalcitrant atopic eczema, leflunomide monotherapy induced a long-lasting remission, whereas in one patient, an acceptable skin response could be obtained only by a combination with medium doses of systemic prednisolone. Owing to the long in-vivo half-life of leflunomide, remissions may outlast the actual duration of therapy by many weeks.

The major side effect of leflunomide consists in elevation of liver function enzymes, which occurs in approximately 5% of patients.

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.

Leukotriene receptor antagonists

Cysteinyl leukotrienes (Cys-leukotrienes) are potent proinflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway. Antagonist drugs to the Cys-leukotriene-receptors, such as montelukast, zafirlukast, and pranlukast, block the effect of Cys-leukotrienes including changes in vascular permeability, inflammatory cell influx, smooth muscle contraction, and increased mucus production in the airways [44]. These drugs alleviate the symptoms of bronchial asthma and allergic rhinitis in randomized clinical trials, but beneficial effects of leukotriene receptor antagonists (LTRAs) have also been demonstrated for other diseases such as atopic eczema. Two recently published randomized, double-blind, placebo-controlled trials investigated the effect of montelukast in children with moderate-to-severe atopic eczema and adults with moderate atopic eczema and show inconsistent results [45,46]. Although montelukast reduced itching, sleep disturbance, disease extent and severity, blood eosinophil count, and serum IgE in children, the data could not support previous reports of efficacy in the treatment of adults.

LTRAs are usually well tolerated, the most common adverse effects are headaches, pharyngitis, and transient raise of alanine aminotransferase. The fact that some studies have observed good clinical effects of LTRAs leaves open the possibility that there is a certain degree of heterogeneity within the population of eczema patients responding or not to LTRAs. Nevertheless, adult patients with atopic eczema showing good clinical response to treatment with LTRAs seem to be rare. However, children might profit from use of LTRAs.

Conclusion

Significant progress has been made in our understanding of atopic eczema, especially regarding recent insights into genetic and immunologic mechanisms, but still, there is no single new treatment as from to date that has proven to be the 'quantum leap' for eczema patients. While novel treatments are being developed and trialed, more studies on the monoclonal antibodies addressing efficacy, optimum dose, and duration of treatment as well as long-term safety data are needed. Further discoveries of key immune pathways that lead to different phenotypes of atopic eczemas will continuously provide new targets for prevention and treatment in the future.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 493–494).

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