

EXPERT OPINION

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Novel investigational therapies for atopic dermatitis

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Introduction: Atopic dermatitis (AD) is a common skin disease. Although most patients are well served by existing therapies, a subset of patients with severe AD are still not adequately treated. An improved understanding of the pathogenic mechanisms behind the disease has led to the development of a range of potential new drugs for this indication.

Areas covered: The authors provide a narrative review of the drugs in Phase II trials listed on Clinicaltrials.gov. The authors supplement this information with recently published literature located through PubMed. The main target of new treatments appears to be the inflammation process, whereas drugs aimed at reducing itching or increasing the barrier function are fewer to nonexistent. A wide range of drugs, including small molecules and antibodies, are being tested.

Expert opinion: The focus on inflammation is not only driven by the limitations posed by our current understanding of biology, but also by the broader scope of these drugs, which may be used in other diseases. In alignment with the recent drug development of other dermatological diseases, antibodies directed at key molecules in the pathogenesis of AD appear to be the most promising.

Keywords: antibodies, atopic dermatitis, drug development, review, small molecules, therapy

Expert Opin. Investig. Drugs [Early Online]

1. Introduction

Atopic dermatitis (AD) is a common and complex eczematous skin disease that affects children and adults. In Western societies, lifetime prevalence rates of 15 – 20% have been described, and contrary to previous dogma, increased prevalence rates have also been described in the adult population [1,2].

The etiology of the disease remains unknown, but genetic, environmental and immunological factors interplay in the development of the disease, with genetically determined filaggrin and ceramide deficiencies reducing the skin barrier and promoting the development of a widely spread irritant dermatitis [3–5]. AD has well-recognized comorbidities in asthma, allergic rhinitis and urticaria [1].

Diagnostic criteria have been defined focusing on history, symptoms and clinical findings. The symptoms include itch, pain and dry skin, and secondary skin infection is common. AD produces a recognizable disease pattern that varies with age and allows the clinical diagnosis to be made in conjunction with the history of the disease [1].

AD has a significant negative impact on the quality of life (QoL) in a large proportion of patients, and in addition to daytime symptoms, the night sleep is often impaired further adding to the morbidity caused [6].

Several treatments are available. Basic treatment consists of irritant avoidance and skin barrier reinforcement with regular use of moisturizers, whereas exacerbations are often managed with topical corticosteroids or calcineurin inhibitors or UV-therapy [7]. In contrast, severe AD is difficult to manage and often represents a clinical challenge. Guidelines for the treatment of severe AD include the use of

Article highlights.

- Although the skin barrier defect is central to the development of atopic dermatitis (AD), no drug development is reported to be aimed primarily at enhancing the skin barrier.
- Extending data from asthma studies, anti-inflammatory mechanisms are being targeted by new treatments.
- The effects of both monoclonal antibodies and small molecules are being explored in AD.
- Currently, small molecules appear to be more extensively tested in this indication than antibodies.

This box summarizes key points contained in the article.

immunomodulating drugs as cyclosporine, systemic corticosteroids, azathioprin, mycophenolate mofetil and methotrexate [8,9].

Although often effective, these drugs present the same problems in AD as they do in other chronic or long-lasting inflammatory dermatoses such as psoriasis: limited or waning long-term effects, associated toxicity and potential serious adverse effects. Therapeutic challenges are therefore not uncommon, and the general clinical situation is accentuated by the large proportion of pediatric patients with AD. Although much can be managed with existing therapy, AD continues to present an unmet need for safe and effective therapy [10].

2. Methods

Two databases were searched – Clinicaltrials.gov and Pubmed.com. – to provide a comprehensive review of drugs in trials.

First, Clinicaltrials.gov data of current Phase II trials investigating new systemic treatments of AD were selected and included in the present study. The search and selection of relevant trials took place in January 2014.

Second, a simple search of www.pubmed.com was conducted to identify published, recent research on treatment with the different drugs selected from the Phase II trials, as well as other novel treatments of AD published in observational studies.

Based on the selected data from Clinicaltrials.com and Pubmed.com, we present a narrative review of novel treatment strategies of AD and their current status of clinical evidence according to postulated mechanism of action.

3. Antibodies or fusion proteins

3.1 TNF- α directed treatment

Data on three TNF- α inhibitors (fusion protein: etanercept; antibodies: infliximab and adalimumab) exist only as small open series or single cases. Conflicting results have been described with the use of TNF- α inhibitors in patients with AD. A case series (n = 9) in which patients with AD received

a standard dosage induction and maintenance treatment with infliximab has suggested that infliximab may have beneficial effect in 2/9 patients with AD, but no convincing data from larger studies exists [11]. Similar cases have been reported by other authors [12,13]. A correspondingly small body of literature suggests that TNF- α blockage may trigger clinical AD-like skin disease in predisposed individuals treated for other diseases [14,15].

3.2 IL-12/23 directed treatment

In 2013, ustekinumab was approved by the Food and Drug Administration for the treatment of moderate and severe psoriasis. Ustekinumab is a human monoclonal antibody directed against interleukins 12 and 23. Two cases of refractory AD successfully treated with ustekinumab have been reported [16,17]. In one of the cases, there was a complete treatment response with clearing of eczema and pruritus. In a case series of four patients treated with ustekinumab 45 mg in week 0, week 4 and then every 12 weeks, marked improvement was found in two patients after two injections and for the other two patients after three injections. The improvement included resolution of episodes of generalized eczema and erythroderma as well as subjective measures of pruritus and QoL [18].

The mechanism of action of ustekinumab in AD is not fully understood, but inhibition of the Th17 pathway preventing the presentation of epidermal autoantigens has been suggested [19,20]. IL-17 and -22 are part of the Th17 pathway and have proinflammatory effects in a variety of cells, and are overexpressed in AD and other inflammatory diseases [21]. Elevated IL-17 has previously been found in the peripheral blood and skin lesions of acute AD. In AD, the expression of IL-17 and IL-22 has been reported to relate to host defense, in particular the production of AMPs [21]. Thus, suppression of the Th17 signaling pathway has been suggested to enhance bacterial infection at lesional sites of the skin. The clinical significance of this is currently not clear, but it is known that enhanced AMP production due to, for example, D-vitamin supplements, may have a beneficial role in the management of some AD patients [22].

3.3 Immunoglobulin E directed treatment

High IgE levels are a characteristic of extrinsic type AD. The efficacy of omalizumab (a monoclonal antibody targeting IgE) in AD is controversial. Omalizumab has shown to be effective in AD, especially in patients without filaggrin mutations and in patients with high levels of IgE [23,24]. Kim *et al.* showed improvement in an open study of 10 patients with AD who received omalizumab treatment for asthma. Patients were treated with a standard regimen, and steady improvement in the objective scores was seen after 6 months of therapy. Similar results were found in nine patients with recalcitrant AD in an open Spanish study [25]. On the other hand, two small randomized controlled studies (RCTs) failed to show clinical improvement in a total of 28 patients treated

16 – 24 weeks [26,27]. These RCTs did however indicate that inflammatory markers changed, suggesting a possible subclinical effect within the study period. A more aggressive combination therapy of omalizumab and rituximab (anti-CD-20) was effective in four out of six patients with severe refractory AD [28]. It may also be speculated that omalizumab may have different effects in intrinsic and extrinsic AD, and it has been suggested to consider omalizumab for treatment-resistant extrinsic-type AD [23].

3.4 Alefacept

Alefacept is a LFA-3/IgG1 fusion protein that inhibits T-cell activation and reduces memory T cells, which was originally introduced for the treatment of psoriasis, where it has been superseded by more effective treatments. In an open trial of nine patients with AD, alefacept i.m. injections were studied. A weekly dose of 30 mg i.m. was given for the first 8 weeks. At week 9, nonresponder patients continued, whereas responders had their dose reduced for the remaining 8 weeks of the trial. At the primary end point, week 18, only two patients had responded [29,30]. The promotion of alefacept was ceased in 2011, and it was never approved for the European drug market.

Efalizumab, a withdrawn LFA-1 subunit antibody, was only effective in 2 of 11 patients in an open study [31].

3.5 Rituximab

Rituximab is a CD-20 antibody that destroys CD-20-positive cells through a variety of mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent toxicity and apoptosis [32]. It has been described that CD-20-positive cells (B cells) are involved in IgE synthesis [33]. In another approach, rituximab has therefore been tried in six patients with recalcitrant AD. All patients had a positive effect on skin symptoms as well as on histological alterations such as spongiosis, acanthosis and dermal infiltrate, including T- and B-cell numbers, and a reduced expression of IL-5 and IL-13 after therapy. Upon rituximab therapy, allergen-specific IgE levels were not altered and total serum IgE levels were only slightly decreased [21,34].

3.6 IL-1-directed therapy

Anakinra, an IL-1 receptor antagonist, has been approved for the treatment of rheumatoid arthritis [35]. IL-1 is a proinflammatory cytokine consisting of two molecular species, IL-1 α and IL-1 β . Anakinra is a recombinant human IL-1 antagonist that blocks the inflammatory effects of both by blocking the IL-1 receptor, which may promote inflammation in AD. Currently, the safety and effectiveness of anakinra is being investigated in a pilot study of children with severe AD. There are no data published yet.

3.7 IL-4-directed therapy

Dupilumab is a fully human monoclonal antibody delivered by subcutaneous injection that targets the α subunit of the IL-4 receptor (IL-4R α) [36]. By blocking IL-4R α , dupilumab

inhibits signaling of both IL-4 and IL-13, drivers of Th2 (type 2 helper T cell) immune response. Dupilumab is currently being investigated as treatment of AD, asthma and nasal polyposis. The drug has shown efficacy in moderate-to-severe asthma and elevated eosinophil levels [36], but no cases or studies of dupilumab used for AD are published yet.

3.8 IL-31-directed therapy

Anti-IL-31 is an inhibitor of *interleukin-31*, a cytokine that is upregulated in AD skin lesions in humans and skin lesions in the NC/Nga mice, a murine model for AD [37]. A current Phase II trial is investigating the effect of the drug (CIM331, Chugai Pharmaceuticals, Japan) used in patients with AD. The primary outcome measure is percent improvement in pruritus visual analogue scale (VAS) from baseline to week 12, and the secondary outcome measures are improvement in Eczema Area and Severity Index (EASI), and improvement in SCORing Atopic Dermatitis from baseline (SCORAD) to week 12 and to week 64. Data are not yet published.

4. Small molecules

4.1 Apremilast

This is an oral phosphodiesterase 4 inhibitor. Apremilast is an anti-inflammatory drug that has been proven effective in the treatment of psoriasis and psoriasis arthritis [38]. Previous studies have shown that leukocytes from patients with AD display elevated phosphodiesterase (PDE) activity compared with normal controls, which leads to leukocyte hyperactivity and inflammation [39,40]. Apremilast inhibits proinflammatory cytokine transcription, neutrophil degranulation, chemotaxis and adhesion to endothelial cells. A pilot study from 2012 showed that apremilast administered 30 mg twice daily resulted in significant improvement in pruritus, Dermatology Life Quality Index (DLQI) and EASI in 16 patients with AD [41]. No adverse effects were found. A Phase II trial in 10 patients with atopic or allergic contact dermatitis using apremilast 20 mg twice daily found significant reduction in Investigators Global Assessment (IGA) in 20% of the patients, and a 75% reduction as well as 50% reduction in EASI in 10%, respectively [42].

4.2 CRTH2

Chemoattractant receptor-homologous molecule expressed on Th2 cells is a G-protein-coupled receptor expressed by Th2 lymphocytes, eosinophils and basophils [43]. The receptor mediates the activation and chemotaxis of these cell types in response to prostaglandin D2 (PGD₂), produced by mast cells. PGD₂ is released through mast cell degranulation in the initial phase of IgE-mediated reactions. This process is also thought to occur at the site of inflammation, amplifying and maintaining the inflammation. These mechanisms are also evident in allergic reactions. There are by now many CRTH2 inhibitors available and have shown to be effective in, for example, asthma [44,45]. In allergic skin diseases, increased expression of CRTH2 on eosinophils has been found [46].

A CRTH2-inhibitor (*OC459*) has been developed for use in moderate-to-severe AD. An ongoing study is investigating the effect of *OC459* on flares in AD with EASI as primary end point. The data have not yet been published. It is anticipated that patients with a highly atopic Th2-dominant form of severe eczema will benefit from treatment with *OC459*.

4.3 Aprepitant

Originally investigated as *VLY 686*, aprepitant is a neurokinin 1 receptor (NK-1R) antagonist that was licensed in 2012 and primarily used for indications as postoperative or chemotherapy-induced nausea and vomiting, alcohol dependence, anxiety, depression and pruritis [47]. An abstract has been published describing effect of aprepitant on an undisclosed number of patients with AD in an open trial. The authors reported reduction of itch and SCORAD after 4 weeks of monotherapy [48]. Currently, a Phase II trial is investigating the effect of this NK-1R antagonist in the treatment of resistant pruritus in AD. NK-1R is highly expressed in neuronal tissue, and in interaction with substance P (SP), neurogenic inflammation and the pain perception pathway are regulated locally. Activation of NK-1R by the natural ligand SP is involved with many physiological processes as pain perception, behavioral stressors, cravings, nausea and vomiting. An inappropriate overexpression of SP may result in pathological conditions as dependence, anxiety, nausea/vomiting and pruritus. Treatment with NK-1 antagonist aims at reducing this overstimulation of NK-1R and has been successfully used in the treatment of chronic pruritus and especially in an AD mouse model [49]. It has been shown that AD patients have a higher level of plasma SP during exacerbation and remission compared with healthy controls, which may suggest efficacy of NK-1R antagonists in these patients [50]. In skin samples from patients with allergic contact dermatitis, a significant increase in the expression of SP in keratinocytes was found compared with those in control skin. Increased expression of a degrading enzyme, ACE, was also found [51].

4.4 Chymase inhibitors

SUN 13834 is an inhibitor of chymase, which is a chymotrypsin-like serine protease exclusively stored in secretory granules of mast cells and has been thought to participate in allergic diseases and to play an important role in the pathogenesis of AD [52-54]. It has already been shown that chymase inhibitor SUN13834 improves dermatitis in NC/Nga mice that spontaneously develop dermatitis resembling AD [55]. The drug is currently under clinical development for the treatment of AD in humans but results have not been posted.

4.5 2-isopropyl-5-[(E)-2-phenylethenyl] benzene-1,3-diol

IPBD, originally investigated as *WBI-1001* is a topical anti-inflammatory agent, and has been presented and tested in two Phase II RCTs [56,57]. This substance, which is derived

from bacteria found on nematodes, inhibits T-cell proinflammatory cytokine secretion *in vitro*. In the two studies, a total of 185 patients were treated in RCTs, with active drug showing significant superiority over placebo on both SCORAD, EASI, BSA and Investigator Global Assessments scores. Two concentrations (0.5 and 1.0%) were tested and well tolerated.

5. Conclusion

Recent general drug developments have been slow to enter the area of AD treatment. The development continues to be dominated by proof-of-concept studies of primarily anti-inflammatory drugs, whereas specific aspects of AD such as the barrier defects and itching remain largely untargeted. The clinically significant aspect of cutaneous inflammation is however not unimportant and both antibody-based treatments and small molecules are being tested in AD that may yet achieve the needed breakthrough in the treatment of this disease. A stronger assessment of the more likely candidates for larger clinical trials however awaits additional data.

6. Expert opinion

Development of new therapies may occur serendipitously but can also be the result of a structured approach directed at targets identified by experimental research into the pathogenesis of a given disease. The current understanding of AD is that the disease is due to a deficient skin barrier and a subsequent dysfunctional immune response. Management is therefore initially directed at improving the skin barrier while at the same time reducing external noxious/allergenic stimuli and inflammation. Sometimes this can be done using the simplest measures, such as moisturizers and sodium hypochlorite cleansers only, but not always [58,59]. Therapy benefits additionally from patient education (adherence to treatment and avoidance of irritants), measures aimed at enhancing the skin barrier and anti-inflammatory measures [60].

For more severe cases, intensified therapy is however necessary, and although many drugs are of use in the management of severe AD, an unmet need for new treatments exists. This need arises partly from the occasional lack of efficiency, partly from the need to minimize the risks to patients associated with long-term use of immunosuppressive drugs.

Interventions aimed at barrier strengthening continue to be useful irrespective of disease severity. Although it may theoretically be possible to develop pharmacological interventions that strengthen the skin barrier, this approach appears to be challenging in reality. Many minor modifications have been suggested to moisturizers, but convincing clinical evidence is more difficult to find [61,62]. Currently, no therapy aimed at correcting filaggrin mutations is published and the only barrier enhancing treatments appear simple lipidization [58,61,62]. In spite of identifying specific ceramide deficiencies in patients with AD, external lipidization applying the appropriate

ceramides does not appear to be more effective than applying other available lipids [63].

Skin barrier defects may also be macroscopic scratches, occurring in response to itching. Therapies primarily aimed at reducing itching may therefore be useful in the management of AD. When effective antipruritic drugs become available, they will however also shed light on the relative role of these macroscopic breaks of the skin barrier that occur following scratching and help to estimate the pathogenetic importance of these. Scratches are however secondary barrier defects and specific antipruritic drugs appear to be in earlier stages of development than drugs targeting inflammation and therefore having a broader scope.

The natural focus on new pharmacological therapies continues to be aimed at the dysfunctional immunological reactions associated with AD. A better understanding of the immunological consequences of the disease has identified several pathways open to manipulation, and the general development of immunomodulatory drugs has provided a number of potential candidates in the treatment of AD. There is good reason to believe that several of the abovementioned drugs may mature and enter general clinical use, not only for patients with AD but for other inflammatory skin diseases as well. The mechanisms however work both ways, and the experimental use of available drugs may also provide important insight into the disease mechanism, as exemplified by, for example, the use of ciclosporin A to show the inflammatory pathogenesis of psoriasis.

A better understanding of the pathophysiological mechanisms of AD, and a broader range of specific drugs provide the opportunity to achieve significant progress in the treatment and understanding of this disease. Development is however not even for the different steps of the pathogenesis. In spite of important progress, current understanding of the mechanisms underlying the barrier defect and itching that are crucial to the development of AD are patchy, with the main focus of the literature being on the inflammatory mechanisms. A broadening of the pathogenic understanding is therefore necessary. This should in particular include data on underlying barrier defect beyond filaggrin and should include a better understanding of the symptom of itching.

The prevalence of AD warrants development of specific drugs, which however are slow in coming as this review shows. The recognition that AD is associated with a specific set of important comorbidities supports the view that drug development in this area will mirror that seen in psoriasis where new drugs reach the field by transfer from related diseases such as rheumatoid arthritis.

The current evidence base for these new treatments is limited, and firm recommendations are not possible at this

early stage, but it is suggested that targeted antibodies or fusion proteins will have an earlier market penetration due to the higher level of maturity of this class of drug and to the conceptual familiarity provided by the introduction of these drug classes in dermatology in general. The necessary head-to-head studies that will offer better proof of the relative utility of these two classes of drugs are unlikely to occur for many years.

Currently, experience from psoriasis also suggests that biologically active antibodies or fusion proteins may be more effective long-term regulators of chronic disease processes than small molecules, but a number of the substances reviewed in the above remain to be tested in a larger clinical setting. There is currently not sufficient data to allow a rational evaluation of the relative merits of the substances discussed due to the limited data available.

Furthermore, AD presents an age-related specific safety aspect, which is less prevalent in, for example, psoriasis. Although most recalcitrant cases appear to occur in adult patients, the highest prevalence of AD is found among children. For any drug to achieve a broad and deep penetration into the market of AD, a firm understanding and description of potential adverse effects in the pediatric population will be necessary.

The current review of registered Phase II trials of new drugs in AD suggests that in spite of the unmet need for treatment beyond the available drugs, development in the field will be dependent on often small exploratory trials of drugs aimed at regulating the inflammatory response. It is hypothesized that any breakthrough will require the development of a better understanding of the barrier defect and itching and the underlying mechanisms in order to identify relevant therapeutic targets. The challenge of this is that these mechanisms are not key targets in other fields of therapeutic development, and therefore drugs are not being developed to cope with analogous diseases. The predominant mode of action of the drugs tested in AD will therefore remain anti-inflammatory for the foreseeable future, limiting the opportunities for identifying a breakthrough in new therapy.

Declaration of interest

GBE Jemec is a consultant for AbbVie and AstraZeneca. He is also on the advisory board of AbbVie, Janssen-Cilag, Pfizer, Inc. and Merck Sharp & Dohme. He is also an investigator of AbbVie, Novartis and Leo Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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