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REVIEW

Novel Therapeutic Approaches to Atopic Dermatitis

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Abstract Atopic dermatitis (AD) is one of the most common inflammatory skin diseases. The number of people affected by AD is relatively high and seems to be rising. Although mild and moderate forms of the disease can be well controlled by the use of emollients, topical corticosteroids, and topical calcineurin inhibitors, treatment of severe is still a huge challenge. The new hope is biologic drugs, magic bullets in allergy, targeted at different points of the complex pathomechanism of inflammation in AD. In this review, novel biologic therapies are discussed, including recombinant monoclonal antibodies directed against various interleukin pathways (such as IL-4, IL-13, TSLP, IL-31, and IL-12/23), on immunoglobulin E, molecules acting as T cells, B cells, etc. Of biological drugs, the most promising seems to be anti-IL-4/IL-13 therapy (dupilumab—the biological agent) and phosphodiesterase-4 inhibitor (crisaborole—a small molecule). A deep understanding of the AD pathomechanism provides a new perspective for tailor-made treatment of severe atopic dermatitis.

Keywords Atopic dermatitis · Immunology · Skin barrier · Biological treatment · Antihistamine

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Introduction

Atopic dermatitis (AD) is a pruritic and chronic inflammatory skin disease with a very high prevalence in western countries. AD frequency varies between 7 and 30% of children and 1–10% of adults resulting in significant decline of the quality of life of affected individuals (Weidinger and Novak 2016). Vast majority of AD cases begin within the first year of life and up to 95% start before the age of five.

Although etiopathogenic sequelae leading to AD are not completely understood, genetic, environmental, and immunologic factors are related to skin barrier deterioration along with immunologic dysregulation. Several therapeutic modalities exist to temporarily control signs and symptoms of AD, but none of them succeed to cure the disease. Taking this into consideration as well as adverse effects of these drugs, there is understandable interest in search for the new drugs that offer a better control over the disease symptoms with minimal secondary adverse effects (Ibler and Jemec 2015).

Many upcoming drugs focus on inhibiting different key pathways of AD inflammation. Published results are promising and launching of many biologicals as the first biological treatment of AD can be expected soon. This will lead to a new era in AD management. In this report, we summarize the current knowledge on the most emerging targets for biological treatments in AD.

The Pathogenesis of AD and Existing Treatments

The pathogenesis of AD is multifactorial including genetic and environmental factors. The disease development is initiated by an impaired skin barrier parallel to a

dysfunctional immune response and trigger factors like diminished bacterial biodiversity and allergic sensitization (Fig. 1). Current management strategies mostly aim at improving the skin barrier and suppressing the exaggerated inflammation. A cornerstone of AD therapy is emollients that restore skin barrier and act by moisturizing dry skin. Their use may radically diminish the need for immunosuppressive treatment and to prevent atopic sensitization. They have recently been demonstrated to reduce the risk of developing AD in high-risk infants if applied from the early infancy (Leitch et al. 2015).

The second most frequently used group of drugs effective in AD are topical glucocorticosteroids (GCS) (Torley et al. 2013). They are offered in different potencies but mid-potent are most widely used. They are highly effective in the treatment of an acute flare but should not be used as a long-term continuous therapy as they induce skin atrophy and GCS-related skin damage. In addition, they can cause steroid acne, steroid rosacea, and peri-oral dermatitis when applied on face and even if inadvertently applied on face. Topical calcineurin inhibitors (TCIs; e.g., tacrolimus and pimecrolimus) act on different immunopathological pathway of AD than GCS (Kwiek et al. 2008; Novak et al. 2005) but can achieve a comparable anti-inflammatory effect and have a more favorable side effect profile. They do not cause skin atrophy or steroid-related skin diseases, but the main limitation is the stinging or burning sensation observed with TCI application.

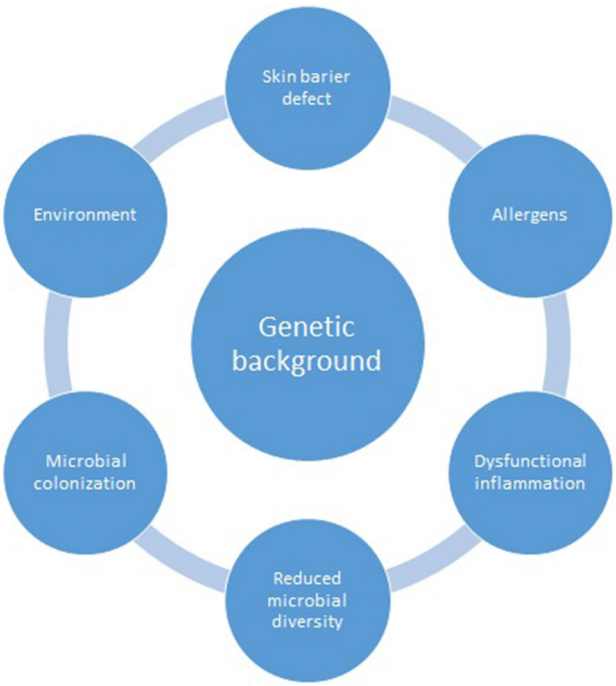

Fig. 1 Factors involved in development and maintenance of atopic dermatitis

Systemic treatment is rarely used, since its mechanism of action is general immunosuppression, and thus, it is limited to patients who fail to control flares with topical medications. The most commonly used drugs are: cyclosporin A (CsA) and oral GCS. The dilemma of systemic treatment is that many of AD patients experience relapses within several weeks after discontinuation. What is more, CsA-treated patients demonstrate numerous adverse effects, such as: hypercholesterolemia, high blood pressure, immunosuppression, kidney dysfunction, and the GCS-treated patients present with hyperglycemia, osteoporosis, and growth failure, respectively. It should be noted that CsA has not been specifically approved by the United States Food and Drug Administration (US FDA) for use in AD; however, in Japan and most European countries, CsA is generally approved for the treatment of patients with severe AD (Bieber and Straeter 2015).

Throughout the last 15 years, only two new medications have been approved for the treatment of AD (tacrolimus and pimecrolimus). Drug development in AD is falling behind in relation to some other inflammatory and malignant skin diseases (Fig. 2), but many patients are peaking out for these drugs, and marketing perspectives seem brilliant. The first and only biologic medicine for the treatment of moderate-to-severe atopic dermatitis has recently been approved (28 March 2017).

Over the last years, investigators have identified mediators, cytokines, and receptors that are decisive for AD development and may become attractive targets for immunotherapy (Eyerich et al. 2015). Current research focuses on different immune cell subtypes, their related cytokines in acute and chronic AD lesions, and on the role of microbial colonization. Many new compounds are monoclonal antibodies depleting cytokines or binding to cytokine receptors to block specifically AD-related immune pathways (Fig. 3). Several clinical trials have tried to transfer drugs that are approved for asthma, psoriasis, or rheumatological diseases to AD treatment, but either drugs showed that a poor efficacy or a beneficial outcome was limited to single subjects. As AD can present in many different clinical ways with heterogeneous courses, ranging from self-limited to chronic disease, another research goal is to characterize specific subtypes to predict disease activity and to individualize medical treatment.

Scientific Rationale and New Therapeutic Targets

AD is a T helper 2 (Th2) cell dominant inflammatory disease like asthma and allergic rhinoconjunctivitis that belong to the group of atopic diseases. The crucial Th2 cytokines are interleukin (IL)-4, IL-5, and IL-13. All of them cause an increased immunoglobulin E (IgE)

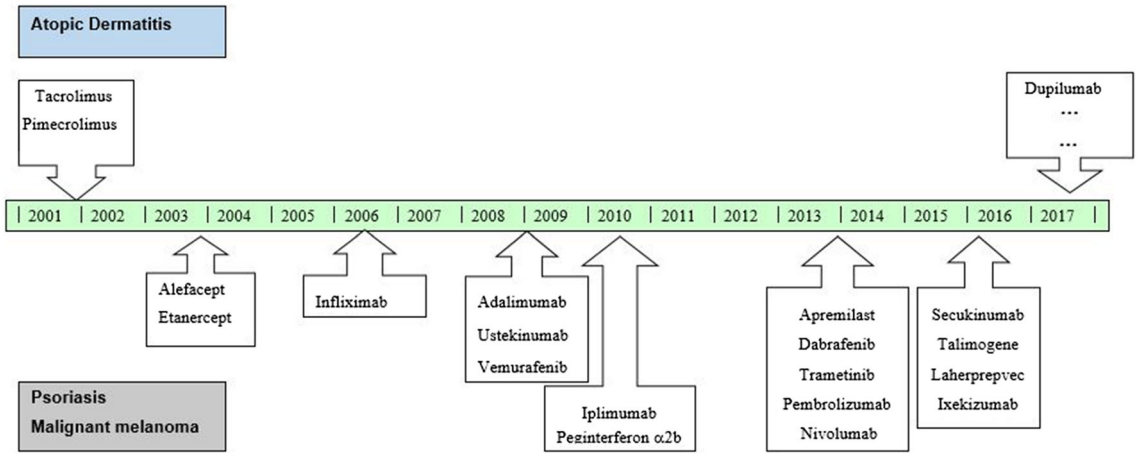

Fig. 2 New agents registered for inflammatory and malignant skin diseases. Timeline demonstrating the introduction and registration by the US FDA of new compounds in the treatment of skin diseases (atopic dermatitis, psoriasis, and malignant melanoma) since 2001

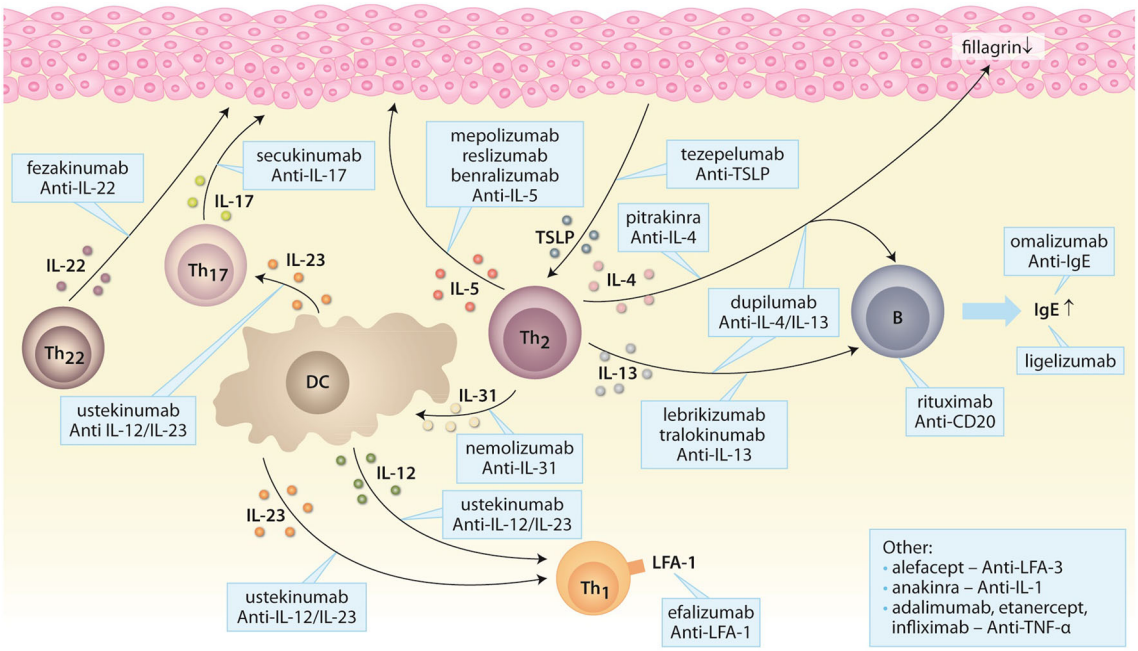

Fig. 3 Overview of atopic dermatitis (AD) pathogenesis and possible therapeutic targets for biologic therapy. AD inflammation is associated with a Th2 imbalance and increased secretion of IL-4, IL-5, IL-13, and IL-31. Th2 cells migrate into the dermis and epidermis, and released cytokines recruit inflammatory cells (including Th1, Th17, and Th22) and additionally drive IgE synthesis by B cells. Th2 cytokines additionally act directly on keratinocytes to disrupt barrier function and lead to epithelial damage with release of TSLP, IL-33, and IL-25. All the mechanisms can be blocked using biologic therapies directed against particular mechanisms, cytokines, or receptors. *Blue boxes* indicate therapeutic approaches that were already tested in clinical trials

production and contribute to allergic sensitization (Fig. 3). Mast cells express FceRI (the high affinity IgE receptor), which binds IgE, that may cross-link after antigen binding. Then, the mast cells release histamine, prostaglandins, and other mediators. They cause an enhanced vascular permeability, local swelling, and itch.

However, AD demonstrate a tendency towards allergic sensitization, mainly due to the impaired epidermal barrier, that allows allergen penetration and ingestion by the antigen-presenting cells within skin. This way of sensitization is currently believed to be the main route of life-threatening type 1 allergy to some food allergens (e.g., peanut) (Brough et al. 2015).

Importantly, the local inflammation differs between acute and chronic AD lesions. At the beginning and sensitization phase, primarily Th2 driven cells as well as Th22 and dendritic cells (DCs) migrate into the skin and secrete high amounts of IL-4, IL-13 and IL-22 (Eyerich and Novak

2013). IL-4 is the key cytokine in driving loco-regional IgE production. Pro-inflammatory cytokine milieu disturbs keratinocyte differentiation, leading to further worsening of skin barrier (Howell et al. 2009). Keratinocytes also release pro-inflammatory mediators, such as thymic stromal lymphopoietin (TSLP), known for propelling Th2-driven responses including production of IL-13 and IL-31 that act in concert with nerve growth factor (NGF) and substance P. Both NGF and substance P were recently identified as strong mediators of itch and serum markers of AD severity (Lauffer and Ring 2016).

In the chronic phase, the Th1 and Th17 lymphocytes also migrate into the lesions, releasing their key cytokines: interferon (IFN)-γ, and IL-17A (Eyerich and Novak 2013; Gittler et al. 2012). These cytokines display strong pro-inflammatory action and contribute to tissue remodeling. Consequently, epidermal barrier stays impaired and permeable stimulating immune cell activation and inflammation. Thus, the chronic AD is characterized by a self-perpetuating inflammation, leading to a vicious circle of immunological activation and defective barrier.

In summary, although the inflammatory component of AD is becoming better understood, the mechanisms behind the drugs used today in clinical practice (GCS, calcineurin inhibitors, and cyclosporine) are based primarily on a local or systemic immunosuppression. Therefore, new approaches are needed for more targeted therapy of AD.

Here, we discuss the current research aiming at the development of new drugs directing on different types of immune cells atopic dermatitis and its exacerbations.

Therapy Directed Against the CD20: Rituximab

Rituximab is a chimeric monoclonal anti-CD20 antibody, which eliminates B cells from the circulation. The CD20 antigen is presented on the surface of pre-B cells and B cells, however, not on plasma cells. The *rituximab* leads to the cell lysis, but its precise mechanism of action has not been fully elucidated. Contrary to the T cells, the B cells and its role in the pathogenesis of AD is not fully understood. Nevertheless, systemic expansion of chronically activated $CD27^+$ memory, plasmablast, and IgE-expressing memory B cells is seen in AD patients, and they are consistently found among the cells migrating to the skin lesions (Czarnowicki et al. 2016). Until now, targeted therapy against CD20 has been widely used in the treatment of proliferative diseases with B cells and autoimmune diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, as well pemphigus vulgaris (Sanchez-Ramon et al. 2013).

In 2008, Simon and Sediva presented two reports on treatment of AD with *rituximab* on six and two patients each. Simon et al. (2008a) initiated treatment of severe atopic dermatitis by intravenous courses of *rituximab* (two doses of 1000 mg 2 weeks apart). Their research demonstrated an impressive clinical and histological improvement during 4–8 weeks of treatment. What is more, all six patients, who participated in that study, did not suffer from any significant adverse effects of *rituximab*.

However, Sediva et al. (2008) did not observe such tremendous results in two patients treated by his group. The SCORAD (SCORing Atopic Dermatitis) index of the first patient decreased 99–58 by week 10, whereas the second patient demonstrated exacerbation (SCORAD index increased 63–74). The most likely explanation for the above-mentioned variance could result from more severe atopic dermatitis as well as insufficient dose (two doses of 500 mg intravenously after 2 weeks apart) that could not eliminate $CD20^+$ B cells effectively enough to improve the clinical condition of the skin or reduce the total concentration of IgE.

At the beginning of 2016, another study with three patients demonstrated no improvement in symptoms [based on index Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI)] at the end of 6-month follow-up (McDonald et al. 2016). Due to the divergent results of studies evaluating the efficacy of *rituximab*, there is a compelling need for a double-blind placebo-controlled study.

Therapy Against IgE

The potential role of IgE in the pathogenesis of AD is equivocal. Increased serum concentration of IgE is observed in about 80% cases of AD, whereas the mast cells in the dermis and epidermis of patients with AD express FcεRI (the high affinity IgE receptors), which binds IgE (Fernández-Antón Martínez et al. 2012). However, one-fifth of patients have normal levels of IgE. Nevertheless, it was hypothesized that interference with IgE activity in skin and blood may be beneficial in AD.

Omalizumab

Omalizumab is a murine monoclonal antibody directed against IgE. The antibody may bind to the IgE receptor-binding site (in both, FcεRI and FcεRII) on the surface of basophils and mast cells, thereby preventing the degranulation and the activation of cellular mediators. In addition, *omalizumab* was also shown to inhibit the FcεRI expression, on the surface of DCs. Therefore, anti-IgE therapy was believed to play a significant role in initiating the inflammatory reaction caused by allergens.

Omalizumab was successfully used for treatment for moderate-to-severe asthma in adolescent and adults with severe asthma. The dosages and schedule are adjusted to the body weight as well as the initial serum of total IgE levels (Fernández-Antón Martínez et al. 2012).

The treatment with *omalizumab* in AD has already been documented in several reports. A recent meta-analysis of available reports (Wang et al. 2016) has demonstrated excellent results in 44 out of 103 analyzed patients. Eleven out of thirteen studies included in the meta-analysis were case series. This antibody was significantly more effective in patients who had total IgE levels below 700 IU/ml. Kim et al. (2013) have shown in an open study that eight treatment cycles with *omalizumab* 300 mg repeated every 14 days resulted in a clinical improvement in all ten patients with AD refractory to systemic treatment [reduction in the SCORAD index and VAS (Visual Analogue Scale) index, improvement in the quality of life-DLQI, and decrease in sleep disorders and itch]. After 2-month follow-up, two patients sustained remarkable improvement (SCORAD index was at least halved); in five cases, it decreased about 25–50%, whereas three patients failed to respond to treatment. Similar effects were observed in school age patients (6–19 years) treated with *omalizumab* (Lacombe Barrios et al. 2013).

A 2010 randomized control trial (RCT) by Heil et al. (2010), with 20 AD patients, demonstrated a reduction in the IgE concentration as well as decreased IgE saturation on the cell surface decreased within 16 weeks of observation. However, these effects were not associated with clinical improvement, suggesting complexity of the immune phenomena and other than IgE-related mechanisms in the pathomechanisms of the disease (Heil et al. 2010). Lack of improvement in two double-blind studies with *omalizumab* highlights the fact of a great need for RCT in AD.

In another study, the immune effect of *omalizumab* and its clinical impact was evaluated in the pediatric population with severe refractory atopic dermatitis (Iyengar et al. 2013). In this report, there was a significant decrease of TSLP, TARC/CCL17 (thymus and activation regulated chemokine), as well as OX40L (OX40 ligand) in the *omalizumab*-treated group. Interestingly the parallel clinical improvement (SCORAD index) was observed both in *omalizumab* and placebo-treated groups.

A new approach to improve the treatment efficacy was based on simultaneous administration of low doses of *omalizumab* (150 mg subcutaneously every 14 days, and increase in the dose to 300 mg after 2 months) and infusion of intravenous immunoglobulin (IVIG) preparation (3-h infusion 10 g IVIG) (Toledo et al. 2012). At 6 weeks of treatment, 75% of patients improved their SCORAD index by more than 50% and this effect was associated with baseline IgE decrease of 50%. Monotherapy with IVIG was shown to be effective in uncontrolled studies (Kwiek and Novak 2010) and that makes it hard to estimate the impact of individual drug on the final outcome.

Another approach to use combined treatment with *omalizumab* was conducted by Zink et al. (2016). Authors have used IgE immunoadsorption followed by *omalizumab* overcoming the problem of very high IgE levels in AD. As with other combined therapies, the question of individual influence of each active compound needs to be addressed in the future, especially that IgE immunoadsorption was successfully used as monotherapy in recalcitrant AD (Kasperkiewicz et al. 2014).

Basing on the observation of the crucial role of IgE in initiation phase of the AD, an interesting approach was proposed by Hotze et al. (2014), who investigated response to treatment with *omalizumab* in patients with primary dysfunction of the skin barrier (filaggrin gene mutation, FLG). They received 14 cycles of *omalizumab* (150 mg) in 14-day intervals, with follow-up therapy in non-responders group. Intriguingly, none of the patients affected by the filaggrin gene responded to treatment (seven patients), whereas patients without this mutations showed a very good clinical response (four patients SCORAD reduction >50%; four patients SOCRAD reduction 25–50% compared to baseline). This study further confirms existence of two arms in the pathology of atopic dermatitis: the role of the immune system and dysfunction of skin barrier plays.

Ligelizumab

A novel potential therapeutic agent in the treatment of atopic dermatitis is *ligelizumab*, an anti-IgE heavy chain IgG1 monoclonal antibody, demonstrating significantly higher avidity for IgE than *omalizumab*. Unfortunately, despite its promising preclinical efficacy profile, studies evaluating the clinical applicability are still lacking (so far examined only the safety and its pharmacokinetics) (Arm et al. 2014).

Th2 Response: Therapy Directed Against IL-4/IL-13

Dupilumab

Since IL-4 and IL-13 are defined as key cytokines in AD pathogenesis, clinical investigations were aimed at assessment of the applicability of monoclonal antibodies directed against these cytokines. IL-4 and IL-13 act via common α subunit of IL-4 receptor (IL-4Rα) and their increased expression results in decreased synthesis of skin barrier proteins (i.e., filaggrin). Skin with disrupted barrier

is more prone to penetration of environmental allergens and pathogens into deeper skin layers (Brough et al. 2015). *Dupilumab*, fully human monoclonal antibody aimed against IL-4Rα blocks binding of IL-4 and IL-13 to the receptor. *Dupilumab*, initially tested in patients with severe asthma, showed improvement of the disease (Wenzel et al. 2013). After these promising results, clinical trials in patients with moderate-to-severe AD who do not respond to topical treatment have started.

Beck et al. (2014) published results of four clinical trials which assessed safety of *dupilumab*. In two clinical studies (phase I), patients were given 75, 150, and 300 mg of *dupilumab* or placebo subcutaneously for 4 weeks. In another trial (phase I), patients were given 300 mg of *dupilumab* or placebo for 12 weeks. The result of these studies was quick, dose-dependent improvement of skin condition measured by EASI and pruritus score. In addition, further improvement was observed after treatment continuation. In 85% of patients treated for 12 weeks, 50% reduction of EASI score was observed in comparison to placebo (35% reduction of EASI because of high effectiveness of emollients), and between weeks 4 and 12, the number of patients with mild or no signs of AD doubled. Fourth clinical trial (phase II) compared efficacy of *dupilumab* with topical corticosteroids to placebo. After 4 weeks, 50% reduction of EASI score was observed in the study group, whereas only half of placebo group had the same outcome. In all clinical studies, mild adverse events were noted without differences between placebo and study group. However, severe adverse events such as exacerbation of atopic lesions and skin infections were more often in the placebo group (Beck et al. 2014).

Thaci et al. (2016) conducted clinical trial (phase II) to compare different doses of *dupilumab*. Patients were injected with 300 mg of *dupilumab* once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks, or placebo once a week. Their data confirmed promising results from the previous studies. In the group receiving 300 mg of *dupilumab* once a week, 50% reduction of EASI was observed in highest percentage of patients, whereas 100 mg every 4 weeks was only slightly better than placebo. Safety profile of *dupilumab* was confirmed in this trial; there were no significant differences in occurrence of adverse events between study and placebo groups (Thaci et al. 2016).

Two phase III trials (SOLO 1 and SOLO 2) comparing *dupilumab* with placebo were published in December 2016 and confirmed positive results from the previous studies. In each trial adult (>18 years), patients with moderate-to-severe AD were given 300 mg of *dupilumab* weekly/every 2 weeks or placebo for 16 weeks. At week 16, significantly more patient receiving *dupilumab* demonstrated an improvement measured with EASI and pruritus intensity. Similarly, a significant improvement was noted in other clinical end points' quality of life, intensity of eczema, or symptoms of anxiety. No significant differences in incidence of adverse events were noted. Serious adverse events such as severe exacerbation of AD were rare. Injection-site reactions and conjunctivitis occurred more often in *dupilumab*-treated patients, whereas exacerbations of AD and skin infections in placebo group (Simpson et al. 2016). A different scientific approach was presented in recently published study (4MAY2017)—the CHRONOS study allowed concomitant use topical drugs (GCS, TCIs) along with *dupilumab*. In group receiving *dupilumab,* 300 mg weekly (plus topical agents) Investigator's Global Assessment score improved in 40% of patients, EASI-75 in 64% after 1 year of treatment. The placebo group plus topical treatment had higher rate of side effects vs. the *dupilumab* (plus topical agents) groups. CHRONOS study and adjunctive therapy provide a practical response to long-term management of moderate-to-severe atopic dermatitis (Strowd and Feldman 2017).

Due to positive result of phase I and II studies and relative good safety profile, *dupilumab* was announced a "Breakthrough Therapy" in moderate-to-severe AD. On 28th March 2017, the US FDA approved *dupilumab* (Dupixent®) injection to treat adults with moderate-to-severe AD, especially with AD not controlled adequately by topical treatment, or when topical therapies are not advisable. Among others IL-13 is known for its antitumor activity, and therefore, increased risk of tumor formation cannot be excluded (Terabe et al. 2004). Moreover, *dupilumab* was studied only in adult population so far. However, due to high incidence of AD in pediatric patients and need for effective treatment, clinical trial assessing safety and tolerability of *dupilumab* in children (aged 6–18 years) has been recently completed and everyone is waiting for publishing the results (NCT02407756 2015).

Pitrakinra

Another drug which targets α subunit of IL-4 receptor and, therefore, blocks the effects induced by IL-4 and IL-13 is human recombinant IL-4 variant—*pitrakinra*. *Pitrakinra* was proven to be effective in patients with asthma (Wenzel et al. 2007). One placebo-controlled clinical study testing *pitrakinra* in atopic individuals was conducted. Phase 2a was completed, but results are not available yet (NCT00676884 2008).

Other Therapies Directed Against IL-13

One of the cytokines playing main part in pathogenesis of allergic diseases including AD is IL-13. IL-13 is produced mainly by Th2 lymphocytes and acts similar to IL-4,

stimulating proliferation, and differentiation B lymphocytes, production of IgE antibodies, and recruitment of eosinophils and mast cells (Shirakawa et al. 2000). Antibodies against IL-13, *lebrikizumab,* and *tralokinumab* were already investigated in the treatment of asthma and the initial results show high efficacy (Hanania et al. 2015). Implications of treatment of patients with AD with anti-IL-13 antibodies were awaited with big expectations. Furthermore, clinical trial assessing efficacy of *lebrikizumab* in comparison to topical corticosteroids has been completed a little while ago. Simpson et al. (2016) presented recently primary efficacy data on *lebrikizumab* activity in AD and they noted 20% reduction in EASI score. Moreover, also topical corticosteroids plus 125 mg of *lebrikizumab* every 4 weeks resulted in a significant improvement in EASI and SCORAD (NCT02340234 2015).

Therapy Against IL-31: Nemolizumab

IL-31 is another AD-related cytokine. It is produced mainly by Th2 lymphocytes but also mast cells and keratinocytes, and it is postulated as crucial cytokine triggering pruritus (Sonkoly et al. 2006). In addition, serum level of IL-31 is correlated with severity of the disease (Raap et al. 2008). The role of IL-31 in exacerbation of the skin lesions is uncertain. In two clinical trials, inhibition of IL-31 was evaluated. The first one showed an impressive reduction in intensity of pruritus and EASI index in nemolizumab group vs. placebo receiving patients (Ruzicka et al. 2017). The second evaluated safety and tolerance of this antibody compared to placebo. This trial is completed; however, its outcomes are not available yet (NCT01614756 2012).

Therapy Directed Against IL-5: Mepolizumab

In many inflammatory, skin diseases such as AD, in the peripheral blood and the skin, eosinophils, and their products are present. IL-5 stimulates the proliferation and release of eosinophils from bone marrow. Furthermore, IL-5 is well known as a chemoattractant for eosinophils. Therefore, there is a strong belief that the reduction of eosinophils may have alleviated symptoms of atopic dermatitis. Therefore, *mepolizumab* (recombinant human monoclonal anti-IL-5) was developed. Two other agents, *reslizumab* and *benralizumab* (currently tested in asthma), also belong to the anti-IL-5 family.

Oldhoff et al. (2005) conducted a randomized double-blind placebo-controlled trial. In this study, 18 patients received two courses of intravenous *mepolizumab* (750 mg every 7 days) and 23 others received placebo. In the group receiving the active compound, a significant improvement in clinical assessment was observed in 22% of patients, while only 5% of placebo-treated patients experienced alleviation of symptoms. However, when averaged results were analyzed, the difference in SCORAD index or itching was not significant in *mepolizumab*-treated group. The authors point out that the duration of the trials was too short to allow for the proper assessment of maintenance of the *mepolizumab* efficacy.

Therapy Directed Against TSLP

TSLP is a cytokine produced mainly by keratinocytes as well as DCs and mast cells. TSLP stimulates transcription of the IL-4 gene. IL-4 is crucial in the Th2 pathway. It promotes differentiation of $CD4^+$ lymphocytes to Th2 and production of various pro-inflammatory cytokines (Tatsuno et al. 2015). IL-4 promotes up-regulation of the TSLP receptor, which enhances the positive feedback loop between these two cytokines. Abnormally high expression of TSLP gene was observed in AD patients (Ziegler et al. 2013); therefore, it is a potential therapeutic target in severe AD. Clinical trial assessing effectiveness of *tezepelumab*, monoclonal antibody against TSLP, in comparison to placebo in patients with severe AD has been recently completed and outcomes of this trial are eagerly expected (NCT02525094 2015).

Non-Th2 Pathways

Although Th2 cytokines are crucial during initiation/exacerbation phases of disease, AD is not clear Th2 disease. Th1 as well as Th17 pathways are believed to play a significant role in its pathogenesis, especially in the chronic, remodeling phase.

Therapy Directed Against IL-12/IL-23: Ustekinumab

Ustekinumab is human monoclonal antibody against p40 subunit which is common to IL-12 and IL-23. IL-12 is produced by macrophages and DCs, and it activates Th1 lymphocytes, whereas IL-23 induces proliferation and activity of Th17 lymphocytes. A number of activated Th1 and Th17 lymphocytes were found in chronic atopic skin lesions (Batista et al. 2015). Inhibition of these cells by blockage of IL-12 and IL-23 may display a novel therapeutic approach in AD management. Regrettably, the only data on the effects of *ustekinumab* use in AD patients are drawn from few case studies. Fernández-Antón Martínez et al. (2014) used *ustekinumab* in four patients with severe, recurrent AD who needed systemic management. Antibody was given in weeks 1 and 4 and subsequently every

12 weeks. A significant improvement in SCORAD and VAS was noted after second or third doses, and there were no serious side effects (Fernández-Antón Martínez et al. 2014). Excellent effects were reported in the two studies in adults (Puya et al. 2012; Shroff and Guttman-Yassky 2014) and other two in teenagers (Agusti-Mejias et al. 2013; Wlodek et al. 2016). However, inadequate or even no response to *ustekinumab* was also observed (Samorano et al. 2016). In view of equivocal outcomes of management AD with *ustekinumab,* role of this antibody remains unclear. Study investigating *ustekinumab* in adults with chronic AD is currently ongoing (NCT01806662 2013).

Therapy Directed Against IL-22

IL-22 which belongs to the IL-10 family is produced mainly by Th17 and Th22 lymphocytes. IL-22 activates keratinocytes which results in up-regulation of pro-inflammatory molecules. It also promotes acanthosis (thickening of epidermis) but inhibits differentiation of keratinocytes (Boniface et al. 2005). Enhanced expression of IL-22 was reported in the skin probes of patients being in the acute as well as chronic phase of AD (Gittler et al. 2012). *Fezakinumab*, human monoclonal antibody against IL-22, previously known from investigations in the treatment of rheumatoid arthritis and psoriasis (trials were discontinued) is being tested in the phase II clinical trial in adults with AD (NCT01941537 2013).

Anti-IL-17 Secukinumab—an anti-IL-17 antibody is currently registered for psoriasis and exhibits excellent efficacy in this disease. The study on its use in AD is currently ongoing (NCT02594098 2015).

Therapy Directed Against TNF-α

Tumor necrosis factor (TNF)-α is a well-recognised pro-inflammatory cytokine in various diseases; however, its role in pathogenesis of AD remains unclear. Several studies suggested that serum level of TNF-α may be elevated in AD, which makes it an interesting potential therapeutic target (Itazawa et al. 2003). Only few studies assessing effectiveness of TNF-α inhibitors in AD individuals have been conducted so far. Buka et al. (2005) used etanercept (human recombinant fusion protein binding to TNF-α) in two patients, showing no satisfactory responses and serious adverse effects (*Staphylococcus aureus* superinfection and viral urticarial rush).

Adalimumab is TNF-α inhibitor (human recombinant monoclonal antibody) used in the management of psoriasis. There is only one case of management AD by this antibody, demonstrating worsening of AD symptoms (Yayli et al. 2013).

Infliximab is chimeric monoclonal antibody against TNF-α. Jacobi et al. (2005) assessed its effectiveness in prospective study in nine patients with severe, chronic AD. During induction phase, a significant improvement was reached according to EASI and intensity of pruritus 2 weeks after the latest dose of medication. Despite initially promising, satisfactory outcome in weeks 10, 14, and 30 six patients was excluded because of lack of further improvement. In week 46, only two patients completed the trial with excellent response to treatment (Jacobi et al. 2005).

Use of TNF-α inhibitors in therapy of AD is controversial. Data on the effects of all the drugs are scarce and contradictory. It is worth mentioned that AD-like adverse events were reported after use of *infliximab* and *etanercept* (Mangge et al. 2003; Wright 2003). To date, there were no clearly promising effects. Further research is essential to state whether TNF-α inhibitors may play the role in the therapy of severe AD.

Therapy Directed Against IL-1: Anakinra

Anakinra is recombinant human receptor directed against IL-1, consisting of two isoforms of IL-1α and IL-1β. IL-1 consists of a group of 11 cytokines, which plays a central role in the regulation of immune and inflammatory responses able to initiate and maintain immune response in the course of autoimmune and chronic inflammatory diseases, including AD (Pazyar et al. 2012). To date, however, there are no promising clinical reports on this drug in the therapy of AD.

Therapy Directed Against LFA-1: Efalizumab

Efalizumab is a recombinant monoclonal antibody which specifically binds to the LFA-1 subunit, CD11. LFA-1 is a T cell surface molecule crucial in the activation and migration of T lymphocytes to the skin as well as the cytotoxicity of T cells. By binding to CD11a, the adhesion between LFA-1 and ICAM-1 (molecule found in the vascular endothelium responsible for adhesion) is blocked.

Therefore, *efalizumab* prevents from the migration of T lymphocytes from peripheral blood to the skin. Its effect is reversible and not associated with a reduction in the number of circulating T cells. Unfortunately, due to risk of the progressive multifocal leukoencephalopathy, a brain infection caused by reactivation of latent JC virus infection, the efalizumab was withdrawn from the European and the US markets.

Therapy Directed Against LFA-3: Alefacept

Alefacept is a fusion protein LFA-3/IgG1, which is adjacent to CD2 on T cells, thereby preventing interaction of LFA-3 and CD2 and induces apoptosis through the perforin-granzyme system. In human studies, anti-LFA-3 therapy results in a decrease of histological changes typical for AD, i.e., diminished hyperkeratosis, acanthosis, spongiosis, and a reduction in the number of B and T lymphocytes, eosinophils in the dermis and epidermis, as well as drop in the concentration of particular cytokines (IL-5, IL-10, IL -13, and IFN-γ) involved in the pathogenesis of atopic eczema. (Simon et al. 2008b). The sale of alefacept has been discontinued since 2011, but this decision was not the result of a safety concern.

Inhibitors of Phosphodiesterase IV

Since the 1980s, it has been known that patients with AD demonstrated a higher activity of phosphodiesterases (PDE), which are responsible for the excessive activation of leukocytes and occurrence of inflammation (Chan et al. 1993). Up to now, 11 different PDE inhibitors have been recognised in the human body. Inhibition of PDE4 (PDE4 is expressed on leukocytes) leads to the accumulation of cAMP which activates protein kinase A and other effectors. This activation results in inhibition of the transcription of not only pro-inflammatory cytokines, but also neutrophil degranulation, chemotaxis, or endothelial cell adhesion.

Crisaborole

Standards in the topical treatment of atopic dermatitis have not changed for 15 years. Crisaborole is non-steroidal topical phosphodiesterase-4 inhibitor that has been just approved as 2% ointment for topical treatment of mild to moderate AD in adults and children older than 2 years. According to physicochemical properties (low-molecular-weight compound—251 g/ml (http://www.chemspider.com/24701949)), crisaborole may fully penetrate through dermis and epidermis to the source of inflammation (Zane et al. 2016). Crisabole-treated patients achieved improvement in Investigator's Static Global Assessment and pruritus (63% reduction at day 29) much faster than vehicle treated patients in a randomized, double-blind, conducted trial conducted in adults and children over 2 years of age (Paller et al. 2016). The most frequent transient adverse effect was the application site pain. Crisaborole represents a promising, novel, non-steroidal topical treatment for patients with mild-to-moderate AD. Also other clinical trials concerning on PDE4 group were completed (E6005, OPA-15406—in pediatric patient).

Apremilast

Apremilast is currently considered as an oral drug that due to blocking PDE4 [molecular weight 450.5 g/mol (http://www.chemspider.com/9736448)], inhibits the production of inflammatory mediators such as TNF-α, IL-12, IL-2, IFN-γ, IL-5, IL-8, LTB4, and adhesion of molecules CD18/CD11b, and also stimulates the production of IL-10, which is known as inhibitor other pro-inflammatory chemokines (Schafer et al. 2010). Despite promising results of first clinical studies (Samrao et al. 2012), the results of the recently updated phase 2 clinical study (April 2017) show that apremilast oral administration failed to demonstrate any efficacy so PDE4 inhibition is unlikely to be an alternative option for the treatment of AD (NCT02087943 2014).

Conclusion and Further Research

For a long time, controlling patients with severe AD has been an enormous clinical challenge. Current systemic therapies are mainly off-label, limited in efficacy, and have an unfavorable side effect profile. After years of stillness, the area of AD medications is just becoming active. Profound understanding of AD pathogenesis allowed the development of new compounds, which selectively inhibit particular AD key pathways. Amongst all drugs, anti-IL-4/IL-13 strategy seems to be the most promising. *Dupilumab* is the furthest advanced biologic from this group. PDE4 inhibitors, members of a small molecule drugs family, are another drugs that are changing our treatment paradigm with crisaborole being already approved for topical treatment. Another PDE4 inhibitor, apremilast already approved for psoriasis treatment, seems to have beneficial effects in AD, as well. Several biologics are in phase II studies, giving reason to expect a fascinating area of clinical application within the next years. Therefore double-blind placebo-controlled trials are so important in the disease in which thorough daily use of emollients may essentially improve the long-term results. High rates of improvement in patients receiving placebo in RCT are at least partially related to study protocols that offer patients unlimited amount of good quality emollients, tools that increase adherence (diaries), and doctor appointments every 1 or 2 weeks.

Despite first successes, this research, however, still faces numerous open questions:

1. Do we understand of AD pathogenesis enough to propose more individualized treatment approaches?
2. Despite overall confidence and negligible side effects are the new biologics safe long-term?
3. Are the particular subtypes of AD defined good enough to early identify those patients that are in the need of a most tailored treatment?

And finally, are we ready for this tremendous change in the management of AD?

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare. All authors have approved the manuscript and agree with submission.

References

Agusti-Mejias A, Messeguer F, García R et al (2013) Severe refractory atopic dermatitis in an adolescent patient successfully treated with ustekinumab. Ann Dermatol 25:368–370

Arm JP, Bottoli I, Skerjanec A et al (2014) Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy 44:1371–1385

Batista DI, Perez L, Orfali RL et al (2015) Profile of skin barrier proteins (filaggrin, claudins 1 and 4) and Th1/Th2/Th17 cytokines in adults with atopic dermatitis. J Eur Acad Dermatol Venereol 29:1091–1095

Beck LA, Thaçi D, Hamilton JD et al (2014) Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 371:130–139

Bieber T, Straeter B (2015) Off-label prescriptions for atopic dermatitis in Europe. Allergy 70:6–11

Boniface K, Bernard FX, Garcia M et al (2005) IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 174:3695–3702

Brough HA, Liu AH, Sicherer S et al (2015) Atopic dermatitis increases the effect of exposure to peanut antigen in dust on peanut sensitization and likely peanut allergy. J Allergy Clin Immunol 135:164–170

Buka RL, Resh B, Roberts B et al (2005) Etanercept is minimally effective in 2 children with atopic dermatitis. J Am Acad Dermatol 53:358–359

Chan SC, Reifsnyder D, Beavo JA et al (1993) Immunochemical characterization of the distinct monocyte cyclic AMP-phosphodiesterase from patients with atopic dermatitis. J Allergy Clin Immunol 91:1179–1188

Czarnowicki T, Gonzalez J, Bonifacio KM et al (2016) Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. J Allergy Clin Immunol 137(118–129):e115

Eyerich K, Novak N (2013) Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. Allergy 68:974–982

Eyerich K, Eyerich S, Biedermann T (2015) The multi-modal immune pathogenesis of atopic eczema. Trends Immunol 36:788–801

Fernández-Antón Martínez MC, Leis-Dosil V, Alfageme-Roldán F et al (2012) Omalizumab for the treatment of atopic dermatitis. Actas Dermosifiliogr 103:624–628

Fernández-Antón Martínez MC, Alfageme Roldán F, Ciudad Blanco C et al (2014) Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients. Actas Dermosifiliogr 105:312–313

Gittler JK, Shemer A, Suárez-Fariñas M et al (2012) Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 130:1344–1354

Hanania NA, Noonan M, Corren J et al (2015) Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. Thorax 70:748–756

Heil PM, Maurer D, Klein B et al (2010) Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course—a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges 8:990–998

Hotze M, Baurecht H, Rodríguez E et al (2014) Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines. Allergy 69:132–135

Howell MD, Kim BE, Gao P et al (2009) Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 124(3 Suppl 2):R7–R12

Ibler KS, Jemec GB (2015) Novel investigational therapies for atopic dermatitis. Expert Opin Investig Drugs 24:61–68

Itazawa T, Adachi Y, Okabe Y et al (2003) Developmental changes in interleukin-12-producing ability by monocytes and their relevance to allergic diseases. Clin Exp Allergy 33:525–530

Iyengar SR, Hoyte EG, Loza A et al (2013) Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. Int Arch Allergy Immunol 162:89–93

Jacobi A, Antoni C, Manger B et al (2005) Infliximab in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol 52:522–526

Kasperkiewicz M, Sufke S, Schmidt E et al (2014) IgE-specific immunoadsorption for treatment of recalcitrant atopic dermatitis. JAMA Dermatol 150:1350–1351

Kim DH, Park KY, Kim BJ et al (2013) Anti-immunoglobulin E in the treatment of refractory atopic dermatitis. Clin Exp Dermatol 38:496–500

Kwiek B, Novak N (2010) Immunosuppressants as treatment for atopic dermatitis. In: Pawankar R, Holgate S et al (eds) Allergy frontiers: therapy and prevention, vol V. Springer, Berlin, pp 291–310

Kwiek B, Peng WM, Allam JP et al (2008) Tacrolimus and TGF-beta act synergistically on the generation of Langerhans cells. J Allergy Clin Immunol 122:126–132.e1

Lacombe Barrios J, Begin P, Paradis L et al (2013) Anti-IgE therapy and severe atopic dermatitis: a pediatric perspective. J Am Acad Dermatol 69:832–834

Lauffer F, Ring J (2016) Target-oriented therapy: emerging drugs for atopic dermatitis. Expert Opin Emerg Drugs 21:81–89

Leitch CS, Chu R, Ray R et al (2015) Preventing atopic eczema from birth using emollients. J Allergy Clin Immunol 135:1663–1664

Mangge H, Gindl S, Kenzian H et al (2003) Atopic dermatitis as a side effect of anti-tumor necrosis factor-alpha therapy. J Rheumatol 30:2506–2507

McDonald BS, Jones J, Rustin M (2016) Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients. Clin Exp Dermatol 41:45–47

NCT00676884 (2008) A phase 2a study to investigate the effects of repeated administration of aeroderm in subjects with atopic eczema. https://clinicaltrials.gov/ct2/show/NCT00676884. Accessed 4 Jan 2017

NCT01614756 (2012) A two-part, phase 1, single-dose study of IL-31 mAb (anti-interleukin 31 monoclonal antibody); in healthy subjects and adults with atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT01614756. Accessed 4 Jan 2017

NCT01806662 (2013) Pilot study of ustekinumab for subjects with chronic atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT01806662. Accessed 4 Jan 2017

NCT01941537 (2013) Randomized Placebo Controlled Study to Determine Safety, Pharmacodynamics and Efficacy of ILV-094 in Atopic Dermatitis. https://clinicaltrials.gov/ct2/show/NCT01941537. Accessed 4 Jan 2017

NCT02087943 (2014) Efficacy and safety study of apremilast in subjects with moderate to severe atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT02087943. Accessed 24 Mar 2017

NCT02340234 (2015) A study of lebrikizumab in patients with persistent moderate to severe atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT02340234. Accessed 4 Jan 2017

NCT02407756 (2015) A study to determine the safety and tolerability of dupilumab in patients aged ≥6 to <18 years with atopic dermatitis (eczema). https://clinicaltrials.gov/ct2/show/study/NCT02407756. Accessed 4 Jan 2017

NCT02525094 (2015) Phase 2a study to evaluate the efficacy and safety of MEDI9929 in adults with atopic dermatitis (ALLEVIAD). https://clinicaltrials.gov/ct2/show/NCT02525094. Accessed 4 Jan 2017

NCT02594098 (2015) Secukinumab for Treatment of Atopic Dermatitis. https://clinicaltrials.gov/ct2/show/NCT02594098. Accessed 4 Jan 2017

Novak N, Kwiek B, Bieber T (2005) The mode of topical immunomodulators in the immunological network of atopic dermatitis. Clin Exp Dermatol 30:160–164

Oldhoff JM, Darsow U, Werfel T et al (2005) Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 60:693–696

Paller AS, Tom WL, Lebwohl MG et al (2016) Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 75(494–503):e6

Pazyar N, Feily A, Yaghoobi R (2012) An overview of interleukin-1 receptor antagonist, anakinra, in the treatment of cutaneous diseases. Curr Clin Pharmacol 7:271–275

Puya R, Alvarez-Lopez M, Velez A et al (2012) Treatment of severe refractory adult atopic dermatitis with ustekinumab. Int J Dermatol 51:115–116

Raap U, Wichmann K, Bruder M et al (2008) Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol 122:421–423

Ruzicka T, Hanifin JM, Furue M et al (2017) Anti-interleukin-31 receptor a antibody for atopic dermatitis. N Engl J Med 376:826–835

Samorano LP, Hanifin JM, Simpson EL et al (2016) Inadequate response to ustekinumab in atopic dermatitis—a report of two patients. J Eur Acad Dermatol Venereol 30:522–523

Samrao A, Berry TM, Goreshi R et al (2012) A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. Arch Dermatol 148:890–897

Sanchez-Ramon S, Eguíluz-Gracia I, Rodríguez-Mazariego ME et al (2013) Sequential combined therapy with omalizumab and rituximab: a new approach to severe atopic dermatitis. J Investig Allergol Clin Immunol 23:190–196

Schafer PH, Parton A, Gandhi AK et al (2010) Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. Br J Pharmacol 159:842–855

Sediva A, Kayserova J, Vernerova E et al (2008) Anti-CD20 (rituximab) treatment for atopic eczema. J Allergy Clin Immunol 121:1515–1516 **(author reply 1516–1517)**

Shirakawa I, Deichmann KA, Izuhara I et al (2000) Atopy and asthma: genetic variants of IL-4 and IL-13 signalling. Immunol Today 21:60–64

Shroff A, Guttman-Yassky E (2014) Successful use of ustekinumab therapy in refractory severe atopic dermatitis. JAAD Case Rep 1:25–26

Simon D, Hosli S, Kostylina G et al (2008a) Anti-CD20 (rituximab) treatment improves atopic eczema. J Allergy Clin Immunol 121:122–128

Simon D, Wittwer J, Kostylina G et al (2008b) Alefacept (lymphocyte function-associated molecule 3/IgG fusion protein) treatment for atopic eczema. J Allergy Clin Immunol 122:423–424

Simpson EL, Bieber T, Guttman-Yassky E et al (2016) Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 375:2335–2348

Sonkoly E, Muller A, Lauerma AI et al (2006) IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol 117:411–417

Strowd LC, Feldman SR (2017) Dupilumab for atopic dermatitis. Lancet 10(389):2265–2266

Tatsuno K, Fujiyama T, Yamaguchi H et al (2015) TSLP directly interacts with skin-homing Th2 cells highly expressing its receptor to enhance IL-4 production in atopic dermatitis. J Invest Dermatol 135:3017–3024

Terabe M, Park JM, Berzofsky JA (2004) Role of IL-13 in regulation of anti-tumor immunity and tumor growth. Cancer Immunol Immunother 53:79–85

Thaci D, Simpson EL, Beck LA et al (2016) Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 387:40–52

Toledo F, Silvestre JF, Munoz C (2012) Combined therapy with low-dose omalizumab and intravenous immunoglobulin for severe atopic dermatitis. Report of four cases. J Eur Acad Dermatol Venereol 26:1325–1327

Torley D, Futamura M, Williams HC et al (2013) What's new in atopic eczema? An analysis of systematic reviews published in 2010–11. Clin Exp Dermatol 38:449–456

Wang HH, Li YC, Huang YC (2016) Efficacy of omalizumab in patients with atopic dermatitis: a systematic review and meta-analysis. J Allergy Clin Immunol 138(1719–1722):e1

Weidinger S, Novak N (2016) Atopic dermatitis. Lancet 387:1109–1122

Wenzel S, Wilbraham D, Fuller R et al (2007) Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. Lancet 370:1422–1431

Wenzel S, Ford L, Pearlman D et al (2013) Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 368:2455–2466

Wlodek C, Hewitt H, Kennedy CT (2016) Use of ustekinumab for severe refractory atopic dermatitis in a young teenager. Clin Exp Dermatol 41:625–627

Wright RC (2003) Atopic dermatitis-like eruption precipitated by infliximab. J Am Acad Dermatol 49:160–161

Yayli S, Irla N, Yawalkar N (2013) Adalimumab in recalcitrant severe psoriasis associated with atopic dermatitis. Case Rep Dermatol 5:332–335

Zane LT, Chanda S, Jarnagin K et al (2016) Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. Immunotherapy 8:853–866

Ziegler SF, Roan F, Bell BD et al (2013) The biology of thymic stromal lymphopoietin (TSLP). Adv Pharmacol 66:129–155

Zink A, Gensbaur A, Zirbs M et al (2016) Targeting IgE in severe atopic dermatitis with a combination of immunoadsorption and omalizumab. Acta Derm Venereol 96:72–76