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Review

Systemic treatments in atopic dermatitis in children

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ABSTRACT

Atopic dermatitis (AD) is a very common skin disease caused by inflammatory reactions, in which the main symptoms of severe itching and recurrent eczema diminish quality of life. As epidermal barrier function and the immune system play a critical role in atopic dermatitis, promoting IgE-mediated sensitization can be the main targets of AD treatment. The goal of AD treatment should be to eliminate the symptoms and obtain long-term eczema control with a multi-step approach adapted to the severity of the disease. Basic management for all patients comprises the use of moisturisers and avoiding triggers. While topical therapy is effective for most children diagnosed with AD, there may also be children who require systemic therapy. The aim of this paper was to present an extensive review of the systemic agents commonly used in childhood atopic dermatitis which mainly target cutaneous inflammation.

Key words: atopic dermatitis (AD), children, systemic treatment.

Atopic dermatitis (AD) is a very common skin disease caused by inflammatory reactions, although the mechanism is still not fully understood.[1,2] Severe itching and recurring eczema are the main symptoms of the disease, causing a significant morbidity burden and diminishing the quality of life of patients and their families.

The target of AD treatment should be to eliminate symptoms and obtain long-term eczema control with a multi-step approach adapted to the severity of the disease. Basic management for all patients comprises the use of moisturisers and avoidance of triggers.[3] Oral antihistaminics are not recommended as there is little evidence for the effectiveness of these drugs, so they have no place in the treatment of AD.

Topical corticosteroids are the main drugs for moderate to severe AD. For more severe AD patients, the use of systemic anti-inflammatory drugs may be needed, but because these drugs can have serious side-effects, treatment is sometimes interrupted, which reduces the effectiveness. Therefore, there has recently been increasing interest in therapies with large protein structures to be injected with targeted biological agents, which will act on the pathways directly responsible for AD, without penetrating the lipid bilayer cell membrane.[4]

In cases where topical treatments and phototherapy are not sufficient, it may be necessary to switch to systemic immunosuppressive therapy.[2]

The objective of this paper was to present an extensive review of the systemic agents commonly used in childhood atopic dermatitis which mainly target cutaneous inflammation.

Pathogenesis of Atopic Dermatitis

Any condition that disrupts the epidermal function is predominant in the pathogenesis of AD.[4,5] A proinflammatory microenvironment can sometimes be seen in AD, even in skin without lesions. This proinflammatory microenvironment is created by an increase in Th-2, Th-22 and sometimes Th-17 cells.[6,7] Allergens, irritants and microbes are the most

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important cause of the disrupted skin barrier, leading to local inflammation and related immune responses.[8]

Atopic dermatitis develops due to a complex interplay of factors, which encompass genetic elements, an ineffective epidermal barrier, and type-2 dominant cutaneous inflammation. Individuals who have a genetic mutation in the filaggrin (FLG) gene have an increased susceptibility to AD. Filaggrin is a protein that is involved in the structure of the skin barrier. Non-adaptation of the barrier, which can also be due to mechanical causes, results in enhanced *S. aureus* settlement, susceptibility to cutaneous infections, recurrent stretching, and changes in the skin microbiome.[9,10]

Cutaneous inflammation in AD sends signals to B cells and promotes antigen-specific IgE production with the expression of IL-13 and IL-4 from activated Th2 cells, and thus Th cell-mediated pathways are formed (Fig. 1).

Cytokine-based endotypes in different age or ethnic groups have helped us comprehend atopic dermatitis. New biologics or small compounds can personalise atopic dermatitis treatment.[11] Four different subtypes were defined in the European-American group. These are acute, chronic, intrinsic, and extrinsic (classic). While the extrinsic form is the more common form with elevated IgE and eosinophilia in the atopic background, the intrinsic form does not increase IgE and does

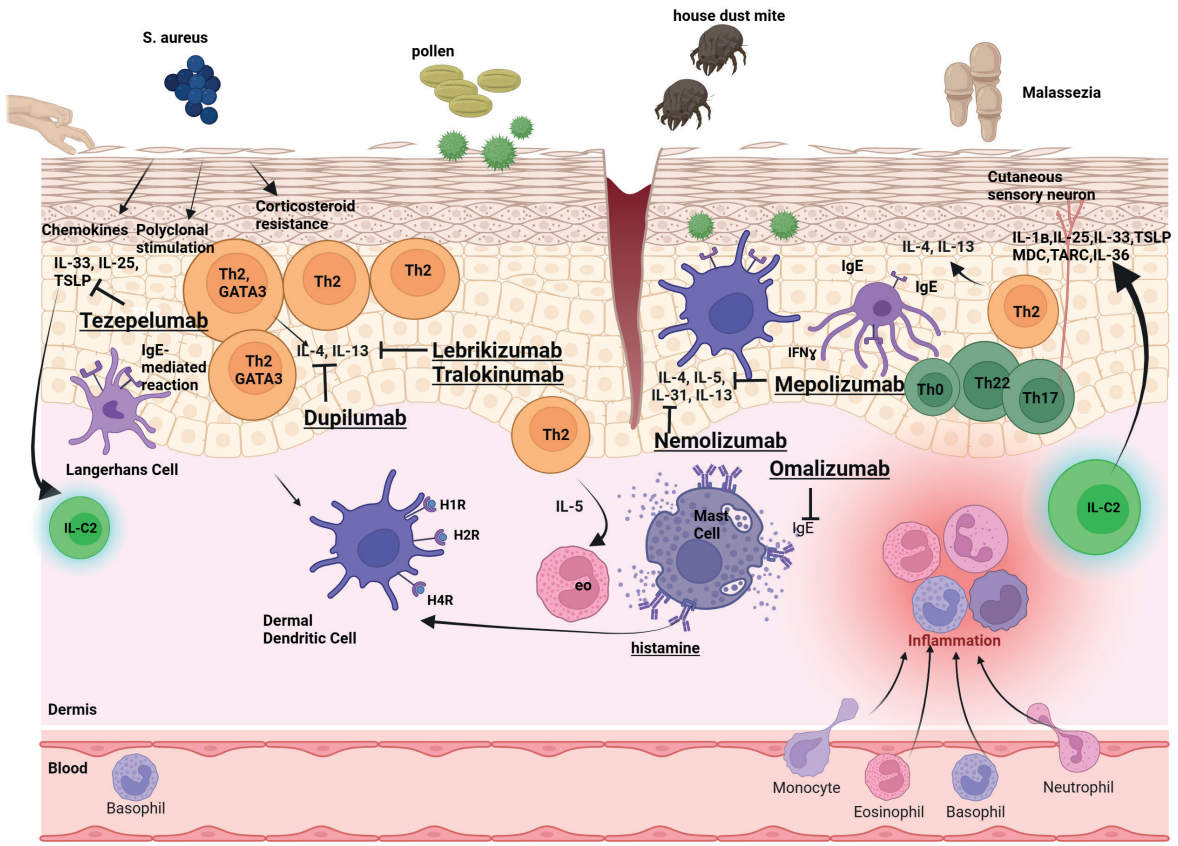

Fig. 1. Pathogenesis and treatment strategies for atopic dermatitis.

It is mediated by epidermal Langerhans cells, inflammatory dendritic epidermal cells and dermal dendritic cells in the lesioned skin of patients with atopic dermatitis.[2] These cells bind to IgE, they can also bind allergens that cause immediate-type allergic reactions and induce delayed-type T cell-mediated reactions. The deterioration of the epidermis and the deterioration of skin integrity are processes that support each other. Chemokines invoking T cells, cytokines that mediate innate immune responses, and Th2 cell and Langerhans cell activation have been demonstrated.[112,113]
(IL-33: Interleukin 33, IL-25: Interleukin 25, TSLP: Thymic Stromal Lymphopoietin, IL-C2: Type 2 Innate Lymphoid Cell, Th:T helper, Eo:Eosinophil).

not show atopic background, but cytokines and epidermal barrier damage are similar.[12] While Th1 is not seen in the pediatric group, Th2 and Th22 are increased in all ethnic groups, and Th17 is increased more in Asians and pediatric groups. Th2-Th22-Th17 are increased more in intrinsic and chronic subtypes.[12]

As a result, epidermal barrier function and the immune system play a critical role in AD and promote IgE-mediated sensitization, and can therefore be the main targets of AD treatment.[13]

Systemic Treatment

Although not safe in the long term and there is a tendency of reversal when discontinued, systemic corticosteroids have long been adopted as the only systemic drug used. Together with phototherapy, immunosuppressants are treatments that can be used as alternatives to steroids and prescribed off-label. However, the use of these drugs is not favored because they require frequent laboratory monitoring, have safety problems, and varying therapeutic benefits. Clarification of the unknown issues about the pathogenesis of AD will enable the development of goal-directed therapy, which may be more effective and safer than the treatments in current use.[14]

Janus Kinase inhibitors (JAKi), which regulate microbial dysbiosis, are new drugs used in the systemic treatment of AD.

Most biological agents for AD treatment are still in the testing phase. Oral JAKis have shown extraordinary efficacy and no serious signs of lack of safety.[15]

Systemic steroids

Corticosteroids are produced by the adrenal gland, which regulates the human stress response and immune system. While these drugs can be given in acute severe eczema flare-ups, they also act as a bridge with other treatments.[16]

The chronic intermittent use of corticosteroids is not recommended in AD, but can be used for transitional therapy in severe, rapidly progressing cases when initiating non-steroidal immunomodulatory agents or phototherapy.[16] Although patients and practitioners may notice immediate improvements in AD with systemic steroids, other systemic medications with fewer side-effects should also be considered.

The main side-effects associated with systemic steroids, which can be seen with prolonged use, include Cushing's syndrome, elevated blood sugar levels, osteoporosis, and gastric complaints.

Cyclosporine (CycA)

Cyclosporine (CycA) shows its effect by inhibiting calcineurin receptors and preventing IL-2 proliferation. This cytokine is vitally important for TH, NK cells, monocytes, and T regulatory lymphocytes. Therefore, inhibiting the activity and proliferation of T lymphocytes is possible by stopping the production of IL-2.[17]

Although it is not approved for use in children under 16 years of age, it is used in patients with refractory and severe AD.[18]

The advised dosage for CycA is 2.5 mg /kg, to a maximum dose of 5 mg/ kg.[17] CycA serum levels should be checked regularly and dose titration should be made according to the increase or decrease of symptoms. When clinical benefit is obtained, the treatment period can be extended up to 12 months.[19]

According to the results of a previous meta-analysis, after 8 weeks of treatment, almost 50% recovery was observed in the disease. The rapid onset of action of CycA allows for short-term use in several 12-week cycles or continuous use for up to 1-2 years.[20]

The most important side-effects include high blood pressure and nephrotoxicity. Therefore, close blood pressure monitoring is required throughout the treatment. In

the follow-up of nephrotoxicity, N-acetyl beta D-glucosaminidase measurements can be performed to determine renal tubular dysfunction, together with plasma creatinine level, and measurement of cystatin c, as in the TReat study.[21]

In a study by Jones et al.[22], in which 27 pediatric patients were treated with CycA for 6 weeks, the patients were followed up for disease activity and side-effects every 2 weeks via visual analog scales and quality of life questionnaires. Significant upgrading in disease activity was detected at all patient visits. Significant improvement or complete clearance was achieved in 22 of the 27 patients, with a significant increase in quality of life for both the patients and their family. The drug was well-tolerated in 25 patients.

In another study, 11 children with severe AD received 8 weeks of treatment with CsA. While 45% of the patients had only *S. aureus* skin colonization, 55% had suppurative *S. aureus* skin infection. All patients had a significant improvement in the clinical findings. The colonized patients showed greater reductions in disease severity and bacterial count with CycA. In conclusion, treatment with CsA in children with severe AD appeared to result in improvement in clinical symptoms.[23]

Choi et al.[24] retrospectively reviewed the use of CycA in dermatology centers. Changes in CycA dose schedules and disease severity were analyzed in 92 (64 eczema, 17 psoriasis) patients. The mean initial dose of CycA was started at 1.53 mg/kg/day and increased to a mean of 2.61 mg/kg/day in 6 months. A response to CycA was observed as early as 2 weeks, and disease control was achieved within 6 months. Although 32 patients used CycA for more than one year, only one patient had a creatinine increase of more than 30%.

In a placebo-controlled randomized study by Jin et al.[25], the SCORAD indices were seen to decrease significantly after the treatment in a population of children with moderate and severe AD unresponsive to topical treatments. Co-administration of glucosamine with CycA did not appear to increase serum CycA levels and there were no adverse events from CycA alone. It was shown that the combination therapy may be beneficial in the treatment of patients with severe AD in order to maintain CycA for a long time.

Permanent use of the drug was found to be more effective than intermittent use, and the dose of the drug should be individualized.

Azathioprine (Aza)

Azathioprine (Aza) is an immunosuppressant used for the treatment of AD, which shows its effect by suppressing proliferating cells. Aza, a purine analog, inhibits DNA-RNA synthesis and inhibits proliferation of B and T cells.[26]

In a study of children with severe AD, Aza was found to have an acceptable effect in the group with a normal thiopurine methyltransferase profile.[27]

Another study of children with a diagnosis of severe atopic dermatitis emphasized that thiopurine methlytransferase activity varied during treatment. Therefore, it was stated that it would be appropriate to make repeated measurements to adjust the dose of Aza.[28,29]

As there are insufficient studies and information about the long-term safety profile, there should be face-to-face discussions with the family if treatment is to be started. Aza has been associated with a number of hematological, hepatotoxic, and long-term cancer-related side-effects, especially non-melanoma skin cancer. As with any systemic therapy, a balance must be struck between the effects on longitudinal growth and neurodevelopment and the need to treat resistant eczema.[30]

The recommended daily dosage is 2-4 mg/kg and this should be checked by performing CBC at regular intervals due to the side-effect of cytopenia.[16]

Although it was stated by the Food and Drug Administration (FDA) in 2011 that there is an increased risk of hepatosplenic T-cell lymphoma, no patient has been diagnosed with this disease to date.[31]

Mycophenolate mofetil (MMF)

Mycophenolic acid (MMF) is a prodrug. MMF, which was used in the treatment of psoriasis in the 1970s and later found use in transplant patients, was also used by dermatologists in other skin diseases with inflammation due to its anti-inflammatory effect. MMF is lymphocyte specific and therefore has a low toxicity profile. Although these features make it a more preferable treatment option, the lack of randomized controlled studies currently limits its use due to potential unknown side-effects and high treatment costs.[32]

In a study which examined 140 patients with AD, there was seen to be a significant decrease in SCORAD scores with the use of MMF. The time of observed first effects was reported to be a mean of 6.8 weeks and relapses occurred in 8.2% of patients.[33]

In a retrospective study, it was determined that 42.8% of the patients switched from Aza treatment to MMF treatment due to intolerance and/or unresponsiveness to the drug. It was stated that 2/3 of the patients showed a significant improvement with the use of MMF and that significant side-effects occurred at a much lower rate.[34]

Methotrexate (MTX)

Methotrexate is an anti-inflammatory agent that acts by inhibiting cell division and lymphocyte proliferation. This effect is shown through the inhibition of the dihydrofolate reductase enzyme, resulting in the prevention of DNA/RNA synthesis and cell division.[35] Low-dose methotrexate is an alternative therapeutic method for severe AD unresponsive to topical treatments. The onset of the effect is slower than that of CycA and systemic corticosteroids. Treatment response typically begins after at least 1.5 months. Dosing in children with AD is 0.2-0.7 mg/kg once a week, and it can be administered orally or subcutaneously.

Purvis et al.[36] reported that it was well tolerated and effective in the results of a study in which 0.33 mg/kg MTX was administered to 43 children aged 2-16 years for 17 months, and improvements in AD were seen in 36 of the 43 patients. A decrease of 50% was determined in patients hospitalized for AD after MTX treatment was started, and the average follow-up period after MTX was two years. Of the children who benefited from MTX, 16% relapsed, and it was stated that MTX should be restarted.

There are few studies on MTX for pediatric AD patients. Only one small study compared MTX with CycA, and the data obtained in the comparison results were generally similar. Previous reports have shown that MTX is cost-effective and clinically effective in pediatric AD patients.[37]

Studies have shown that a low dose (5-15 mg/week orally) is effective for AD.[38]

The most important side-effects of methoteraxate are nausea, elevated liver enzyme levels, and bone marrow supression.[21] It has also been shown that pulmonary fibrosis, although extremely rare, can also be a complication.

Other Therapies

Phototherapy

Phototherapy is an alternative treatment for AD patients, which has been widely used as a proven second-line therapy. However, it has only been evaluated for short-term control and has only been tested in intensive programs of two or three sessions per week. Long-term control of the disease requires a new phototherapy regimen that balances the risks from ultraviolet (UV) exposure and patient acceptance.

In a study by Clayton et al.[39], 50 children (83%) received at least 10 narrow-band UVB treatments. In 40% of these children, complete or minimal recovery was obtained. It was stated that good improvement was obtained in 23% of the children, while a moderate improvement was obtained in 26%. The mean remission period of the treatment was found to be 3 months, which was accepted as an indication that the treatment was easily tolerated.

Narrow-band UVB centered at 311-313 nm is accepted as the first choice agent for some photosensitive dermatoses because it is safer and easier to apply than psoralen-UVA. Studies have shown that narrow-band UV phototherapy is much more effective and less erythematogenic than broadband phototherapy.

Phototherapy may be a suitable treatment alternative for AD patients who do not benefit adequately from topical treatments. Wavelength and treatment plan should be determined according to the patient and the severity of the disease.[16] Although home phototherapy application methods have been shown to reduce the treatment burden for other diseases, no clinical studies have been found on AD.

Extracorporeal photochemotherapy is not recommended for the routine treatment of AD because it varies considerably between patients.[16]

Allergen immunotherapy

Atopy is present in 70% of AD patients, and exposure to aeroallergens is one of the major causes of acute exacerbations.[40]

The preventative function of allergen immunotherapy to prevent atopic march, which is a serious problem in children with AD, has not been proven as yet.[41] There are studies indicating that allergen immunotherapy can be used in the treatment of patients with severe AD if they also have allergic rhinitis and/or asthma.[42,43]

There are many studies showing the efficacy and safety of AIT in AD. Although it is generally seen as a risk that may cause worsening of the disease when used in AD, it can be said to be an option that improves the course of AD when used in appropriate cases.[44]

Biological Agents and New Treatment Strategies

Dupilumab

The development of biological therapies targeting AD is very important. Dupilumab is the only biological agent that received FDA approval for the following indications in 2019: adolescents aged 12 years and above; children aged 6 years and above; and most recently, neonates aged 6 months and above (as of June 2022). It provides patients with a safe and long-lasting alternative.[45] Accelerated FDA approval was obtained after comparing dupilumab in combination with topical corticosteroid (TCS) and TCS alone in terms of efficacy and safety (Table I).[46,47]

Dupilumab is a monoclonal antibody that inhibits the production of IL-4 and IL-13 while maintaining immune system functionality.[48] Patients aged 12 years and over, diagnosed with moderate-to-severe asthma or patients with chronic sinusitis with nasal polyps are suitable patients for the use of dupilumab. There are extended reports of sustained benefits in adolescent patients continuing dupilumab therapy, resulting in greater enhancement in EASI scores at 1 year.[49]

In a study of combined dupilumab + TCS treatment for 16 weeks in patients with severe AD who did not benefit sufficiently from topical treatments, there was a significant and rapid enhancement in clinical findings. As most measures of efficacy show improvement at week 16, greater benefit is possible with a longer treatment duration. A significantly greater improvement in the treatment group compared to the placebo group was demonstrated at week 16 (73% and 18%, respectively).[50]

In a study by Bosma et al.[51], adults and children who started treatment with dupilumab were evaluated with the aim of comparing dupilumab with other immunosuppressant treatments. Although efficacy was similar to other systemic immunomodulatory drug treatments, dupilumab was found to be the most preferred treatment for severe disease requiring systemic agents. This was suggested to be due to a lack of availability or responsiveness to other immunomodulatory therapies rather than access to new systemic agents and disease severity.

In a study of dupilumab in an adolescent patient population, conducted by Simpson et al.[52], dupilumab monotherapy was found to result in statistically and clinically noteworthy improvements in disease signs and symptoms. Dupilumab has an adequate safety profile.

Omalizumab

Omalizumab is another monoclonal antibody produced by recombinant technology, which binds free IgE. It inhibits the binding of IgE to IgE receptors on cells such as mast cells and basophils.[53-55]

In addition to premedication in allergen-specific immunotherapy, it has been used in the treatment of many allergic diseases.

In a randomized controlled trial (RCT) by Iyengar et al.[56] of 8 patients with severe, treatment-resistant AD, 50% of the patients received omalizumab and the other 50% received a placebo. Previous eczema medications were standardized among the patients. Basal blood IgE levels were documented. All medications were discontinued one week before the start of the study. AD scoring was performed using the SCORAD index at monthly visits. A 20-50% decrease in SCORAD values was noted in the omalizumab group, compared to a 45-80% decrease in the placebo group. Both small RCTs failed to demonstrate the superiority of omalizumab over a placebo in AD.[57]

In the ADAPT study by Chan et al.[58], 62 children were recruited and evaluated. The difference between the groups in the improvement of the SCORAD index measured at week 24 was -6.9. Children's Dermatology Life Quality Index in the omalizumab group was improved. Although less potent topical corticosteroids were used in the group receiving omalizumab, a greater decrease in the severity of the disease was determined. Considering the positive side-effect profile, further studies on omalizumab are required to investigate its use in this difficult-to-treat patient group (Table I).

The benefit of the treatment became more pronounced towards the 24th week and it was observed that the effects continued after the treatment was stopped. More studies are needed on the optimal duration of treatment.[59]

Mepolizumab

Mepolizumab is a monoclonal IL-5 antibody, which reduces eosinophils in the blood. In a study of 40 patients diagnosed with AD, it was shown that mepolizumab was not effective. Although a decrease was detected in the amount of eosinophils in the blood, when the skin biopsy was examined, it was not found to have caused any change in the number of eosinophils in the tissue (Table I).[60]

Rituximab

It is known that CD20 is predominant in the pathogenesis of AD. Rituximab is a monoclonal anti-CD20 antibody developed against CD20. In a study using rituximab in patients with AD, 2 doses of 1000 mg of rituximab were given at 2-week intervals, and the EASI score, which was 29.4 at baseline was measured as 8.4 in the 8th week.[61]

Interferon- gamma (IFN- ɣ)

It is known that in AD, IgE levels increase while IFN gamma (IFN- ɣ) production decreases.[53,62] IFN- ɣ is one of the cytokines that has an important place in both the innate and acquired

immune systems. While the production of natural killer cells increases with the effect of IFN-ɣ, it also increases the oxidation of macrophages.

Studies have shown that IFN-ɣ is moderately effective in the treatment of AD, so IFN-ɣ should only be considered as an alternative drug in refractory patients who do not respond to other systemic treatments or phototherapy, or in patients with contraindications.[63] Fatigue, fever, nausea, vomiting, and myalgia are side-effects that can be seen after use. There is no specific recommendation for the pediatric age group.[16]

Biological Agents in Trials

Nemolizumab

Nemolizumab is another monoclonal antibody that blocks IL31 receptors.[64] IL31 is an important cytokine that mediates the formation of pruritus, which is known to occur during the itch-scar cycle in AD that causes disruption of the skin barrier.[65]

In a randomized controlled study, patients were separated into 3 groups, given 0.1 mg/kg, 0.5 mg/kg and 2 mg/kg nemolizumab treatment for 4 weeks, respectively. When the results were compared with the placebo in the 12th week, although the SCORAD-50 and SCORAD-75 results of the patients receiving 0.5 mg/kg were found to be better, no superiority was determined over the placebo when the EASI-50 and EASI-75 results were examined. There was no difference between the placebo group and other groups in terms of patients who dropped out of the study due to adverse events (Table I).[66]

Ongoing Phase 2/3 studies are examining the effects of nemolizumab on infants and adolescents (NCT03921411, NCT04921345, NCT03985943, NCT03989349, NCT03989206). Current research suggests that in conjunction with nemolizumab (rescue therapy), topical treatments including moisturisers, topical corticosteroids, and calcineurin inhibitors may have a synergistic effect in the treatment of AD and associated pruritus.[18]

Tezepelumab

Tezepelumab is an IgG2 monoclonal antibody that binds to TSLP.[67] When the lesions of acute or chronic AD patients were examined, it was observed that there was TSLP over-expression in keratinocytes.[68] At the same time, high levels of TSLP were detected in the blood of AD patients.[69]

TSLP is a key AD molecule, according to research. TSLP produced by epidermal keratinocytes in response to stimuli interacts with a subpopulation of sensory neurons, enhancing Th2 itch responses. For AD prevention or improvement, TSLP is a prospective therapeutic target.[70,71] Tezepelumab is a human monoclonal IgG2λ antibody. Tezepelumab circulates TSLP by binding to the receptor and disrupting TSLP's interaction with it, suppressing downstream inflammatory processes.[72] Tezepelumab is used in phase 1 (NCT00757042) and phase 2a (NCT02525094) randomised, double-blind, placebo-controlled AD investigations.[73]

A phase II study on this has been conducted on an adult population, but as yet there is no pediatric study in the literature (Table I).

Tralokinumab- lebrikizumab

These drugs are monoclonal antibodies which have been developed against IL-13. By binding to free IL-13 with high affinity, they are involved in the prevention of factors that cause damage to the epidermal barrier.[74] Consequently, IL-13 cannot bind with IL-4Ra, and thus IL-4Ra / IL-13 receptor alpha 1 heterodimerization cannot be established[75] Il-13 also inhibits the production of the filagrin protein.[76]

Tralokinumab works in much the same way, but by inhibiting IL-13 from binding to both IL-13 receptor alpha 1 and IL-13 receptor alpha 2.

The FDA approval of tralokinumab is "indicated for the treatment of adults with moderate-to-severe AD, when adequate control is not achieved with topical prescription treatments or the use of these treatments is not recommended".[77] The European Medicines Agency (EMA) approval of tralokinumab is "indicated for the treatment of adolescent and adult patients 12 years of age and older with moderate-to-severe AD who are candidates for systemic therapy".[78]

Lebrikizumab is a high affinity humanized IgG4 mAb that inhibits IL-13 signaling by blocking IL-13Rα. Adolescent and adult studies of lebrikizumab are under submission for FDA approval.

In a randomized controlled study, it was shown that lebrikizumab was effective on many clinical signs in adults with moderate-to-severe AD, and had a favourable safety profile. If these results are also obtained in phase 3 studies, then the drug can be approved for use in the treatment of AD. However, no study has been started in the pediatric age group (Table I).[79]

ISB-830

ISB-830 is another monoclonal antibody developed to inhibit OX40.[80] OX40 (CD 134) is a co-stimulatory molecule of the TNF family, predominantly expressed in T cells. The interaction of this molecule with OX40L increases cytokine production by bridging the Th2 and Th1 pathways. It has been shown that there is greater expression of OX40 in AD lesions and the number of OX40L +DCs is greatly increased in AD patients.[81]

An evidence-based clinical trial by Yassky et al.[80] was the first to target a co-stimulatory immunomodulatory molecule to treat AD patients. It was found that anti-OX40 antibodies administered 1 month apart provided significant improvements in clinical scores and cutaneous findings, lasting up to day 71 (Table I).

Anti IL-17 therapy

IL17 and its associated cytokines have some functions in the inflammatory process of AD. Expression of IL-17 in the skin is thought to cause the skin to form a defence mechanism against foreign substances.[82]

Small Molecules "Janus Kinase Inhibitors"

The small molecules of these drugs make them ideal for topical or oral use. Small molecule therapies are reported to be safer in terms of side-effects when compared to other systemic immunosuppressant agents. The most important reason for this is that these drugs suppress the immune pathways more selectively. Janus kinase inhibitors prevent the signal created by the activation of certain cytokine receptors, and have the advantage of oral use with flexible dosing regimens.[83,84]

The JAK family includes four molecules (Fig. 2) that are necessary for intracellular signaling via multiple cytokine receptors, including for type 2 interleukins.[83,85]

JAK inhibitors can be used orally as well as in topical forms. The fact that they do not increase immunosuppression and their pharmacokinetics are clear may make them superior to other drug groups.

Abroticinib

Abrocitinib inhibits JAK1 in a selective inhibitor. For the multicenter JADE-MONO study, patients older than 12 years with an EASI score greater than 16 and an IGA score greater than 3 were randomised into 100 mg, 200 mg, or placebo groups. Monotherapy with once-daily oral abrocitinib for patients with moderate to severe AD was demonstrated to be effective and well tolerated.[86]

In another RCT (JADE TEEN), two groups of adolescent patients were given 100 mg and 200 mg of abrocitinib, respectively, and the results were compared with a placebo. When

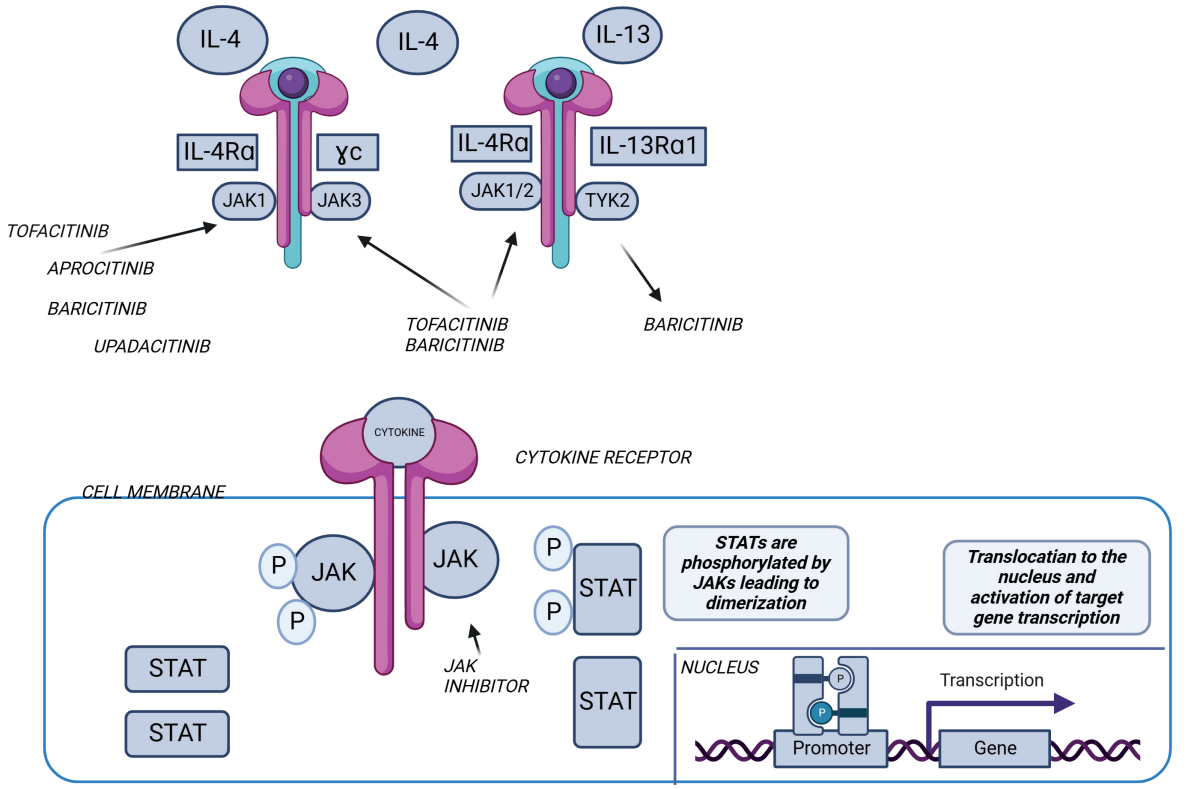

Fig. 2. JAK-STAT Signaling Pathway and JAK Inhibitors Treatment for Atopic Dermatitis.
IL: Interleukin, STAT: Signal transducer and activation of transcription, JAK: Janus kinase.

primary outcomes were evaluated, a greater improvement was found in the patients receiving abrocitinib therapy (Table II).[87]

In another study, which compared dupilumab with abroticinib, no significant difference was found between the outcomes of patients receiving abroticinib and dupilumab at week 16.[88]

Abrositinib FDA approval is "indicated in the treatment of children aged 12 years or older with moderate to severe atopic dermatitis and adults, when adequate control cannot be achieved with other systemic treatments (including biologics) or the use of other treatments is not recommended".[89]

Abrositinib EMA approval is for adult patients aged 18 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy.[89]

Nasopharyngitis, nausea and headache are the most common complaints in patients receiving abroticinib treatment. In addition, transient thrombocytopenias have been observed depending on the drug dose in patients using abroticinib, but these changes were not considered significant. Inhibition of JAK also affects the hematopoietic system and platelet homeostasis.[90]

Upadacitinib

The selective JAK1 inhibitor upadacitinib has been approved for the treatment of moderate-to-severe AD in patients 12 years and older.[91] The recommended dose is 15-30 mg once a day, depending on the severity of the disease.[92]

In a study comparing patients treated with 15 mg and 30 mg upadacitinib to a placebo group, both upadacitinib groups achieved primary goals for EASI and IGA scores at

week 16. According to the results at 52 weeks, upadacitinib was determined to be sufficiently effective and safe.[93]

In a similar study involving patients older than 12 years, 15 mg and 30 mg upadacitinib doses were administered to patients and compared with a patient group receiving topical corticosteroids. The most significant decrease in EASI and IGA scores at week 16 was observed in both upadacitinib groups (Table II).[94,95]

In another study of adult patients, when the adverse effects seen in patients treated with dupilumab and upadacitinib were evaluated, eczema herpeticum, herpes virus infections and other infections were more common in the upadacitinib group, and conjunctivitis and wound infections were more common in the dupilimab group.[96]

Upadacitinib, which has received approval from the Food and Drug Administration (FDA), is prescribed for the management of moderate-to-severe atopic dermatitis in children and adults aged 12 years or older and weighing a minimum of 40 kg. This treatment is indicated when other systemic treatments (including biologics) fail to achieve satisfactory control or when the use of alternative therapies is not advised.[89]

Systemic therapy is authorised by the European Medicines Agency (EMA) and is available to patients with moderate to severe atopic dermatitis who are 12 years of age or older.[97]

Baricitinib

JAK1 and JAK2 are selectively inhibited by baricitinib.[91] Baricitinib's pharmacokinetic efficacy in paediatric patients with moderate to severe AD is the subject of an ongoing Phase III study that has not yet reached a conclusion (Table II).[98]

According to the results obtained from previous studies conducted on adults, upper respiratory tract infections and herpes simplex infection were stated as the most common side-effects, and the most serious side-effects were evaluated as eczema herpeticum, cellulitis and pneumonia. When the results of studies on baricitinib were evaluated in general, cardiovascular events and thromboembolic events were stated as the two major side-effects.[15,99,100]

Conclusion

A better understanding of the pathogenesis of AD has provided a step-by-step approach supporting the use of targeted therapies with biological agents in treatment. However, there are still many issues that need to be clarified, such as the definition of treatment response, strategies to increase the response rate, the duration and regimen of treatment (in-clinic or at home), cost-effectiveness, and long-term safety.[101]

In order to demonstrate how safe the drugs described above are, long-term follow-up of the patients is required after the treatment. Therefore, there is a need for RCTs to be conducted in this way. It is not only very difficult to elucidate the pathogenesis of AD, but the treatment of the disease is also just as difficult and complex.

Author contribution

The authors confirm contribution to the paper as follows: DIG, OS made the literature search and wrote the whole paper, UMS supervised the whole process and prepared the structure of the review.

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Conflict of interest

The authors declare that there is no conflict of interest.

Table I. Biologics for moderate to severe atopic dermatitis.

Molecule	Target	Clinical Development Phase	Advantages	Disadvantages
Dupilumab (Regeneron/Sanofi)	IL-4Ra	Phase 4	Decrease pruritus, eruption[102] and TARC, periostin, IL-22[103] Does not affect pharmacokinetics of medications metabolized by CYP enzymes[104]	Injection site reaction Conjunctivitis[52]
Omalizumab (Xolair) Novartis Pharmaceuticals	Anti-IgE	Phase 4	Bind and neutralized free circulating IgE58 Decrease basophil and dendritic cell FcεRI expression[105]	Anaphylactic reactions[105]
Mepolizumab (GlaxoSmithKlein)	IL-5	Phase 2	No meaningful differences were observed.[106]	Diarrhea Impetigo[106] No study in the pediatric age group
Rituximab	Anti -CD20	Not applicable	Histological alteration (Hyperkeratosis, spongiosis, acanthosis Depletion B cell and T cell activation in blood[61]	Further clinical studies are needed[61]
Tezepelumab (Astra Zeneca Amgen)	TSLP	Phase 2b	No significant change in EASI50 from baseline[107]	No study in the pediatric age group
Lebrikizumab (Eli Lily and Company)	IL-13	Phase 3	Decrease pruritus Well tolerated in adults No efficacy and safety data results[108]	Conjuctivitis Upper respiratory tract infection Headache Nasopharyngitis İnjection site reaction[109] No efficacy and safety data results There are currently ongoing phase 3 trials in pediatric patients[108]
Tralokinumab (LEO Pharma)	IL-13	Phase 3	Decrease pruritus No efficacy and safety data results[108]	Upper respiratory tract infections Conjuctivitis Headache Nasopharyngitis[109] Currently undergoing phase 3 trials in pediatric patients[108]
Nemolizumab (Galderma)	IL-31	Phase 2	Decrease pruritus[110,111] No efficacy and safety data results[108]	Upper respiratory infection Nasopharyngitis Injection site reaction Triggered asthma symptoms (in patients with a history of asthma) No efficacy and safety data results Currently undergoing phase 3 trials in pediatric patients[108]
ISB-830 Ichnos Sciences SA Glenmark Pharmaceuticals SA	OX-40	Phase 2b	Well tolerated Changes in epidermal hyperplasia and gene expression Reduce keratin, ki67, epidermal thickness, mRNA expression[72]	Intravenous administration Nasopharyngitis[72] No study in the pediatric age group

CYP: cytochrome P450, TARC: thymus- and activation-regulated chemokine.

Table II. Janus Kinase Inhibitors for the treatment of moderate to severe atopic dermatitis.

Molecule	Target	Clinical Development Phase	Advantages	Disadvantages
Abrocitinib (Pfizer)	JAK 1	Phase 3	Selective inhibitor Orally once daily Decrease pruritus	Acne Nasopharyngitis Headache Upper respiratory tract infection Herpes Zoster Conjunctivitis[88] Currently ongoing phase 3 trials in pediatric patients
Upadacitinib (AbbVie)	JAK 1	Phase 3	Selective inhibitor Orally once daily Decrease pruritus[96]	Acne Conjunctivitis Transaminase elevation Egzema herpeticum and Herpes zoster One death reported (due to influenza associated pneumoniae)[96] Currently ongoing phase 3 trials in pediatric patients
Baricitinib (Eli Lily and Company)	JAK1/2	Phase 3	Orally once daily Rapid and sustained reduction in itch sensation[99]	Viral infections Herpes Simplex, eczema herpeticum, Headache Venous thrombosis[13] Currently ongoing phase 3 trials in pediatric patients

JAK: Janus kinase.

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