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Breakthrough in Pediatric Atopic Dermatitis Therapy: The Role of Monoclonal Antibodies as a New Hope for Targeted Treatment in Children

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Introduction and purpose:
Atopic dermatitis is a common skin condition, affecting about 15-20% of children. [1] It is characterized by chronic inflammation of skin, with the main symptoms being dryness and itchiness of the skin. It is a condition that not only has a negative effect on the general well-being of the child affected by it, but also usually takes a toll on the parents as well as society in general. [2] Since it is an important medical concern, there has been a lot of focus put on developing new therapeutic options. Over the last decade, new treatments have been approved by the EMA, with the biological therapeutics being the most promising. [1] In this review, different available forms of monoclonal antibody therapy are discussed. Furthermore, their mode of action and possible side effects are discussed. Finally, past and current clinical trials in the pediatric population are mentioned.
Material and methods:
A systematic review of scientific and medical literature was conducted using PubMed and Google Scholar databases. Researchers included only studies that mentioned monoclonal antibodies approved by EMA (European Medicines Agency) or that are being currently researched for use in pediatric population with AD.

Keywords: atopic dermatitis; children; monoclonal antibody therapy; SCORAD index; dupilumab; nemolizumab

Definition

Atopic dermatitis is a heterogenous skin condition, characterized by chronic inflammation of skin, with the main symptoms being dryness and itchiness of the skin.

In some cases, the atopic dermatitis is part of the so-called "atopic march", which consists also of asthma, rhino conjunctivitis, and eosinophilic esophagitis. [2] Moderate to severe AD is characterized by intense, persistent and debilitating itch (pruritus), which can have a profoundly negative impact on the patients' quality of life and sleep. [3]

Clinical assessment of severity of AD and effectiveness of its treatment:

Severity Scoring of Atopic Dermatitis (SCORAD) index was developed in 1993 for use in the pediatric population. It consists of the interpretation of the extent of the disorder, the intensity composed of six items and subjective symptoms. It is crucial for physicians to remember to use the most representative lesion for scoring purposes rather than the most severe or mildest lesion. The distribution of the score is calculated using the following formula $A/5 + 7B/2 + C$. The maximum achievable score is 103. The downside of using this score comes with the fact that the ending score can often be influenced either by the subjective grading of the skin lesions by the physician performing the physical examination or influenced by gradings of the subjective symptoms by the patient or their caregivers. Some physicians also argue that it is a time consuming procedure. [4, 5] The components included in the assessment of atopic dermatitis using the SCORAD scale are presented in Table 1.

Table 1. SCORAD index

Category	Explanation of the category	% of the total score
A - extent of the disorder	After physical examination, the physician has to map out the areas of the body that are affected by AD, according to the rule of the nines.	20
B - intensity of the disorder	Examining physician has to rate the intensity of 6 symptoms of AD in the representative area of patient's skin: ● erythema ● oedema / papulae ● oozing / crust formation ● neurotic excoriations ● lichenification ● dryness of unaffected skin Each symptom has a grading of o to 3, with 0 meaning absence of symptom and 3 meaning severe.	60
C - subjective symptoms	The patient or their caregiver are asked to use the Visual analog scale	20

	to determine the average intensity of pruritus and sleep loss for the last 3 days or nights, with a score from 0 to 10 for each symptom.	

The concerns about the SCORAD index also stem from the fact that AD is a chronic condition characterized by periods of flare ups or remission and it is impossible to adequately monitor patients' course of the disease by their physicians, using only data obtained from professional physical examination. With the rise of patient-oriented medicine and to address various concerns regarding the original SCORAD index, the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) was proposed. [6] It is based on the elements of the clinical picture assessed in the SCORAD and is similarly divided into three parts- extent, severity of AD and subjective symptoms declared by patients or their caregivers. The extent of the disease is assessed by the patient or their caregiver and is visualized by coloring or shading the affected body parts on the drawing attached to the questionnaire. The severity of the disease is assessed by answering questions regarding the dryness of unaffected skin and the questions about the eczema and skin lesions over the last 3 days. Finally, the subjective symptoms of itchiness and sleep disturbances are marked using a visual analog scale similar to the one found in the SCORAD index, with 0 meaning no itch/sleeplessness and 10 being the worst imaginable itchiness/sleeplessness. The PO-SCORAD has been proven to be particularly useful during the COVID-19 pandemic, since it allowed to monitor the course of patients' AD remotely. [7, 8] In two independent studies carried out in 2009 and 2011 PO-SCORAD has been proven to be feasible and useful scale, since there was a correlation between patient's and physician's score. [6, 7]

The Eczema Area and Severity Index (EASI) was first developed in 1998 and has since become the most used severity score in AD trials. The assessment is performed by the physician and includes area score, which depends on the percentage of body area affected by AD (0-6) and EASI calculator, which assesses the severity of AD in four body regions - head and neck, trunk, upper and lower extremities. In each body area, the physician performing the examination grades the severity of eczema symptoms - erythema, oedema / papulae, excoriations and lichenification on a scale from 0 - clear/absent to 3 - severe. The score obtained in this part of examination is then multiplied according to the patient's age, since the multipliers are different in the EASI calculator for adults and for children under the age of 8. The final EASI score is a sum of 4 regions' scores and can range between 0 to 72. [9] EASI has been validated as a consistent and objective scoring method with good intraobserver reliability, moderate interobserver reliability, and sufficient responsiveness. Utilizing EASI, at the very least, in upcoming trials concerning atopic eczema is advised to enhance evidence-based communication. A commonly used measure of treatment effect in atopic dermatitis (AD) clinical trials is based on EASI SCORE and includes a 75% reduction from baseline in the Eczema Area and Severity Index (EASI-75). [5]

Children's Dermatology Life Quality Index was developed in 1995 as a simple questionnaire designed to measure the quality of life (QOL) in children with skin diseases.

It is based on the Dermatology Life Quality Index used in the adult population. [10] The questionnaire has 10 questions concerning the impact skin disease has on a patient's life over the last week.
The topics included revolve around important parts of children's life, such as friendships, hobbies, playing, sports, school, holidays as well as the feeling of embarrassment, sleep loss, bullying by peers, need for special clothes, severity of pruritus and the impact of treatment. Each question has 4 possible answers, scored 0 to 3, with the maximum score being 30. The CDLQI has been validated for use in children aged 4 to 16 years and is available in a text version, which includes 10 questions and in a cartoon version for children that are unable to read. Both of those versions yielded similar results during various studies. [10, 11]

Pathophysiology

Although the pathophysiology of atopic dermatitis is being intensively researched, there are still a lot of unanswered questions. As of now, it is universally accepted that the pathophysiology of this disease is complex and includes genetic predispositions, altered immune response, cutaneous microbiome -particularly colonization by *Staphylococcus aureus* - and external factors, which contribute to the onset and persistence of symptoms. [2, 3] Innate and adaptive immune responses play a key role in AD pathophysiology and collectively contribute to clinical manifestations of AD. The pathological immune responses are triggered by keratinocytes that activate in response to mechanical or inflammatory injury. When stimulated by an injury to the epidermis, keratinocytes produce Antimicrobial Peptides (AMPs) such as cathelicidin (LL-37) and human β-defensins 2 and 3, as well as pro-inflammatory cytokines. All those molecules play a key role in the pathophysiology of barrier damage and the activation of the innate immune response. AMPs induce the keratinocytes to release molecules, which are called "alarmins". Alarmins, which include IL-33, IL-25 and thymic stromal lymphopoietin , have a pro-inflammatory effect. They activate innate lymphoid cells 2 and other dermal lymphoid cells, such as dendritic cells and Langerhans cells. Upon activation, these cells then produce IL-5 and IL-13, which, in turn, amplify the adaptive type 2 immune response. The inflammatory cycle repeats and becomes self-reinforcing, triggered by the influence of AMPs on the skin barrier and keratinocytes. [12]
Alongside the defects in the epidermal barrier and disruptions in skin microbiota homeostasis, an important role plays the immunologically abnormal activity of the Th2 cell system, characterized by excessive activity of cytokines such as IL-4 and IL-13, as well as cytokines secreted by Th17, Th22, Th1 lymphocytes, and cytokines originating directly from the damaged epidermis (IL-33, TSLP, IL-25). [13] Various drugs used in treatment address different parts of the pathophysiology of AD and biological therapy is usually reserved for patients with moderate to severe symptoms that do not respond well to first-line therapy. [14] The target of biological therapy is the Th2 inflammatory reaction, which is key to the pathophysiology of atopic dermatitis and is a universal cause of current inflammation present in AD, independent of patients' ethnicities or environmental factors. [13, 15]
Currently approved monoclonal antibodies in the treatment of AD and their targets in AD's pathophysiology are detailed in Table 2.

Table 2. Target points of monoclonal antibody therapy in the pathophysiology of AD

Monoclonal antibody	Role in the pathophysiology of AD	Target of the therapy	Approved by + age limit
Dupilumab	IL-4 and IL-13 - key drivers of type 2 inflammation	the interleukin-4 receptor alpha (IL-4Rα) subunit - inhibits signaling of Il-4 and IL-13	EMA: ➢ moderate to severe AD in patients aged 12 years and older ➢ severe AD in patients from 6 months up to 12 years old
Omalizumab	IgE - initiates mast cells degranulation and the release of inflammatory mediators	anti-IgE - prevents IgE from binding to its receptor on mast cells and basophils	
Nemolizumab	IL-31 - main pruritogen, enhances the secretion of other pruritogens, promotes the release of brain-derived natriuretic peptide to the dorsal root ganglions and skin cells	IL-31 receptor - blocks IL-31 from binding to its receptors in the peripheral sensory nerve fibers in the epidermis and dermis	
Tralokinumab	Il-13 - inhibits the production of the filaggrin protein, causing damage to the epidermal barrier	the α1 and α2 receptors of IL-13-selectively inhibits the activity of IL-13	EMA: moderate to severe AD - children aged 12 years old and older
Lebrikizumab	IL-13Rα1/IL-4R α heterodimer receptor signaling complex - induces Th2 inflammatory response	soluble IL-13 cytokine - prevents the formation of the IL-13Rα1/IL-4R α heterodimer receptor signaling complex	EMA: moderate to severe AD - children aged 12 years old and older and weighing at least 40 kg

Results:

Dupilumab:

Dupilumab has been the biologic drug that revolutionized the treatment of AD. [14] It is a fully human monoclonal antibody that targets the α receptor shared by interleukins 4 and 13, eventually blocking their signaling. [16, 17] Those two Th2 cytokines play a key role in AD pathogenesis. [18] As of now, dupilumab has been approved in the treatment of pediatric patients with moderate-to-severe AD aged as young as 6 months. The efficacy and safety of dupilumab in the treatment of AD in pediatric patients was supported by many different clinical trials, which showed a significant improvement of symptoms of AD, with acceptable safety and tolerance. The most notable clinical trial including dupilumab was LIBERTY AD PRE-SCHOOL, a multicenter, randomized, double-blinded, phase 3 clinical trial, which included patients aged 6 months to younger than 6 years. This study included 162 patients which were randomly assigned either to dupilumab or placebo, with both groups receiving low-potency topical corticosteroids at the same time. The conclusions of this study included consistent beneficial effects of dupilumab therapy, such as the significant improvements on the extent and severity of atopic dermatitis. Patients and caregivers reported improvement in the severity of skin pain, pruritus and also improvement in patients' sleep quality and quality of life of patients and caregivers alike. In the dupilumab group the weekly use of topical corticosteroids was lower and the use of emergency medications, such as strong oral corticosteroids was also lower than in the placebo group. Both of those outcomes suggest a steroid-sparing effect of dupilumab, which is relevant given safety concerns surrounding long-term usage of corticosteroids in young children. [19] The adverse effects of dupilumab therapy were no more severe than the ones in the placebo group, but the ocular side effects present in LIBERTY AD PRE-SCHOOL and other studies show the necessary precautions that should be taken when prescribing the patient with dupilumab. The ocular side effects include conjunctivitis, keratitis and blepharitis. [20] In the LIBERTY AD PRE-SCHOOL a higher incidence of narrow conjunctivitis occurred in the dupilumab group. In the LIBERTY AD PEDS study, which targeted children aged 6-11 years and was completed in September 2019, conjunctivitis was also one of the adverse side effects with higher incidence in dupilumab group, but the severity was mostly mild to moderate. [18] On the other hand, rates of non-herpetic skin infections were lower in the dupilumab treated group than in the placebo group in both studies. [21] The patients treated with dupilumab also had lower incidences of systemic infections, skin infections and herpes virus infections, as well as reduced incidence of exacerbation of other typ2 inflammatory diseases. [22] Those results suggest that while the development of ocular side effects is a viable concern, the general safety profile of dupilumab is broad and in turn does not require frequent laboratory controls. [23] Currently, the recommended dose of dupilumab is dependent on the patients' age and bodyweight. If the child is aged 12 to 17 years, the starting dose is 400 mg (two 200 mg injections) for body weight less than 60 kg and 600 mg (two 300 mg injections) for body weight 60 kg and more. The subsequent doses are 200 mg every 2 weeks and 300 mg every 2 weeks, accordingly. For children between the ages 6 and 11, the starting dose is 300 mg, with one 300 mg injection on day 1, followed by 300 mg injection on day 15, if the body weight is 15 kg to less than 60 kg. The subsequent doses start 4 weeks after the day 15 dose and include 300 mg every 4 weeks, but may be increased to 200 mg every 2 weeks, based on the physician's assessment of the patient.

Children aged 6 to 11 with a body weight of 60 kg or more start with the dose of 600 mg, which includes two 300 mg injections, and continue with 300 mg doses every 2 weeks. [24]

Omalizumab:
Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that prevents IgE from binding to its receptor on mast cells and basophils, inhibiting their activation. [16, 20] In turn, the depletion of serum IgE downregulates its receptors in mast cells and basophils, which stabilizes those cells and inhibits mast cells degranulation and inflammatory mediator release. [16, 18] Omalizumab is the first and only commercially-available anti-IgE antibody. The first clinical trials with omalizumab in the pediatric population with AD were conducted as early as 2004. The study conducted then showed that patients receiving omalizumab had significantly decreased levels of cytokines that were involved in Th2 polarization, but the improvement in clinical outcomes did not show efficiency of this treatment. [18] Moreover, two randomized controlled trials including children aged 4 years and above showed that omalizumab was not better than placebo for the SCORAD score and clinical improvement. [20] However, in the ADAPT study by Chan et al., 62 children aged 4-18 were recruited and split into omalizumab and placebo groups and then evaluated at the end of 24 weeks long study. [20, 25] The difference between the groups in improvement of the SCORAD index measured at week 24 was -6.9 and the children's dermatology life quality index in the omalizumab group was improved. A significant decrease in the severity of AD in patients receiving omalizumab was determined, despite the usage of mild topical corticosteroids. Considering the possibility of new therapeutic option with a relatively good safety profile for difficult-to-treat patients, further studies on omalizumab are required to determine its usefulness in the treatment of patients with moderate to severe AD. [25]

Nemolizumab:
Nemolizumab is a human monoclonal antibody that blocks IL-31 receptors. IL-31 is sometimes referred to as "itch cytokine", since it is an important cytokine that mediates the formation of pruritus, which occurs during itch-scratch cycle in AD that causes further disruption of the skin barrier. [18, 25, 26] Itch-scratch cycle in AD refers to a vicious cycle in which pruritus drives repeated scratching, which in turn further exacerbates pruritus either directly by mechanical sensitization or indirectly by releasing trauma-induced inflammatory mediators. [27] IL-31 binds to its receptors in the peripheral sensory nerve fibers in the epidermis and dermis and enhances the secretion of other pruritogens and also promotes the release of brain-derived natriuretic peptide to the dorsal root ganglions and skin cells, which further contributes to the itchy sensation. [26] In August of 2020 a multicenter phase II single-group study was completed, which included 20 patients aged 12 to 17 years, who were prescribed subcutaneous injections of 30 mg of nemolizumab for 16 weeks, with a loading dose of 60 mg on day 1. There was a significant improvement in rash, itchiness and sleep quality. By week 16, a 66.5% improvement of EASI score was reported. The pharmacokinetics profiles of the adolescent patients in this study were similar to that of adults. [18] A phase 3 clinical trial of 215 Japanese patients aged 13 and older was reported in 2020. [28, 29] In the 16 week trial 143 patients were assigned to receive 60 mg subcutaneous nemolizumab every 4 weeks. [28]

The study showed 43% reduction in pruritus per visual analog scale compared to 21% for patients on placebo at 16 weeks. The EASI score improvement from baseline was 46% in the nemolizumab group versus 33 % on placebo. The only adverse effects that were reported in this study were injection-site reactions and elevated creatine phosphokinase levels. [29] As of now, nemolizumab has been approved in Japan for use in patients 13 years and older, when prior treatment is insufficiently effective in alleviating itch associated in AD.[27] There is an ongoing clinical trial launched in 2021 to further assess the pharmacokinetics, safety and efficacy of nemolizumab in pediatric patients aged 2 to 11 years with moderate to severe AD. In 2019, a phase III prospective, multicenter, long-term study with approximately 1700 participants aged 12 years and older was launched. It is estimated to conclude in August 2026. [18] Nemolizumab shows great promise for pruritus treatment in AD, but more studies are needed. [20]

Tralokinumab:

Tralokinumab is a fully human IgG4 monoclonal antibody that selectively inhibits the activity of IL-13, by binding both the α1 and α2 receptors of IL-13. [24, 30] IL-13 cytokine is preferentially expressed in keratinocytes and the upregulation of this cytokine has been consistently documented in the lesional skin of AD patients. IL-13 is also a central cytokine involved in AD pathogenesis, causing disruption of the skin barrier, keratinocyte- mediated amplification of the inflammatory response and activation of the neuronal itch response. [29] A phase 2a trial showed promising results in adolescents aged 12 and above with the decrease in pruritus score within a week of the study. [16] A clinical trial ECZTRA 6 results were published in June of 2023. This randomized trial included 289 patients aged 12 to 17 years with moderate to severe AD and was conducted across 10 countries in North America, Europe, Asia and Australia. The patients were enrolled either in the placebo or tralokinumab group (receiving 150 or 300 mg) for 16 weeks. Patients who received tralokinumab and achieved clinical improvement measured by 75 % or higher improvement in EASI were switched to open-label tralokinumab, 300 mg, every 2 weeks. This treatment was well tolerated, without frequency of the most common adverse effect – conjunctivitis, increasing through week 52. [31] Other adverse effects, such as nausea and herpes simplex infections were low during the tralokinumab treatment and comparable tralokinumab and placebo groups. [32] The ongoing 5 year ECZTEND trial aims at evaluating the long-term safety and efficacy of tralokinumab treatment. Currently, after 2 years of this trial, the treatment was reported to be well tolerated and maintained long-term control of AD signs and symptoms. [33] TRAPEDS 1 is a study started in 2022, with estimated completion in 2026 and is aimed at targeting the pharmacokinetic and safety of tralokinumab in children under 12 years old. [18] Tralokinumab has been approved in the USA and Europe in 2023 to treat pediatric patients aged 12 to 17 years old with moderate to severe AD, with initial dose of 300 mg and subsequent dose of 150 mg every other week. [21, 27]

Lebrikizumab

Lebrikizumab is a novel high-affinity monoclonal antibody that binds to soluble IL-13 cytokine, at an epitope that overlaps strongly with the binding site of IL-4Rα, thus preventing the formation of the IL-13Rα1/IL-4R α heterodimer receptor signaling complex. [18, 34]

In turn, this prevents IL-13 from inducing Th2 inflammatory response. Results from the phase 2b clinical trial of lebrikizumab with the dose of 250 mg every 2 weeks suggest that blocking IL-13 systemically alone may be sufficient to improve itch significantly in patients with moderate to severe AD. [24, 35] Lebrikizumab has demonstrated efficacy and safety in patients with moderate-to-severe AD during the 16 weeks of Adhere trial. The trail was conducted from February 3, 2020 to September 16, 2021 and included sites across Germany, Poland, Canada and the USA and included adolescent patients aged 12 and older, as well as adults. Patients were administered a dose of 500 mg subcutaneous at baseline and week 2, followed by 250 mg every 2 weeks, as well as topical corticosteroids. The results showed improved outcomes in adolescent and adults treated with combination of Lebrikizumab and corticosteroids compared to treatment dependent only on topical corticosteroids. 75% improvement in the EASI index was seen in 69.5% of patients in the Lebrikizumab group. The most serious adverse events reported by patients in that group included conjunctivitis, headaches and herpes infections. [36] The results of clinical studies on Lebrikizumab are promising, but there is still not enough data to determine safety and efficacy in the pediatric population. [25] A randomized, double-blind 16 week study aimed at measuring the effect, safety and pharmacokinetics of lebrikizumab in the pediatric population from 6 months to 18 years old is already in progress. [37]

Dosing and age limits regarding monoclonal antibodies mentioned above are compiled in Table. 3.

Table 3. Age limits and dosing regimens of monoclonal antibodies approved by EMA

Substance	Age limit	Dosage
Dupilumab	6 months	patients aged 12 - 17 years: ➢ starting dose: ○ 400 mg (two 200 mg injections), if the body weight is < 60 kg ○ 600 mg (two 300 mg injections)for body weight > 60 kg and more. ➢ subsequent doses: ○ 200 mg every 2 weeks for body weight < 60 kg ○ 300 mg every 2 weeks for body weight > 60 kg patients aged 6 months to 12 years old: ● starting dose - 300 mg ● second dose - 300 mg injection on day 15, if the body weight is 15 kg - < 60 kg. ● subsequent doses- 300 mg every 4 weeks, start 4 weeks after the day 15 dose (may be increased to 200 mg every 2 weeks) ● body weight of 60 kg or more: ● start with the dose of 600 mg (two 300 mg injections) ● continue with 300 mg doses every 2 weeks
Tralokinumab	12 years old	● initial dose - 300 mg ● subsequent dose - 150 mg, every other week
Lebrikizumab	12 years old	● initial dose - 500 mg (two 250 mg injections) at both week 0 and week 2,

		• subsequent does - 250 mg (every other week up to week 16) • Once clinical response is achieved, the recommended maintenance dose of lebrikizumab is 250 mg every fourth week.

Discussion:

Monoclonal antibody therapy has emerged as a promising treatment option for pediatric patients with moderate to severe atopic dermatitis (AD). Clinical trials have demonstrated that these therapies can significantly alleviate symptoms such as pruritus and improve the overall quality of life for affected children. This is particularly important in pediatric populations, where severe AD can severely impact daily activities and psychosocial well-being. One of the challenges with monoclonal antibody therapy in younger children is the need for injections, which can be distressing for both the patients and their caregivers. However, the infrequency of these injections, which are often required only every few weeks, can in turn make the treatment of AD more manageable for patients and their families and facilitate better adherence to the therapeutic regimen. While monoclonal antibodies like dupilumab and nemolizumab have shown effectiveness and safety in adult AD patients, further studies are essential to evaluate their long-term safety and efficacy specifically in the pediatric population. The success of current monoclonal antibodies in treating AD also opens the door for the development of new therapies targeting different components of AD pathophysiology. As the underlying mechanisms of AD are researched and understood better, innovative monoclonal antibodies can be developed, potentially offering even more effective and tailored treatment options for children suffering from this debilitating condition. Thus, continuous research and clinical trials are important for advancing pediatric AD management and improving patient outcomes.

Conclusions:

Monoclonal antibody therapy offers a promising advancement in treating moderate to severe atopic dermatitis (AD) in children, providing significant symptom relief and improving quality of life. The less frequent dosing, despite potential injection discomfort, enhances manageability for patients and families.

While the efficacy is encouraging, ongoing research is crucial to establish long-term safety and effectiveness in the pediatric population. As clinical trials continue, monoclonal antibodies could become integral to AD management, offering hope to children who have not responded to traditional therapies and significantly improving their care and quality of life.

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