INTERNATIONAL JOURNAL
of PEDIATRIC DERMATOLOGY

Special Issue, 2025
ISSN 3035-1006 online

Review

New Therapies for Moderate-to-Severe Atopic Dermatitis in Pediatric Patients

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KEYWORDS

Atopic dermatitis,
Skin barrier alterations,
Dysregulated immune activity,
IL13 inhibitors,
JAK inhibitors,
Crisaborole,
Ruxolitinib,
Tapinarof,
Nemolizumab

ABSTRACT

In pediatric patients with severe atopic dermatitis, novel therapeutic options have recently become available - options that were not accessible until a few years ago. The authors outline the principal agents currently approved for systemic treatment, as well as those undergoing advanced clinical investigation.

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Introduction

Atopic dermatitis (AD), is a chronic inflammatory skin condition that affects 15%–20% of children and its pathophysiology involve genetical factors, alterations of skin barrier functions and dysregulated immune activity (1, 2). Severe clinical manifestation of AD are characterized by diffuse eczema lesions, intense itch and a negative impact on quality of life (QoL); the severity of the disease in calculated by the Eczema Area and Severity Index (EASI) and pruritus Numerical Rating Scale (NRS) (3) (Fig. 1-3). Most recent studies have demonstrated the role of Interleukin 13 (IL13) as a key cytokine in the pathogenesis of AD and in Th2 cell-mediated responses (2). This has led to the development of new systemic therapies that can effectively control disease symptoms over the long term. At this moment, in Italy are available tree IL 13 inhibitors and tree Janus Kinase JAK inhibitors for the treatment of moderate-to-severe AD.

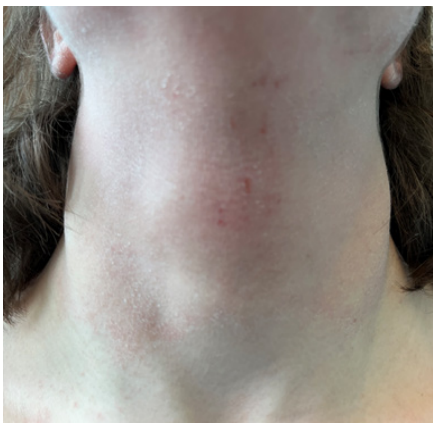

Fig. 1. *Clinical manifestations of AD.*

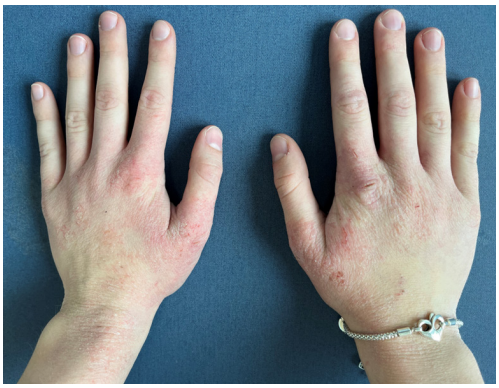

Fig. 2. *Clinical manifestations of AD.*

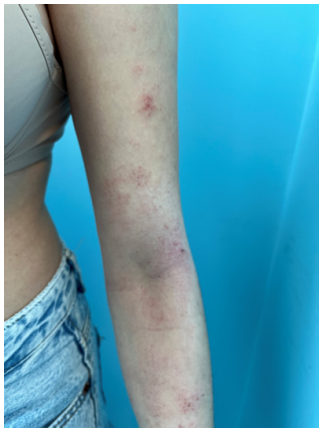

Fig. 3. *Clinical manifestations of AD.*

New systemic treatment for moderate-to-severe AD

In Italy, the treatment of moderate-to-severe AD with the following therapies is indicated in patients with EASI > 24 or Involvement of visible or sensitive areas, RNS > 7 and CDLQI > 10 (Table I).

Table I. *Therapies for moderate-to-severe AD in paediatric patients.*

CLASS	GENERIC NAME	TARGET	METHOD OF ADMINISTRATION
IL4/13 inhibitor	Dupilumab	IL4 and IL13	Subcutaneous
IL13 inhibitor	Tralokinumab	IL13	Subcutaneous
	Lebrikizumab	IL13	Subcutaneous
JAK inhibitor	Upadacitinib	JAK1, JAK1/3	Oral
	Baricitinib	JAK1, JAK2	Oral
	Abrocitinib	JAK1	Oral

IL13 inhibitors

IL-13 inhibitors are a class of biological drugs that target IL-13, which is involved in the persistent inflammation of the skin in patients with atopic AD. They are characterized by an high level of efficacy in EASI 75; the most common side effects are represented by injection site reactions and conjunctivitis. The administration of the treatment is by subcutaneous injection.

Dupilumab

It is a human monoclonal antibody that acts as an IL4 and IL13 receptor antagonist. It is approved for the treatment of moderate-to-severe AD in children aged from six months. The efficacy in paediatric population showed an EASI 75 response rates around 79.4% to 85.8% by week 16 to week 52 without severe adverse events (AE) (4). From a practical standpoint, solid foods should be introduced after 6 months of age, never at 4 months, based on the baby's chewing ability and neuromotor development. Introduce solid foods such as pureed vegetables and fruit around 6 months, ensuring the baby is ready. Offer cooked and uncooked eggs as the first solid food and introduce peanuts during weaning in an appropriate form even at high risk children, performing the skin prick tests only in patients with severe atopic dermatitis.

Tralokinumab

It is a human monoclonal antibody that works by blocking IL-13 and it is approved for moderate-to-severe AD in patients aged 12 and older combined to the application of topical corticosteroids. In clinical trials, 57.8% of adolescent patients achieving EASI-75 by week 52 without severe AE (5).

Lebrikizumab

It is a humanized monoclonal antibody that acts blocking IL-13 and it is approved for moderate-to-severe AD in patients aged 12 and older. Clinical trials demonstrated the efficacy of Lebrikizumab: the EASI mean percentage improvement from baseline to Week 52 was 86.0% (6).

JAK inhibitors

JAK inhibitors are a class of oral drugs medications that acts by blocking Janus kinase (JAK) enzymes, which disrupts the JAK-STAT signalling pathway that transmits signals related to inflammation. This class of drugs are used in several immune-mediated inflammatory diseases. JAKs are intracellular enzymes that activate cytokine-mediated signals through the JAK-STAT metabolic pathway, which is involved in a wide range of cellular processes, including inflammatory responses, haematopoiesis, and immune surveillance.

The JAK enzyme family includes: JAK1, JAK2, JAK3, and TYK2 (tyrosine kinase 2), which act in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs) at various levels and with different selectivity. JAK1 is primarily involved in inflammatory cytokine signalling, JAK2 is predominantly involved in signals for red blood cell maturation and JAK3 plays a role in immune surveillance and lymphocyte function. This class of drugs demonstrated high efficacy in the treatment of AD; most common side effects are represented by upper respiratory infections, headache, nausea, diarrhoea, acne, elevated cholesterol levels, and changes in blood cell counts. The administration of the treatment is orally.

Upadacitinib

It acts blocking JAK 1 and JAK 1/3 activity. It is approved for moderate-to-severe AD in patients aged 12 and older. The efficacy and safety were evaluated in randomized clinical trial involving 542 adolescents. At week 76, EASI-75 was achieved in 84.4% to 89.1% of patients (dose 15 mg/day) and in 82.7% to 96.1% (dose 30 mg/day) (7).

Baricitinib

It acts blocking JAK 1 and JAK 2 activity; it is approved for moderate-to-severe AD in patients aged 2 and older. The efficacy and safety were evaluated in randomized clinical trial involving 483 patients. At week 16, patients treated with a dose of 4 mg/day achieved EASI-75 and EASI 90 in 52.5% and 30% of cases respectively (8).

Abrocitinib

It acts blocking JAK 1 activity; It is approved for moderate-to-severe AD in patients aged 12 and older. The efficacy and safety were evaluated in randomized clinical trial involving 124 patients. EASI 75 was achieved by 68% and 72% of patients treated with a dose of 100 mg/day and 200 mg/day (9).

New drugs in the pipeline

Continuous progress in the study of pathogenesis of AD, in addition to currently approved drugs, has allowed for the development of new molecules that are still in the study phase and will likely be available soon. Here are some drugs in advanced stages of clinical trials.

Crisaborole

It acts as an inhibitor of Phosphodiesterase 4 (PDE4). Efficacy outcomes of the treated individuals who achieved ISGA success (clear (0)) on day 29. ISGA (Investigator Static Global Assessment). Several studies have also evaluated the topical use of crisaborole in terms of efficacy and safety in paediatric patients (10).

Ruxolitinib

It acts as JAK 1 and 2 inhibitors. In the TRuE-AD studies, patients 12 years of age and older with AD were randomized in a 2:2:1 ratio to apply 1.5% ruxolitinib cream twice daily, 0.75% ruxolitinib cream, or a vehicle continuously for 8 weeks, with benefits lasting up to 1 year of therapy (11).

Tapinarof

Tapinarof is a topical aryl hydrocarbon receptor (AhR) agonist. In two Phase 3 studies, tapinarof 1% cream, applied once daily, demonstrated significant efficacy and was well-tolerated in patients as young as 2 years old with AD (12).

Nemolizumab

Nemolizumab is a subcutaneously administered humanized monoclonal antibody that blocks the interleukin-31 alpha receptor (IL-31RA). Two phase III clinical trials demonstrated the safety and the efficacy of long-term treatment with nemolizumab for paediatric patients with AD, over 68 weeks of treatment (13).

Conclusions

The current therapeutic landscape for treating AD is constantly and rapidly evolving. Even for paediatric patients, there are now treatment options that were not available just a few years ago. Furthermore, the development of new therapies already in advanced stages of study will surely make it possible to effectively control the symptoms of this chronic condition.

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