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Guidelines

GUIDELINES FOR SYSTEMIC TREATMENT OF PATIENTS WITH ATOPIC DERMATITIS AT THE UNIVERSITY CLINIC FOR DERMATOLOGY IN SKOPJE

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Abstract

This Guideline was developed for the needs of the University Clinic (UC) for Dermatology in Skopje and is based on the European Guidelines for the Systemic Therapy of Atopic Dermatitis (AD) from 2020 and 2021 (EuroGuiDerm Guideline). Dermatologists from the UC for Dermatology with extensive experience in pediatric dermatology and treating patients with AD participated in the process. The Guideline was adopted by the Expert Board of the UC for Dermatovenerology in Skopje in February 2025.

This part of the Guideline contains general information about the goals and scope, the health issues covered in the Guideline, the target groups, and a methodology section. The Guideline provides guidelines for identifying patients who should be treated with systemic therapy and recommendations and information for each systemic drug. In addition, the Guideline provides recommendations and information on each systemic drug. The first section describes systemic treatment options, such as conventional immunosuppressive drugs (azathioprine, cyclosporine, glucocorticosteroids, methotrexate, and mycophenolate mofetil), biologic agents (dupilumab, lebrikizumab, nemolizumab, omalizumab, and tralokinumab) and Janus kinase inhibitors (abrocitinib, baricitinib, and upadacitinib).

Objectives of the guidelines

This Guideline aims to guide treating patients with varying severity of AD for all age groups. The specific objectives are:

- To develop treatment recommendations and algorithms that include topical therapy, phototherapy, and new and established systemic therapies for AD, updated according to the latest available evidence.
- To provide guidelines for the management of patients with AD during pregnancy and patients with other comorbidities.

Target group of users of the guidelines

The Guideline is primarily intended for dermatologists at the University Hospital for Dermatology in Skopje.

Methodology

These guidelines are based on EuroGuiDerm, Manual of Methods version 1.3., available on the EDF website: https://www.guidelines.edf.one/guidelines/atopic-ezcema[1]

Guideline development and consensus process

These guidelines and recommendations were developed by a working group of dermatologists with extensive experience in pediatric dermatology and treating patients with AD. Resident physicians were also involved in the technical preparation of the text.

Each chapter and all recommendations were reviewed, discussed, and amended where necessary. The Expert Collegium and then the Management Board of the the University Clinic for Dermatology in Skopje, reviewed and adopted the Guideline with the necessary consensus.

Evidence

The systematic review by Drucker et al.[2] was used as the evidence base for the decision-making framework. The certainty of the evidence compared to placebo[3] is added for each evidence-based recommendation.

Conventional systemic drugs

Azathioprine (AZA)

The efficacy of AZA is comparable to methotrexate (MTX) but inferior to dupilumab and cyclosporine in the remission of clinical signs of AD [2].

Dosage

- Not licensed for long-term use.
- Commonly used dose: Adults and children: 1–3 mg/kg body weight daily.
- If no improvement in AD is observed within 3 months, discontinuation of AZA should be considered.

Safety

Adverse effects include hepatotoxicity, myelotoxicity, and gastrointestinal disorders. Hypersensitivity reactions (e.g., fever, rigors, myalgia, arthralgia, and occasionally pancreatitis) may also occur [4]. It has a carcinogenic potential (e.g., squamous cell carcinoma of the skin and non-Hodgkin lymphoma), especially in combination with other immunosuppressants [5].

Monitoring

- TPMT activity if available.
- Screening for chronic infections (hepatitis B/C, HIV) before starting therapy.
- Follow-up: Bood count, hepatic and renal evaluation twice monthly for 2 months, then once monthly for 4 months, then every other month, and when the dose is increased.
- Pregnancy test before and during AZA therapy is indicated[6].

Combination with other treatments

May be combined with topical corticosteroids (TCS) and/or calcineurin inhibitors (TCIs). Due to the potentially increased risk of developing skin cancer, AZA should not be combined with UV light (UVA, UVB, and PUVA). Not licensed for the treatment of AD in children.

Table 1. General recommendations for systemic medications in adults with atopic dermatitis

	Conventional systemic treatments			**Biologics**		**JAK – inhibitors**		**Rescue therapy**
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑
Dose for adults [1]	licensed ≥ 16 years standard dosage adults: 2.5-5 mg/kg per day in two single doses	Off-label; commonly used dosage adults: initial dose: 5-15mg/ per week, maximum dose 25mg / per week	Off-label; commonly used dosage Adults: 1-3mg/kg per day	Licensed ≥6 years; adults: initially 600mg s.c. day 1, followed by 300mg Q2W	Licensed for adults; initially 600 mg s.c. Day 1, followed by 300mg Q2W. Consider Q4W dosing at week 16 in those achieving clear or almost clear skin	Licensed for adults: 4mg per day, reduction to 2 mg per day possible, depending on treatment response	Licensed ≥12 years; dosage for adults is 15-30mg per day based on individual patient presentation; for age ≥65, it is 15mg per day. The lowest effective dose for maintenance should be considered.	General license for adults and children: Dosage maximum: 1mg/kg per day
Time to response (weeks) [2]	1-2	8-12	8-12	4-6	4-8	1-2	1-2	1-2
Time to relapse (weeks) [2]	<2	>12	>12	>8	>8	<2	<2	<2

Monitoring	Complete blood count, renal and liver profile, blood pressure	Complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections	Complete blood count, renal and liver profile, TPNT activity if available, screen for chronic infections	Not required	Not required	Complete blood count, lipid profile, liver profile	Complete blood count, lipid profile, liver profile	Not required for short-term treatment, consider blood glucose testing for adrenal gland suppression with high doses/ longer-term treatment
Selection of most relevant adverse events	Serum creatinine ↑, blood pressure ↑	Nausea, fatigue, liver enzymes ↑, myelotoxicity	Gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity	Conjunctivitis, upper respiratory tract infections, arthralgia	Conjunctivitis, upper respiratory tract infections	Upper respiratory tract infections, increase in LDL cholesterol, thrombocytosis, nausea and abdominal pain, herpes virus infections	Upper respiratory tract infections, acne, headache, anemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain, herpes virus infections	Skin atrophy, weight gain, sleep disturbance, mood change, hyperglycemia or new-onset diabetes, peptic ulcers/gastritis, osteoporosis

[1] SmPC, [2] expert experience, ↑ rise, LDL- low-density lipoprotein, PIIINP- procollagen III N- Terminal propeptide, TPMT- Thiopurine-S- Methyltransferase

Cyclosporine

Cyclosporine is approved for the treatment of AD in adolescents ≥16 years of age and adults and is considered a first-line treatment for patients with severe disease [2].

Dosage

In the short-term treatment of AD, higher doses of cyclosporine (5 mg/kg/day) lead to a more rapid response and are more effective than lower doses (2.5-3 mg/kg/day) [7].

Safety

Cyclosporine has a narrow therapeutic index and requires close monitoring of blood pressure, renal function, liver profile, and complete blood count (e.g., initially at 4 weeks and then 3 months)[8]. Screening for hepatitis B/C and HIV should be considered before initiating therapy.

Combination with other treatments

Topical TCS and TCIs may be used. Cyclosporine should not be combined with UV light (UVA, UVB, and PUVA).

Systemic glucocorticosteroids

In studies conducted in children and adults, systemic glucocorticosteroids do not induce long-term remission, and a rebound effect is often observed after therapy[9].

Dosage

- Exacerbation: The initial dose is usually 0.5 mg/kg body weight per day. Treatment should be discontinued or systematically reduced as soon as possible.
- Combination with emollients and/or local antiinflammatory therapy in patients with AD.

Safety

Systemic glucocorticosteroids have a wide therapeutic index of efficacy. Toxicity is related to the mean dose, cumulative dose, and duration of use. For adverse effects, see (Table 1). When used for no longer than 3 weeks, therapy with even fairly high doses can be simply discontinued without reduction[10].

Methotrexate (MTX)

MTX has been used for years in the treatment of moderate to severe forms of AD. Studies suggest that MTX can be considered a moderately effective, relatively safe, and well-tolerated treatment for severe AD in both children and adults[11,12]. If oral once weekly is ineffective or poorly tolerated, subcutaneous administration is an alternative.

Dosage

- most commonly used dose:
  - adults: 10-15mg (moderate dose) to 25mg per week (maximum dose)
  - children: 0.4mg/kg/week, usually given in two divided doses
- Concomitant use of folic acid should also be considered to reduce gastrointestinal and other side effects.

Safety

Adverse effects include nausea, fatigue, and elevation of liver enzymes, while pancytopenia and idiopathic pulmonary fibrosis are of key importance but are rare.

Monitoring

Complete blood count and renal and hepatic profile before and every 4 weeks for the first 3 months of starting therapy or after a dose increase, then every 8-12 weeks.

Screening for chronic infections (hepatitis B-/C, HIV, tuberculosis) before therapy. Due to liver or bone marrow function deviations, the dose should be reduced, or the drug should be temporarily or completely discontinued.

Combination with other treatments

May be combined with TCS and TCIs, or UV phototherapy. Concomitant use of cyclosporine is a relative contraindication.

Mycophenolate mofetil (MMF)

A recent systematic review and meta-analysis including 18 studies with a total of 140 evaluated adult and pediatric patients with AD for the efficacy of MMF outside of the approved use[13].

Dosage

- most commonly used dose:
  - adults: 1–3 g per day
  - children: 30–50 mg/kg body weight per day, usually given in two divided doses

Safety

The most common side effects include headaches and gastrointestinal symptoms, followed by infections, especially during long-term therapy. Hematological side effects are rare and include anemia, leukopenia, neutropenia, and thrombocytopenia.

Monitoring

- Complete blood count, renal and hepatic profile, screening for chronic infections (hepatitis B/C, HIV) before starting therapy, then every 2 weeks for 1 month; monthly for 3 months; then every 2–3 months.
- Pregnancy testing before and during MMF therapy.

Combination with other treatments

May be combined with TCS and/or TCIs.

Biological therapy

Dupilumab

Dupilumab is used for the treatment of AD in adults over 2 years of age, and in some countries, it is approved for adolescents and children >6 years of age. It significantly affects the intensity of pruritus[14].

Dosage

- Adults: 600 mg subcutaneous loading dose, followed by maintenance doses of 300 mg every other week.

- Children: licensed for ≥6 years; ages 6–11: from 15 kg <60kg, initially 300mg s.c. days 1 and 15, followed by 300mg every fourth week; ages 12–17: <60kg: initially 400mg s.c. on day 1, once every two weeks; when the patient is ≥60kg: therapeutic adult dose.

Safety

No routine laboratory tests are recommended, but a significant number of patients develop conjunctivitis (over 30%), most of which are mild to moderate[15]. Topical treatment with eye drops is often sufficient[16].

Combination with other treatments

Combination therapy with TCS, TCIs, and UV light is well established.

Omalizumab

Most patients with AD have elevated serum IgE levels, but the pathogenic role of IgE in AD remains unknown.

Omalizumab's safety profile is very good[17], but its unpredictable and statistically low efficacy prevent a general recommendation for its use in the treatment of AD.

Dosage

- Adults: Doses range from 150-450mg every 2 or 4 weeks.
- Children: The dose of the drug was determined based on the baseline total IgE level (range: 30 to 1500 IU/mL), measured before the start of therapy, and body weight (kg) and was calculated using the formula: 0.016 × body weight (kg) × total IgE level (kU/L) in 2–4 weekly injections.

Safety

The possibility of intestinal parasitic infections in patients treated with omalizumab is of concern. The incidence of anaphylaxis was 0.14%.

Monitoring

No follow-up studies have been reported. IgE levels increase after omalizumab administration and may remain elevated for up to 1 year after drug discontinuation.

JAK inhibitors

The JAK family, which includes JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)[18].

Baricitinib

Baricitinib is an oral, selective inhibitor of JAK1 and JAK2. The drug has been tested in one phase 2 and several phase 3 trials in adults with moderate to severe AD, showing significant improvement in EASI from baseline to week 16, particularly at the two higher doses[19,20].

Dosage

- Adults: 1, 2, and 4 mg daily

Safety

The most common adverse reactions are increased LDL cholesterol, upper respiratory tract infections, and headaches. Acne is less common than with other JAK inhibitors. Infections

such as herpes simplex, eczema herpeticum, cellulitis, and pneumonia may also occur. Transient elevations of CPK may occur, especially after exercise.

Monitoring

Recommended laboratory monitoring includes a complete blood count and renal, hepatic, and lipid profiles. Before starting treatment, chest X-ray, creatinine kinase level, and screening for infections (HIV, hepatitis B/C, TB) are recommended. Screening for hematological abnormalities is also recommended.

Laboratory tests 4 weeks after the start of treatment and every 3 months thereafter are recommended.

Upadacitinib

Upadacitinib is licensed for AD in adolescents (12 years and older) and adults[21].

Dosage

- Adults: 15 mg and 30 mg.

Safety

The main adverse events are upper respiratory tract infections and acne.

Monitoring

Recommended laboratory monitoring includes a complete blood count, renal and liver function, and lipid profile. Before starting treatment, chest X-ray, creatinine kinase level, and screening for HIV, hepatitis B and C, and TB infections are recommended. Screening for hematological abnormalities is also recommended no later than 12 weeks.

Laboratory tests at 4 weeks after the start of treatment and every 3 months thereafter are recommended.

Other systemic therapies

Alitretinoin

Licensed in some European countries for the treatment of chronic palmar eczema, regardless of its pathogenesis[22].

Dosage

- Adults: 10–30 mg daily for 3 to 6 months (suitable for long-term therapy).

Safety

All women of childbearing age must adhere to a birth control program.

Monitoring

Before and during therapy: liver enzymes, lipid status, basal thyroid stimulating hormone (TSH), free thyroxine (fT4), blood count, and pregnancy test in women of reproductive potential.

Combination with other treatments

Topical therapy with CSs, CNIs, and emollients is possible.

Conflict of interest statement. None declared.

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