Review paper

Methotrexate in the treatment of atopic dermatitis

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Adv Dermatol Allergol 2025; XLII (3): 243–247
DOI: https://doi.org/10.5114/ada.2025.149551

Abstract

Atopic dermatitis (AD) is a common inflammatory skin disease. Most cases start in children although some have been reported in adults. Moderate to severe cases of AD not responding to topical treatments may need systemic therapy. Methotrexate may be considered in patients with severe AD who did not achieve the expected improvement after cyclosporine, or who had adverse effects and no possibility of biological treatment with monoclonal antibodies or Janus kinase inhibitors.

Key words: atopic dermatitis, systemic therapy, methotrexate.

Atopic dermatitis (AD) is a common, chronic recurrent inflammatory dermatosis. It affects about 11–20% of children and 5–8% of adults. Approximately 30% of children and half of adults have moderate to severe disease [1–3]. The therapy of atopic dermatitis aims to control the inflammation of the skin, reduce the symptoms of the disease, reduce pruritus, improve the quality of life of the patient, and prevent recurrences [4]. The basic treatment of AD is intensive skin care with emollients and the use of topical anti-inflammatory preparations, i.e. topical glucocorticosteroids (TCS) and calcineurin inhibitors (TCI) [4, 5]. When the local treatment is ineffective, especially in severe forms of AD, there are indications to implement systemic therapy [6]. According to current recommendations, before using systemic drugs, the reasons for failure of previously applied treatment should be analysed in each case. This action includes consideration of the change of emollients, optimization of previously applied treatment (wet dressings, phototherapy, baths in sodium hypochlorite), avoidance of factors provoking and exacerbating the disease, exclusion of coexisting inflammatory diseases, including skin infections, and sometimes even verification of the diagnosis [6, 7].

Cyclosporine (CsA) is recommended as the first-line therapy for systemic AD, and in the absence of efficacy or in the case of contraindications or side effects, other drugs such as dupilumab, methotrexate (MTX), systemic glucocorticosteroids (SCS), azathioprine (AZA), or mycophenolate mofetil (MMF) may be included [8, 9].

MTX is a derivative of folic acid. It is a cytotoxic compound from the antimetabolite group. The mechanism of action of the drug is based on the inhibition of dihydrofolate reductase, responsible for the reduction of dihydrofolate to the active form of folic acid, tetrahydrofolate, which is an important compound in DNA synthesis. It also inhibits the synthesis of RNA, purines, and T-lymphocytes [10]. MTX was registered in 1958 for the treatment of oncological diseases, but it is not uncommon for it to be included in the treatment of many inflammatory conditions with a severe course. In dermatology, it is registered for the treatment of severe forms of psoriasis and psoriatic arthritis. The drug's efficacy has also been confirmed in lymphomas, bullous diseases, and other autoimmune disorders [11–13].

There are reports in the literature about the safety and efficacy of MTX in the treatment of AD; this is also confirmed in everyday clinical practice [6]. MTX may be used in patients with severe AD when other drugs are ineffective or poorly tolerated [14]. Similarly to AZA, MTX is a second-line treatment in patients with AD, but it is not registered in this indication, therefore it can be used for off-label indications [15].

The expert group of the European Academy of Dermatology and Venereology (EADV) in its guidelines for the treatment of AD recommends MTX in adult patients with severe AD when CsA treatment is ineffective or contraindicated [16]. Similar information is found in the recommendations of Werfel *et al.* of 2016 [17]. In a recent meta-analysis summarizing the available studies on sys-

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Received: 18.09.2024, **accepted:** 28.01.2025, **online publication:** 15.04.2025.

temic therapy of AD, the authors presented, among others, the results of the efficacy and safety of MTX therapy. This drug proved to be as effective as CsA and AZA in short-term therapy, while the effect of clinical improvement lasted longer after MTX compared to CsA [18, 19]. In an open-label study in a group of 12 adults with moderate to severe AD, treated with MTX at a starting dose of 10 mg/week, a very good effect of the therapy was obtained, assessed both by a decrease in the skin lesion severity index, as well as a significant improvement in the quality of life, measured by the severity of pruritus and sleep disturbances [20]. In a study comparing MTX and AZA in the treatment of AD, both drugs gave comparable improvement of the skin condition assessed by a decrease of the SCORAD index. Both preparations were well tolerated; there were also no significant differences in the observed adverse effects [21–23]. On the other hand, in a multicentre randomized study comparing the efficacy of MTX (at a baseline dose of 15 mg/week) and CsA (at a baseline dose of 2.5 mg/kg/day) in a group of 97 adult patients with moderate to severe AD, MTX showed lower efficacy assessed at week 8 of the therapy, while at week 20 the efficacy of both drugs was comparable, but MTX appeared to have a better safety profile [24]. In a study comparing the long-term therapy with both drugs (25 patients treated with CsA and 32 patients treated with MTX), it was shown that the reason for discontinuation of CsA treatment was most often the adverse effects of the drug, while in the case of MTX – obtaining good disease control. In addition, the time of maintaining remission after the end of treatment was significantly longer with MTX therapy [19, 25–27].

A meta-analysis published in 2020 in JAMA Dermatology, presented data on the efficacy of systemic medications in AD based on results from 39 reports evaluating a total of 6360 patients' symptoms. Most of the studies were conducted in adults and follow-up was less than 16 weeks [28]. Dupilumab and CsA had higher efficacy than MTX and AZA. However, the authors emphasize that the short time of patient follow-up does not allow a complete and objective assessment, because it favours drugs with a rapid onset of action, and as shown in earlier studies, methotrexate is more effective in long-term therapy [25].

The literature provides few data on the efficacy and safety of MTX in children, and the results are inconclusive. The authors of the previously cited guidelines emphasize the lack of sufficient data in this age group. On the other hand, a study conducted in Egypt showed that MTX used in low doses in children is effective and well tolerated [29]. The authors of this study compared the effect of MTX and CsA treatment in a group of 40 children with severe AD, obtaining, after 12 weeks of therapy, a reduction in the SCORAD index in both treatment groups (–49% for MTX and –45% for CsA).

According to the literature analysis, MTX is much more frequently used in the paediatric population in North American countries than in Europe. Both European guidelines and the American Academy of Dermatology (AAD) recommendations lack clear guidelines on the use of MTX in children with AD [30, 31] however, in recent years there have been more and more reports on its possible use in this age group. Anderson *et al.* used MTX in a group of 55 young patients (3–19 years old) with severe AD, in whom previous treatment methods were ineffective, achieving improvement in 42 (76.4%) patients [32]. No serious adverse events were reported during the follow-up of patients. Analysing the available treatment methods in children with severe AD, the authors emphasize that CsA often gives a quick beneficial effect of the therapy, however, the improvement achieved is short-lived in many cases. AZA, on the other hand, is characterized by a late but long-lasting therapeutic effect, however, due to its unfavourable safety profile, it should not be recommended for long-term therapy in the youngest patients. Dupilumab, which shows high efficacy in the majority of patients, due to its limited availability and high cost, remains for the time being a treatment option in those patients in whom other methods fail [33]. Tralokinumab, baricitinib and upadacitinib registered for the treatment of moderate and severe AD in Poland are still not included in the drug programme [9].

Based on previous reports and own observations, the authors recommend MTX as an effective, safe, and inexpensive therapeutic method in the paediatric population with a severe form of AD [31]. On the other hand, in the material collected from several hundred American and Canadian clinicians, it has been shown that among systemic drugs used in children with severe AD, MTX was the second most commonly used preparation after CsA; 29.6% of patients in this group were treated with it [34]. Based on non-European experience, in the Italian consensus published in 2016, MTX is mentioned as an alternative to CsA in the treatment of severe and recurrent forms of AD in children. However, the authors emphasize the need for further studies in this age group to develop an optimal safe dose and duration of therapy [35]. According to the data in the product characteristics, MTX is not recommended for use in children younger than 3 years because of insufficient data on efficacy and safety in this age group [10]. However, in a study from Ireland, MTX was used in children from 2 years of age with severe atopic dermatitis. A retrospective study evaluated the efficacy and safety of MTX in 47 children aged 2 to 18 years treated between 2010 and 2015 at three clinical centres. Due to the late onset of the therapeutic effect obtained after MTX treatment, only patients who had been using the drug for at least 3 months were evaluated. The drug was applied at a dose of 0.2 to 0.5 mg/kg body weight in a single weekly dose. The results of the study allowed the authors to evaluate MTX as an effective and safe thera-

peutic option in children with severe atopic dermatitis. In including MTX in patients in such a young age group, the researchers relied on both previous reports of its use in patients with AD as well as the beneficial effects and mild side effects of this drug used in young children with oncological and inflammatory diseases, including psoriasis, linear scleroderma, inflammatory bowel disease, or juvenile idiopathic arthritis [36].

The dosage and duration of therapy depend on the severity of the disease and the patient's tolerance of MTX. Most commonlythe drug is used at a dose of 7.5–25 mg per week in adults and 0.2–0.7 mg/kg body weight per week in children (Table 1) [37]. The weekly dose of MTX can be given as a single, fasting dose immediately before a meal. In case of gastrointestinal adverse events, it is possible to change the dosing schedule from once a week to a dose divided over 2 days. Maximum therapeutic efficacy is usually achieved after 8–12 weeks [10, 15, 37]. Apart from the oral route of MTX administration, a subcutaneous form of MTX in the form of ready-to-use autoinjectors has been available for several years. When there is insufficient improvement with oral MTX after 8–12 weeks, the subcutaneous route of administration could be tried before discontinuing MTX treatment [37]. MTX in semi-automatic pens has also appeared on the Polish market [38]. According to the available studies, the administration of MTX by the subcutaneous route improves the bioavailability of the drug to a clinically relevant extent, which has an impact on increasing its efficacy and improving tolerance [39–43]. If patients are afraid to inject MTX, it is worth considering the possibility of administering the drug using pens. Such injection is less painful and accompanied by even fewer side effects. This route of administration is preferred by parents of young patients starting MTX treatment [44].

Contraindications for the use of MTX include hypersensitivity to the drug or any of its excipients, severe hepatic and renal impairment, hematopoietic disorders, immune deficiencies, severe acute and chronic infections, oral ulcers, and active gastric or duodenal ulcers. The drug must also not be used during pregnancy and breastfeeding.

MTX therapy is usually well tolerated, and many reports indicate that this therapy is safe; however, because of the possibility of serious side effects, this therapy must be closely monitored [15]. Gastrointestinal symptoms are among the most commonly observed side effects that may occur during MTX therapy [45]. In light of the available knowledge, it is now known that the gastrointestinal tolerability of MTX can be improved by administering the drug subcutaneously. With subcutaneous administration, MTX is absorbed practically in 100% and the number of gastrointestinal side effects is lower, and the drug is much better tolerated [40]. In one study, Rutkowska *et al.* compared the incidence of nausea, vomiting, loss of appetite, abdominal pain and diarrhoea in patients treated

Table 1. International consensus on MTX dosing for patients with atopic dermatitis [37]

No test dose is needed when starting MTX.
MTX should be administered in a single, weekly dose.
MTX should be tried for at least 8–12 weeks before the effect can be assessed.
Dose increases of MTX should be done gradually, for example, 2.5–5 mg/week with evaluation every 2–3 months.
When there is insufficient improvement with oral MTX after 8–12 weeks, the SC route of administration could be tried before discontinuing MTX treatment.
In case of gastrointestinal adverse events, the route of administration could be switched from oral to subcutaneous.
MTX treatment can be stopped all at once (as opposed to requiring a taper).
There is no maximum treatment duration with MTX, assuming the treatment is well tolerated and efficacious.
The cumulative dose of MTX does not need to be recorded in routine clinical practice.
Folic acid should be supplemented when prescribing MTX.
The preferred dose of folic acid is 5–6 mg/week in one single weekly dose or multiple daily doses.
Adults
Irrespective of whether a test dose with MTX is given, the initial dose is usually* 15 mg/week.
The maximum dose is 25 mg/week.
Children
MTX dosing should be based on weight (mg/kg).
Irrespective of whether a test dose with MTX is given, the starting dose should be 0.2–0.4 mg/kg/week.
The maximum dose should be 0.7 mg/kg/week and should not exceed 25 mg/week.

MTX – methotrexate, SC – subcutaneous.
**This means that adjustments are possible depending on, for example, renal function or age.*

orally or subcutaneously with MTX at a dose of 7.5 mg or 15 mg/day. A higher intensity of gastrointestinal side effects was observed in patients receiving oral MTX. In addition, it was noted that the intensity of symptoms was correlated with the dose of MTX taken orally. Vomiting and loss of appetite were significantly more frequent in patients receiving oral MTX ($p < 0.05$). In contrast, among patients taking MTX subcutaneously, nausea and loss of appetite were observed more frequently in the group of patients receiving 15 mg of MTX. In contrast to patients taking MTX orally, vomiting and diarrhoea were not observed in any of the patients receiving MTX subcutaneously. The data obtained indicate better tolerability of subcutaneous MTX compared with oral MTX in patients with long-standing RA. In the group of patients receiving subcutaneous MTX, 14.6% also showed the possibility of a 50% reduction in doses of other disease-modifying drugs when used concurrently [43].

MTX may have genotoxic effects – it affects spermatogenesis and ovum development, which may result in reduced fertility – these effects disappear after the discontinuation of the therapy. The drug also has a toxic effect on the embryo; it can cause foetal defects and miscarriage. Therefore, during MTX treatment and 6 months after its completion, patients and their sexual partners should use effective methods of pregnancy prevention [10].

Because of possible effects on the immune system, MTX may impair the effectiveness of vaccinations and cause false results on tests that evaluate immune response. Live vaccines must not be administered during treatment with MTX.

Before starting MTX treatment, a complete blood count with smear and platelet count determination, bilirubin and liver enzyme levels, renal function parameters should be performed. A chest X-ray is also indicated. Blood tests should be repeated at least once a month for the first 6 months of therapy, and then every 3 months [10]. Before starting MTX, it is also necessary to analyse all drugs and medical devices previously used by the patient, because of the possibility of pharmacokinetic interactions.

The most common adverse reactions to MTX include elevated liver enzyme activity and bilirubin levels, ulcerative stomatitis, and bone marrow dysfunction, usually in the form of leukopenia and decreased resistance to infection. Most adverse reactions are reversible if recognized early. The incidence and severity of adverse effects are thought to be related to the dose and frequency of administration [10].

Conclusions

Taking into account the current recommendations as well as the available clinical data, MTX may be considered in patients with severe AD who did not achieve the expected improvement after CsA, or who had adverse effects and no possibility of biological treatment with monoclonal antibodies or Janus kinase (JAK) inhibitors. Off-label MTX is expected to maintain its relevance due to its cost-effectiveness, established safety profile, and widespread availability.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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