Methotrexate

We **suggest** using methotrexate in AE patients who are candidates for systemic treatment.	↑	**100%** Evidence and consensus based see, Evidence Report

methotrexate: off-label; commonly used dosage
adults: initial dose: 10-15 mg per week; maximum dose: 25 mg per week
children: 0.3–0.4 mg/kg per week; maximum dose: 25mg per week

Certainty of evidence: Network meta-analysis from 2022[1, 2]:

Short term (up to 16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

⊕⊕◯◯ LOW for standardized mean difference change in signs -0.6 (-1, -0.2), QoI -0.4 (-0.9, 0.1), itch -0.6 (-1.2, 0)

For methotrexate versus other drugs, see Evidence Report

Mechanisms of action and efficacy

MTX is a folic acid antagonist that impedes cell division, DNA/RNA synthesis and repair and protein synthesis, altogether suppressing the activity of the immune system. Although its exact action in AE is not fully understood, inhibition of the JAK/STAT pathway has been proposed.[3]

MTX has been used in the treatment of moderate and severe AE for years, but clinical trial evidence is limited. Consequently, recommendations have been primarily based on expert consensus[4-7], but there is one controlled study comparing MTX with AZA in adults[8-10], one investigator-blinded randomised controlled trial comparing MTX with ciclosporin in children (TREAT trial)[11] and an open-label randomised multi-centre study in children, again comparing MTX with ciclosporin.[12] Altogether these studies support that MTX can be considered effective, relatively safe, and well-tolerated treatments for severe AE both in children and adults - findings also in keeping with recent retrospective studies.[13-15]

In the TREAT trial (n=103) ciclosporin showed a better response after 12 weeks (4 mg/kg/day), but MTX (0.4 mg/kg/week) was superior after this time point, with more sustained disease control seen up to week 60, even after treatment was stopped at 36 weeks (lower disease severity measured by EASI and o-SCORAD, as well as less patient-reported flares and reduced need for the use of topical anti-inflammatory treatment), suggesting potential disease modification through MTX. Both MTX and ciclosporin improved QoL above the minimally important difference for the CDLQI. Importantly, ciclosporin was significantly more expensive than MTX (£0.55 per week) vs ciclosporin (£24.33 per week, UK National Health Service prices 2023), which should be taken into account when treatment with either drug is considered.[11]

In the living network meta-analysis, which only included adults, the efficacy of MTX was comparable to AZA and lower than dupilumab and ciclosporin in clearing clinical signs of AE at week 16. In addition, the UK-Irish Atopic Eczema Systemic TherApy register (A-STAR) recently published a real-world comparison of MTX versus ciclosporin and dupilumab.[16, 17] Ciclosporin and dupilumab were superior to MTX with regard to treatment effectiveness, while all three medications had a similar impact on QoL.

It is important to keep in mind that gradual up-dosing was commonly used in those receiving MTX in the A-STAR analysis, while the TREAT trial regimen involved patients receiving the full treatment dose from the outset.[4-6] One adult study suggests that patients who do not benefit from a moderate weekly dose (10–15 mg) of MTX over a three-month treatment period will probably not benefit from an increased dosage. However, slow gradual up-dosing of MTX might underestimate the therapeutic potential of the drug in AE. In children 0.4 mg/kg/week is recommended, which is significantly higher than dosing in adults.[4] 25 mg per week are the widely used maximum treatment dose for adult and paediatric AE patients.[7]

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage
    - adults: initial dose: 10-15 mg per week; maximum dose: 25 mg per week (given in a single, weekly dose). No test dose is needed.
    - children: 0.2–0.4 mg/kg per week acute flare and short-term: no relevant dosing
- Oral and subcutaneous delivery are considered equivalent options of administration. For patients in whom MTX 15 to 25 mg orally once weekly is ineffective or poorly tolerated, a trial of subcutaneous MTX administration is an alternative.
- We recommend combining MTX, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- Concomitant use of folic acid should be considered to reduce gastrointestinal and other side-effects related to the folic acid antagonistic effect of the drug.[18]

Safety

As MTX is a commonly used drug in dermatology, the safety profile is well recognized, with nausea, fatigue and raised liver enzymes as main side effects, while pancytopenia and idiopathic pulmonary fibrosis is of key concern but only very rarely seen.

MTX is generally well tolerated and is considered safe for long-term treatment, based on experience and multiple studies including both adults and children suffering from psoriasis and rheumatologic disease.[19, 20]

Screening and monitoring

Screening for chronic infections (e.g. hepatitis B-/C, HIV, tuberculosis) before therapy should be considered (see also section 8.1 Introduction conventional immunomodulatory drugs).

Screening and follow up monitoring: Complete blood count, renal and liver profile before and every 4 weeks for the first 3 months or, after increasing the dose, then every 8-12 weeks.

In patients undergoing long-term MTX therapy, a fibroscan may be considered as an option to monitor liver fibrosis in accordance with national and local guidelines. An emerging alternative is the fibrosis-4 index, combining age, AST, ALT and platelet count to identify those at increased risk of liver fibrosis.[21]

Any noteworthy impact on liver or bone marrow function should give cause to dose reduction or transient or total discontinuation of treatment.

Combination with other treatments

We recommend combining methotrexate, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients. There is experience from rheumatoid arthritis for combining with the JAK-Inhibitor baricitinib.

Special considerations

MTX may be used for treatment of AE in both adults and children.

Subcutaneous administration increases bioavailability and tolerability, as well as adherence, compared to oral treatment.

MTX affects fertility and is highly teratogenic. Effective contraception is advised for women of childbearing potential. According to the SmPC, the same applies to men treated with MTX who could potentially father a child.

References

1. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. *JAMA Dermatol* 2022;158(5):523–32.
2. Drucker AM. Systemic immunomodulatory treatments for atopic dermatitis: a living systematic review and network meta-analysis. 2022. Available at: https://eczematherapies.com/research/ (last accessed 12 May 2025).
3. Alqarni AM, Zeidler MP. How does methotrexate work? *Biochem Soc Trans* 2020;48(2):559–67.
4. Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 2007;156(2):346–51.
5. Goujon C, Bérard F, Dahel K, Guillot I, Hennino A, Nosbaum A et al. Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006;16(2):155–8.
6. Lyakhovitsky A, Barzilai A, Heyman R, Baum S, Amichai B, Solomon M et al. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. *J Eur Acad Dermatol Venereol* 2010;24(1):43–9.
7. Caron AGM, van Huizen AM, Musters AAH, Gerbens LAA, Middelkamp Hup MA, Flohr C et al. International consensus on methotrexate dosing for patients with atopic dermatitis: An eDelphi study. *J Eur Acad Dermatol Venereol* 2025;39(2):331–9.
8. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol* 2011;128(2):353–9.
9. Roekevisch E, Schram ME, Leeflang MMG, Brouwer MWD, Gerbens LAA, Bos JD et al. Methotrexate versus azathioprine in patients with atopic dermatitis: 2-year follow-up data. *J Allergy Clin Immunol* 2018;141(2):825–7.e10.
10. Gerbens LAA, Hamann SAS, Brouwer MWD, Roekevisch E, Leeflang MMG, Spuls PI. Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial. *Br J Dermatol* 2018;178(6):1288–96.
11. Flohr C, Rosala-Hallas A, Jones AP, Beattie P, Baron S, Browne F et al. Efficacy and safety of ciclosporin versus methotrexate in the treatment of severe atopic dermatitis in children and young people (TREAT): a multicentre parallel group assessor-blinded clinical trial. *Br J Dermatol* 2023;189(6):674–84.
12. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013;172(3):351–6.
13. Deo M, Yung A, Hill S, Rademaker M. Methotrexate for treatment of atopic dermatitis in children and adolescents. *Int J Dermatol* 2014;53(8):1037–41.
14. Taieb Y, Baum S, Ben Amitai D, Barzilai A, Greenberger S. The use of methotrexate for treating childhood atopic dermatitis: a multicenter retrospective study. *J Dermatolog Treat* 2019;30(3):240–4.
15. Shah N, Alhusayen R, Walsh S, Shear NH. Methotrexate in the Treatment of Moderate to Severe Atopic Dermatitis: A Retrospective Study. *J Cutan Med Surg* 2018;22(5):484–7.
16. Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B et al. Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis. *JAMA Dermatol* 2020;156(6):659–67.
17. Alexander H, Malek R, Prieto-Merino D, Gribaleva E, Baden M, Beattie P et al. A prospective observational cohort study comparing the treatment effectiveness and safety of ciclosporin, dupilumab and methotrexate in adult and paediatric patients with atopic dermatitis: results from the UK-Irish A-STAR register. *Br J Dermatol* 2024;191(6):988–99.

18. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. *J Rheumatol* 1998;25(1):36–43.
19. Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. *Clin Exp Dermatol* 2013;38(6):573–88.
20. Weinblatt ME. Methotrexate in rheumatoid arthritis: a quarter century of development. *Trans Am Clin Climatol Assoc* 2013;124(16–25.
21. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010;59(9):1265–9.