Methotrexate

We suggest using methotrexate in AE patients who are candidates for systemic treatment.

Certainty of evidence

Short term (8-16 weeks) vs placebo (NMA medications used in clinical practice or likely to be approved soon)

\[\text{LO} \text{W for standardized mean difference change in signs, QoL, itch}\]

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 only a limited number of non-randomised controlled trials have examined the effect and treatment regimens. Consequently, recommendations have been primarily based on case series and expert consensus\(^4\-^6\), one controlled study comparing MTX with AZA in adults\(^7\) and an open-label randomised multi-centre study in children.\(^8\) Altogether these studies support that MTX can be considered moderately effective, relatively safe, and well-tolerated treatments for severe AE both in children and adults - findings also in keeping with recent retrospective studies.\(^9\-^{11}\) The efficacy of MTX was comparable to AZA and lower than dupilumab and ciclosporin in clearing clinical signs of AE at week 16. However, there are no long-time follow up head-to-head studies available for further comparison.\(^12\) The onset of action takes several weeks and peak efficacy is seen after months, but speed of treatment effect onset depends on the dosing regimen.\(^4\-^6\) 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 0.4mg/kg/week is recommended, which is significantly higher than dosing in adults.\(^4\) 25mg per week are the widely used maximum treatment dose for adult and paediatric AE patients.

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage
  - adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week
- children: 0.3–0.4 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.  

**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.  

**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.

Type III procollagen peptide (PIIINP) should be monitored according to national and local guidelines when available. Fibroscan or liver biopsy when necessary in selected cases.

Screening for chronic infections (e.g. hepatitis B-/C, HIV, tuberculosis) before therapy should be considered.

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**

Combination with TCS, TCI or narrow band UV phototherapy are established treatment combinations and considered safe. Concomitant use of ciclosporin is a relative contraindication. 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 teratogenic. Fertile women should use effective contraception. The same is recommended for men treated with MTX living with a woman of childbearing potential.
References


