Azathioprine (AZA)

We **suggest** using azathioprine in AE patients who are candidates for systemic treatment.	↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

azathioprine: off licence; commonly used dosage
adults: 1-3 mg/kg per day
children: 1-3 mg/kg per day

Certainty of evidence(1, 2):

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

⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs**

⊕⊕◯◯ LOW for standardized mean difference QoL, itch

For azathioprine versus other drugs, see Evidence Report

Mechanisms of action and efficacy

AZA is a pro-drug which is rapidly converted in vivo to the anti-metabolite 6-mercaptopurine (6-MP), following cleavage of its imidazole side chain. It is believed to exert its primary immunosuppressant effect via metabolites of 6-MP, thioguanine nucleotides (TGNs), which are subsequently incorporated into DNA, inhibiting its synthesis.(3)

The efficacy of AZA is comparable to that of MTX but lower compared to dupilumab and cyclosporine A in clearing clinical signs of AE.(4)

Randomized clinical trials report a significant superiority of AZA vs placebo, with a decrease in clinical scores such as Six Area, Six Sign Atopic Dermatitis and Scoring Atopic Dermatitis (SASSAD) by 26% to 39% after 12 weeks.(5) However, results from retrospective studies are less favorable with a percentage of AZA treatment failure varying from 30 to 57% due to adverse effects or lack of effectiveness.(6-8) An observational follow-up study of 36 adult patients with severe AE treated with MTX or AZA over a 24-week period demonstrated less improvement in subjects with filaggrin mutations (36%, 13/36) compared to those without filaggrin mutations.(5)

Long-term studies on adult patients treated with either AZA or MTX showed a relative reduction in SCORAD of 53% ($P < .01$) and 63% ($P < .01$) after 2 years, and 54% and 53% after 5 years, respectively.(5, 9) Patients with a Filaggrin mutation seemed to have slower but prolonged effects of therapy compared with patients without a mutation.(5, 9)

Dosage: acute flare, short term, long term

- off licence
- commonly used dosage
    - adults and children: 1-3 mg/kg bodyweight per day

  - If no improvement of AE occurs within 3 months, withdrawing azathioprine should be considered.

- We recommend combining AZA, as any systemic treatment with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.
- If timely thiopurine S-methyltransferase (TPMT) activity measurement is available, the following dosing of AZA has been suggested:
  - very low activity (< 2.5 per mL red blood cells [RBC]), treatment should not be started
  - intermediate activity (2.5-7.5 nmol/h/mL RBC): 0.5 mg/kg bodyweight per day for the first 4 weeks and then increase to 1.0 mg/kg bodyweight per day
  - normal activity (>7.5 nmol/h/mL RBC): 2.0 mg/kg bodyweight per day for the first 4 weeks and then increase to 2.5-3.0 mg/kg bodyweight per day

Low azathioprine doses (0.5-1.0 mg/kg bodyweight per day) for the first 4 weeks were shown to reduce gastrointestinal side-effects.(10)

If TPMT results are not available prior to starting AZA therapy, then half the standard treatment should be given for about 4-6 weeks under close monitoring of full blood count and liver profile, prior to going up the full treatment dose.

Safety

In the short and medium term, the most commonly reported serious dose-dependent effects are hepatotoxicity and myelotoxicity, together with gastrointestinal disturbances. Further, idiosyncratic hypersensitivity reactions (e.g. fever, rigours, myalgia, arthralgia and occasionally pancreatitis) may occur.(11)

Concerns have been raised about the potential carcinogenecity induced by long-term treatment with azathioprine (predominantly squamous cell skin cancer and n on-Hodgkin's lymphoma), especially if AZA is combined with other immunosuppressants regimens.(12)

Monitoring

- Baseline: Complete blood count, renal and liver profile
- TPMT activity if available.
- Screening for chronic infections (e.g. hepatitis B-/C, HIV) before therapy should be considered
- Follow up: Complete blood count, renal and liver profile twice monthly for 2 months, monthly for 4 months, then every other month and with dose increases
- Pregnancy testing before and during AZA therapy where indicated

Combination with other treatments

Concomitantly to AZA, topical therapy with corticosteroids and or calcineurin inhibitors can be applied.

Because of a potentially increased risk to develop skin cancer, AZA should not be combined with UV light (UVA, UVB, PUVA).

Special considerations

There is a theoretical risk of teratogenesis with AZA. This is based on studies in animals in which very high doses of AZA were used. However, in practice AZA has been used for over 30 years in sexually active men and women and no definite association between the drug and the incidence of foetal abnormalities has been observed. There also seems to be no effect on fertility.

According to a recent position paper by ETFAD(13), AZA use during pregnancy should be avoided as there are better options, but may be used off-label in the absence of other alternatives as continuation of treatment in women already receiving this treatment at the time of conception. According to experts' opinion of the ETFAD, the dosage of azathioprine should be reduced by 50% if it is continued during pregnancy. Initiation of azathioprine after conception is not recommend.

The use of AZA during lactation is debated. The WHO has recommended that the potential side-effects of AZA outweigh the effects and benefits of the treatment(14), and studies suggest that AZA intake during breastfeeding could increase the longterm risk of immunosuppression and carcinogenesis in the child.(15)

AZA is not licensed for the treatment of AE in children but it has proven beneficial in several retrospective pediatric case series. The main disadvantage of AZA is that it reaches its maximum treatment effect only after 3-4 months.(16)

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