Ciclosporin

We recommend using ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	↑↑	>75%  (14/15) Evidence and consensus based, see Evidence Report

ciclosporin: in licence for ≥ 16 years of age
standard dosage adults: 2.5-5 mg/kg per day in two single doses
commonly used dosage children: 2.5-5 mg/kg per day in two single doses

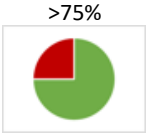
Certainty of evidence: Network meta-analysis from 2022[1,2]:

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

Higher dose
⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -1 (-1.6, -0.4)
⊕⊕⊕◯ MODERATE for standardized mean difference **QoL** -0.7 (-1.3, -0.1)
⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.5, 0.2)

Lower dose
⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -0.7 (-1.4, -0.1)
⊕⊕◯◯ LOW for standardized mean difference QoL -0.5 (-1.1, 0.2)
⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.6, 0.3)

For ciclosporin versus other drugs, see Evidence Report

We **recommend** to start with higher ciclosporin dosages in order to achieve a more rapid response in AE patients who are candidates for systemic treatment.	↑↑	>75%  (14/15) Expert Consensus
We **recommend** close follow-up for potential blood pressure elevation and signs of renal impairment in AE patients on ciclosporin.	↑↑	100%  (15/15) Expert Consensus

Mechanisms of action and efficacy

Ciclosporin inhibits T cell activation and proliferation by blocking nuclear factor of activated T cells (NFAT)-dependent cytokine production.

Ciclosporin has been approved for treatment of AE in adults in many European countries and is considered as first line option for patients with severe disease if other, novel therapies are not available or indicated. Ciclosporin is very effective for AE in both children and adults with a better tolerability in children.[3-5] Although similarly effective in the above NMA meta-analysis evaluating adult trials up to 16 weeks and in a real world analysis from the UK-Irish Atopic Eczema Systemic TherApy Register (A-STAR) among both adults and children[6], real life data reveal a longer drug survival of dupilumab compared to ciclosporin after 16 months, but similar effectiveness.[7,8] In head-to-head adult trials ciclosporin was superior to MTX, prednisolone, IVIG, UVA and UVB, and similarly efficacious as enteric-coated mycophenolate sodium (EC-MPS).[9,10]

In an investigator-blinded randomised controlled trial comparing ciclosporin (4 mg/kg/day) with MTX (0.4 mg/kg/week) in children aged 2 to 16 years (n=103), participants receiving ciclosporin showed a faster response to treatment by 12 weeks (TREAT trial). However, MTX 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.[11] Both drugs improved QoL above the minimal important difference for the CDLQI and were adequately tolerated and there were no serious adverse events attributed to either medication. In addition, there was no significant impact on either treatment on renal tubular function, using sensitive tubular biomarkers.[11] In the short-term treatment of AE, higher ciclosporin dosages (5 mg/kg per day) lead to a more rapid response and are more efficacious than lower dosages (2.5-3 mg/kg per day).[9] Longterm use of ciclosporin up to 1 year can be recommended based on several trials, however, their evidence is limited because of the open-label design and high dropout rates.[9]

Dosage: acute flare, short term, long term

- licensed ≥ 16 years of age
- standard dosage adults: 2.5-5 mg/kg per day in two single doses
    - Acute flare, short-term: 4-5 mg/kg body weight per day
    - Long-term: 2.5-3 mg/kg body weight per day
- commonly used dosage children: 2.5-5 mg/kg per day in two single doses
    - We recommend combining ciclosporin, as any systemic treatment, with emollients and, whenever needed, topical anti-inflammatory treatment in AE patients.

Safety

Ciclosporin has a narrow therapeutic index and requires a close follow-up for blood pressure and signs of renal impairment. To note, clinically relevant increase of creatinine seems less common than expected, as recently confirmed in the TREAT trial, which showed no abnormal renal profiles due to ciclosporin, even when sensitive tubular function biomarkers were used (see above).[4,11,12]

Monitoring

- Blood pressure, full blood count, renal and liver profile (including GGT) according to national guidelines (e.g. at baseline, 4 weeks and then 3-monthly).
- Screening for hepatitis B/C and HIV before therapy should be considered.

Combination with other treatments

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

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

Special considerations

Ciclosporin has been shown to be effective, safe and well tolerated in children and adolescents.[3,5,13]

Ciclosporin can be considered in pregnant woman with severe AE. So far, no increased risk of congenital malformations or fetal death compared to the background populations have been reported. An increased risk of low birthweight cannot be ruled out.[14] Where systemic therapy is likely to be needed throughout pregnancy, ciclosporin is first choice therapy.[14]

References

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