Ciclosporin - UC Only - Full Clinical Guideline

Reference No: CG-T/2014/208

Intravenous Ciclosporin Regime for Ulcerative Colitis Treatment

Please note that Ciclosporin use for Ulcerative Colitis (UC) is an *unlicensed indication*

Ciclosporin is used in steroid refractory patients with severe UC. Alternatives include infliximab. Ciclosporin should only normally be started on consultant advice.

Before starting IV Ciclosporin:

- Blood pressure
- Urinalysis
- Check blood results before starting ciclosporin for the following
  - U+Es as drug can cause renal impairment and high potassium levels
  - Magnesium as drug can cause low magnesium levels
  - Cholesterol as drug causes high cholesterol levels

The risk of seizures is increased in patients with a low cholesterol (<3.0 mmol/l or magnesium (<0.50 mmol/l). *Neoral oral solution,* which is an oral micro-emulsion of ciclosporin (dosed at 5-6 mg/kg) is a safe alternative as it is not associated with the seizures provoked by a chromophore in the intravenous preparation[1]. The IV preparation should be first line for all other patients, as the vast majority of the evidence is based on this preparation.

Other UC treatment should be continued whilst on this drug

Dose:

2mg/kg/day given by continuous IV infusion for up to 10 days. Doses up to 125mg should be given in 100ml sodium chloride 0.9%, doses above this in 250 ml sodium chloride 0.9%, over 24 hours, through a dedicated cannula (can be given peripherally or centrally)[2].

Doses should be rounded to the nearest 10mg for ease of measurement.

Dosing should be based on **ideal body weight**[3]

To prescribe on iCM:

In the *Dose* box enter the dose for 24 hours (i.e. 2mg/kg rounded to nearest 10mg)
In the *Frequency* box enter *once daily at* and choose the start time (may need to use the user schedule function if desired start time isn't in the drop-down list).
In the *Infusion Duration* over box enter *24 hours.*

Manufacture:

Drug is stable for 24 hours only if made in a PVC free infusion bag[4]. Freeflex or Baxter brand bags are PVC free, Maco brand bags are not.

Monitoring:

- This drug can cause anaphylactic reactions. Make sure there is an in-date anaphylaxis box on the ward and monitor patient closely during the first 30 minutes of infusion. Thereafter observations should be carried out 4 hourly[5]

- Check levels after 36-48 hours. The level must be taken from the opposing arm to that with the infusion going in. 5ml of blood is required for the level to be taken, this is sent in a potassium-EDTA tube (lilac top, same as FBC) to biochemistry[6,7]

- Adjust the dose if necessary to achieve drug level of 100-200 micrograms/litre[1,2] (see table for details of how to adjust doses). Thereafter levels should be taken twice weekly whilst on intravenous therapy.

- Continue infusion whilst waiting for levels to come back as they can take a few days depending on the day of the week the sample is taken. Ciclosporin samples are only tested twice weekly, on Tuesdays and Fridays. Pathology require samples being received in the laboratory before 10 am on the Tuesday or Friday to ensure analysis is undertaken on that day.

- Urgent analysis of ciclosporin will only be undertaken after a Consultant to Consultant request, and need at least 24 hours notice. The service will not be routinely available at weekends and bank holidays.

- Bloods should be taken at least alternate days to monitor for nephrotoxicity, hyperkalaemia, liver toxicity, hypomagnesaemia.

- Other ulcerative colitis treatments should be continued whilst on ciclosporin

Cautions[8]

Use with caution in patients with GFR<30ml/min – seek advice from renal team before starting (drug not renally cleared but very nephrotoxic).

Use with caution in infections, history of seizures and malignancies, see BNF for more information.

This drug has several interactions, importantly:

- **Metoclopramide, clarithromycin, erythromycin, doxycycline, fluconazole, verapamil, diltiazem** and **grapefruit juice** all increase ciclosporin levels – monitor levels carefully after starting/stopping.
- **NSAIDs, gentamicin** and **trimethoprim** all increase the risk of nephrotoxicity – if possible do not use concurrently
- **ACE inhibitors, ARBs, spironolactone** all increase the risk of hyperkalaemia
- **Diclofenac** dose needs to be halved.
- Avoid **rosuvastatin** and **tacrolimus**
- Combination with products containing *Hypericum perforatum* (St John´s Wort) (see section 4.5).
- Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren (see section 4.5).
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For further cautions see the SPC/BNF

Side Effects[8]

- Anaphylaxis (monitor during the first 30 minutes of infusion)
- Nephrotoxicity (one third of patients, monitor at baseline and at least alternate days. Reduce dose by 25% if serum creatinine rises above 30% above baseline.)
- Hyperkalaemia (monitor)
- Liver toxicity (monitor, reduce ciclosporin dose by 25% if any LFT values double from baseline)
- Hypertension (treat if necessary, reduce ciclosporin dose by 25% if BP remains over 150/90 despite antihypertensive treatment, discontinue if hypertension remains despite dose reduction)
- Hypercholesterolaemia

Other effects include tremor, parasthesia, GIT disturbances, hypetrichosis, gingival hypertrophy, convulsions (rare), nausea, opportunistic infections, hyperglycaemia.

Dose adjustments

Level	Action (IV dosing)	Action (oral dosing)
<100	Increase daily dose by 20mg, recheck levels in two days	Increase daily dose by 25mg BD, review in one week
100-200	Continue	Continue
200-300	Decrease daily dose by 20mg, recheck levels in two days	Decrease daily dose by 25mg BD, review in one week
>300	Decrease daily dose by 40mg, recheck levels in two days	Decrease daily dose by 50mg BD, review in one week
>500	Stop and recheck levels	Stop and recheck levels

Switching to oral

After 5-7 days responders should be converted to oral ciclosporin. Bioavailability of the capsule is one third of the intravenous drug, and so oral therapy is dosed at 5-6mg/kg/day (choose a measurable dose, capsules come in 25mg, 50mg and 100mg strengths). This is given in two divided doses in addition to oral steroid treatment. To switch, stop the infusion at the same time as the first oral dose is given (normally 8am)

Check levels of oral ciclosporin after 48 hours, aiming for 100-200 micrograms/L. The sample should be taken as a trough level, normally pre-morning dose. If needing to re-check levels, e.g. after a dose change, wait at least 2-3 days before doing this to allow steady state to be reached.

This should then be converted to azathioprine or vedolizumab for long-term maintenance treatment (2.5mg/kg/day). Azathioprine is started whilst on oral ciclosporin, and the ciclosporin is stopped (no weaning needed) after 3 months cross-over period.

Any patient on 3 or more immunosuppressant drugs should have co-trimoxazole 960mg three times a week added as PCP prophylaxis (i.e steroids + ciclosporin + azathioprine whilst switch over is taking place) – note risk of nephrotoxicity with these drugs, monitor U+Es carefully.

References

1. Mowat C et al. on behalf of the British Society of Gastroenterology, Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;1-37

2. Van Assche G, D'Haens G, Noman M *et al*. Randomised, double blind comparison of 4 mg/kg vs 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;125:1025–31

3. Flechner SM, *et al*., The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. *Transplantation* 1989;4:806-10

4. Trissell LA. Handbook of Injectable Drugs accessed online at http://www.medicinescomplete.com/mc/hid/current/ June 2011

5. Summary of Product Characteristics for Ciclosporin intravenous infusion accessed via www.medicines.org.uk June 2011

6. Travis SPL, Farrant JM, Ricketts C *et al*. Predicting outcome in severe ulcerative colitis. *Gut* 1996;38:905–10

7. Gupta SK, Bakran A, Johnson RWG, Rowland M (1989) Pharmacokinetics of cyclosporine: influence of rate-duration profile of an intravenous infusion in renal transplant patients. Br J Clin Pharmac. 27 353-357

8. British National Formulary BNF 62 September 2011

9. Lichtiger S, Present DH, Kornbluth A *et al*. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–5

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