Joint Trust Guideline for the Administration of Ciclosporin for the Treatment of Ulcerative Colitis in Adults

A clinical guideline recommended for use

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<th>In:</th>
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<tbody>
<tr>
<td>By:</td>
<td>Registered nurses, Medical Staff, Pharmacists</td>
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<tr>
<td>For:</td>
<td>Patients with Ulcerative Colitis requiring the administration of ciclosporin</td>
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.
Quick reference guideline/s

INDICATION

Severe steroid resistant colitis (unresponsive to:

- IV methylprednisolone 40mg twice daily (NNUH)
  or
- IV hydrocortisone 100mg 6 hourly (JPUH).

This is an unlicensed indication and informed patient consent should be sought.

DOSE

2mg per kg body weight (total daily dose)

PRESCRIPTION

Prescribe on the infusion section of the drug chart. Divide total daily dose into four 6-hour infusions, each one made in 50ml of sodium chloride 0.9%. For patients <50kg, the dilution volume is 25ml.

e.g.  70kg patient total daily dose = 140 mg

\[ \text{:.35mg in 50mL made up with sodium chloride 0.9% given over 6 hours then repeated} \]

ADMINISTRATION

Give each 6-hour infusion immediately after the previous one to form a continuous infusion.

Each time the infusion is changed the giving set should also be changed.

MONITORING REQUIREMENTS

Cholesterol – Do not prescribe IV ciclosporin if cholesterol <3.0 (But consider oral ciclosporin)
Magnesium – pre-ciclosporin assessment. Magnesium should be corrected before starting ciclosporin.
Renal function – serum creatinine and urea before and during ciclosporin therapy.
Blood Pressure (stop infusion if significant hypertension)
Ciclosporin levels (At least twice per week)
Liver function
Abdominal X-Ray
Daily CRP, serum potassium and stool chart

During Infusion

On day 1 of the infusion close observation for at least 30 minutes.
Temperature, pulse, and BP every 6 hours. As infusion is continuous, observations on subsequent days should continue at 6hrly intervals.
PROPHYLAXIS AGAINST PJP (PCP)

Clinicians should consider prescription of co-trimoxazole for the duration of ciclosporin therapy, at a dose of 960mg once a day three times a week although this is not mandatory.

FURTHER INFORMATION

For further information refer to full protocol, manufacturer’s literature, or contact James Harris (Gastroenterology Pharmacist ext ****)

Objective/s

The aim of this document is to ensure the safe administration of ciclosporin in patients receiving treatment for ulcerative colitis.

Rationale

Ciclosporin is an unlicensed drug in the treatment of ulcerative colitis. The drug itself has a narrow-therapeutic range, requires therapeutic drug monitoring, and has complex requirements for prescription and administration.

This guideline is based on the current CONSTRUCT trial protocol, the Leeds Teaching Hospital Policy 2010 and evidence from clinical trials.

Broad recommendations

1. WHAT IS CICLOSPORIN

Ciclosporin is a potent immunosuppressant, commonly used to prevent organ transplant rejection. There is evidence (Grade A) that intravenous ciclosporin can be effective for patients with severe corticosteroid resistant ulcerative colitis, with initial response rates of 80%.1,2,3 In reported case series the likelihood of avoiding colectomy over 2-3 years is 40-50%.4

2. INDICATIONS FOR USING CICLOSPORIN

IV ciclosporin is indicated in acute severe ulcerative colitis refractory to IV corticosteroids, where surgery would not be the first choice therapy. This is an unlicensed indication, and informed patient consent should be sought.

Ciclosporin should be considered after 3 days of IV steroids where improvement is not being seen (stool frequency >8/day or CRP >45mg/L at 3 days has been shown to predict the need for surgery in 85% of cases5)

Those patients who respond favourably to IV ciclosporin will normally be switched to oral ciclosporin (see later for dose conversion).
3. CONTRA-INDICATIONS

- Known hypersensitivity to ciclosporin
- Concomitant use of tacrolimus
- Known hypersensitivity to polyethoxylated castor oils (anaphylaxis risk)
- Low serum cholesterol (high likelihood of side effects)
- Uncorrected hypomagnesaemia (likelihood of seizures)

4. DOSAGE AND ADMINISTRATION

Total daily dose = 2 mg / kg

The total daily dose (or closest approximation) should be equally divided into four 6-hour infusions, given continuously. Each dose should be given in 50ml of sodium chloride 0.9%, unless the patient is less than 50kg. In this case make up to 25ml with sodium chloride 0.9%.

\[
\text{e.g.} \quad \begin{align*}
\text{70kg patient,} & \quad \text{total daily dose} = 140 \text{ mg} \\
\therefore & \quad 35\text{mg in 50ml made up with sodium chloride 0.9% given over 6 hours then repeated}
\end{align*}
\]

5. CONCOMITANT IBD THERAPY

Corticosteroids

Patients should normally be maintained on

- IV methylprednisolone 40mg twice daily (NNUH)
  or
- IV hydrocortisone 100mg 6 hourly (JPUH)

during initial ciclosporin dosing until clinical improvement allows conversion to oral steroid dosing and then steroid dose reduction to commence.
Oral mesalazine

Patients already taking oral mesalazine therapy should have their current dose continued during ciclosporin therapy.

Rectal Therapy

Rectal therapy with corticosteroids and/or mesalazine preparations may also be continued during ciclosporin therapy if appropriate.

6. DRUG INTERACTIONS

Drugs known to have nephrotoxic effects should be used with extreme caution in patients on ciclosporin. Commonly used potentially nephrotoxic drugs include

- NSAIDs (e.g. aspirin, diclofenac etc)
- aminoglycosides (e.g. gentamicin)
- ciprofloxacin

A number of drugs may increase or decrease the plasma or whole blood levels of ciclosporin within the body. Refer to the product data sheet for a full list of these agents.

Patients should be advised to avoid grapefruit juice during oral ciclosporin dosing as it has been reported to increase bioavailability.

7. ADVERSE REACTIONS

Side effects are usually dose-dependent and responsive to dose reduction

A frequent and potentially serious complication is a dose-dependent and reversible increase in serum creatinine and urea during the first few weeks of therapy. Less frequently renal structural changes may develop - this is more common with long term treatment and is therefore less likely to be a problem in our patients.

Apart from impaired renal function, the most frequently observed side effects include hypertrichosis, tremor, hypertension, hepatic dysfunction, fatigue, gingival hypertrophy, gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea) and burning sensations of the hands and feet (usually during the first week of treatment).

A full list of side effects can be found in the product monograph.¹

8. MONITORING REQUIREMENTS

Magnesium

Hypomagnesemia is a common finding of ciclosporin treated patients and has been proposed as both a cause and a consequence of induced nephrotoxicity. Hypomagnesemia should be corrected before commencing ciclosporin. Refer to policy on management of hypomagnesaemia.
Cholesterol

Ciclosporin is a highly lipophilic drug. Studies in transplant patients have suggested that the risk of neurotoxicity is increased in patients with hypocholesterolaemia (the other major risk factor being ciclosporin toxicity itself)\(^7\).

Patients being considered for IV ciclosporin therapy should therefore have a pre-treatment cholesterol level measured. A level of >3 mmol/L is considered acceptable for dosing at 2mg/kg/day IV. A level of <3mmol/L does not preclude the patient from treatment but the risk of neurotoxicity may be increased. This should be a Consultant decision.

If a patient develops signs of neurotoxicity on ciclosporin a dose reduction or discontinuation of therapy should alleviate the symptoms.

Renal Function (Serum creatinine, urea and potassium)

Ciclosporin can impair renal function. This is a frequent and potentially serious complication of therapy. Close monitoring of creatinine and urea is required and dose adjustment may be necessary. Increases in these values during the first few weeks of therapy are usually dose-dependent and respond to dosage reduction. The dose should be reduced if serum creatinine increases by 30% above baseline.

Liver Function

Ciclosporin may affect liver function, and dosage adjustment based on the results of billirubin and liver enzyme monitoring may be necessary. The dose should be reduced if serum liver enzyme values increase by 50% from base line.

Blood Pressure

Ciclosporin can cause hypertension and regular monitoring of blood pressure is required during therapy. If hypertension develops, appropriate antihypertensive therapy must be instituted. The dose of ciclosporin should be reduced where diastolic blood pressure remains consistently over 90 mm Hg despite antihypertensive therapy.

Other Tests

Abdominal X-Ray at baseline then as indicated.
Daily CRP and stool chart

Adverse Effects

Refer to section 7 of these guidelines for a list of common adverse effects which can be experienced with ciclosporin.
Ciclosporin Levels

The measurement of ciclosporin levels is recommended to give an indication of appropriate dosing and to inform dose adjustment as appropriate.

**Levels**

Aim for 150-250 nanograms/millilitre². Ciclosporin toxicity can occur above 300 nanograms/millilitre.

**Timing**

Steady state will not have been reached till approximately 72hrs. Levels should not be taken until at least the middle of the 3rd day (approx 60hrs).

**Frequency**

Ciclosporin levels should be taken twice weekly while on IV therapy and week 1 of oral therapy, then once weekly thereafter until levels are stable or for six weeks. Thereafter levels can be taken monthly until ciclosporin is stopped. Should doses need to be adjusted the frequency should return to weekly again until stable.

9. THE NURSE’S RESPONSIBILITY WHEN GIVING CICLOSPORIN

Ciclosporin injection contains polyethoxylated castor oil which has been reported to cause anaphylactoid reactions. These reactions consist of flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received IV injections or infusions containing polyethoxylated castor oils, or in patients with allergic conditions.

On day 1 of the infusion, closely observe patient for at least 30 minutes. Monitor temperature, pulse, and BP every 30 minutes for the first 2 hours, then every 6 hours. As infusion is continuous, monitoring should continue every 6 hours on subsequent days.

If anaphylaxis occurs, the infusion should be discontinued and the patient managed in accordance with common clinical practice.

Side effects are usually dose dependent and responsive to dose reduction. Any adverse effects or changes in the above clinical observations must be reported to the medical team.

10. CONVERSION TO ORAL THERAPY

IV ciclosporin will normally be given for up to 7 days depending on response (unresponsive patients are likely to require surgical intervention), following which patients will routinely be converted to oral therapy.

The brand **CAPIMUNE** has a more predictable bioavailability than the older NEORAL brand and should be prescribed by brand name.

For patients not previously treated with IV ciclosporin CAPIMUNE should be initiated at a total daily dose of 5.5mg / kg. The total daily dose should be given in two equal divided doses, morning and evening.
For patients previously receiving IV ciclosporin with appropriate drug therapeutic levels the correct total daily oral dose is 3 x the total daily IV dose. The total daily oral dose should be given in two equal divided doses, morning and evening.

Monitoring

Regular weekly monitoring (blood pressure, renal and hepatic function, magnesium and trough ciclosporin levels) should continue for the first 6 weeks of ciclosporin therapy, thereafter monthly monitoring if all parameters are stable. Ciclosporin levels should fall into the range quoted previously.

11. PNEUMOCYCTIS JIROVECI PNEUMONIA (PJP) PROPHYLAXIS

Most patients should receive prophylaxis against PJP with co-trimoxazole at a dose of 960mg once a day three times a week. This is a decision for the consultant responsible for the patients care.

12. FURTHER INFORMATION

For further information regarding the use of ciclosporin or for clarification of any part of these guidelines contact James Harris (ext **** – Gastroenterology Pharmacist) or consult the manufacturer's literature.

13. REFERENCES

7. de Groen PC et al. Central nervous system toxicity after liver transplantation. The role of ciclosporin and cholesterol. NEJM 1987; 317: 861-966

This guideline was adapted from the Leeds Hospital protocol for administration of ciclosporin for ulcerative colitis.