Protocol for IV ciclosporin in severe ulcerative colitis - Prescribing summary

**INDICATION**
Acute, severe steroid-resistant colitis (unresponsive to IV hydrocortisone 100mg QDS)
This is an unlicensed indication and informed patient consent should be sought.

**DOSE**
2mg per kg body weight, as total daily dose

**PRESCRIPTION**
Prescribe on an IV infusion chart.
The total daily dose should be diluted in 100ml sodium chloride 0.9%.
If patient weights >125kg, the total daily dose should be diluted in 250ml sodium chloride 0.9%.

**ADMINISTRATION**
Administer as a 24 hour intravenous infusion.

**MONITORING REQUIREMENTS**
Serum magnesium level (part of pre-course assessments)
Serum cholesterol (part of pre-course assessments)
Renal function, i.e. serum creatinine and urea
Liver function
Blood pressure (hypertension)
Serum ciclosporin levels (every 72 hours)
Abdominal X-ray as required

**During Infusion**
Day 1: Continuous observation for at least 30 minutes. Temperature, pulse, and blood pressure every 30 minutes for first 2 hours, then every 6 hours.
Day 2 onwards: Continue at 6 hourly observations.

**PROPHYLAXIS AGAINST PCP**
Patients on combined immunosuppressive therapy should be prescribed co-trimoxazole while on ciclosporin therapy, at a dose of 960mg daily.

**FURTHER**
For further information, refer to full protocol, manufacturer’s literature, or contact Shy Lih Teo (Lead Pharmacist Emergency Care, bleep 1563)
Protocol for IV Ciclosporin in Inflammatory Bowel Disease

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 acute, severe corticosteroid-resistant ulcerative colitis, with initial response rates of 80\%\textsuperscript{1,2,3}. In reported case series the likelihood of avoiding colectomy over 2-3 years is 40-50\%\textsuperscript{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 freq >8/day or CRP >45mg/L at 3 days has been shown to predict the need for surgery in 85\% of cases\textsuperscript{5}).

Those patients who respond favourably to IV ciclosporin, and who are not candidates for surgery, 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 (risk of anaphylactic reaction)

4. DOSAGE AND ADMINISTRATION

- Dosage and Prescribing

Intravenous ciclosporin should be prescribed for up to 7 days as a once daily infusion to run over 24 hours.

\textbf{Total daily dose} = 2 \text{ mg} / \text{ kg}

The total daily dose should be prescribed in 100ml sodium chloride 0.9\%.

For patient weights >125kg, the dose should be prescribed in 250ml sodium chloride 0.9\%.
• **Presentation of Medicine**

Intravenous ciclosporin is supplied from Pharmacy Department as:

Ampoules containing ciclosporin 50mg in 1ml concentrate for solution for infusion, or Ampoules containing ciclosporin 250mg in 5ml concentrate for solution for infusion

Which require further dilution for administration.

• **Administration**

The requested amount of concentrate intravenous ciclosporin should be calculated and diluted in 100ml sodium chloride 0.9% (or 250ml sodium chloride 0.9% for patient weights >125kg) to give slowly by continuous infusion using an infusion pump.

The excipient polyethoxylated castor oil is not compatible with polyvinyl chloride (PVC) therefore containers and giving sets for infusion must be PVC free.

Even though it is not essential, administration via central venous access device may be preferable if infusing at the highest recommended concentration to avoid potential venous irritation due to high osmolarity. If central access is unavailable, assess the benefits and risks of peripheral administration for the individual patient (e.g. timeliness of therapy, clinical status of patient). If given peripherally, choose a large vein and monitor the infection site closely using a recognised infusion phlebitis scoring tool.

Flush with sodium chloride 0.9% or glucose 5%.

Please also refer to Section 9 The Nurse Responsibility When Giving Ciclosporin for monitoring requirement during administration of intravenous ciclosporin.

5. **CONCOMITANT IBD THERAPY**

• **Corticosteroids** Patients should usually be continued on IV hydrocortisone 100mg QDS while on ciclosporin therapy, until clinical improvement is seen which allows conversion to oral steroid dosing and subsequent steroid dose reduction.

• **Oral mesalazine** Oral mesalazine therapy should be 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 (eg aspirin, diclofenac etc)
- aminoglycosides (eg gentamicin)
- ciprofloxacin
- trimethoprim (not strictly nephrotoxic, but may result in raised serum creatinine, therefore avoid to simplify picture)

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 ciclosporin 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.\(^6\)

8. **MONITORING REQUIREMENTS**

- **Magnesium**

Ciclosporin enhances the clearance of magnesium; hypomagnesemia is a common finding in ciclosporin-treated patients and has been proposed as both a cause and a consequence of induced nephrotoxicity. Hypomagnesemia should be corrected before commencing ciclosporin.
• **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 >3mmol/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.

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

• **Renal Function (Serum creatinine and urea)**

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 bilirubin and liver enzyme monitoring may be necessary. The dose should be reduced if serum liver enzyme values increased by 50% from baseline.

• **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 mmHg despite antihypertensive therapy.

• **Adverse Effects**

Refer to section 7 of this guideline for a list of common adverse effects which can be experienced with ciclosporin.

• **Ciclosporin Levels – Monoclonal Assay**

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

  *Assay* Two assays are used in practice. The monoclonal antibody assay measures the level of ciclosporin alone. The polyclonal assay measures both ciclosporin and its metabolites. For simplicity, samples should be sent for monoclonal assay.
Assay should be requested on Trust request form and sample taken via peripheral veins with EDTA anticoagulated whole blood tube (purple top). When sending blood samples from the ward to our laboratories at DRI, ring specimen reception in advance (Extn: 3131) to let them know that the sample will need sending to Northern General Hospital Clinical Chemistry Department (Direct dial: 0114 2714716) and results will be needed back that evening. Samples will need to be sent to our laboratories before midday for results to be reported that evening. Ensure the contact number of whom the results should be communicated when they arrive back is clearly endorsed on the request form. As results will only be visible via ICE system 2-3 days after samples sent, it is medical team’s responsibility to chase the results with NGH laboratories (Direct dial: 0114 2714716) if have not heard back from them. Please note that therapeutic range of ciclosporin levels varies. Advice on the interpretation of the levels can be sought from Clinical Chemistry Department at NGH (Direct dial: 0114 2434343). They will not be able to advise dose changes, however.

**Timing**

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

Patient should be placed under continuous observation for at least the first 30 minutes after the start of the infusion, and temperature, pulse, and blood pressure should be monitored every 30 minutes for the first 2 hours and then every 6 hours. As infusion is continuous subsequent days, continue at 6 hourly observations.

**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 reported during the infusion should be referred to the medical team.

SL Teo, Lead Pharmacist Emergency Care (adapted from protocol written by D Greer, Lead Pharmacist GI Medicines, Leeds TH)  
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10. **CONVERSION TO ORAL THERAPY with NEORAL**

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 **NEORAL** has a more predictable bioavailability than the older Sandimmun brand and should always be prescribed (specify the brand NEORAL on prescriptions).

NEORAL should be initiated at a total daily dose of 5.5 mg/kg. The total daily dose should be given in **two divided doses**, morning and evening.

**Monitoring**

Regular weekly monitoring (blood pressure, renal and hepatic function, ciclosporin levels) should continue for the first 2 weeks of ciclosporin therapy, thereafter monthly monitoring if all parameters are stable\(^8\). Ciclosporin levels should be aimed at the range quoted previously.

11. **PNEUMOCYTIS CARINII PNEUMONIA PROPHYLAXIS**

All patients receiving combined immunosuppressive therapy should receive prophylaxis against PCP with co-trimoxazole at a dose of 960mg daily, for the duration of ciclosporin treatment.

12. **FURTHER INFORMATION**

For further information regarding the use of ciclosporin or for clarification of any part of this guideline, contact Shy Lih Teo (Lead Pharmacist Emergency Care, bleep 1563) or consult the manufacturer literature.

13. **AUTHORSHIP**

This protocol has been written by Daniel Greer (Lead Pharmacist, Medical Gastroenterology) with input from the GI Consultants at Leeds Teaching Hospitals and applied to the use of IV ciclosporin in patients with ulcerative colitis, which has later been adapted for use locally by Shy Lih Teo, Lead Pharmacist Emergency Care.
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