

**Gastroenterology Guideline: Administration of Ciclosporin for the Treatment of Acute Severe  
Ulcerative Colitis in Adults**

## 1. Introduction

Ulcerative colitis (UC) presents as an acute severe flare in between 10% and 15% of new cases. Severe attacks requiring hospitalisation and intravenous steroids occur in 15% of patients with established disease.<sup>1</sup> First line treatment for such patients is infliximab,<sup>2</sup> but for those in whom this is contraindicated or unsuitable, due to previous infliximab treatment, intravenous ciclosporin therapy has been shown to be rapidly effective.<sup>3</sup> Intravenous ciclosporin (with or without continued intravenous corticosteroids) is effective in between 50% and 80% of patients with severe ulcerative colitis.<sup>4</sup>

## 2. Indications for use

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 thus informed patient consent should be sought. The decision to use ciclosporin must be made by a consultant gastroenterologist.

IV ciclosporin can be prescribed in ulcerative colitis patients who:

- Have not shown clinical or biochemical improvement after 3 days of IV hydrocortisone at a dose of 100mg QDS<sup>5</sup>
- Cannot tolerate intravenous corticosteroids or where they are contraindicated
- Are unsuitable for rescue treatment with infliximab due to contraindications to anti-TNF or due to current maintenance treatment with anti-TNF
- Have failed infliximab for acute severe colitis – there is limited data to support the use of ciclosporin as a second-line salvage treatment following infliximab failure

## 3. Contraindications

- Known hypersensitivity to ciclosporin or any excipients
- Concomitant use of any interacting drugs (see section 8)
- Known hypersensitivity to polyethoxylated castor oils (anaphylaxis risk)
- Uncorrected hypomagnesaemia (defined as magnesium levels <0.5mmol/L)<sup>6</sup>
- Hypocholesterolaemia (defined as cholesterol levels <3.0mmol/L)<sup>7</sup>

## 4. Cautions

- Alcohol sensitive patients (ciclosporin IV contains around 34.4% volume ethanol)
- Hyperkalaemia (defined as potassium levels of >5.0mmol/L) or co-administration with potassium sparing or containing medicines
- Hyperuricaemia (defined as urea levels of >7mg/dL)
- Hypertension (defined as blood pressure of >150/90mmHg)
- Infection – stool cultures should be negative for infection and prescribers aware that activation of latent polyomavirus infection may lead to polyomavirus associated nephropathy (PVAN)

- Liver impairment
- Malignancy – ciclosporin increases the risk of developing lymphomas and other malignancies, particularly those of the skin
- Renal impairment
- Vaccination – live attenuated vaccines should be avoided and vaccination may be less effective<sup>6</sup>

## 5. Dosage and administration

Total daily dose = 2 mg/kg – given as a continuous 24-hour IV infusion for **UP TO 7 DAYS**

Actual body weight should be used to calculate this dose unless BMI is over 30, in which case ideal body weight should be used instead. The dose should be prescribed on an infusion chart as 2mg/kg over 24 hours and a ‘see additional chart’ prompt added to EPMA. Rates are as per table 1.

Weight (kg)	Ciclosporin 50mg/50mL Rate of infusion mL/hour
45	3.75
50	4.2
55	4.6
60	5.0
65	5.4
70	5.8
75	6.25
80	6.7
85	7.1
90	7.5

*Table 1: Rate of Ciclosporin Infusion*<sup>8</sup>

### Administration:

Ciclosporin should be diluted to a concentration of 50mg in 50mL sodium chloride 0.9% or glucose 5% and given using a 50mL syringe and polyvinyl chloride (PVC) free administration set.<sup>7</sup> The excipient polyethoxylated castor oil is incompatible with PVC thus **polyethylene (PE) lined sets must be used** instead.<sup>6</sup>

### Expiry:

Infusions should be replaced on a continuous basis and any dose remaining after 24 hours should be discarded and a new infusion prepared.

## 6. Monitoring Requirements<sup>9</sup>

Test	Baseline	Frequency during IV infusion	Frequency during PO
Abdominal X-ray	✓	N/A	N/A
Varicella zoster serology	✓	N/A	N/A
Hep B and C serology	✓	N/A	N/A
Albumin	✓	Daily	Monthly
HbA1c	✓	N/A	At 3 and 6 months of treatment
Blood glucose	N/A	Random BMs	N/A
U&Es, FBC, CRP, magnesium, LFTs	✓	Daily	Every 2 weeks until on a stable dose for 6 weeks, then monthly for 3 months, then every 3 months
Blood pressure	✓	Four times a day	
Ciclosporin levels	N/A	After 72 hours and then twice a week	Weekly for 2 weeks, then monthly for 3 months, then every 3 months
Blood lipids	✓	N/A	After 1 month of treatment
Observations	N/A	Every 30 minutes for the first 2 hours and then 6 hourly	N/A
Stool chart	Entirety of inpatient stay		
Thiopurine Methyltransferase	✓ Ensure appropriate to start thiopurine	N/A	

During the first hour the patient should be monitored every 15 minutes for signs of an allergic response, such as wheezing, urticaria and hypotension. If anaphylaxis occurs, the infusion should be discontinued and the patient managed as per Trust guidance.<sup>8</sup>

### Magnesium

Hypomagnesemia should be corrected, as per the Trust policy, before commencing ciclosporin as ciclosporin use in those with hypomagnesaemia can result in nephrotoxicity.

### Blood lipids

Ciclosporin is a highly lipophilic drug thus the risk of neurotoxicity with treatment is higher in those with hypocholesterolaemia and, as such, baseline cholesterol levels are required before treatment is initiated.

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

#### Renal Function, U&Es

Dose dependent increases in serum creatinine and urea may be seen in the first few weeks of therapy and may necessitate dose reduction. If creatinine increases by 30% or more from baseline, ciclosporin dose should be reduced by 25% and then stopped altogether if there is no subsequent improvement in renal function.<sup>10</sup>

Ciclosporin also increases the risk of hyperkalaemia, particularly in those with renal dysfunction or co-administration of potassium-sparing drugs. Hyperkalaemia should be treated as per the Trust policy, if it occurs.

#### Liver Function

If there is a more than 2-fold rise in the upper limit of normal in liver enzymes or bilirubin then the ciclosporin dose should be reduced by 25%. It should be stopped altogether if there is continued derangement of LFTs following a dose reduction.

#### Blood Pressure

If hypertension develops, appropriate antihypertensive therapy must be initiated with preference given to a drug that does not interfere with ciclosporin pharmacokinetics (see section 8).<sup>6</sup>

The dose of ciclosporin should be reduced by 25% - 50% if diastolic and systolic blood pressure remain consistently over 90mmHg and 150mmHg respectively despite antihypertensive therapy. Stop IV ciclosporin if there is no improvement after a dose reduction.

#### Ciclosporin Levels

- Sampling time: Steady state takes approximately 76 hours to reach so levels should be checked on the **morning of day 4 of treatment** and then every 2 days after this whilst the patient is receiving IV ciclosporin. The sample should be taken during a 15-minute interval between syringes.
- Sample type: Purple top 4mL EDTA tube<sup>11</sup>
- Reference range: 150-250ng/mL, toxicity can occur at levels of above 300ng/mL<sup>12</sup>
- Turnaround time: Results are expected within 1 week but ciclosporin can be ordered as an urgent test if clinically indicated. In this case, results can be obtained by the end of the working day (Monday–Friday) if received in the laboratory in the morning.

## 7. Adverse Drug Reactions<sup>6, 13</sup>

Very common ( $\geq 1/10$ ): Hyperlipidaemia, tremor, headache, hypertension, hirsutism, renal dysfunction.

Common ( $< 1/1$ ,  $\geq 1/100$ ): Leucopenia, hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia, convulsions, paraesthesia, flushing, nausea, vomiting, abdominal discomfort/pain, diarrhoea, gingival hyperplasia, peptic ulcer, acne, hypertrichosis, myalgia, muscle cramps, pyrexia, fatigue.

Uncommon ( $< 1/100$ ,  $\geq 1/1000$ ): Thrombocytopenia, anaemia, encephalopathy, allergic rashes, oedema, weight increase.

Rare ( $< 1/1,000$ ,  $\geq 1/10,000$ ): Haemolytic uraemic syndrome, microangiopathic haemolytic anaemia, motor polyneuropathy, pancreatitis, muscle weakness, myopathy, menstrual disturbances, gynaecomastia.

Very rare ( $< 1/10,000$ ): Optic disc oedema.

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

## 8. Drug Interactions<sup>6</sup>

Ciclosporin interacts with a large number of medicines and some foods, those commonly seen in practice are detailed below but for more information consult the ward pharmacist, medicines information, the BNF or summary of product characteristics.

Drugs that decrease ciclosporin levels - Inducers of CYP3A4 and/or P-glycoprotein – e.g.:

- Barbiturates (e.g., phenobarbital)
- Carbamazepine, oxcarbazepine
- Phenytoin
- *Hypericum perforatum* (St. John's Wort)
- Orlistat
- Rifampicin

Drugs/foods that increase levels - Inhibitors of CYP3A4 and/or P-glycoprotein – e.g.:

- Metoclopramide
- Macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin)
- Azole antimycotics (i.e., fluconazole, itraconazole, voriconazole, posaconazole)
- Diltiazem, verapamil and nifedipine
- Amiodarone

- Oral contraceptives
- Grapefruit (during oral ciclosporin dosing)
- Allopurinol

Combinations with increased risk for nephrotoxicity

- Aminoglycosides (e.g., gentamicin, vancomycin)
- Amphotericin
- Ciprofloxacin
- NSAIDs (e.g., aspirin, naproxen, ibuprofen, diclofenac)

Ciclosporin may reduce the clearance of

- Digoxin
- Colchicine
- Prednisolone
- Statins

Caution is also required when ciclosporin is used alongside other potassium-sparing medicines.

## 9. Concomitant IBD Therapy

Corticosteroids: Patients should be maintained on IV hydrocortisone 100mg QDS during initial ciclosporin dosing until clinical improvement allows conversion to oral steroid dosing. Typical oral prednisolone reducing regime: 40mg OD for 1 week, reducing by 5mg/week until stopped.

Azathioprine/ Mercaptopurine: Should be started alongside oral ciclosporin at a dose of 2-2.5mg/kg daily (azathioprine) or 1-1.5mg/kg daily (mercaptopurine).

Oral Mesalazine: Evidence shows that mesalazine reduces the occurrence of bowel cancer<sup>14</sup> but in some instances concurrent use in the acute phase can cause worsening of symptoms. The decision over whether or not to continue treatment should be at the consultant's discretion.

Rectal Therapy: Rectal therapy with corticosteroids and/or mesalazine preparations can be continued if considered appropriate.

Current biologic treatment: Ciclosporin as a rescue treatment for acute severe colitis may be chosen if patients are already on maintenance biological treatment, including anti-TNF.

Biologic	Half-life (days)	Washout period (weeks)
Infliximab	8-9.5	6
Adalimumab	14	8-10
Vedolizumab	26	14-18
Ustekinumab	21	12-15

*Table 2: Biologic washout periods*

JAK-inhibitor	Half-life (hours)	Washout period (days)
Filgotinib	7-19	1.5-3
Upadactinib	9-14	2-3
Tofacitinib	3	0.5 -1
Ozanimod	21	4-5

*Table 3: JAK-inhibitor and small molecule washout periods*

## 10. Conversion to Oral Therapy

IV ciclosporin should be given for up to 7 days if a response is seen. After this, patients should be converted to oral therapy. Oral ciclosporin therapy does not appear to be effective in maintaining UC remission thus use should be limited to a duration of 3-6 months<sup>15</sup> during which time thiopurines can be introduced as maintenance therapy.<sup>16</sup>

Dose: 5mg/kg total daily dose given in **two equal divided** doses in the morning and evening<sup>3</sup> (capsules are available in strengths of 25mg, 50mg and 100mg)

Brand Prescribing: The brand prescribed should **always** be specified as there are variations in bioavailability between brands. Generic brands should be prescribed.

See section 6 for monitoring requirements for oral therapy

## 11. Pneumocystis jiroveci pneumonia (PCP) Prophylaxis

Patients should receive prophylaxis against PCP with co-trimoxazole at a dose of 960mg once a day three times a week<sup>17</sup> for the duration of the oral ciclosporin course<sup>18</sup>

Patients who are exposed to high dose triple therapy following second-line salvage treatment with ciclosporin following failed infliximab rescue within 2 weeks should also be considered for PCP prophylaxis.

## 12. References

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