Ciclosporin or infliximab as salvage therapy for acute, severe ulcerative colitis

Ciclosporin is an immunosuppressant that inhibits the production of interleukin 2 by activated T lymphocytes through a calcineurin dependent pathway. It also down regulates the synthesis of other inflammatory cytokines. Studies have shown that ciclosporin is effective in the management of acute severe UC, which has failed to respond to corticosteroid therapy. The first studies used a dose of 4mg/kg/day, but concerns were raised in relation to adverse effects and death in some patients. A recent trial demonstrated that a dose of 2mg/kg/day was as effective as 4mg/kg/day, but with fewer side effects. However, ciclosporin is not licensed for the treatment of UC and therefore should only be initiated by a consultant Gastroenterologist only.

Approximately 50% of patients will respond to ciclosporin but half of these will relapse when therapy is stopped. Even if patients relapse, the time bought can be useful to allow other immunosuppressants such as azathioprine or 6-mercaptopurine to become therapeutic. For patients who are already on azathioprine and failing or losing response then infliximab may be an alternative option. NICE (2008) states that infliximab can be considered for acute exacerbations of UC when ciclosporin is contra-indicated (see below) or clinically inappropriate. Infliximab is a monoclonal antibody that binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF)α, thereby inhibiting its functional activity. TNFα is a pro-inflammatory cytokine that plays a key role in the pathophysiology of ulcerative colitis

Inclusion Criteria for ciclosporin
• Confirmed diagnosis of a moderate to severe flare acute exacerbation of UC that has failed to respond to 72 hours of intravenous (IV) corticosteroids or patient has previously been intolerant to corticosteroids
• Patient has given informed consent and is aware of other treatment options including surgery
• Stool cultures have been performed and are negative for infection, including clostridium difficile
• There is no other suspected infection or sepsis
• The ward pharmacist is informed of iv ciclosporin use in the patient

Exclusion Criteria for ciclosporin
• Patients who are known to have hypersensitivity to ciclosporin
• Patients concurrently using tacrolimus and rosuvastatin
• Patients known to have hypersensitivity to polyethoxylated castor oils
• Patients with uncontrolled hypertension > 150/90
• Patients with serum cholesterol < 3.0 mmol/L (increased risk of seizure)
• Patients with serum magnesium < 0.50 mmol/L (increased risk of seizure)
• Hyperkalaemia > 5.0mmol/L
• Patients with renal and/or liver failure
• Patients with any kind of malignancy
• Patients who are pregnant/breastfeeding
• Patients with epilepsy
• Absolute indication for surgery
• Patient not under the care of a Consultant Gastroenterologist

Inclusion Criteria for infliximab
• Confirmed diagnosis of a severe acute exacerbation of UC that has failed to respond to 72 hours of IV corticosteroids
• Patients have given informed consent and are aware of other treatment options including surgery
• Stool cultures have been performed and are negative for infection, including clostridium difficile
• Ciclosporin is contra-indicated or clinically inappropriate
Exclusion Criteria for infliximab

- Patients with previous or current Tuberculosis (TB) or recent contact with TB
- Patients with other suspected infection or sepsis
- Patients with heart failure (NYHA class III/IV)
- Patients with a history of hypersensitivity to infliximab, to other murine proteins, to any of the excipients.
- Patients with multiple sclerosis
- Patients who are pregnant /breast feeding

Suggested use of salvage therapy in acute severe ulcerative colitis

Assess after 72 hours iv steroids

Stool frequency of >8/day or 3-8/day + CRP >45 mg/l

Check Magnesium & cholesterol levels; obtain Consultant colorectal surgeon review, stoma nurse review and consider use of salvage therapy after discussion with patient and colorectal team

Consider ciclosporin

Ciclosporin contraindicated or not clinically appropriate

Consider Infliximab
Use of ciclosporin
Consider stopping IV hydrocortisone on commencement of ciclosporin. If remission is achieved then convert to oral prednisolone 40mgs for two weeks then to 30mgs for 2 weeks, then reduce by 5mg/week to zero.

Continue other immunosuppressants unless risk is thought to outweigh benefit. Aminosalicylates should be continued during therapy.

- Patients should be advised to avoid grapefruit and grapefruit juice since it may increase ciclosporin levels.5
- Patients should continue ciclosporin for up to three months unless patients develop any adverse reactions or events.7

Patients should be commenced on prophylactic antibiotics against opportunistic infection: Oral co-trimoxazole 960mg on alternate days (Three times a week) whilst on intravenous ciclosporin.

Dose and Administration

Intravenous
IV ciclosporin is available but patient should be warned of the increased risks of seizures, the starting dose is 2mg/kg every 24 hours.2

As UC patients are generally underweight, the actual body weight should be used to calculate the ciclosporin dose. Only if the patient is overweight should ideal body weight be used instead. Ciclosporin levels will inform any necessary dose adjustments.

IV ciclosporin is prepared on the ward. It is available as 50mg/ml and 250mg/5ml ampoules. The dose should be diluted to a concentration of 50mg in 50ml of either glucose 5% or sodium chloride 0.9%. The infusion should be administered in a 50ml syringe using a syringe pump. The drug should not be added to PVC containing infusion bags, to avoid the risk of leaching of plastic into the infusion.

The rate of infusion should be calculated as follows:
- The dose should be prescribed on the blue IV prescription chart and expressed as “Ciclosporin 50mg in 50ml sodium chloride 0.9% (or glucose 5%), run at x ml/hour”
- The hourly rate $\frac{x}{2} = \frac{2 \times \text{weight (kg)}}{24(\text{hrs})}$

See Table 1 for hourly rate $\frac{x}{2}$ according to patient weight.

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

Table 1 – Ciclosporin hourly rate $\frac{x}{2}$ in ml/hr according to patient weight

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Hourly rate $\frac{x}{2}$ (ml/hr)</th>
<th>Weight (kg)</th>
<th>Hourly rate $\frac{x}{2}$ (ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>3.3</td>
<td>75</td>
<td>6.25</td>
</tr>
<tr>
<td>45</td>
<td>3.75</td>
<td>80</td>
<td>6.7</td>
</tr>
<tr>
<td>50</td>
<td>4.2</td>
<td>85</td>
<td>7.1</td>
</tr>
<tr>
<td>55</td>
<td>4.6</td>
<td>90</td>
<td>7.5</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
<td>95</td>
<td>7.9</td>
</tr>
<tr>
<td>65</td>
<td>5.4</td>
<td>100</td>
<td>8.3</td>
</tr>
<tr>
<td>70</td>
<td>5.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Take a random ciclosporin level early on Day 4 (72hrs to reach steady state) and Day 7. The infusion does not need to be stopped prior to levels being taken. Ciclosporin levels are analysed at Royal Liverpool Hospital only. This service is only available Monday to Friday. Samples need to be sent by taxi from the ward to Biochemistry at Royal Liverpool Hospital to arrive by 12noon to be processed on the same day. It is the responsibility of the ward pharmacist to contact Biochemistry.
at the Royal Liverpool Hospital for the result by 5pm and liaise with the medical team to adjust the
dose as necessary to achieve ciclosporin levels of 100-200ng/ml. If the level is low, check no gaps
between infusions.

If IV ciclosporin is started on a Wednesday, a random ciclosporin level should be taken early on
Friday morning. This is to check for toxicity only. As ciclosporin takes 72 hours to reach steady
state, do not increase dose if level reported as sub-therapeutic at this stage.
If IV ciclosporin is started on a Thursday, a random ciclosporin level should be taken early on the
following Monday morning.
Clinical response should be monitored over the weekend. Deterioration in renal function could
indicate ciclosporin toxicity. A sub-therapeutic ciclosporin level may result in treatment failure.

IV ciclosporin should be continued for 7 days before converting to oral therapy.

**Monitoring**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily U&amp;E whilst on intravenous ciclosporin</td>
<td>If any renal deterioration: either reduce the dose or stop therapy (if Cr rises to more than 150 (or by more than 30% of the starting value) the dose of ciclosporin should be reduced by 25%. If the Cr exceeds 200 or the trend is not reversed, the dose should be further reduced or drug stopped)</td>
</tr>
<tr>
<td>Daily LFT whilst on intravenous</td>
<td>If liver enzymes or bilirubin become significantly affected (twice the upper limit) reduce the dose by 25% or stop therapy.</td>
</tr>
<tr>
<td>Daily Magnesium whilst on intravenous (0.7-1.0mmol/L)</td>
<td>Add IV Magnesium if any hypomagnesaemia as per WUTH Medicines Guide</td>
</tr>
<tr>
<td>4 hourly MEWS as per Acute Severe UC &amp; Crohn’s Colitis Guidance (more often if deterioration)</td>
<td>If hypertension, dose reduction by 25% or initiation of appropriate anti-hypertension therapy. If hypertension uncontrolled then stop therapy.</td>
</tr>
<tr>
<td>Ciclosporin levels at Day 4 and Day 7 whilst on intravenous. Trough ciclosporin levels on oral therapy before morning dose - weekly for 2 weeks (or until dose stable) and then monthly. If dose adjustment weekly again until stable</td>
<td>Adjust dose accordingly for levels of 100-200ng/ml</td>
</tr>
<tr>
<td>Daily FBC &amp; CRP whilst on intravenous</td>
<td>Stop if WCC &lt; 3.0 or PLTS &lt; 120 CRP to monitor progress</td>
</tr>
</tbody>
</table>

Monitor patient for first 30mins of the first infusion since the polyethoxylated castor oil can cause
anaphylactic reactions (flushing of face and upper thorax, acute respiratory distress, tachycardia,
blood pressure changes). Monitor temperature, pulse and blood pressure every 30mins for first 2 hrs of the first infusion.

If starting Azathioprine to check thiopurine methyltransferase (TPMT) level
Oral therapy
- 5mg/kg/day in 2 divided doses (aiming for a ciclosporin level of 100-200ng/ml) for 3-6 months.\textsuperscript{7}
- Since ciclosporin has not proved to be beneficial in maintaining remission in UC consider commencing azathioprine or 6-mercaptopurine if appropriate and not contraindicated.\textsuperscript{7}

Undesirable effects \textsuperscript{5, 8}

Minor side effects (31-51%)

Tremor, paraesthesiae, malaise, headache, abnormal liver function, gingival hyperplasia and hirsutism.

Other common side effects include: gastrointestinal disturbances (anorexia, nausea, vomiting and diarrhoea), hypertrichosis, hypertension, hyperlipidaemia (reversible), hyperkalaemia, hypomagnesaemia, hyperuricemia.

Major side effects (0-17%)

Renal failure, infection, neurotoxic effects such as seizure

Mild, reversible renal impairment is common during the first few weeks of therapy. It may necessitate a dose reduction of discontinuation
There are only isolated reports of serious renal failure (likely due to short duration of therapy)

See BNF or Summary of Product Characteristics (SPC) for full list of side effects.

Drug Interactions \textsuperscript{5}

The ward pharmacist should been contacted and concurrent medication checked for interactions which could reduce or increase ciclosporin levels.

Increase ciclosporin levels
- Grapefruit juice
- Metoclopramide
- Erythromycin / Clarithromycin
- Fluconazole / Ketoconazole / Miconazole / Itraconazole / Voriconazole
- Diltiazem / Verapamil / Nicardipine
- Amiodarone
- Oral contraceptives
- Ursodeoxycholic acid

Reduce ciclosporin levels
- Phenytoin
- Carbamazepine / Oxcarbazepine
- Phenobarbitone
- Rifampicin
- St John’s Wort

Increase risk of nephrotoxicity
- Aminoglycosides
- Amphotericin
- Ciprofloxacin
- NSAIDs
- Trimethoprim / Co-trimoxazole
Increased risk of muscle toxicity when given with statins or colchicine (avoid / reduce dose as per SPC).
See BNF or Summary of Product Characteristics (SPC) for full list of interactions.

Use of infliximab

Patient needs an up to date chest x-ray to help exclude tuberculosis (TB). Infliximab treatment should not be delayed pending a TB ELISpot test result.

Continue IV hydrocortisone on commencement of infliximab. If remission is achieved then convert to oral prednisolone 40mgs for two weeks then to 30mgs for 2 weeks, then reduce by 5mg/week to zero.
If clinical response and patient avoids colectomy give additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion.

Dose and Administration

5mg/kg body weight infused intravenously in 250ml Sodium Chloride 0.9% over a 2-hour period. Infliximab must be administered via 0.2 micron filter.

Prepared in the Pharmacy Aseptic Unit – DO NOT SHAKE.

Patients receiving infliximab are at risk of allergic/anaphylactic reactions (see below)

Prescribe:

For patients not already on steroids / azathioprine or 6-mercaptopurine or who have had a previous infusion reaction:

- Hydrocortisone iv bolus 100mg prior to infliximab infusion

For all patients

- Hydrocortisone iv bolus 100-200mg prn ‘Moderate infliximab hypersensitivity only’
- Chlorpheniramine iv bolus 10-20mg prn ‘Moderate infliximab hypersensitivity only’ (maximum 40mg in 24hrs) –
- Chlorpheniramine tablets 4mg prn ‘Mild Infliximab hypersensitivity only’ (maximum 24mg in 24hrs)
- Paracetamol tablets 1g prn ‘Mild Infliximab hypersensitivity only’ (maximum 4g in 24hrs)

Check the anaphylaxis kit is available at the patient’s bedside.

Check MEWS score before infusion and every half hour during infusion and for 2 hours post infusion.
<table>
<thead>
<tr>
<th>Infusion reaction</th>
<th>Action</th>
</tr>
</thead>
</table>
| Mild hypersensitivity [pruritus, rash, headache and NO respiratory or cardiovascular distress] | • Halve rate of infusion  
• Inform medical staff  
• If rash present give 4mg chlorpheneramine orally  
• If headache present give 1g paracetamol orally  
• If improvement continue infliximab infusion at reduced rate and monitor |
| Moderate hypersensitivity [urticaria/rash, mild hypotension, tachycardia, mild wheeze, nausea] | • STOP infusion  
• Lay patient flat and secure airway  
• Check MEWS  
• Inform medical staff  
• Give 100-200mg hydrocortisone IV and 10-20mg chlorpheneramine by slow iv injection |
| Severe hypersensitivity [Hypotension, respiratory distress, swollen lip, obstructed airway, loss of consciousness, reduced oxygen saturation, flushed or pale] | • STOP infusion  
• Follow resuscitation protocol  
• Inform medical staff |

**Undesirable effects**

**Very common effects (≥1/10) include:**

Viral infection, upper respiratory tract infection, sinusitis, headache, infusion-related reaction, pain, abdominal pain and nausea.

**Common effects (≥1/100 to <1/10) include:**

Bacterial infection (including lower respiratory tract infection, conjunctivitis and urinary tract infection), blood disorders (including neutropenia, leucopenia, anaemia, lymphadenopathy) allergic respiratory symptom, depression, insomnia, fatigue, fever, chills, injection site reaction, vertigo, dizziness, flushing, oedema, hypo or hypertension, hypoaesthesia, paraesthesia, tachycardia, chest pain, gastrointestinal effects (e.g. haemorrhage, diarrhoea, dyspepsia, constipation), altered LFTs and dry skin.

**Severe but rare effects (≥1/10,000 to <1/1,000) include:**

Tuberculosis, septicaemia and hepatitis B reactivation

Cardiac failure (new onset or worsening), Skin reactions (including toxic epidermal necrolysis and stevens-johnson syndrome), (autoimmune) hepatitis, jaundice, interstitial lung disease, circulatory failure, cyanosis, pericardial effusion, endophthalmitis, demyelinating disorders, lymphoma, leukaemia

See BNF or Summary of Product Characteristics (SPC) for full list of side effects.
References

2. Quan VA, Saunders BP, Hicks BH, Sladen GE. Cyclosporin treatment for ulcerative colitis complicated by fatal Pneumocystis carinii pneumonia. BMJ 1997; 314: 363-364
3. Van Assche G, D’haens G, Noman M et al. Randomized, Double-Blind Comparison of 4mg/kg versus 2mg/kg Intravenous Cyclosporine in Severe Ulcerative Colitis. Gastroenterology 2003; 125: 1025-1031