Ciclosporin for Patients Receiving Allogeneic Blood and Marrow Transplantation

Ciclosporin (CSA) is a cyclic polypeptide with potent immunosuppressive properties. CSA blocks lymphocytes in G0 or early G1 phases of the cell cycle and inhibits cytokine (such as IL-2) release. In BMT recipients it is used as prophylaxis against graft-versus-host disease.

Starting ciclosporin

1. CSA is started 3 days before cell infusion (day –3).
   CSA should be commenced orally (unless there is severe GI disturbance) at 5mg/kg/day (i.e. 2.5mg/kg/bd). Capimune oral formulation should be prescribed. It is important to emphasise, that many patients still need IV CSA at some point during the transplant. There should be a very low threshold for switching to IV when mucositis occurs.

2. The intravenous (IV) starting dose of CSA is 3mg/kg/day (i.e.1.5mg/kg/bd) and should be diluted to a concentration of 50mg in 20 – 100mls of sodium chloride 0.9% then infused over 2 - 4 hours.

Body weight should be calculated from the lean or actual weight which ever is the less.

Oral to IV conversion is usually a reduction of one third of the oral dose.

It is worth noting that malabsorption of oral ciclosporin may present as an oily film on stools/diarrhoea; this should be reported to the medical team.

Monitoring inpatient ciclosporin levels

CSA levels are monitored on day -1, then twice weekly, on Monday and Thursday. A CSA ‘lumen’ should be identified on the drug chart and the CSA level should be taken from the lumen of the central line which has not been used to give CSA (as the IV drug adheres to the line). Alternatively, a sample from a peripheral vein may be taken.

The samples should be collected just before the patient has their morning dose of CSA. The blood should be taken into EDTA (a full blood count bottle) and sent with a biochemistry request.

Monitoring outpatient ciclosporin levels

Oral CSA levels are monitored at each clinic appointment. This is usually weekly in the early months post discharge and continues until tapering has commenced. Patients should be advised not to take the morning dose on the day of their appointment but, to bring the dose with them to take post blood sampling, and to take the previous evening dose approximately 12 hours prior to their appointment time. This will help to promote a true trough level. As above, samples should be taken in EDTA and sent with a biochemistry request.
Target ciclosporin levels
T-replete transplants: CSA levels should be between 200-300ng/mL.

T-deplete (i.e. Alemtuzumab or ATG conditioned) transplants: CSA levels should be between 100-200ng/mL.

If the CSA level is low the dose of CSA should be increased by 25%. Levels above 400ng/mL may be ignored if the patient has no signs of toxicity (see later) but the assay should be repeated 24 – 48 hours later. Persistent, very high levels may require a dose reduction at the discretion of the consultant or SpR looking after the patient.

Please note that specific clinics trials may have differing target CSA levels, please see trial documentation.

Ciclosporin and deteriorating renal function
Dose adjustments of CSA are essential in patients with deteriorating renal function, discuss with consultant. Specifically where there is a rapid increase of creatinine within 24 hours of 50% or more, miss 1-2 doses of ciclosporin and restarting at a lower dose. Discuss specific dosing strategies with transplant consultant.

Registrars should personally review allograft blood test results daily inclusive of weekends

Converting intravenous to oral ciclosporin (Capimune)
Patients should be started on at 1.5 x the last intravenous dose that the patient was receiving. This dose, like the IV dose, is given in two divided doses.

Full dose Ciclosporin (Capimune) is continued until day 100 after which, in the absence of graft versus host disease, it can be tapered by 25-50mg per week and stopped by day 180.

Ciclosporin levels should be monitored once weekly and the dose modified as described above for patients receiving the intravenous formulation.

Side effects of ciclosporin
- Nausea and vomiting
- Tremor
- Hypertension
- Headache
- Fluid retention
- Renal impairment

When administered IV, rate reduction, analgesia and anti-emetics are the first steps in managing headache, nausea and vomiting.

Dose reduction is the next step in managing these side effects and should be discussed with the consultant or SpR looking after the patient. Dose reduction is often indicated in the first few days of transplantation in patients developing headaches or having significant problems with nausea and vomiting. Reduce dose by 50% initially and then gradually increase over the following few days. Patients will often become more tolerant of ciclosporin with fewer such side effects with time.
Other side effects include neurological symptoms, such as fits, particularly in patients with raised blood pressure and hypomagnesaemia or hypocalcaemia, hypertrichosis and occasionally, a HUS or TTP type disorder. For a full list of possible side effects the data sheet should be consulted.

**Pharmaceutical Interactions**

*The patient should be told to avoid grapefruit juice for 2 hours before and after oral ciclosporin dose as this can raise the ciclosporin levels, increasing the risk of toxicity.*

Voriconazole and posaconazole increase the levels of ciclosporin. Twenty four hours after starting voriconazole/posaconazole, reduce ciclosporin dose by 50% and monitor levels closely.

NSAIDs: interact with ciclosporin and can cause significant renal impairment. If possible patients should not receive NSAIDs. If NSAIDs have to be used, then monitor renal function carefully and try to limit NSAID administration to a few days only e.g. in the treatment of gout.

Colchicine: ciclosporin inhibits P-glycoprotein and reduce colchicine excretion, increasing the risk of myopathy, rhabdomyolysis or neuromyopathy. For treatment of gout, colchicine dose should be reduced to a single dose of 500 microgram, repeat after 72 hours if necessary.

**Drugs that decrease ciclosporin levels:**

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine i.v, rifampicin, octreotide, probucol, orlistat, hypericum perforatum (St John's Wort), ticlopidine, sulfipyrazone, terbinafine, bosentan.

**Drugs that increase ciclosporin levels:**

Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole; diltiazem, nicardipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors, imatinib; colchicines; nefazodone

This list is not conclusive. Please consult your pharmacist for advice.
Applicable Jacie Standard: 5th Edition
B3.4.4.7 Diagnosis and management of acute and chronic graft versus host disease

Audit
These processes are subject to the OxBMT audit programme.

Authors
Tim Littlewood, BMT Programme Director, Original and Version 2, 2004,
Denise Wareham, BMT Co-ordinator – Version 3, 2008 and amendments 2009

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