

## **Ciclosporin (CsA) for Patients Receiving Allogeneic Blood and Marrow Transplantation**

### **Indication**

Prophylaxis of graft-versus-host disease (GvHD), in patients undergoing allogeneic Blood and Marrow Transplantation (BMT).

### **Dosing**

Starting dosing of ciclosporin

**CSA is started 3 days before cell infusion (day -3).**

CSA should be commenced orally (unless there is severe GI disturbance). 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.

**Oral route:** ciclosporin 2.5mg/kg TWICE daily (i.e. total daily dose 5mg/kg in two divided doses)

**Intravenous route:** ciclosporin 1.5mg/kg TWICE daily (total daily dose 3mg/kg in two divided doses) via intravenous infusion over 2-4hours.

**The dose needs to be adjusted in case of concurrent drug interactions, particularly with azole antifungal prophylaxis- see drug interaction section below for guidance.**

**Duration:** Full dose CSA is continued until day +100 after which, in the absence of graft versus host disease, it can be tapered by 25-50mg per week, aiming to stop within four weeks.

For patients with high risk disease treated with Flu/Mel/Campath conditioning, consider tapering CSA from day +60

### **Dosing/prescribing considerations:**

- **The dose needs to be adjusted in case of concurrent drug interactions, particularly with azole antifungal prophylaxis- see drug interaction section below for guidance.**
- Ciclosporin must be prescribed and dispensed by BRAND NAME to minimise the risk of inadvertent switching between products, and avoid confusion and the potential for patients receiving the wrong formulation. There are a number of ciclosporin brands and pharmaceutical forms available, and they are NOT INTERCHANGEABLE.
- 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.

### **Oral to IV conversion:**

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

### **IV to oral conversion:**

When switching patients from intravenous to oral route, the total daily oral CSA dose should be 1.5 x the total daily intravenous dose, that the patient was receiving and given in two divided doses.

### **Dosing in 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, omit 1-2 doses of ciclosporin and restart at a lower dose. Discuss specific dosing strategies with transplant consultant.

Registrars should personally review blood test results on all allograft patients daily inclusive of weekends and discuss ciclosporin dosing with the on-call consultant if they are unsure.

### **Therapeutic Drug Monitoring**

CsA levels are measured at 12 h after a dose (trough level before the next infusion/dose).

### **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 clinical trials may have differing target CSA levels, please see trial documentation.

### **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 EPR 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.

### Side Effects

- 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, an HUS or TTP type disorder. For a full list of possible side effects the product data sheet should be consulted.

### Drug Interactions

(This list is not conclusive. Please consult your pharmacist for advice).

#### Drugs that increase ciclosporin levels:

All inhibitors of CYP3A4 and/or P-glycoprotein may lead to increased levels of ciclosporin. Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole; diltiazem, nifedipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors, imatinib; colchicines; nefazodone

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

#### Drugs that decrease ciclosporin levels:

All inducers of CYP3A4 and/or P-glycoprotein are expected to decrease ciclosporin levels. Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine iv rifampicin, octreotide, probucol, orlistat, hypericum perforatum (St John's Wort), ticlopidine, sulfapyrazone, terbinafine, bosentan.

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

**Food interactions:** The concomitant intake of grapefruit and grapefruit juice has been reported to increase bioavailability of ciclosporin and must be avoided.

**Effect of ciclosporin on other medicinal products:**

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.

**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

**Circulation**

**NSSG Haematology Website**

**Review**

Name	Revision	Date	Version	Review date
Dr A Peniket BMT Programme Director	Generic ciclosporin, additional pharmaceutical Information insertion of Jacie standards into document	Jan 2013	3.2	Jan 2015
Dr A Peniket	Change of initial CSA management to oral where tolerated	Sept 2014	3.3	Jan 2015
Dr T Littlewood, Consultant Haematologist Cheuk-Kie Cheung, Specialist Cancer Pharmacist	Minor amendments  Additional minor amendments and drug advisory information	Feb 2017	3.4	Feb 2019
Andy King, Haematology SpR Nadjoua Maouche, Lead Haematology Pharmacist, Cristina Ovas, BMT Quality and Data Manager	Indication. Dosing and prescribing considerations. Drug interactions. Restructuring of sections/information	July 2019	3.5	July 2021
Nadjoua Maouche, Lead Haematology Pharmacist  Robert Danby, Consultant Haematologist	Minor update. Removal of lean body weight CSA reduction schedule	Oct 2020	3.6	Oct 2022
James Davies, Consultant Haematologist and Rob Danby, Consultant	Minor update	June 2023	3.7	June 2025

Department of Clinical Haematology  
Oxford BMT Programme

Haematologist				
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