Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

CICLOSPORIN FOR USE IN DERMATOLOGY, NEUROLOGY and GASTROENTEROLOGY
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for ciclosporin therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc , the BNF and the Shared Care Protocol - Responsibilities.

BACKGROUND FOR USE

Ciclosporin is a potent immunosuppressant and disease modifying drug. **This protocol is for non-transplant patients only**. Its uses in this protocol are limited to:

Dermatology
- Psoriasis (licensed) plus other severe inflammatory skin disease
- Atopic dermatitis (licensed)

Gastroenterology
- Induction and remission of ulcerative colitis (unlicensed)

Neurology
Used as a second-line therapy (unlicensed) for a range of neurological disorders including:
- myasthenia gravis,
- inflammatory myopathies and neuropathies
- vasculitis and other immune-mediated central and peripheral nervous system diseases

Rheumatology – see separate protocol

For all renal patients, supply of this medication will be provided in secondary care.

SUPPORTING INFORMATION

It is important that ciclosporin is prescribed by BRAND name, due to the associated risk of either toxicity or rejection should the patient receive the wrong formulation. The MHRA advises that patients should be stabilised on a single brand and the same brand should always be prescribed and dispensed. Capimune is the branded generic of choice. All new patients starting therapy should be initiated on Capimune, with the exception of transplant patients who will continue to be initiated on Neoral first line. Any existing patients currently taking Neoral should be continued on this.

CONTRAINDICATIONS AND PRECAUTIONS

CONTRAINDICATIONS	
Uncontrolled hypertension	Do not use
Severe electrolyte imbalance, e.g. hyperkalaemia	Do not use
Uncontrolled infections	Do not use
Breastfeeding	Do not use
Malignancy	Do not use
Other immunosuppressants	Do not use unless recommended by specialist
Renal impairment	See monitoring below
Hypersensitivity	Do not use
PRECAUTIONS	

Pregnancy/Family Planning	Effective contraception is advised. Patients (both male and female) on ciclosporin who are considering starting a family should discuss issues with the specialist. Patients who are on the drug and do conceive should be referred back to clinic as soon as possible.
Immunisation with LIVE vaccines	Patients receiving ciclosporin must NOT receive immunisation with LIVE vaccines. Inactivated polio is available although sub-optimal response may be seen.
Chickenpox /shingles	Withhold ciclosporin and inform specialist. For those with exposure to chickenpox or shingles and no history of previous infection/vaccination, passive immunisation should be carried out using VZIG.
Excessive sun exposure	Avoid excessive exposure to UV light, including sunlight. Recommend diligent use of high SPF (25 or more) sunscreens.
Elderly	Use with caution as renal impairment. Drug interactions more common.
Epilepsy	Use in caution with anti-epileptics
Grapefruit juice	Increases plasma concentrations of ciclosporin (toxicity). Avoid for 1 hour prior to taking ciclosporin

DOSAGE

Indication	Dose
Dermatology	Starting dose usually 2.5 mg/kg daily in two divided doses. This is adjusted according to clinical response and haematological tolerance. The maximum dose is 5 mg/kg daily.[2]
Ulcerative Colitis	Usually initiated on intravenous ciclosporin in hospital (provided cholesterol level > 3). The oral dose is 2.5mg/kg twice a day (12 hours apart) for 3- 6 months.
Neurology	Starting dose of ~1mg/kg /day in two divided doses and increasing, if there are no adverse effects, to 2.5-3mg/kg.

TIME TO RESPONSE

Up to 3 months for most indications. Within 48-72 hours for acute severe UC.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- FBC
- U&Es (check renal function twice 2 weeks apart to obtain mean creatinine value) and eGFR.
- LFTs and fasting lipid profile.
- BP must be <140/90 before treatment, on 2 occasions 2 weeks apart. If over 140/90 treat hypertension before commencement.
- In patients with psoriatic arthritis, assess if patient received PUVA therapy. If total dose received >1000J discuss with dermatologists.
- Cholesterol (for IV)

ONGOING MONITORING SCHEDULE [2]

Ciclosporin can cause dose-related reduction in GFR and careful monitoring of the renal function and BP is essential. Irreversible renal damage is associated with high doses >5 mg/kg daily.

Parameter	Frequency and Result
Blood pressure & pulse	Check at 2 weeks, then every month (or as directed by consultant, some specialities vary). Maintain <140/90
U&Es including creatinine/eGFR	Every 2 weeks for 2 months. Then every month to 3 months. Monitor more frequently if dose increased or concomitant NSAIDs introduced or increased.
LFTs, FBC, ESR or CRP	Monthly for first 3 months, then every 3 months once stable
Fasting serum cholesterol and triglycerides	Every 6 months
Blood level	Every 2 weeks then monthly or within 48 hrs dose titration. 12 hour trough level. Target range for UC is 100-200ng/ml

In addition to absolute values for haematological indices, a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends it is recommended that all blood test results are entered in patient held monitoring booklet.

ACTIONS TO BE TAKEN

Side effects[2]	Action
WBC <3.5 x 10^9/l Neutrophils <2 x 10^9/l	Withhold and discuss with specialist.
Platelets <150 x 10^9/l	Withhold until discussed with specialist.
>2-3 fold rise in ALT/AST from upper limit of reference range	Withhold. Look for alternative cause. N.B may be of muscle origin in myositis. Repeat LFT's. If abnormal discuss with specialist.
Hyperkalaemia	Withhold until discussed with specialist
Significant rise in lipids	Withhold until discussed with specialist
Rise in serum creatinine >30% above baseline on 2 occasions 1 week apart	Withhold until discussed with specialist. In **dermatology** patients, if there is a sustained rise in serum creatinine exceeding 30% above the baseline value, the dose should be reduced by 0.5 to 1 mg/kg daily and review intervals should not exceed one month. If the creatinine has risen by more than 50%, larger dose reductions may be required.If the creatinine fails to return to within 130% of baseline consideration should be given to use of an alternative treatment.
BP >140/90 on 2 consecutive readings 2 weeks apart	Discuss with a specialist and consider 50% dose reduction (although not always necessary). Treat BP (but note interactions with antihypertensive drugs). If BP difficult to control stop ciclosporin and discuss with specialist.
Gastro-intestinal disturbances	Abdominal pain, anorexia, nausea, vomiting, diarrhoea; should be managed symptomatically. Consider 25 - 50% dose reduction if persists.
Abnormal bruising	Check FBC immediately. Withhold until discussed with specialist.
Abnormal sensations/ neuropathies	A burning sensation may be experienced in the hands and feet in the first 1 - 2 weeks of therapy. This is transient.
Hypertrichosis	Mild, common in 4 - 8 weeks in all patients. If significant, withhold and discuss with specialist.
Gum hyperplasia	If severe withhold and discuss with specialist.
Headache, tremor	Common and dose related. Consider other causes. Consider 25 - 50% dose reduction or cessation.

NOTES
In all patients annual flu vaccine is recommended (warning: do not use the live paediatric nasal spray) and pneumovax can be considered.

DRUG INTERACTIONS [2,3]

**** TAKE CARE WHEN CHANGING ALL TREATMENTS IN PATIENTS ON CICLOSPORIN ****

Agents increasing ciclosporin levels: Allopurinol, amiodarone, amlodipine, chloramphenicol, chloroquine, cimetidine, clarithromycin, danazol, diltiazem, erythromycin, ezetimibe, fluconazole, fluoroquinolones; grapefruit juice, hydroxychloroquine, itraconazole, ketaconazole, H_2 blockers, high dose methylprednisolone (risk of fits), metoclopramide, miconazole, nicardipine, oestrogens, omeprazole, progestogens, tacrolimus, verapamil, vitamin E.
(Avoid where possible and monitor ciclosporin levels and U&E if initiating or changing doses.)
Agents which may increase the risk of nephrotoxicity: Include aciclovir, bezafibrate, colchicine, doxycycline, fenofibrate, NSAIDs (use minimum dose and monitor effects on renal function when increasing NSAID dose), quinolones, thiazide diuretics, trimethoprim.
Agents which increase the risk of hyperkalaemia: ACE inhibitors, aldosterone antagonists, angiotensin receptor antagonists, potassium salts, potassium sparing diuretics.
Ciclosporin increases levels of the interacting drug: Darifenacin (manufacturers say avoid with ciclosporin), digoxin, methotrexate, (doses concurrently to be established by a specialist), nifedipine (increased risk of nifedipine toxicity), prednisolone (note may be co-prescribed but dose of prednisolone should be titrated gradually). Simvastatin, atorvastatin, rosuvastatin (may increase risk of rhabdomyolysis), sulphonamides (risk of myopathy).
Agents decreasing ciclosporin levels: Barbiturates, carbamazepine, griseofulvin, modafanil, orlistat, oxcarbazepine, phenytoin, primidone, rifampicin, sevelamer, St John's Wort, sulphadiazine, sulfinpyrazone, terbinafine.

BACK-UP INFORMATION/ADVICE

Contact Details	Oxford University Hospitals NHS Trust	
Dermatology	Dermatologist	01865 741155 ask for SR
Gastroenterology	Dr Simon Travis 01865 228753 simon.travis@ndm.ox.ac.uk Dr Oliver Brain Oliver.brain@ouh.nhs.uk	
Neurology	Dr David Hilton-Jones neurology consultant Neurology Registrar on call	Tel 01865 231893 Hospital switchboard: 01865 741166 Bleep Registrar on call
Medicines Information	Tel 01865 221505	

REFERENCES

1. Chakravarty-K et al. BRS/BHPR guideline for DMARD therapy in consultation with the British Association of Dermatologists. Rheumatology, 2008 1-16.
2. Ciclosporin (Neoral®) SPC http://www.medicines.org.uk/emc/ last updated 6th March 2014.
3. BNF No 68, September 2014.
4. The British Society of Gastroenterology. http://www.bsg.org.uk/
5. Ulcerative colitis: Management in adults, children and young people, NICE CG 166, June 2013
6. The European Crohns and Colitis organization. https://www.ecco-ibd.eu/

Acknowledge:
Adapted from Buckinghamshire CCG Shared Care Protocols