788FM.2.1 CICLOSPORIN FOR USE IN DERMATOLOGY, GASTROENTEROLOGY AND RHEUMATOLOGY
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for ciclosporin therapy. It should be read in conjunction with the Buckinghamshire responsibilities for amber protocol medicines (appendix 3 of Buckinghamshire Joint Formulary Policy), the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

BACKGROUND FOR USE

- Ciclosporin is a potent immunosuppressant and disease modifying anti rheumatic drug (DMARD).
- Its uses in this protocol are limited to:

Dermatology

- Psoriasis (licensed)
- Atopic dermatitis (licensed)

Rheumatology

- Rheumatoid arthritis (licensed)
- Psoriatic arthritis, Behçet's disease, myositis, systemic lupus erythematosus (SLE) (all unlicensed)
- Ciclosporin can be used in combination with other DMARDs such as methotrexate with careful monitoring

Gastroenterology

- Induction of remission of ulcerative colitis (unlicensed)

SUPPORTING INFORMATION

CONTRAINDICATIONS AND PRECAUTIONS

CONTRAINDICATIONS	
Hypersensitivity	Do not use
Uncontrolled hypertension	Do not use
Severe electrolyte imbalance, e.g. hyperkalemia	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
PRECAUTIONS	
Pregnancy	Effective contraception is advised. Avoid ciclosporin unless potential benefits outweigh risks.
Chickenpox/shingles	Withhold ciclosporin and inform specialist. For those with exposure to chickenpox or shingles and no history of infection/vaccination, check that immunity to Varicella zoster virus (VZV) infection has been checked. If the patient is susceptible, a course of oral aciclovir or valaciclovir is recommended unless there are significant concerns of renal toxicity or malabsorption. Discuss with a Microbiologist.
Excessive sun exposure	Avoid excessive exposure to ultraviolet (UV) light, including sunlight. Recommend diligent use of high sun protection factor (SPF) (30 or more) sunscreens.
Elderly	Use with caution as renal impairment. Drug interactions more common.

DOSAGE

Indication	Dose
Dermatology indications	Starting dose usually 2.5 mg/kg PO daily in two divided doses. This is adjusted according to clinical response and haematological tolerance. Doses should not normally exceed 5 mg/kg daily.[2]
Rheumatology indications	Starting dose 2.5 mg/kg daily PO in two divided doses for 6 weeks. It can be increased at 2 to 4 week intervals by 25 mg until clinically effective or maximum dose of 4 mg/kg daily is reached.[2]
Gastroenterology indication Ulcerative colitis (severe, acute)[5]	Usually initiated as ciclosporin in hospital at a dose of 2 mg/kg/day IV. It is then continued as an oral preparation at a dose of 2 mg/kg PO every 12 hours[5].

Prescribing points

- Patients should be stabilised on a particular brand of oral ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration.
- Neoral® is the ciclosporin brand on the Buckinghamshire formulary. It provides greater predictability than other ciclosporin brands.
- Prescribing and dispensing should be by brand name.
- Prescriptions must state the dosage form, strength, dose and directions in full.
- The use of 'as directed' in prescribing should be avoided. A specific dose must be applied to each prescription.

TIME TO RESPONSE

Up to 3 months.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- Full blood count (FBC)
- Urea and electrolytes (U&Es) (check renal function twice 2 weeks apart to obtain mean creatinine value) and estimated glomerular filtration rate (eGFR).
- Liver function tests (LFT) 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 psoralen and ultraviolet A (PUVA) therapy. If total dose received >1000J discuss with dermatologists.

VACCINATION (recommended by the Specialist to the patient and GP)

- Pneumococcal vaccination should be administered as a single dose polysaccharide PPV-23 (Pneumovax®), if possible, prior to initiation of ciclosporin therapy or as soon as possible afterwards.
- Annual influenza vaccine should be recommended to all patients.
- Live vaccines should not be given to patients who are receiving or have received immunosuppressive therapy in the past three months[7].
- Patients who have received a live vaccine should wait until their immune response has been established before commencing immunosuppressive therapy. For most viral live vaccines, a period of up to four weeks should be sufficient[7]. Inactivated polio vaccine is available although a sub-optimal response may be seen.

ONGOING MONITORING SCHEDULE[2]

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

Parameter	Frequency and Result
Blood pressure	Every 2 weeks for 2 months, then every month. Maintain BP <140/90.
U&Es including creatinine/eGFR	Every week for 1 month, every 2 weeks for 1 month, then every month. Monitor more frequently if dose increased or concomitant NSAIDs introduced or increased.
LFTs, FBC, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)	Monthly
Fasting serum cholesterol and triglycerides	At baseline, after one month, then every 6 months.

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.

ROLES AND RESPONSIBILITIES

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Unless otherwise stated in the protocol, the responsibilities are as follows:

Specialist

- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Where appropriate, provide advice to the patient on the impact of ciclosporin on fertility, pregnancy and breastfeeding.
- Provide a copy of patient information leaflet and drug monitoring card where appropriate.
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria and how often monitoring should be done.
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments.
- Be available to give advice to GP and patient throughout treatment.

GP

- Prescribe medication once the dose is stable and shared care is agreed.
- Ensure all monitoring is completed in accordance with the specific shared care protocol.
- Check and record results then advise the specialist of any deteriorations or abnormal results.
- Notify the specialist regarding any changes in patient's condition, any adverse drug reactions or failure to attend tests.

Patient

- Agree to treatment and monitoring after making an informed decision.
- Agree to being under the shared care of the GP and specialist.
- Attend for blood tests and monitoring when required.
- Ensure monitoring card is kept up to date and is brought to all appointments.
- Report any side effects to the GP or a member of the specialist team.

Note: If the patient does not attend blood monitoring, then treatment will be stopped. If the patient is more than 4 weeks late with their monitoring, then treatment should be stopped.

ACTIONS TO BE TAKEN

Side effects[2]	Action
White blood cell count (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 fold rise in alanine transaminase (ALT)/aspartate aminotransferase (AST) from upper limit of reference range	Withhold. Look for alternative cause. Repeat LFTs. If abnormal discuss with specialist.
Hyperkalaemia above upper limit of normal (ULN) (after excluding pseudohyperkalaemia)	Withhold until discussed with specialist
Significant rise in lipids	Withhold until discussed with specialist
Rise in serum creatinine >25% above baseline or reduction of eGFR >25% below baseline on 2 occasions 1 week apart	Withhold until discussed with specialist. If the creatinine fails to return to within 125% of baseline consideration should be given to use of an alternative treatment.
BP >140/90 on 2 consecutive readings 2 weeks apart	Consider 50% dose reduction (although not always necessary). Discuss with a specialist. Treat BP (but note interactions with antihypertensive drugs). If BP difficult to control stop ciclosporin and discuss with specialist.
Gastrointestinal disturbances	Abdominal pain, anorexia, nausea, vomiting, diarrhoea; should be managed symptomatically. Consider 25 - 50% dose reduction if persists. Discuss with specialist.
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. Discuss with specialist.

DRUG INTERACTIONS[2,3]

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

- **Agents increasing ciclosporin levels:** Allopurinol, amiodarone, amlodipine, aprepitant, bosentan, chloramphenicol, chloroquine, cimetidine, clarithromycin, danazol, diltiazem, dronedarone, erythromycin, ezetimibe, fluconazole, fluoroquinolones; grapefruit juice, hydroxychloroquine, imatinib, itraconazole, ketaconazole, H_2 blockers, high dose methylprednisolone (risk of fits), metoclopramide, miconazole, nicardipine, oestrogens, omeprazole, progestogens, protease inhibitors 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 when used concurrently:** Include aciclovir, bezafibrate, colchicine, doxycycline, fenofibrate, non-steroidal anti-inflammatory drugs (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:** Angiotensin converting enzyme (ACE) inhibitors, aldosterone antagonists, angiotensin receptor antagonists, potassium salts, potassium sparing diuretics.

- **Ciclosporin increases levels of the interacting drug:** Dabigatran (dose may need adjusting), darifenacin (manufacturers say avoid with ciclosporin), digoxin, methotrexate, (doses concurrently to be established by a specialist), nifedipine (increased risk of nifedipine toxicity), and prednisolone (note may be co-prescribed but dose of prednisolone should be titrated gradually), rifaximin. 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	Wycombe and Amersham	Stoke Mandeville
Dermatology	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01494 526161 **Email:** bht.dermatologysecretaries@nhs.net	09:00 – 17:00 contact on-call registrar or consultant via switchboard 01296 315000 **Email:** bht.dermatologysecretaries@nhs.net
Rheumatology	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries) In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Reg: Bleep 905/907 via switchboard **Email:** bht.rheumatology@nhs.net	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries) In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Reg: Bleep 905/907 via switchboard **Email:** bht.rheumatology@nhs.net
Gastroenterology	**Routine queries:** Advice and guidance via ERS. **Urgent queries:** via switchboard, bleep 543 **Gastroenterology secretaries:** **email** buc-tr.whgastro@nhs.net Consultant secretary: Dr Cullen 01494 425267 Dr Gorard 01494 425267 Dr Johns 01494 425595 Dr Maggs 01494 425595 **Dedicated IBD patient helpline** 01296 315105	**Routine queries:** Advice and guidance via ERS. **Urgent queries:** via switchboard, bleep 543 **Gastroenterology secretaries:** **email** buc-tr.whgastro@nhs.net Consultant secretary: Dr Sekhar 01296 312599 Dr Hossain 01296 312599 Dr Blackwell 01296 312599 Dr Khan 01296 312599 **Dedicated IBD patient helpline** 01296 315105
Medicines Resource Centre	Email: bucks.medicinesresourcecentre@nhs.net Tel: 01494 425355 (Monday to Friday 0900 to 1700)	

SHARED CARE AGREEMENT FORM

Available on DocGen. When not available, use the Word version linked here.

REFERENCES

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7. Contraindications and special considerations: the green book chapter 6, page 5 updated April 2017. Gateway number 2017523 G https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf

See also:
Guideline 280FM Management of Patients on Immunosuppressants admitted with Suspected Infections

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