Oxford University Hospitals NHS
NHS Foundation Trust

NHS
Oxfordshire
Clinical Commissioning Group

CICLOSPORIN FOR USE IN ADULT RHEUMATOLOGY
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 and the BNF.

Shared Care Protocol – Responsibilities

Shared care assumes communication between the rheumatology 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. See Rheumatology Shared Care Responsibilities document for further information.

Rheumatology Specialist Team

At the start of treatment:

- Complete pre-treatment assessments, including baseline tests, in accordance to the specific shared care protocol
- Initiate treatment by prescribing the first 56 days
- Supply the patient with 3 blood cards (for FBC, U&E and LFTs) and inform patients to book and attend blood tests at 2, 4 and 6 weeks after starting treatment
- Ensure that patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly, as part of obtaining informed agreement to shared care
- Provide a copy of the drug-specific patient information leaflet (or direct patient to Versus Arthritis website https://www.versusarthritis.org/about-arthritis/treatments/drugs/)
- Provide a copy of OUHFT 'Rheumatology Shared Care Monitoring Card' to the patient and/or carer, which includes contact details for the rheumatology advice line
- Send a letter to the GP requesting shared care once dose is stable, confirming the above has been completed. Include any results from pre-treatment assessments if appropriate. Provide details of the dose to be continued. Outline shared care protocol criteria and/or direct them to the relevant document on the Oxfordshire CCG website

After 2-6 weeks of treatment:

- Check blood test results from week 2, week 4 and week 6 (available on EPR for Oxfordshire patients/contact GP practice for blood results if patient's GP practice is not in Oxfordshire)
- Ensure any abnormal results are acted upon promptly

After 4-6 weeks of treatment:

- Conduct a consultation with the patient and/or to check that the patient is not experiencing any issues or side effects.
- Confirm that the patient is stable (no side effects, tolerating the drug and established on monthly blood tests). Communicate this information in a shared care handover letter to the GP. Shared care can now commence.
- If the patient is not stable requiring change in the treatment regime, the patient will remain under the care of the specialist until they become stable, as above.

Unless any concerns are raised by the GP within 14 days, shared care will be assumed and the patient will collect the next prescription from the GP. [1]

During treatment:

- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Be available to give advice to GP and patient
- If the dose is increased, patient's bloods will be monitored as above
- If dose is decreased, additional monitoring may not be required at discretion of the rheumatology specialist - this will be clearly communicated in the clinic letter and the existing monitoring schedule should continue

GP

- Ensure that provision has been made for the patient to have blood monitoring as per local arrangements
- Prescribe medication once the dose is stable or shared care is agreed
- Ensure all monitoring is completed in accordance to 'Recommended monitoring schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)'
- Check results then advise the specialist of any deteriorations or abnormal results. Results should be recorded on the monitoring card if the GP practice is outside of Oxfordshire.
- Notify the specialist to any changes in patient's condition, any adverse drug reactions or failure to attend tests
- If a patient fails to attend for monitoring:
  - Only issue a 28 day prescription and book them in for the next available appointment for a blood test
  - If they fail to attend a second blood test then contact the specialist team for advice and to discuss suitability for continuing treatment before supplying further prescriptions

Patient and/or carer

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Ensure that they are booked in for blood test monitoring as per local arrangements and attend as required
- Attend all hospital and GP appointments as scheduled
- Ensure monitoring card is kept up to date and is brought to all appointments (especially patients whose GPs are out of Oxfordshire)
- Report any side effects to the GP or a member of the specialist team

BACKGROUND FOR USE

Ciclosporin is a potent immunosuppressant and disease modifying drug. It is used to treat the following conditions:

- Rheumatoid arthritis (licensed)
- Psoriatic arthritis, Behcet's disease, myositis, systemic lupus erythematosus, adult-onset Still's disease (unlicensed).

DOSAGE

- Usual starting dose 1.25mg/kg twice daily for 6 weeks, rounded to the closest 25mg.
- 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.

- **Capimune** is the branded generic of choice. 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.
- Can be taken in combination with low-dose weekly methotrexate in patients who have an insufficient response to methotrexate alone. Can also be taken in combination with corticosteroids and/or NSAIDs.
- Time to response: 3 months

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

- FBC
- U&Es (check renal function at least 2 weeks apart – a recent result can be used) and eGFR.
- LFTs and lipid profile.
- BP must be <140/90 before treatment. 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.

ONGOING MONITORING

More information available in separate guideline; 'Recommended Monitoring Schedule for patients taking disease-modifying anti-rheumatic drugs (DMARDs)'

Baseline assessments should include height, weight, blood pressure, FBC, U&Es, LFTs and CRP.

Standard Monitoring Schedule as per British Society of Rheumatology Guidelines[3]:

- Following initiation or dose change: Check FBC, U+Es and LFTs **every 2 weeks** until on stable dose for **6 weeks**
- Once on stable dose, check FBC, U+Es and LFTs **monthly** for **3 months**
- Thereafter, check FBC, U+Es and LFTs **every 3 months**.
- More frequent monitoring is appropriate in patients at higher risk of toxicity (extremes of body weight, CKD3 or above, pre-existing liver disease, significant other medical co-morbidity, age over 80 years and previous DMARD toxicity)

Exceptions and Additions to the Monitoring Schedule:

Drug	Laboratory monitoring	Other monitoring
Ciclosporin	Extend monthly monitoring longer term (reduced frequency of monitoring after 12 months on an individual patient basis)	BP and glucose at each monitoring visit. Fasting glucose is preferred but may not be practical. If conducting a non-fasting test, be aware of false positives and repeat as necessary.

Abnormal Laboratory Results and Action to be Taken:

Please note that in addition to absolute values for haematological indices a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance.
Some patients may have abnormal baseline values; specialist will advise if so. e.g. some patients with cirrhosis will have pre-existing pancytopenia and lupus patients may have leucopenia because of lymphopenia.

Laboratory Result	Action
WBC less than 3 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
Neutrophils less than 1.6 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
Platelets less than 140 x 10^9/l	Withhold and discuss with Rheumatology. Bone marrow suppression can occur abruptly.
MCV greater than 110 fl	Withhold and discuss with Rheumatology. May be able to continue if chronic increase. Check folate and $B_{12.}$ If level low, start appropriate supplementation.
Creatinine increase greater than 30% over 12 months and/or calculated GFR less than 60ml/min/1.73m^2	Discuss with Rheumatology as dose adjustments or further investigations may be required.
Adult liver function ALT greater than 2.5 x upper limit of normal or over 100U/l	Withhold and discuss with adult rheumatology.

CONTRAINDICATIONS AND PRECAUTIONS

CONTRAINDICATIONS	
Uncontrolled hypertension	Do not use
Severe electrolyte imbalance, e.g. hyperkalaemia	Do not use
Uncontrolled infections	Do not use
Malignancy	Do not use
Other immunosuppressants	Do not use unless recommended by specialist
Hypersensitivity	Do not use

PRECAUTIONS	
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.

SIDE EFFECTS & ACTIONS TO BE TAKEN

Side effects	Action
Hyperkalaemia	Withhold until discussed with specialist. Review medications to identify drug interactions. Check if patient has a potassium-rich diet.
Significant rise in lipids	Withhold until discussed with specialist as a dose reduction may need to be considered. Advise patient to restrict dietary fat.
Rise in serum creatinine >30% above baseline on	Withhold until discussed with specialist. Patients on long term therapy can be at risk of developing structural changes to the kidney

Side effects	Action
2 occasions 1 week apart	(interstitial fibrosis).[4]
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 is difficult to control, stop ciclosporin and 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.
Gingival hyperplasia	Advise on good oral hygiene. May be associated with calcium-channel blockers. If severe, withhold and discuss with specialist.
Headache, tremor	Common and dose related. Consider other causes. Consider 25 - 50% dose reduction or cessation.
High fasting blood glucose	Repeat the same test again to confirm, do not do a HbA1c level. If the repeat test is raised, discuss with specialist.

DRUG INTERACTIONS [4,5]

(Please note that this is not an extensive list. Refer to BNF and SPC for any specific drug interaction queries)

Please note that CYP3A4 inducers and inhibitors can either decrease or increase ciclosporin plasma levels. Similarly, as Ciclosporin is an inhibitor of CYP3A4, it can increase plasma levels of medications that are substrates of this enzyme.

Take care when changing all treatments for patients on Ciclosporin.

Agents increasing ciclosporin levels: Allopurinol, amiodarone, azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole, voriconazole), chloramphenicol (IV or oral), danazol, diltiazem, ezetimibe, grapefruit juice (avoid for 2 hours before and after taking Ciclosporin) , macrolide antibiotics (azithromycin, clarithromycin, erythromycin), high dose methylprednisolone (risk of fits), nicardipine, oestrogens, progestogens, protease inhibitors, quinolones, verapamil. *(Avoid where possible and monitor ciclosporin levels and U&E if initiating or changing doses.)*

Agents decreasing ciclosporin levels: Barbiturates, bosentan, carbamazepine, griseofulvin, modafanil, orlistat, oxcarbazepine, phenytoin, primidone, rifampicin, sevelamer, St John's Wort, sulphadiazine, sulfinpyrazone, terbinafine.

Agents which may increase the risk of nephrotoxicity: Include aciclovir, aminoglycosides, bezafibrate, colchicine, fenofibrate, H_2 blockers (cimetidine and ranitidine), NSAIDs (use minimum dose and monitor effects on renal function when increasing NSAID dose), quinolones, tacrolimus (avoid), 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: Dabigatran (contraindicated), digoxin, edoxaban, methotrexate, (doses concurrently to be established by a specialist), felodipine, lercanidipine and nifedipine (increased risk of toxicity), repaglinide, 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).

FAMILY PLANNING

Follow advice from secondary care

VACCINATIONS

Check Department of Health green book guidance and if not covered, discuss with secondary care

BACK-UP INFORMATION AND ADVICE

Contact Details	**Oxford University Hospitals NHS Foundation Trust**	
Rheumatology	Rheumatology Helpline (Adult and Paediatric) Monday to Friday 8am - 2pm (answerphone service) Closed on weekends and bank holidays Rheumatology Registrar/Consultant on call Monday to Friday 9am-8pm Weekends and bank holidays 9am-5pm	Tel: 01865 737656 Email: Rheumatology.NOC@nhs.net OUH switchboard number: 0300 304 7777, ask for Rheumatology on call
Medicines Information	Tel: 01865 221505 (Monday to Friday 9am - 5pm) Email: Medicines.information@ouh.nhs.uk	

REFERENCES

1. Shared Care Protocols (SCP) Best Practice Guidelines. March 2019. Available from: https://clinox.info/clinical-support/local-pathways-and-guidelines/Prescribing/Shared%20Care%20Protocol%20Best%20Practice%20Guidelines.pdf
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3. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, Gordon P, Christidis D, Galloway S, Hayes E, Jeffries A. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. (2017) *Rheumatology*. Jun 1;56(6):865-8
4. Summary of Product Characteristics. Capimune 50mg tablets (Mylan). Last updated on eMC: 12/2015 (Accessed via www.medicines.org.uk on 26/07/19)
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