North and East Devon healthcare community shared care prescribing guideline ~ Ciclosporin (Neoral) for rheumatological disease

This shared care guideline sets out details for the sharing of care of patients with rheumatological disease prescribed ciclosporin. These guidelines provide additional limited information necessary to aid in the treatment of rheumatology patients. **As with all shared care guidelines they highlight significant prescribing issues but should be used in conjunction with the ABPI summary of product characteristics (SPC/Data sheet) and do *not* replace them.**

Indications for the purposes of this guideline

Treatment of **adults** with severe active rheumatoid arthritis. **Please note that this drug should only be initiated in secondary care.**

Ciclosporin should be prescribed by brand. The Devon Formulary recommended brand is Neoral.

Dosage

The usual starting dose in secondary care is 1.5 - 2.5mg/kg per day for six weeks, increasing usually to 3.5mg/kg per day according to response and tolerability. **The dose should not exceed 4mg/kg per day**. The dose will be made clear in clinic correspondence. Doses are given orally in two divided doses.

Contraindications

- Combination with tacrolimus
- Abnormal renal function
- Uncontrolled hypertension
- Uncontrolled infections
- Malignancy
- Under 18 years of age
- Pregnancy. This drug is contra-indicated in pregnancy as it has the potential to affect the development of the unborn child. Men and women of childbearing age should be advised to use a reliable method of contraception during treatment. When planning a pregnancy it is important that both men and women on this drug discuss medication with the Rheumatology Team (at least six months before conception) since all drugs can potentially affect the unborn child.
- Breastfeeding

Precautions

- Patient should avoid contact with infections such as chicken pox or shingles.
- Abnormal renal function. Renal function will always be checked and the decision to use the drug will depend on the severity of renal impairment.
- High dietary potassium intake – potassium intake should be reduced and potassium sparing diuretics or potassium supplements should be avoided.
- Hyperuricaemia.
- Porphyria.
- Taking other drugs - there are multiple drug interactions with ciclosporin, see side effects section and the BNF appendix for full list of interactions. Particular care should be taken with prescribing compounds known to have nephrotoxic effects.

Monitoring

Baseline assessments and frequency of ongoing monitoring is based on recommendations of the British Society of Rheumatology (2017).

Baseline assessment to be completed by the specialist service provider:

- At baseline:
    - Height & weight
    - Blood pressure
    - Full blood count (FBC)
    - creatinine / eGFR
    - ALT and/or AST, and albumin
    - Chest x-ray
    - Consider patient risk factors for viral infections and screen for occult viral infections (hepatitis B and C and HIV) where appropriate
    - Baseline blood lipid levels

Ongoing monitoring during treatment to be completed by the GP:

See table overleaf

<table>
<tr><th>Test</th><th>Frequency</th><th>Results</th><th>Action</th></tr>
<tr><td>FBC</td><td rowspan="3">Every two weeks until on stable dose for 6 weeks, then every month for at least 12 months before considering reduced frequency on an individual patient basis (specialist to advise).
Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then as above.
Patient factors where continued monthly monitoring is recommended (unless otherwise specified):
• Previous toxicity or deranged FBC or LFTs while on DMARDs
• Chronic kidney disease (CKD 3 or worse)
• Pre-existing liver disease</td><td>WCC < 3.5 x 10^9/L
Neutrophils < 1.6 x 10^9/L
Eosinophils >0.5 x 10^9/L
Platelets < 140 x 10^9/L
MCV > 108fl</td><td rowspan="3">If results meet specified criteria, stop treatment and refer to specialist.
If isolated MCV rise, check for other causes (B12, folate, thyroid function and alcohol consumption). If results are normal, refer to specialist.
If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.
If deterioration in renal function, dose adjustment may be necessary; if toxicity suspected or dosing advice required refer to specialist team.</td></tr>
<tr><td>Creatinine/eGFR</td><td>Creatinine increase >30% over 12 months and/or
eGFR <60ml/min/1.73m^2</td></tr>
<tr><td>ALT and/or AST and albumin</td><td rowspan="2">Additional urgent monitoring tests should be carried out within 24 hours for any patient with acute kidney injury (AKI).</td><td>ALT and/or AST >100 U/L
Albumin unexplained reduction to <30g/L</td></tr>
<tr><td>Blood pressure</td><td rowspan="2">At each monitoring visit (as above) to promptly identify and minimise cardiovascular risks</td><td>Raised BP</td><td>Treat hypertension as per local formulary guidance. A rise in BP does not indicate withdrawal of ciclosporin unless resistant to treatment – refer to specialist team.</td></tr>
<tr><td>Glucose</td><td>Raised glucose</td><td>Consider alongside patient and cardiovascular risk factors using appropriate screening tools. Treat as appropriate and discuss with specialist if continued concern.</td></tr>
<tr><td>Warning signs and symptoms</td><td colspan="3">For patients experiencing mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, rash, unexplained illness or infection, additional urgent monitoring tests (as above) should be carried out within 24 hours. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday</td></tr>
<tr><td colspan="4">Other factors that may increase risk of toxicity include moderate renal impairment, extremes of body weight, polypharmacy (especially other haematotoxic/ hepatotoxic/ nephrotoxic drugs), comorbidities, age > 80 years. Where more frequent ongoing monitoring is required due to a combination of patient factors this will be advised by the specialist prescriber.</td></tr>
</table>

Infections

Contact microbiology if a patient not known to be immune to chickenpox comes into contact with **shingles or chickenpox**, for advice on whether varicella-zoster immune globulin (VZIG) or other treatment is indicated.

In patients suffering from chickenpox or active skin lesions from shingles, withhold. Patients with chickenpox: contact microbiologist for consideration of admission to hospital for IV antivirals. Patients with shingles: if any vesicles are still present (regardless of the time of onset), treat with aciclovir (800mg five times a day for 7 days).

During a **serious** infection STOP ciclosporin. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant high-risk of infection where an individual patient plan should be made.

Vaccines

Live vaccines are contraindicated for patients on ciclosporin. These vaccines include measles, mumps and rubella; BCG; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.

Flu and pneumococcal vaccines should be given (see GP responsibilities below).

Shingles vaccination **can** be given to eligible patients on ciclosporin. Specialist advice should be sought if uncertain

Side effects

Patients must report mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, and any unexplained illness/infection and should be seen urgently for clinical assessment, full blood count and liver function tests. (via out of hours service e.g. NHS 111 if their GP practice is closed for weekend/bank holiday)

- Some patients feel a burning sensation in their hands and feet during the first weeks of therapy. This may disappear with continued therapy, if not discuss this with your rheumatology team.
- The most important side effects, which needs monitoring, are impairment of renal function and hypertension.
- All patients put on this medication will be warned of the theoretical but as yet unquantifiable risk of lymphoproliferative disorders and other malignancies in the future.

Very common > [1 in 10] > Common > [1 in 100] > Uncommon > [1 in 1000] > Rare > [1 in 10000] > Very rare

Very common/ Common – these include

Hypercholesterolaemia, hyperkalaemia, hypomagnesaemia, hyperuricaemia, renal dysfunction, gout, gastrointestinal disturbances, gingival hyperplasia, hepatic dysfunction, hypertrichosis, muscle disorders, tremor, paraesthesia, headache, predisposition to infection.

Uncommon / Rare

Haemolytic anaemia, thrombocytopenia, haemolytic uraemic syndrome, menstrual disorders, gynaecomastia, diabetes, pancreatitis, allergic rash, muscle weakness, myopathy, oedema, weight increase, signs of encephalopathy or demyelination (e.g. convulsion, confusion etc.), motor polyneuropathy.

Very Rare

Optic disc oedema including papilloedema with possible visual impairment secondary to benign intracranial hypertension, colitis, cortical blindness.

Common / significant drug interactions

This list is **NOT exhaustive**, the data sheet and BNF should be consulted for a more comprehensive list of potential drug interactions.

- Food: Grapefruit or Grapefruit juice (not to be ingested for 1 hour prior to dose of ciclosporin
- Interference with the p450 system.
- Drugs that **reduce** ciclosporin blood levels (Increased dosage required - danger of rejection) e.g. St. Johns Wort (Hypericum perforatum), carbamazepine.
- Drugs that **increase** ciclosporin blood levels (Reduced dosage required - danger of toxicity) e.g. Macrolide antibiotics, Amiodarone, Grapefruit or Grapefruit juice (not to be ingested for 1 hour prior to dose of ciclosporin), 'Conazole' antifungals.
- Nephrotoxic drugs e.g. Aminoglycoside antibiotics, quinolones, trimethoprim, co-trimoxazole, amphotericin, melphalan, colchicines.
- Drugs that increase potassium levels e.g. ACE inhibitors, A2RBs.
- Drugs that increase ciclosporin nephrotoxicity e.g. non-steroidal anti-inflammatory drugs, allopurinol.
- Drugs that increased hepatotoxicity e.g. Danazol, anabolic steroids and oral contraceptives.
- Other drug interactions
    - An increased risk of myopathy occurs with statins.
    - Nifedipine - avoid in patients who develop gingival hypertrophy with ciclosporin. May also occur with other dihydropyridine calcium channel blockers.
    - Live attenuated vaccines should be avoided. For additional information refer to the British Society of Rheumatology guidance on vaccinations for immunosuppressed patients at: http://www.rheumatology.org.uk/guidelines/clinicalguidelines/vaccineguideline

Product information

- Neoral® 10, 25, 50 or 100mg soft gelatin capsules
- Neoral® 100mg/ml oral solution – to be diluted immediately before being taken.
- Solutions should be stored between 20°C and 30°C.

CICLOSPORIN SHOULD BE PRESCRIBED BY BRAND.

References

- Summary of Product Characteristics. http://emc.medicines.org.uk/: January 2008.

Areas of responsibility for the sharing of care

These are suggested ways in which the responsibilities for the management of patients with rheumatoid arthritis who are prescribed oral ciclosporin can be shared between the specialist and the general practitioners.

GPs **are invited** to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical.**

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and be accepted by them.

The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Specialist

- Initiate oral ciclosporin, supply 28 days' medication.
- Discussion with the patient regarding the benefits and side effects of treatment. Refer patient to specialist nurse service where appropriate (e.g. new patient) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom.
- A booklet for recording test results may then be issued.
- Ask the GP whether they are willing to participate in shared care.
- Prompt communication with GP of any changes in treatment, results of monitoring undertaken and assessment of adverse events.
- Specify review dates at clinically relevant time intervals for both the GP and the consultant.
- Advice to GPs on when to stop treatment.
- Ensure clear arrangements for back-up advice and support.
- Reporting adverse events to the CSM.

GP

- Reply to request for shared care as soon as practical.
- Continue to prescribe oral ciclosporin in accordance with these guidelines.
- Monitoring as outlined in the shared care guideline.
- Prompt referral to a specialist if there is a change in the patient's status.
- Reporting to and seeking advice from a specialist on any aspect of patient care which is of concern to the GP and may affect treatment.
- Reporting adverse events to specialist and CSM.
- Stopping treatment in the case of a severe adverse event or as per shared care guideline
- Offer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check that the patient has had one dose of pneumococcal vaccine (revaccination is not recommended, except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia) – see BNF or Green Book

Patient/carer

- Take ciclosporin as prescribed
- Report any adverse effects (see section above) to their GP and/or specialist whilst being treated with oral ciclosporin.
- Ensure that they have a clear understanding of their treatment.
- Ensure they attend for monitoring requirements as per shared care guideline.
- Aware that treatment will be stopped if patient does not attend for monitoring.
- Dispose of unused or unwanted ciclosporin appropriately

Back-up advice and support

Contact details	Telephone No	E-mail address
Dr R Haigh	(01392) 403705	richardhaigh@nhs.net
Dr S Earl	(01392) 406351	Susannah.earl@nhs.net
Dr M Brown	(01392) 403567	mary.brown11@rnhs.net
Dr R Mascarenhas	(01392) 406355	r.mascarenhas@nhs.net
Dr M Abusalameh	(01392) 403772	m.abusalameh@nhs.net
Dr M Cates	(01392) 403707	matthewcates1@nhs.net
Dr S Kyle	(01271) 311571	stuartkyle@nhs.net
Dr R Manhas	(01271) 311571	roopemanhas@nhs.net
Dr V Arya	(01271) 311571	vivek.arya2@nhs.net
RD&E rheumatology dept		rde-tr.rheumatology@nhs.net
NDHT rheumatology dept		ndht.rheumatology@nhs.net

Please do not use rheumatology department emails for enquiries relating to patients receiving DMARDs under the care of other specialties e.g. dermatology, gastroenterology etc.

Partially updated: October 2019, March 2021

Shared Care Agreement Letter - Consultant Request

To:	**Dr:**
	Practice Address:
Patient Name:	
NHS Number:	
Date of birth:	
Address:	

Diagnosed condition: ……

I recommend treatment with the following drug: ……

At the following dosage: ……..……

I request your agreement to continue the care of this patient according to the Shared Care Guidelines for this drug. The patient has been initiated on treatment and stabilised in accordance with the appropriate Shared Care Guidelines.

The results of any relevant baseline tests and any additional supportive information (target range, date of last blood test etc.) are included below:

Principles:
GPs are invited to participate, but **if the GP is not confident to undertake these roles then they are under no obligation to do so.** If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Continuing the care assumes communication between the specialist, GP and patient; the intention should be explained to the patient and accepted by them.

Remember: the doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed:			**Date:**
Consultant name:			
Telephone number:		**Fax number:**	
Email address:			
Department email:			

Please sign below and return promptly. Remember to keep a copy of this letter for the patient's records. If this letter is not returned sharing of the care for this patient will not commence.

GP Response

I agree / do not agree* to share the care of this patient in accordance with the Specialised Medicines Guideline.

Signed: …….. Date: …….

GP name: …… *Delete as appropriate.

Patient agreement

I understand and agree to my responsibilities as described above.

Signed: …….. Date: …….

Name: