Shared Care Guideline

Leflunomide in rheumatic diseases

Executive Summary

- Leflunomide is used as a disease-modifying agent to induce and maintain remission of rheumatoid arthritis (RA), and psoriatic arthritis. It is also used off-label to treat sarcoidosis
- A loading dose of 100mg daily for 3 days may be prescribed but this may increase the risk of adverse effects and is optional.
- The usual maintenance dose is 20mg daily, reduced to 10mg daily if prescribed in combination therapy with another potentially hepatotoxic disease-modifying antirheumatic drug (DMARD) such as methotrexate.
- Response can usually be seen in 4-6 weeks with further improvement during the next four to six months.
- Due to teratogenicity in male and female patients, female patients must use adequate contraception for the duration of leflunomide therapy, and for two years after discontinuation of therapy unless a drug washout procedure has been done. In the latter case risk should be discussed with the specialist.
- The risk of hepatotoxicity and haematotoxicity are increased if leflunomide is prescribed with other drugs known to have similar toxicities.
- The responsibilities of the hospital specialist, GP and patient for this shared care guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/ carer. 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. The doctor/ healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Cross-boundary: Trust and general practice in adult patients.

2. Aim

To provide guidance in the use of leflunomide as a disease-modifying agent in the treatment of rheumatoid arthritis and sarcoidosis

3. Introduction

Leflunomide is an immunosuppressive agent, which reduces the signs, symptoms and progression of rheumatoid arthritis,psoriatic arthritis and sarcoidosis. This shared care guideline outlines the responsibility of primary and secondary care clinicians using leflunomide in rheumatic diseases.

4. Abbreviations

AIDS	Acquired immune-deficiency syndrome
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BP	blood pressure
CPK	creatine phosphokinase
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
FBC	full blood count
GGT	gamma-glutamyl transferase
GP	general practitioner
LDH	lactate dehydrogenase
LFTs	liver function tests
LLN	lower limit of normal
NICE	National Institute for Health and Clinical Excellence
WBC	white blood cell count
ULN	upper limit of normal

5. Dose and Administration

- Optional loading dose of Leflunomide 100mg daily for three days followed by the maintenance dose. Omitting the loading dose may reduce the risk of adverse effects.
- The usual maintenance dose of leflunomide is 20mg daily.
- The dose may be reduced to 10mg or lower if side effects occur.
- The dose is 10mg daily if leflunomide is prescribed in combination therapy with another potentially hepatotoxic disease-modifying antirheumatic drug (DMARD) such as methotrexate.
- For sarcoidosis the usual starting dose is 10mg daily with further dose up-titration if clinically indicated
- Clinical response usually starts in 4-6 weeks with further improvement during the next four to six months.
- NSAIDs and glucocorticoids may be continued if already being taken by patients when starting leflunomide.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (https://www.medicines.org.uk/emc/medicine/26345)

6. Adverse Effects

Common (≥ 1 in 100 and < 1 in 10)

- Diarrhoea or colitis
- Nausea and vomiting
- Anorexia and weight loss
- Asthenia
- Mild allergic reactions including maculopapular rash
- Oral mucosal disorders (e.g. mouth ulceration, aphthous stomatitis)
- Abdominal pain
- Mild increase in blood pressure
- Elevation of ALT or AST (less commonly ALP, GGT, bilirubin)
- Increased hair loss
- Leucopaenia WBC <3.5 $x10^9$/L
- Elevation of creatine phosphokinase (CPK)
- Skin reactions such as eczema, rash, pruritus, dry skin
- Tenosynovitis

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Taste disturbances
- Urticaria
- Anaemia
- Mild thrombocytopenia
- Ulcerative stomatitis
- Eosinophilia
- Hypokalaemia
- Hyperlipidaemia
- Hypophosphataemia
- Tendon rupture
- Anxiety

Rare (but significant) (≥ 1 in 10000 and < 1 in 1000)

- Severe liver injury (especially if taken concurrently with other hepatotoxic drugs) including hepatitis, jaundice or cholestasis
- Severe infections, including sepsis
- Pancytopaenia
- Leucopaenia WBC < 2 $x10^9$/L
- Pneumonitis (interstitial lung disease)
- LDH increase
- Severe increase in blood pressure
- Progressive Multifocal Leukoencephalopathy (PML)

Very rare (< 1 in 10000)

- Agranulocytosis
- Severe anaphylactic/anaphylactoid reactions
- Vasculitis
- Stevens Johnson syndrome or toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
  Further information can be found in the Summary of Product Characteristics:

7. Cautions

- Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) **should be used with caution**
- The active metabolite of leflunomide has a long half-life, usually 1 to 4 weeks. Serious undesirable effects may continue or occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even after treatment with leflunomide has stopped.
- Patients should be advised to avoid alcohol during treatment with leflunomide.
- Leflunomide persists in the body for a long time even after therapy is stopped. If switching to another DMARD, *the washout procedure may be performed to reduce the risk of adverse effects* ***[closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching]***
- Leflunomide is immunosuppressant and increases the patient's susceptibility to infections, including opportunistic infections.
- Male patients must be warned of possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide must be guaranteed.
- The immune response to vaccination may be impaired. Patients should not receive live attenuated vaccines, although shingles vaccine [Zostavax] is not contraindicated with oral DMARDs.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (https://www.medicines.org.uk/emc/medicine/26345)

8. Contraindications

- Hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the active substance or to the principal active metabolite (teriflunomide);
- Patients with impaired liver function.
- Patients with severe immunodeficiency states such as AIDS.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis (because the risk of haematological toxicity is increased).
- Patients with serious infections
- Patients with moderate to severe renal insufficiency.
- Patients with severe hypoproteinaemia such as in nephrotic syndrome (because leflunomide is highly protein-bound).
- Pregnant women or women of childbearing potential who are not using reliable contraception during treatment with leflunomide. Pregnancy must be excluded before start of treatment with leflunomide.
- Leflunomide and its metabolite enter breast milk so it is not advised for use in breast-feeding women.

Further information can be found in the British National Formulary and the Summary of Product Characteristics (https://www.medicines.org.uk/emc/medicine/26345

9. Interactions

Combination of leflunomide with other hepatotoxic or haematotoxic medicines increases the risk of toxicity.

If taken with warfarin or other coumarin anticoagulant, INR must be closely monitored as there is a risk of increased INR.

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

Pre-treatment by the hospital rheumatology team.	• FBC including differential WBC and platelet count, U&Es, eGFR LFTs. • Check BP. If > 140/90, treat hypertension before starting leflunomide. • Record body weight
Initiation to stabilisation monitoring by the hospital rheumatology team (or GP if in agreement).	Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every: • Two weeks until on stable dose for 6 weeks then • Once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months • Thereafter FBC, creatinine/calculated GFR, ALT, and/or AST and albumin at least every 12 weeks
On-going monitoring by GP once stable.	• After six months, check FBC, LFTs, BP and weight every two months. • If co-prescribed with another immunosuppressant or potentially hepatotoxic drug, continue monitoring at least once a month
Legend: ALT: alanine transaminase; AST: aspartate transaminase; BP: blood pressure; FBC: full blood count; LFTs: liver function tests; RFTs: renal function tests; U&Es: urea and electrolytes; WBC: white blood cell count	
All results to be recorded in a patient-held record book	

The following table includes advice on what action to take if test results rise or fall below defined limits or if the patient reports one of the adverse events below:

Test results	Action
• ALT or AST between 2- 3 times upper limit of normal (ULN)	Reduce dose to 10mg, **recheck weekly**. If normalised – continue 10mg; if remains elevated withdraw drug and discuss with specialist team.
• ALT/AST >3 x upper limit of normal	Stop drug, **recheck within 72 hours**. If still > 3x, withdraw drug and consider washout (see section 12).
• Blood pressure rises above 140/90mmHg on 2 consecutive readings 2 weeks apart.	Treat in line with NICE guidance. If patient develops severe hypertension which remains uncontrolled despite optimal antihypertensive treatment, stop leflunomide and consider washout (see section 12).
• Leucopaenia WBC < 3.5 x10^9/L	Stop leflunomide and contact rheumatologist or rheumatology practitioner 01223 254933. See contact list below. **If severe haematological reaction, including pancytopaenia, leflunomide and any concomitant myelosuppressive medication must be discontinued and leflunomide wash out procedure initiated (see section 12)**
• Neutropenia < 1.5 x10^9/L	
• Thrombocytopenia platelets <150 x10^9/L	
• >10% weight loss with no other cause identified	Reduce dose, or stop and consider washout. Discuss ongoing therapy with the hospital rheumatology team.
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Symptoms/side effects	**Action**
• Pulmonary symptoms, such as dry cough and/or shortness of breath	Stop leflunomide at once and seek urgent medical advice
• Peripheral neuropathy	Discuss ongoing therapy with the hospital rheumatology team.
• Unexplained chronic diarrhoea	Discuss ongoing therapy with the hospital rheumatology team.

11. Shared Care Responsibilities

a. Hospital specialist:

- Send a letter to the GP requesting shared care for the patient. Agreement to shared care will be assumed unless GP advises otherwise.
- Ensure accurate details of patient's prescription are communicated.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- Provide any advice to the patient/carer when requested.
- Initiate treatment and prescribe the first month of treatment.
- Routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose and most recent test results are stated.
- Evaluate any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Ensure that backup advice is available at all times.

b. General Practitioner:

- Agree to shared care guideline by the GP.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Monitor patient's overall health and well-being.
- Prescribe the drug treatment as described.
- Monitor blood results (FBC, LFTs) and BP in line with recommendations from hospital specialist.
- Help in monitoring the progression of disease.

c. Patient or parent/carer:

- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Do not exceed the recommended dose.
- Patients must attend their scheduled test appointments to assist health professionals to provide effective, safe, appropriate treatment.
- Take effective contraceptive precautions (male and female patients).
- Avoid drinking alcohol.
- Inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.
- Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
- Share any concerns they have in relation to treatment with leflunomide.

12. Washout procedure

- Either colestyramine 8 g three times a day for 11 days or activated powdered charcoal 50g four times a day for 11 days.

13. Funding for treatment with Leflunomide tablets

Funding for oral leflunomide is from the usual secondary or primary care drug budgets as these indications are 'in tariff' and leflunomide is not a high cost excluded from tariff drug.

14. Contact numbers for advice and support

Cambridge University Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone**
Eilis Rahill	**Lead pharmacist division A (surgery)**	**01223 274804**
Medicines Information department		**01223 217502**
Rheumatology Department Decisions to alter or discontinue treatment are usually discussed via the Rheumatology Helpline on 01223 254933. The on-call rheumatology specialist registrar (SpR) may also be contacted via the Addenbrooke's Contact Centre.		
Specialist	**Post**	**Telephone**
Jill Bloxham; Nancie Gachie, Sherly Paul, Tracey Nash, Jane How	Rheumatology practitioners	01223 254933, option 3
Dr G Clunie, Dr FC Hall, Dr D Jadon, Dr N Jordan, Dr M Lillicrap, Dr A Malaviya, Dr A Negoescu, Dr K Poole, Dr N Shenker. Dr C Chan	Consultant rheumatologist	01223 254933, option 4

Papworth Hospital NHS Foundation Trust	
Medicines Information department	**01480 364179**

Respiratory Medicine ILD Department		
Specialist	**Post**	**Telephone**
Dr Muhunthan Thillai	Consultant Respiratory Physician	01480 364530
Dr Helen Parfrey	Consultant Respiratory Physician	01480 364530
Dr Nicola Simler	Consultant Respiratory Physician	01480 364521
Dr Christine Fiddler	Consultant Respiratory Physician	01480 364521
Duncan Grady	Thoracic directorate pharmacist	01480 830541 bleep 845
Emma Harris Katie Hart	ILD Specialist Nurses	01480 830541 bleep 109 or 01480 364184

15. Monitoring compliance with and the effectiveness of this document

Specialties will regularly review their incidents and feedback from GPs with regard to the use of this drug and update the guideline accordingly.

16. Equality and Diversity Statement

This document complies with the Cambridge University Hospital NHS Foundation Trust service Equality and Diversity statement.

17. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

18. Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics (https://www.medicines.org.uk/emc/medicine/26345)