DMARDs in Adult Rheumatology - Shared Care Information

Leflunomide

Please also refer to the Shared Care Guidelines - Principles of Shared Care and Responsibilities of Speciality Team, GP, Pharmacist & Patient

Indications:
- Rheumatoid arthritis (RA) and Psoriatic arthritis (PsA)
- Not licensed for use in Psoriasis

Presentation and Availability:
- 10mg and 20mg tablets (100mg tablets available for loading dose)

Time to response:
- 8-12 weeks (longer if loading dose not employed)

Contraindications:
- Severe immunodeficiency
- Serious infections
- Hepatic impairment due to any cause (see monitoring)
- Hypersensitivity to Leflunomide or any of the other excipients
- Severe unexplained hypoproteinaemia
- Renal impairment (moderate to severe)
- Impaired bone marrow function such as anaemia, cytopenias or thrombocytopenia due to causes other than RA or PsA

Cautions:
- Localized or systemic infection such as Hepatitis B or C and history of tuberculosis
- Drug potentiation by haematotoxic or hepatotoxic drugs (e.g. methotrexate although this combination has been used by rheumatologists)
- Potentially hepatotoxic especially when used with other hepatotoxic drugs (methotrexate) or if evidence of current or recent Hepatitis B or C infection. Severe life-threatening hepatotoxicity has been rarely reported, usually in the first 6 months of treatment and in the setting of multiple risk factors for hepatotoxicity. Liver function monitoring must be adhered to (see dosage and monitoring). If liver abnormality persists, the washout procedure should be initiated. Patients should limit alcohol intake to 4-8units per week

Side effects:
- *Common:* Mild blood pressure increase, headaches, dizziness, diarrhoea (more common when loading doses are used), nausea, vomiting, weight loss
- *Less Common:* Taste disturbance, anaemia, mild thrombocytopenia, alopecia
- *Rare Serious:* Hepatotoxicity, severe infection, Stevens Johnson Syndrome, toxic epidermal necrolysis, pulmonary infiltration, pneumonitis reactions

SPC for a list of full side effects: http://www.medicines.org.uk/emc/default.aspx

Pregnancy and Breastfeeding:
- Leflunomide is teratogenic and is contraindicated in pregnancy
- Women should discontinue the drug 2 years prior to conception or undergo a washout procedure to rapidly remove its active metabolite
- Women must use effective contraception while on Leflunomide and for up to 2 years after treatment is stopped and for up to 3 months after treatment is stopped in men
- Before conception, active metabolite blood levels must be measured and fall below 0.02mg/L

Drug Interactions:

Owing to its long half- life (2 weeks), drug interactions can be potentially serious and a drug washout procedure in addition to discontinuation of Leflunomide may be required

- Warfarin – possible increase in anticoagulant effect of warfarin. Monitor INR closely
- Tolbutamide – possible increase in hypoglycaemic effects of tolbutamide
- Phenytoin – possible increase in levels of phenytoin
- Methotrexate – risk of toxicity with concomitant use (see above)

See SPC for further clarification of drug interactions: http://www.medicines.org.uk/emc/default.aspx

Vaccination:

- See Appendix i

Leflunomide – Dosage and Monitoring

Dosage and Administration:

Rheumatoid Arthritis:

- 10- 20mg once daily
- 10mg daily when used in combination therapy with other hepatotoxic DMARDs

Psoriatic Arthritis:

- 20mg daily

Loading dose:

- 100mg daily for 3 days. Speeds up the onset of effect but rarely prescribed due to unacceptable gastrointestinal side effects (diarrhoea). Avoid in combination DMARD therapy

Pre-treatment Assessment:

- FBC, U&Es and Creatinine, LFTs
- Blood pressure - if > 140/90mmHg on 2 occasions 2 weeks apart, treat prior to starting drug
- Weigh to allow assessment of weight loss that might be attributable to Leflunomide

During Treatment:

See 'Responsibilities of Speciality Team, GP, Patient and Pharmacist in Shared Care Agreement'

Investigation	Frequency	Specialist	GP
FBC	Monthly for 6 months (initial 3 months by specialist)	✓	✓
	2 monthly thereafter if stable		✓
	Monthly (at least) blood checks if co-prescribed with another immunosuppressant or hepatotoxic drug		✓
LFTs	Monthly for 6 months	✓	
	2 monthly thereafter if stable		✓
BP & Weight	At each monitoring visit	✓	✓

- Please monitor CRP/ ESR (usually every 3 – 6 months) to assess disease activity as requested by specialist team

Action to be taken if:

WBC <3.5 x 10^^{9}/l	Withhold until discussed with specialist team
Neutrophil <2.0 x 10^{9}/l	Withhold until discussed with specialist team
Platelets <150 x 10^{9}/l	Withhold until discussed with specialist team
AST, ALT 2-3 times upper limit of reference range	Reduce dose to 10mg daily if above this and recheck LFTs weekly until normalised. If AST & ALT remain normal, continue 10mg daily. If remain elevated, withhold until discussed with specialist team
AST, ALT >3 fold rise from upper limit of reference range	Recheck LFTs within 72 hours If still >3 times the upper limit, discontinue and consider washout
Rash, itch, hair loss	Consider dosage reduction with or without antihistamines If severe, stop and consider washout
Abnormal bruising or sore throat	Check FBC immediately and withhold until results are available
Hypertension	If BP >140/90mmHg, treat in accordance with NICE guidance. If remains uncontrolled, stop Leflunomide and consider washout
Severe GI upset & headaches	If severe or persistent stop and consider washout
Weight loss	Monitor carefully. If > 10% reduce dose or stop. Consider washout
Breathlessness	If increasing shortness of breath occurs, stop leflunomide and consider washout

Washout Procedure (rapid drug removal):

Simple dose reduction is unlikely to produce a rapid diminution of adverse effects owing to Leflunomide's long half-life (2 weeks). If a rapid response is required consider washout e.g. in cases of serious adverse effect, or before starting another DMARD or before conception. Stop treatment and give either colestyramine 8g three times daily for 11 days or activated charcoal 50g four times daily for 11 days. The active metabolite concentration after washout should be less than 0.02mg/L (measured on 2 occasions, 2 weeks apart) in men and women before conception. The process can be repeated as necessary.

Appendix i

Guidelines for vaccinations in patients taking immunosuppressants, steroids and biological therapies

This is the BSR's most recent guidance and is subject to revision and formal review

GENERAL INFORMATION LIVE VACCINES

- Live vaccines are contraindicated while on immunosuppressive therapy
  - e.g Azathioprine, Ciclosporin, Leflunomide, Mycophenolate, Cyclophophamide
- Immunosuppressive therapy should be stopped for 3 months prior to live vaccine administration
- Live vaccines if needed should be ideally given at least 2 weeks, preferably 4 weeks, before immunosuppressive therapy is commenced
- In immunosuppressed patients, the immunological response may be suboptimal. Consider repeating 3 months after therapy has ceased if viral titres low
- Consider using immunoglobulins if contact risk is significant (e.g. Varicella, Measles)

INACTIVE VIRUS VACCINES

- In immunosuppressed patients, the immunological response may be suboptimal but can be given in accordance with national recommendations
- There is an increased risk in the immunocompromised from secondary bacterial infections following influenza
- Pneumococcal and the Annual flu vaccination is recommended in patients with autoimmune inflammatory rheumatic disease
- Immunisation against Meningococcal, Haemophilus B, Tetanus and Hepatitis B infection might be indicated. Check Hepatitis B titres 3 months after the 3rd injection
- Check Varicella zoster titres prior to immunisation if appropriate

VACCINES FOR TRAVEL ABROAD

- Yellow fever vaccine must not be given. Patients should be advised not to travel to countries requiring this e.g. mid-Africa. If travel necessary, an exemption statement may be accepted but the patient will be at risk
- Polio vaccine - the oral live polio vaccine (OPV) must not be given. Killed inactivated vaccine can be given but may need to be obtained from abroad so adequate notice must be given
- Typhoid vaccine - the live form should not be given. Killed vaccine is available but only 70% protective
- Inactive viruses can be given e.g. Rabies, Anthrax, Cholera, Plague

VACCINES FOR HOME

- Polio - OPV is contraindicated and in household contacts. Inactivated form (IPV) can be used
- Measles, Mumps, Rubella (MMR) - all three live vaccines is contraindicated but not in household contacts. Exposure to measles should be treated with immunoglobulin regardless of prior immunization
- BCG is contra-indicated. Consider giving it in juvenile arthritis 4 weeks before immunosuppressives started. Juvenile arthritis patients should be brought up to date with vaccination schedules prior to receiving methotrexate

Zostavax (Zoster Vaccination)

- A live attenuated vaccine with high antigen level of varicella zoster virus
- Eligible individuals previously not immunised should receive a single dose of vaccine at least 14 days (preferably a month) before starting immunosuppressive therapy as the risk and severity of shingles is considerably higher amongst immunosuppressed individuals
- Zostavax should not be given to a person who is receiving immunosuppressive therapy such as high-dose corticosteroids
- Zostavax can be given to patients receiving low dose corticosteroids, low dose methotrexate (<0.4/kg/week) and azathioprine (<3.0mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis and sarcoidosis

- Immunosuppressed individuals who are inadvertently vaccinated with Zostavax should be urgently assessed by a clinician to establish the degree of immunosuppression and the need for prophylactic acyclovir. If a varicella rash develops following inadvertent vaccination, patients can be treated with aciclovir

See link for full guidance:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239892/2013181_Shingles_QA_for_healthcare_professionals_final.pdf

PATIENTS ON STEROIDS

- Live vaccines must not be given to patients taking moderate or high doses of steroids for longer than 2 weeks
- Long-term moderate to high dose steroids should be stopped for 3 months before live vaccines can be administered

There are no contra-indications to using live vaccines if steroid therapy is:

- for less than 2 weeks
- by topical application
- by intra-articular or soft tissue injection
- used as replacement therapy in physiological doses e.g. adrenal insufficiency
- long-term low dose steroids (10mg per day or less)

BIOLOGICS

- Live vaccines should not be given concurrently with biological therapies as no data is available on the effects of vaccination in these patients e.g. anti- TNF therapy, Tocilizumab or Anakinra

LEFLUNOMIDE

- The long half- life of Leflunomide should be considered when contemplating administration of a live vaccine after stopping the drug

References

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with British Association of Dermatologists. Rheumatology. 2008 K Chakravarty *et al* http://rheumatology.oxfordjournals.org/content/suppl/2008/05/31/kel216a.DC1/kel216b.pdf

- SPC (Summaries of Product Specification) for each drug are available on the EMC website: http://www.medicines.org.uk/emc/default.aspx Please ensure you refer to the correct brand where appropriate (especially for ciclosporin and mycophenolate mofetil) as some information is brand specific.

- Vaccinations in the immunocompromised person guidelines for the patient taking immunosuppressants, steroids and the new biologic therapies January 2002 http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/v/vaccinations_in_the_immunocompromised_person.pdf

- BSR statement on Vaccination in Adult Patients with Rheumatic Diseases November 2011