DMARD MONITORING GUIDELINES – FOR GP INFORMATION
10.10.08

Leflunomide

A. Indications: (Licensed) RA and psoriatic arthritis (PsA). Not used in Psoriasis. BAD: Dermatologists generally do not use this drug.

B. Dose: Grade of evidence: C

Typical dose is:

RA: 10–20 mg once a day [1–3] when monotherapy is used. In cases of combination therapy with another potentially hepatotoxic DMARD like methotrexate, 10 mg once a day is recommended (therapeutic efficacy may be reduced with the reduced dosage.

PsA: 20mg once a day.

Loading dose: 100mg once daily for 3 days may be used to speed up the onset of effect. Unacceptable gastrointestinal (GI) side effects such as diarrhoea may occur when a loading dose is given and this is often omitted in routine practice. A loading dose is not recommended when used as part of combination therapy.

C. Route of administration: Oral

D. Time to response: 8–12 weeks (longer if loading dose is not employed)

E. Caution: Grade of evidence: A & C

(1) Localized or systemic infection including hepatitis B or C and history of tuberculosis.
(2) Drug potentiation: Haematotoxic or hepatotoxic drugs such as methotrexate. Leflunomide SPC states caution if used together with methotrexate although combination therapy using these drugs has been used.

F. Contraindications: Grade of evidence: C

(1) Severe immunodeficiency.
(2) Serious infections.
(3) Impaired liver function due to any cause.
(4) Severe unexplained hypoproteinaemia.
(5) Renal impairment (moderate to severe).
(6) Impairment of bone marrow function as indicated by anaemia and cytopenias due to causes other than RA and PsA.
leflunomide

NB. Simple dose reduction is unlikely to produce a rapid diminution of adverse effects as the half-life of the drug is 2 weeks (1–4 weeks). If a rapid response is required, consider washout and liaise with the rheumatologist.

I. Caveats

leflunomide
(1) Immunization
(a) Patients receiving leflunomide must not receive immunization with live vaccines. Inactivated polio is available although suboptimal response may be seen.
(b) Annual flu vaccination is recommended.
(c) In patients receiving leflunomide exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG.

(2) Pregnancy and lactation: Leflunomide is teratogenic and must not be given to pregnant women or women of child bearing potential unless reliable contraception is used. Women planning to have children should either discontinue the drug 2 yrs prior to conception or have a rapid removal of its active metabolite by following the washout procedure. Men should use effective contraception for 3 months after stopping leflunomide.

(a) Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following wash out. Any pregnancy within 2 yrs of discontinuation of leflunomide should be discussed with rheumatologist if drug washout has not been performed. Notify pharmaceutical company in the event of pregnancy while on leflunomide.

(b) Breast feeding should be avoided as animal studies indicate that metabolites of leflunomide are secreted in the breast milk.

(3) Hepatic toxicity: Leflunomide is a potentially hepatotoxic drug and caution is advised when using leflunomide concomitantly with another hepatotoxic drug, such as methotrexate, or if there is evidence of current or recent hepatitis with Hepatitis B or C viruses. Rare cases of severe liver injury (some with fatal outcome) have been reported during treatment with leflunomide. Most cases occurred within 6 months and in a setting of multiple risk factors for hepatotoxicity. It is highly recommended that LFTs be monitored closely (at least once a month) if leflunomide is co-prescribed with potentially hepatotoxic drugs, such as methotrexate. Patient should be asked to limit alcohol intake well within national limits 4–8 units a week (National Survey data 2005).

(4) Drug interactions: Leflunomide can interact with many drugs, particularly with phenytoin, tolbutamide and may enhance the effects of these drugs although significant interaction is unlikely. Leflunomide also interacts with warfarin and the International normal ratio (INR) should be very closely monitored for several weeks even after stopping the leflunomide. As leflunomide has an extremely long half-life (2 weeks) the interactions can potentially be serious and more actions may be required beside just discontinuation of the drug such as washout. This may be of practical importance when changing from leflunomide to another DMARD.

(5) GI effects: Diarrhoea often occurs early in therapy when full loading doses of 100 mg/day for 3 days are given. Such effects lead to patient dissatisfaction and issues related to compliance and subsequent withdrawal of the drug in some circumstances. Omission of loading dose is acceptable with the knowledge that there may be a slight delay in response time.

(6) Hypertension: Regular monitoring of blood pressure is necessary during treatment and if there is a significant rise in blood pressure, then this should be treated. However, it is important to undertake a risk – benefit assessment at all times. In severe uncontrolled cases it is necessary to consider stopping the drug and washout if necessary.

(7) Infections: Any infection should be treated on its own merit. All types of infection can occur and a cautious vigilance is necessary to detect early evidence of infection.

(8) Pulmonary infiltration/pneumonitis/reactions: Pulmonary infiltration/pneumonitis as an acute allergic reaction has been described in a small number of patients after starting leflunomide
leflunomide. Patients should be made aware of this rare complication (see drug SPC) and if they become short of breath they should stop the tablets at once and seek urgent medical advice. If combination therapy is used with methotrexate, the patient should be made aware of the possible added risk even though this may not be clinically significant.

Consultant: ........................................
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