Objectives. To determine, by consensus, the optimal use of leflunomide in rheumatoid arthritis (RA), using a multidisciplinary panel of experts and performing meta-analyses of available data

Methods. A multidisciplinary panel of experts in RA was convened. Important questions, pertinent to the use of leflunomide in the treatment of RA, were defined by consensus at an initial meeting. Each question was allocated to subgroups of two or three members, who worked separately to prepare a balanced opinion, based on published literature, data from individual patients taking part in phase II and phase III clinical trials provided by Aventis, and data from a USA-based medical claims database (AETNA). The full group then reconvened to agree on an overall consensus statement. Recommendations concerning efficacy and tolerability versus comparator drugs and placebo were derived from two new meta-analyses.

Results. Leflunomide was at least as effective as sulphasalazine and methotrexate, and equally well tolerated on meta-analysis of trial data. Overall withdrawal rates for all adverse events were similar for all three drugs. Avoidance of the loading dose reduces ‘nuisance’ side-effects (e.g. nausea), but probably delays the onset of action. Adverse events could usually be managed by dose reduction and/or symptomatic therapy.

Conclusions. On the basis of efficacy, safety and cost, leflunomide should be considered in patients with RA who have failed first-line DMARD drug therapy. In refractory cases, leflunomide may be used in combination with, for example, methotrexate before biological agents. Therapy should be initiated by a specialist, but repeat prescribing in general practice on a shared care basis is acceptable using agreed protocols. Clear mechanisms are required to monitor toxicity, with good communication between the patient and rheumatologist to manage nuisance side-effects and avoid unnecessary discontinuation of leflunomide.

KEY WORDS: Leflunomide, Rheumatoid arthritis, DMARDs, Combination therapy, Adverse events.
Leflunomide in RA: consensus recommendations

Methods
A multidisciplinary panel was convened consisting of eight rheumatologists with experience of using leflunomide from teaching hospitals and district general hospitals across the UK, a general practitioner (GP) with a special interest in rheumatic diseases, nurse practitioners from two additional rheumatology units and a patient with RA. At an initial meeting, eight questions pertinent to the use of leflunomide in the management of inflammatory arthritis were defined.

1. How effective is leflunomide?
2. How well tolerated is leflunomide in comparison with other DMARDs?
3. Can leflunomide be used in combination?
4. Who should prescribe leflunomide?
5. How should leflunomide be given?
6. How should side-effects be managed?
7. What is the ideal model of care for treatment with leflunomide?
8. What does the patient need to know?

Subgroups of up to three members of the panel were allocated each question to consider by systematically reviewing available data to reach a balanced opinion.

New meta-analyses were also performed for questions 1 and 2. The analysis for question 1 pooled data from individual patients enrolled in three Phase III, multicentre, international, randomized, double-blind trials reported in peer review publications [4–10], that compared the clinical efficacy of leflunomide with placebo and comparator drugs. A total of 1817 patients were included. Baseline demographic data and numbers of patients available for follow-up at 12 and 24 months are given in Table 1. The trials collected swollen joint counts (28 joints), tender joint counts (28 joints), pain scores (on a 100 mm visual analogue scale), patient and physician global responses (on 100 mm visual analogue scales), ESR and CRP levels and Health Assessment Questionnaire (HAQ) scores. These data were used to determine the American College of Rheumatology (ACR) response rates (ACR20 and ACR50). Data from these trials were analysed for all drugs in all units and a patient with RA. At an initial meeting, eight questions pertinent to the use of leflunomide were defined.

### Table 1. Meta-analysis of leflunomide efficacy versus comparator DMARDs: patient demographics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>LEF (n = 807)</th>
<th>MTX (n = 669)</th>
<th>SSZ (n = 132)</th>
<th>PLC (n = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr): mean</td>
<td>57.4</td>
<td>66.5</td>
<td>58.9</td>
<td>56.4</td>
</tr>
<tr>
<td>Patients with disease for &lt;6 months (%)</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Patients with disease for &gt;24 months (%)</td>
<td>58</td>
<td>57</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Patients completing 6 months’ treatment</td>
<td>623</td>
<td>547</td>
<td>86</td>
<td>105</td>
</tr>
<tr>
<td>Patients enrolled on 12 months’ extension</td>
<td>450</td>
<td>421</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Patients completing 24 months’ treatment</td>
<td>392</td>
<td>357</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

LEF, leflunomide; MTX, methotrexate; SSZ, sulphasalazine; PLC, placebo.

The analysis for question 2 also pooled individual patient data from dose-ranging phase II studies, allowing the safety of the 25 mg daily dose regimen to be evaluated (Supplementary data, Appendix 2). Additional data allowing the safety of the 25 mg daily dose regimen to be evaluated (Supplementary data, Appendix 2). Additional data were obtained from the USA-based healthcare claims database AETNA [11]. This provided useful information on the use of leflunomide in over 40,000 RA patients versus comparator DMARDs.

**Recommendations**

1. **How effective is leflunomide?**

   **Meta-analysis of published trials on leflunomide.** ACR response rates were better in the leflunomide group than in the placebo group. At 6 months and 12 months respectively, an ACR20 (20% improvement in ACR criteria) response was seen in 60 and 53% of leflunomide patients and in 27 and 26% of placebo patients. Similarly, an ACR50 response (50% improvement in ACR criteria) was seen in 29 and 34% of leflunomide-treated patients and in 11 and 8% of placebo-treated patients at the same time points (Supplementary data, Appendix 1).

   Sulphasalazine (maximum dose 2 g daily), methotrexate (maximum dose 15 mg weekly) and leflunomide (maximum dose 20 mg daily) were similar in all clinical, imaging and laboratory parameters, apart from a greater lowering of erythrocyte sedimentation rate (ESR) observed with sulphasalazine and methotrexate than leflunomide.

   Leflunomide-treated patients showed a significant improvement in disability, with mean HAQ scores decreasing at 12 months by 0.37 [95% confidence interval (CI) 0.33, 0.41] compared with an increase in placebo HAQ scores of 0.06 (95% CI –0.03, 0.16) at 12 months. Comparable results to leflunomide were observed in patients taking sulphasalazine and methotrexate. The 2-yr extension studies showed that the decrease in mean HAQ scores was maintained in patients taking each of the DMARDs.

   Analysis of Sharp scores revealed significantly less radiological progression with leflunomide than placebo (leflunomide versus placebo: 6-month study, \(P = 0.0004\); 12-month study, \(P = 0.0007\)) [12].

   In a subset of patients initially treated with leflunomide or methotrexate for 12 months (MN302 protocol), dynamic gadolinium-enhanced magnetic resonance imaging (DEMRI) was compared at baseline and at 16 weeks. Whilst indistinguishable in terms of ACR response criteria, the DEMRI parameters (initial rate of synovial enhancement and maximal signal intensity enhancement) showed significant improvement in leflunomide-treated patients and a slight deterioration in the methotrexate group at this early time point [13].

   Leflunomide therefore satisfies OMERACT criteria for a DMARD, is at least as effective as sulphasalazine and methotrexate and appears to have a faster onset of action with respect to pain and reduction in synovial vascularity.

2. **How well tolerated is leflunomide in comparison to other DMARDs?**

   **Study withdrawals and infections.** In clinical trials leflunomide had a tolerability profile intermediate between that of methotrexate and sulphasalazine in terms of all-cause withdrawal rates and infections. AETNA data revealed greater withdrawal rates with leflunomide in clinical practice (30–50% after 1 yr), with adverse events (especially gastrointestinal tract-related, the main reason for withdrawal). Since most patients studied received leflunomide 20 mg daily and relatively few were on
other doses, it was difficult to say whether side-effects were dose-related or idiosyncratic. However, where a dose effect was apparent this is mentioned.

The most prevalent adverse events for leflunomide, methotrexate and sulphasalazine were hypertension, gastrointestinal and dermatological symptoms, occurring in higher frequency in patients on any of these three drugs compared with placebo. Serious adverse events were similar to the comparator DMARDs except severe weight loss and severe dermatological toxicity, which were higher in leflunomide and an increase in liver function tests (LFTs) greater than three times the upper limit of normal, which was more common with methotrexate.

Nausea and diarrhoea. The prevalence of significant nausea (requiring withdrawal of treatment) was less in leflunomide (1.3%)-treated patients than seen with methotrexate (2.4%) or sulphasalazine (3.5%). Diarrhoea was more prevalent than significant nausea for all three drugs, and the withdrawal rate was higher in leflunomide (1.9%)-treated patients than in those on methotrexate (1.5%) or sulphasalazine (0.75%).

Daily doses of leflunomide 20 mg were associated with more nausea and diarrhoea than the 10 mg/day dose. The rates of diarrhoea requiring withdrawal in patients receiving loading doses of 100 or 50 mg/day leflunomide were identical (2.1%) and higher than with lower doses.

Hepatotoxicity. The cumulative incidence of hepatic enzyme concentration elevation three times the upper limit of normal was highest with methotrexate (17%), followed by leflunomide (5%), sulphasalazine (4%) and placebo (1%). This was also the case in the AETNA database; where hepatic adverse events were more common with methotrexate compared with methotrexate or other DMARD groups.

Dermatological. The prevalence of all dermatological adverse events was comparable for leflunomide (28%), methotrexate (32%) and sulphasalazine (35%), but leflunomide was associated with a higher incidence of serious dermatological adverse events (this higher rate was only evident with the use of the 25 mg daily dose and apparent from 3 months within the clinical trial data reviewed). The AETNA database was insufficient for comparable analysis.

Hypertension. Withdrawals due to hypertension occurred rarely in the placebo-treated group (0.93%) and the leflunomide (0.77%) and sulphasalazine (0.75%) groups, but these were a little higher than methotrexate (0.28%). In contrast, the AETNA data showed less hypertension in the leflunomide group than all other DMARDs.

The use of leflunomide 100 mg/day as a loading dose for 3 days was associated with hypertension in 3.4% of 1322 study participants, but in only 1.2% of patients who received a loading dose of 50 mg/day. Confounding factors, such as NSAID use, could not be determined from this meta-analysis.

Other adverse events. Neither the meta-analysis nor the AETNA database provided data to suggest that leflunomide was associated with significant haematological toxicity, including cytopenias or solid or haematological malignancies.

Serious adverse events therefore do not seem to be increased with leflunomide compared with methotrexate or other DMARDs and anecdotal evidence that dermatological adverse events and hypertension are more common with leflunomide than other DMARDs was not supported.

3. Can leflunomide be used in combination?

NSAIDs. Although the active metabolite of leflunomide, A771726, inhibits cytochrome P450 2C9, which metabolizes many NSAIDs, published clinical trial data suggests that NSAIDs can be used effectively with leflunomide [14]. There are no published data considering COX-2-specific NSAIDs and leflunomide.

DMARDs

Methotrexate. Pharmacokinetic data have revealed no clinically significant interaction between methotrexate and leflunomide [15]. A 24-week randomized, double-blind trial [16] reported that the addition of leflunomide to the treatment of patients with persistently active RA on stable methotrexate therapy resulted in a significantly better outcome than when placebo was added to the methotrexate, with acceptable toxicity (including manageable rises in transaminases).

The AETNA database corroborated these findings, further supporting the efficacy and safety of leflunomide and methotrexate combination therapy. However, it is highly recommended that all patients receiving methotrexate plus leflunomide are monitored closely for LFTs.

Sulphasalazine. In a 12-month trial (the RELIEF study) a favourable but not significant benefit of combining leflunomide and sulphasalazine vs sulphasalazine alone was reported, with between-treatment similarity in terms of safety [17].

Infliximab. To date, there are no randomized, controlled trials to assess the feasibility of a leflunomide/infliximab combination. However, data from two prospective [18, 19] and two retrospective cohort studies [20, 21] have been reported. These showed that leflunomide plus infliximab was an effective combination in patients failing on or intolerant to methotrexate, or those having an inadequate response to leflunomide mono-therapy. However, until further evidence is available, caution is advised concerning dosing and adverse events.

Adalimumab. In the Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR) study [22], adalimumab or placebo injections were given to RA patients receiving DMARD polypharmacy, of whom 13.4% received leflunomide alone or as combination therapy. No relationship between adverse events and a specific DMARD was found.

4. Who should prescribe leflunomide?

The current Summary of Product Characteristics for leflunomide (March 2001) states that only ‘specialists experienced in the treatment of rheumatic diseases’ should prescribe it. The European Medicines Evaluation Agency (EMEA) [23] statement (12 March 2001), which addressed hepatic adverse events, reiterated this advice. Therefore, the initiation of leflunomide in primary care is precluded in all but exceptional cases where the prescribing physician has the relevant training and experience.

Repeat prescribing of leflunomide on a shared care basis is acceptable under the guidance of mutually agreed protocols (Table 2).

5. How should leflunomide be given?

Loading dose. The use of a loading dose of 100 mg daily for 3 days results in steady-state plasma levels within 3–5 days. Omitting the loading dose delays steady-state plasma levels on a daily dose of 20 mg to approximately 2 months. It will take at least 6 months to reach therapeutic drug levels with 10 mg daily without a loading dose and sometimes a therapeutic level is not achieved. Loading doses are associated with a higher incidence of nuisance side-effects, particularly nausea and diarrhoea [3], increased discontinuation [24], and higher chance of adverse events [25]. It is now common UK (but not EU) practice to omit the loading dose (Aventis, personal communication). Whilst further research is required to determine the association between loading dose and adverse events, it may be sensible to omit the loading dose in frail or adverse event-prone patients, reserving it for patients where a rapid clinical effect is required.
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Table 2. Shared care recommendations

Recommendations for a leflunomide shared care protocol

Essential elements

The provision of clearly written guidelines outlining the responsibilities of the hospital specialist and the primary care physician undertaking the shared care
The availability of the necessary contact details to enable the primary care physician to gain ready access to the local on-call rheumatology service
The transfer of details of the laboratory investigations undertaken by the primary care physician to the hospital specialist at each clinic visit
The provision of drug information for patients outlining the benefits and risks of treatment, and the need to adhere to safety monitoring recommendations
The provision for the monitoring of treatment by the hospital specialist in situations where the primary care physician is unable or unwilling to undertake shared care

Responsibilities of the GP

Monitoring the patient’s overall health status and well-being
Prescribing DMARDs and monitoring coprescribing of other drugs
Ensuring safety monitoring is conducted according to the shared care protocol
Adverse event monitoring and being aware of the risks involved in using each DMARD
Managing minor and major adverse events

Responsibilities of the hospital specialist

Initiating DMARDs and monitoring patient response to treatment
Evaluating the results of the community and hospital drug safety monitoring
Managing minor and major adverse events
Informing the primary care physician of any proposed changes to treatment
Providing ready access to the primary care physician for specialist advice on the treatment

Recommendations for some leflunomide-related care management issues

<table>
<thead>
<tr>
<th>Care issue</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuisance symptoms</td>
<td>Establish a clear line of communication between the patient and the department (e.g. help-lines, e-mail, routine telephone call from the department after 1 and 2 weeks’ treatment) to ensure prompt action (e.g. reassurance, symptomatic treatment, dose reduction) thereby potentially facilitating treatment adherence</td>
</tr>
<tr>
<td>Routine blood pressure and blood monitoring</td>
<td>The GP must ensure he/she takes responsibility for this to ensure blood pressure and routine blood monitoring takes place according to the agreed protocol</td>
</tr>
<tr>
<td>Non-compliance with monitoring</td>
<td>There should be a means of identifying patients who have not complied with monitoring requirements and a strategy for repeat prescription cessation</td>
</tr>
<tr>
<td></td>
<td>There should be an agreed clear line of communication between the department and GP regarding the interpretation of monitoring data. This may be facilitated by the production of guidelines.</td>
</tr>
<tr>
<td></td>
<td>Efficacy should be monitored at regular intervals—ideally 6-weekly until disease control is achieved. Responsibility for action taken (e.g. dose modification, discontinuation, washout, symptomatic treatment) usually lies with the consultant and must be clearly defined</td>
</tr>
</tbody>
</table>

Daily maintenance dose. The consensus of the group is that the recommended daily leflunomide dose, based on trying to achieve a balance between therapeutic benefit and the risk of side-effects, is 20 mg. This is supported by a head-to-head study [26] showing that leflunomide 20 mg daily was more effective than 10 mg without compromising tolerability. However, in patients receiving other potentially hepatotoxic drugs (e.g. methotrexate) or who are renally impaired, 10 mg is recommended, although the dose can be cautiously increased to 20 mg daily if necessary.

Use of leflunomide in special situations. Recommendations for the use of leflunomide in special populations, (such as children, the elderly, pregnancy, and hepatic dysfunction) are presented in the Supplementary data (Appendix 3).

What monitoring is required? Recommendations regarding monitoring for adverse events in leflunomide-treated patients are given in Appendix 3 of the Supplementary data. Since there are no data to suggest an increase in blood dyscrasias attributable to leflunomide, recommendations for full blood count (FBC) monitoring are less stringent than those suggested in the Summary of Product Characteristics.

6. How should side-effects be managed?

Published reports in general provide minimal detail regarding how adverse events are managed [2-8, 15, 16, 27, 28], though they indicate that most appear to be self-limiting [6-8] and in long-term studies lead to leflunomide discontinuation in a minority of cases [6, 7, 16]. Detailed recommendations of how to manage adverse events are given in the Supplementary data (Appendix 4).

Many adverse events can be managed simply by reducing the drug dose or by concomitant administration of symptomatic therapy. Patients may have preferences about this and these should be incorporated in the decision-making process. A dose reduction from 20 to 10 mg is unlikely to produce a rapid diminution of adverse events, as the half life is ~2 weeks. If a rapid response is required, a partial washout with cholestyramine (8 g three times daily for 1–3 days) will quickly reduce plasma levels, lead to prompt diminution of the adverse event, and allow the 10 mg dose to commence without delay. If drug dose reduction has controlled a specific adverse event, it may be possible to reintroduce the drug at the original dose if required.
7. What is the ideal model of care for treatment with leflunomide?

Figure 1 illustrates a proposed model of care for leflunomide. The decision to initiate treatment is usually made by a rheumatologist, although a suitably trained nurse practitioner working alongside a rheumatologist could also do so. A detailed discussion covering benefits and risks, the time to onset of action, nuisance symptoms and strategies to reduce other adverse events (e.g. low alcohol intake) may lessen the chance of premature discontinuation. A nurse practitioner may be best at providing this information, especially if he/she is subsequently the contact between the patient and department at times of crisis. This preliminary consultation may require considerable time, and written information is advocated. The responsibility for issuing repeat prescriptions should be clearly defined and shared care guidelines followed (Table 2).

8. What does the patient need to know?

Educating patients about disease and therapies has been shown to facilitate long-term compliance with drug regimes [29, 30]. The degree of discussion and provision of information to patients may vary enormously and are dictated by many factors, such as the patient’s desire to be involved in their treatment. A good rapport will help successful management of adverse events with leflunomide. This may include allowing the patient a choice of symptomatic treatment, partial washout or dose reduction. The use of written information to reinforce verbally communicated advice is strongly advocated [31–33].

Overall conclusions

What is the position of leflunomide as DMARD therapy for RA?

Both the existing literature and two new meta-analyses presented here show clearly that leflunomide has comparable efficacy and tolerability to methotrexate and sulphasalazine in RA. There still remains a place for other DMARDs in RA management and optimal care should be tailored to the individual patient’s requirements. This group concluded by consensus that methotrexate should remain the first-line DMARD for RA because it is effective, has a low incidence of serious side-effects and is of relatively low cost [34]. For patients who fail to respond to methotrexate or who suffer intolerable adverse events [35], the available evidence suggests that sulphasalazine or leflunomide may be suitable as monotherapy [2, 36]. The meta-analyses above suggest no significant differences between these drugs with respect to efficacy or adverse effects and therefore the choice
of drug may depend upon factors such as sulphonamide allergy, serious co-existing hypertension or cost. Alternatively, sulphasalazine or leflunomide may be successfully added to methotrexate in cases of failure of efficacy of monotherapy with this drug [15, 37] (Fig. 2). Finally, there is as yet no firm evidence base to best inform how to place leflunomide with biological therapy in RA. There is evidence that leflunomide is more cost-effective for the average RA patient who has failed methotrexate than combination therapy with biologicals, although head-to-head trial data are not yet available [38, 39]. Some units, therefore, require failure of leflunomide therapy as well as methotrexate before starting biologicals; others treat biological failures with leflunomide. Perhaps most importantly, there are many patients who cannot take biological therapy because of chronic infection. Therapy with leflunomide would allow these patients access to an effective DMARD without the risk of severe infection.

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Supplementary data

Supplementary data are available at Rheumatology Online.