The Efficacy of Leflunomide Monotherapy in Rheumatoid Arthritis: Towards the Goals of Disease Modifying Antirheumatic Drug Therapy

JOSEPH S. SMOLEN, PAUL EMERY, JOACHIM R. KALDEN, PIET L.C.M. VAN RIEL, MAXIME DOUGADOS, C. VIBEKE STRAND, and FERDINAND C. BREEDVELD

ABSTRACT. This expert review of results from the leflunomide phase II and III clinical trials database demonstrates that leflunomide meets all 3 goals desired of disease modifying antirheumatic drug (DMARD) therapy: reducing the signs and symptoms of the disease; inhibiting structural damage; and improving physical function. Further, leflunomide has a rapid onset of action, sustained efficacy, and is effective in early and late disease, regardless of whether patients have received other DMARD previously. The consistent efficacy of leflunomide across phase III clinical trials is confirmed by the findings from clinical practice. Experts agreed that it is important to observe a patient under leflunomide monotherapy for at least 3–4 months before assessing efficacy. It is possible to start maintenance therapy, with either a daily dose of leflunomide 10 mg, subsequently changing to 20 mg, or the reverse. The decision to use a loading dose when initiating leflunomide therapy depends primarily on the balance between the tolerability and rapid efficacy associated with a loading dose, and the balance desired for an individual patient. In general, the use of both maintenance and loading doses requires a flexible approach to the treatment of rheumatoid arthritis. During the first few weeks of leflunomide therapy, patient dropout can be avoided by using prednisolone rather than a loading dose. Moreover, to ensure good tolerability and compliance in patients receiving a loading dose, information and adequate support should be provided throughout treatment. (J Rheumatol 2004;31 Suppl 71:13–20)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LEFLUNOMIDE TREATMENT MONOTHERAPY

The treatment of rheumatoid arthritis (RA) has 3 primary goals: to improve signs and symptoms; to reduce structural damage, as demonstrated by radiographic evaluation of erosions and joint space narrowing; and to improve physical function, as measured by health-related quality of life (HR-QOL) instruments. The leflunomide database of phase II and III studies, which contains findings from 2390 RA patients, of whom 1339 received leflunomide, represents one of the largest databases of RA patients studied in a clinical trial setting (data on file). The data show a good efficacy and safety profile for leflunomide and also show that this novel agent meets all 3 primary goals of an appropriate treatment for RA.

The primary objective of this review is to define recommendations for the optimal use of leflunomide, based on the review of key studies by international experts in rheumatology at a panel meeting held in Paris in 2003. The following section summarizes the data from leflunomide studies presented at the Expert Panel Meeting.

IMPROVEMENT IN SIGNS AND SYMPTOMS OF RHEUMATOID ARTHRITIS

This section reviews key findings from the 3 pivotal, randomized, double-blind phase III studies conducted with leflunomide, including one US-based study (US301)[1,2] and 2 multinational studies (MN301 and MN302)[3-5]. The studies US301 (n = 482) and MN301 (n = 358) were placebo-controlled; the active comparator in US301 was methotrexate (7.5–15 mg/wk) and in MN301 it was sulfasalazine (0.5–2 g/day). In MN302 (n = 999) the active comparator was methotrexate.

Disease duration ranged from 3.7 (MN 302) to 7.0 years (MN 301); 33–53% of treated patients were DMARD-naïve, and the other patients had received a mean of one disease

From the Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, and the 2nd Department of Medicine, Lainz Hospital, Vienna, Austria; Department of Rheumatology and Rehabilitation, University of Leeds School of Medicine, Leeds, UK; Department of Internal Medicine III, Universitaet Erlangen-Nuremberg, Erlangen, Germany; Department of Rheumatology, University Medical Centre Nijmegen, Nijmegen, The Netherlands; Institute of Rheumatology, Hospital Cochin, Paris, France; Division of Immunology, Stanford University, Portola Valley, CA, USA; and Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands.

J.S. Smolen, MD, Lainz Hospital; P. Emery, MA, MD, University of Leeds School of Medicine; J.R. Kalden, MD, Universitaet Erlangen-Nuremburg; P.L.C.M. van Riel, MD, University Medical Centre Nijmegen; M. Dougados, MD, Hospital Cochin; C.V. Strand, MD, Stanford University; F.C. Breedveld, MD, Leiden University Medical Centre.

Address reprint requests to Prof. J.S. Smolen, Department of Internal Medicine III, Division of Rheumatology, Wahringer Gurtel 18-20, University of Vienna, A-1090 Vienna, Austria.
E-mail: smj@2me.khl.magwien.gv.at

modifying antirheumatic drug (DMARD) previously (Table 1). Leflunomide was given as a loading dose of 100 mg daily on days 1 to 3, then 20 mg daily thereafter.

Rapid onset, consistent and sustained efficacy

Response to leflunomide is consistent across clinical trials, whether measured by American College of Rheumatology (ACR) 20% response rate, or change in tender or swollen joint count, or in physician or patient global assessment. Symptoms of disease, measured as improvement in the number of ACR 20% responders, improved within a month of starting treatment, and improvement was maintained in the longterm (Figure 1)[1,4,6,7]. In all 3 trials (MN301, MN302, and US301) the ACR 20% response rate at 4 weeks was substantially greater in the leflunomide-treated patients than in the active comparator arms. In US301, for example, the responder rate in the leflunomide arm was 37.6% compared with 23.9% and 19.5% in the methotrexate and placebo arms, respectively (leflunomide vs placebo, $p \leq 0.032$; leflunomide vs methotrexate, $p = 0.0904$)[8]. This response was sustained over time, with 52% and 79% of patients in US301 demonstrating an ACR 20% response at 1 and 2 years, respectively[1]. Moreover, this good ACR response was sustained for 5 years in the 214 patients from the 2 multinational trials (MN301 and MN302) who subsequently entered an open-label extension study (Figure 2)[9]. These data, therefore, indicate that leflunomide has both an early and a sustained efficacy in improving the signs and symptoms of RA.

Table 1. Baseline characteristics for leflunomide phase III studies[1,3-5].

	US301	MN301	MN302
Patients, n	482	358	999
Control	Placebo	Placebo	NA
Methotrexate	7.5–15 mg/week	NA	7.5–15 mg/week
Median dose	15	NA	11
Sulfasalazine	NA	0.5–2 g/day	NA
Treatment duration, mo	12–24	6–24	12–24
Mean RA duration, yrs	6.7	7	3.7
Patients ≤ 2 years' disease duration	33–40%	38–42%	43–44%
Mean DMARD failed	0.9	1	1.1
DMARD-naïve patients	40–45%	40–53%	33–34%
Mean HAQ-DI	1.3	1.7–1.9	1.5
Patients using folate, %	100	NA	10

DMARD: Disease modifying antirheumatic drug; HAQ-DI: Health Assessment Questionnaire Disibility Index; RA: Rheumatoid arthritis.

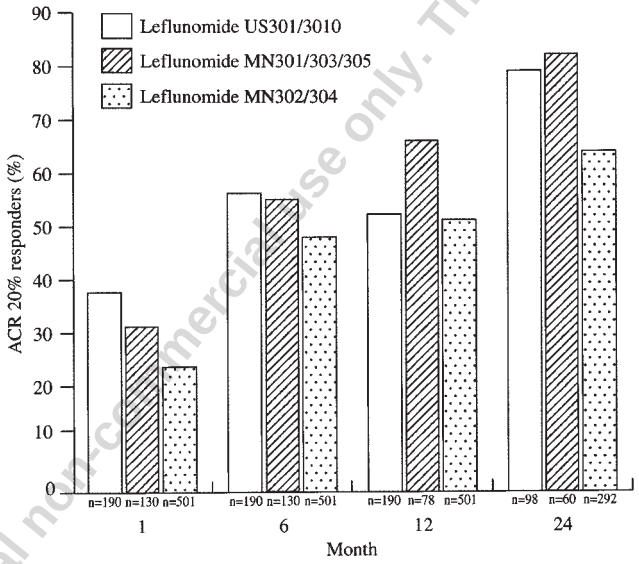

Figure 1. ACR 20% response rate for leflunomide-treated patients in Phase III pivotal studies and their open-label extension over 2 years. Adapted from previous reports[1,4,6,7].

Efficacy in early and late rheumatoid arthritis

The subgroup analysis of placebo-controlled studies MN301 and US301 also shows that the efficacy of leflunomide is similar in both early (< 2 years of disease duration) and late disease (> 2 years of disease duration) (Figure 3)[10].

The efficacy of leflunomide is at least comparable to that of either sulfasalazine or intermediate dose methotrexate. In MN301, 58% and 52% of patients with early and late disease, respectively, were ACR 20% responders to leflunomide compared with 41% and 60% of those randomized to sulfasalazine[10]. In US301, the respective response rates in early and late disease were 56% and 50% with leflunomide and 45% and 46% with methotrexate[11].

Efficacy in DMARD-naïve and DMARD-treated patients

A post hoc analysis of 3 phase III pivotal studies showed leflunomide has similar efficacy in patients previously treated with DMARD and in those who are DMARD-naïve (Figure 4) (data on file).

Subgroup analysis of placebo-controlled studies US301 and MN301 shows the efficacy of leflunomide to be at least comparable to that of either methotrexate or sulfasalazine. In US301, leflunomide response rates were 51.5% in the DMARD-treated and 48.8% in the DMARD-naïve groups; in the methotrexate arm, 45.5% of the DMARD-treated and 41.8% of the DMARD-naïve patients responded. In MN301, 50.6% of DMARD-treated versus 60.8% of DMARD-naïve patients responded to leflunomide; the response rate in the sulfasalazine arm was 53.8% in DMARD-treated patients and 58.2% in DMARD-naïve patients.

Efficacy in clinical practice

A one-year, multinational, multicenter study, **R**heumatoid Arthritis **E**valuation of **L**eflunomide: Further **I**nsights into its **Ef**ficacy (RELIEF), was designed to investigate the efficacy of leflunomide in a patient population comparable to that treated in routine clinical practice[12]. In the first 24-week phase of the study, 969 patients with active RA, as classi-

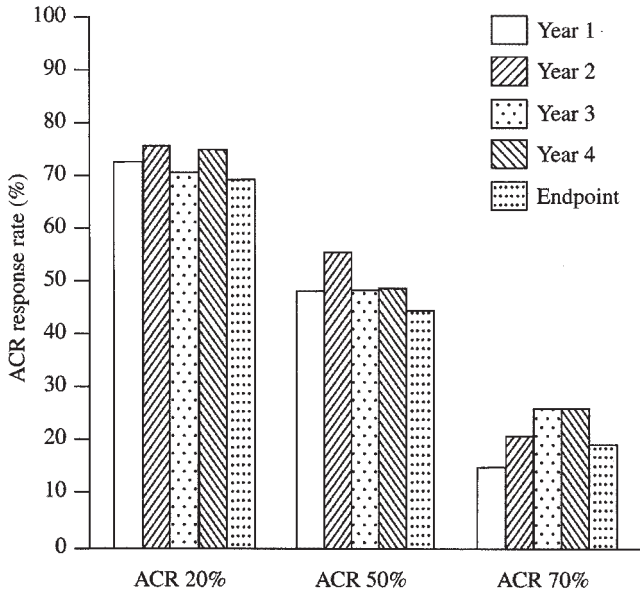

Figure 2. ACR response rates for leflunomide-treated patients (n = 214) in open-label extension of MN301 and MN302[9].

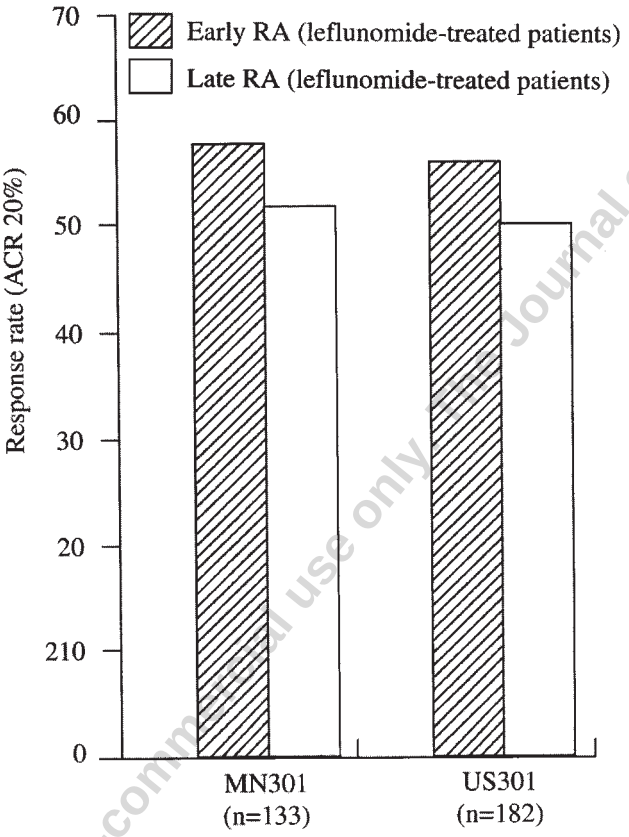

Figure 3. Efficacy of leflunomide in early and late RA. Subgroup analysis[10,11].

fied by the Disease Activity Score (DAS > 3.2), received open-label therapy with leflunomide 100 mg for 3 days, followed by 20 mg daily thereafter. Of the 969 patients treated with leflunomide for 24 weeks, 69% were good or moderate responders at week 24 according to DAS 28 criteria[13]*.

In the second phase of the study, patients who had responded to treatment with leflunomide continued monotherapy for the 24-week treatment period, while the nonresponders were randomized to a further 24 weeks: double-blind treatment with either sulfasalazine (2 g/day) and leflunomide (at the same dose) or sulfasalazine plus placebo. At week 48, 71% of the patients receiving leflunomide were classified as responders according to the DAS 28 criteria, 13.3% fulfilled the disease remission criteria (DAS 28 < 2.6), with 25% having a low DAS 28 score of ≤ 3.2 (Figure 5)[12]. Similar findings were obtained using the ACR 20% response rate.

These results demonstrate that the consistent and sustained efficacy of leflunomide observed in the pivotal clinical trials is confirmed in a setting more akin to everyday practice.

REDUCTION OF STRUCTURAL DAMAGE AS SHOWN BY X-RAY OF EROSIONS AND JOINT SPACE NARROWING LESIONS

RA is characterized by chronic joint inflammation and damage, which has been shown to occur within the first 2 years of disease onset[14]. Moreover, the rate of joint damage increases with disease duration, and this rate remains fairly constant during the 10–20 year course of the disease[15]. Data demonstrating that leflunomide reduces structural damage in RA extend to more than 5.8 years. Change in total Sharp score at endpoint (at 6 or 12 mo, or when the patient left the study prematurely) was significantly less with leflunomide than with placebo in both US301 and MN301 trials, and was also significantly less than with methotrexate at one year[16]. Slowing of disease progression with leflunomide, observed as early as 6 months, was maintained in patients who continued for more than 5.8 years of leflunomide treatment (Figure 6)[17].

IMPROVEMENT IN PHYSICAL FUNCTION AND HEALTH RELATED QUALITY OF LIFE

Although physician-rated measures of efficacy and safety are clearly important in the assessment of the risk:benefit ratio of new therapies, patient-rated measures should also be used, since they correlate well with disease activity and reflect outcome of treatment. Moreover, treatment standard effect sizes may even be greater relative to placebo using patient-reported measures (Figure 7)[18,19]. Patient-reported measures include: the Health Assessment Questionnaire

*Good responders: patients with a significant change (> 1.2) and low disease activity (DAS 28 ≤ 3.2)

Moderate responders: patients with a significant change (> 1.2) and moderate or high disease activity (DAS 28 > 3.2) or patients with a change ≤ 1.2 and > 0.6 and low or moderate disease activity (DAS 28 ≤ 5.1)

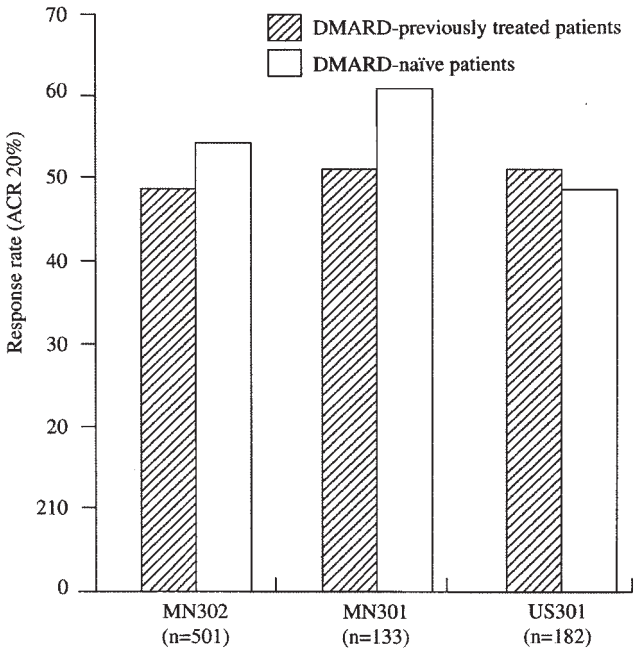

Figure 4. Efficacy of leflunomide in DMARD-treated and DMARD-naïve patients. Subgroup analysis (data on file).

Disability Index (HAQ-DI); the Problem Elicitation Technique (PET) (in which patients are asked to rate the importance of different activities in the HAQ); and the Medical Outcome Study Short Form-36 (SF-36). The minimum clinically important difference on these various instruments provides a measure of the improvement that a patient would perceive as meaningful (Table 2)[19-25].

The leflunomide integrated global database is one of the first to include data on such measures of HR-QOL and, thus is of considerable importance. Findings from the phase III studies show significant improvements in HAQ-DI, PET, and SF-36 with leflunomide across all studies. HAQ-DI at endpoint also improved significantly more with leflunomide than methotrexate in US301 (–0.45 vs –0.26)[2], and HAQ score at endpoint also improved significantly more than with sulfasalazine (–0.50 vs –0.29) in MN301[5]. In MN301, the leflunomide group showed a statistically significant improvement in HAQ score versus both the placebo ($p < 0.001$) and the sulfasalazine group ($p < 0.05$) as early as 4 weeks and up to 6 months. There were also substantial improvements, compared with methotrexate, in all domains of the SF-36 at year one, which reached statistical significance ($p < 0.05$) for bodily pain and vitality[26]. These differences in HAQ scores between leflunomide and methotrexate or sulfasalazine were maintained at year two[1,6].

WHEN AND HOW TO START LEFLUNOMIDE MONOTHERAPY

Optimal ways to switch a patient to leflunomide from another DMARD

Two different clinical scenarios were considered: one in which the previous DMARD had been ineffective and the other in which it had been poorly tolerated.

Ineffective previous DMARD. Three different strategies were discussed. The first was to switch immediately to leflunomide; the second was an overlap strategy in which the existing DMARD was continued for 2–4 weeks to cover the introduction of leflunomide; the third possibility was to switch immediately to leflunomide but to use corticosteroids to cover the intervening period until therapeutic levels of leflunomide had been attained, after which the corticosteroid dose could be reduced.

Poorly tolerated previous DMARD. It is important to distinguish between subjective side effects such as alopecia and nausea and objective side effects such as leukopenia or raised transaminase levels. Objective side effects may require a washout of the previous DMARD before starting leflunomide, but the duration of washout depends on the rapidity of side-effect resolution and on concurrent disease activity. Conversely, in a patient with active disease, leflunomide may be started immediately following resolution of the side effect(s) for which the previous DMARD was withdrawn.

Leflunomide: optimal dosing schedule

Maintenance dose. Phase II clinical trials, using several different doses of leflunomide (5 mg, 10 mg, and 25 mg), have demonstrated that steady-state plasma levels of the active metabolite (A77 1726) after 24 days of treatment were directly proportional to the administered dose[27]. However, a logistic model of the relationship between steady-state concentrations and probability of clinical success after 6 months of treatment showed half-maximal efficacy at 10 mg/l and a plateau at 13 mg/l, (i.e., the therapeutic threshold) (Figure 8). The higher dose of 25 mg did not increase the probability of clinical success[27]. A dose of 20 mg daily was calculated to achieve concentrations above the therapeutic threshold concentration of 13 mg/l in at least 95% of patients. Therefore, the recommended dose for phase III clinical trials was 20 mg daily[27].

In their questionnaire responses, 90% of the members of the Expert Panel (n = 21) reported they most frequently used leflunomide 20 mg daily as a maintenance dose. Only one-quarter reported frequently altering the maintenance dose during therapy, the majority starting with a 20 mg dose but subsequently reducing it to 10 mg in case of adverse events.

However, as can be seen from the experts' responses, a flexible approach to dosing is both feasible and effective.

Loading dose. Computer simulations, based on data from phase I and II studies, demonstrate a faster onset of action of leflunomide when a loading dose is used and indicate that, without a loading dose, attainment of a steady-state plasma level above the therapeutic threshold of 13 mg/l would require 4 weeks' continuous treatment at a dose of 20 mg

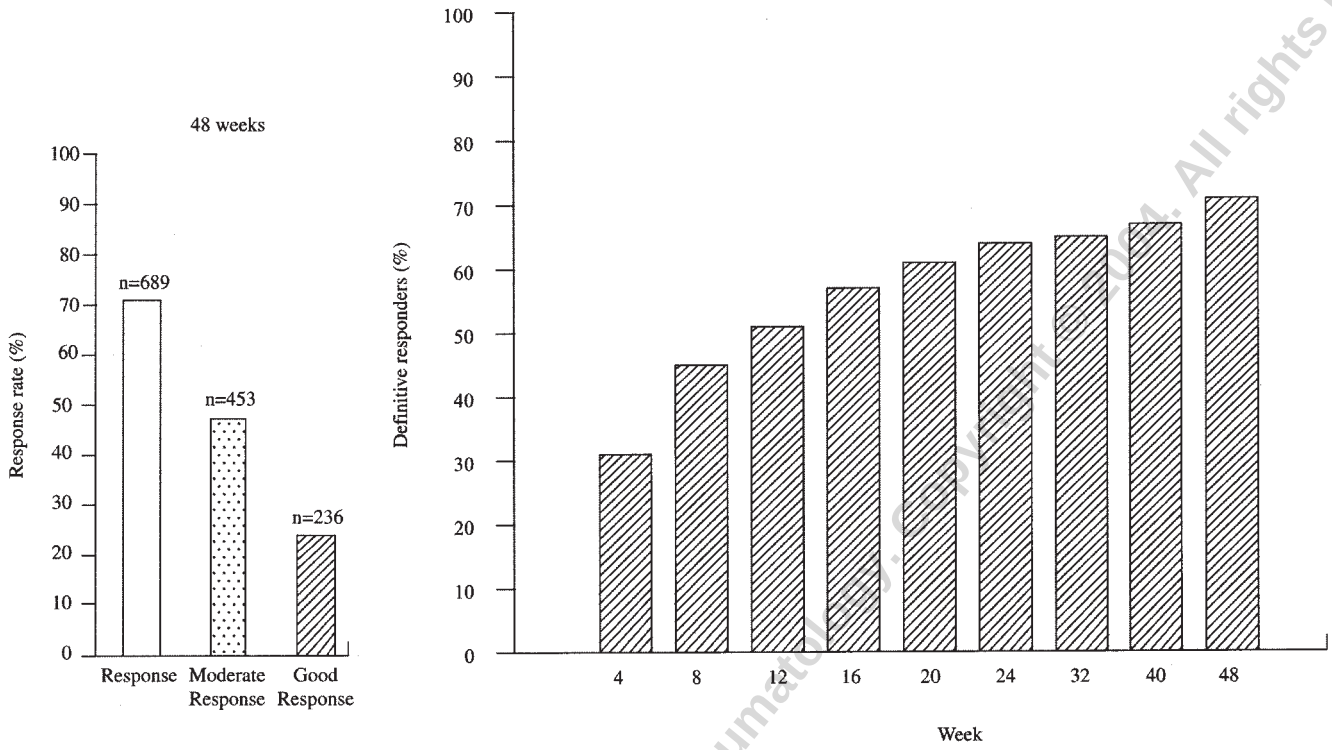

Figure 5. Cumulative "definitive" response rate for patients treated with leflunomide (DAS/EULAR criteria)[12].

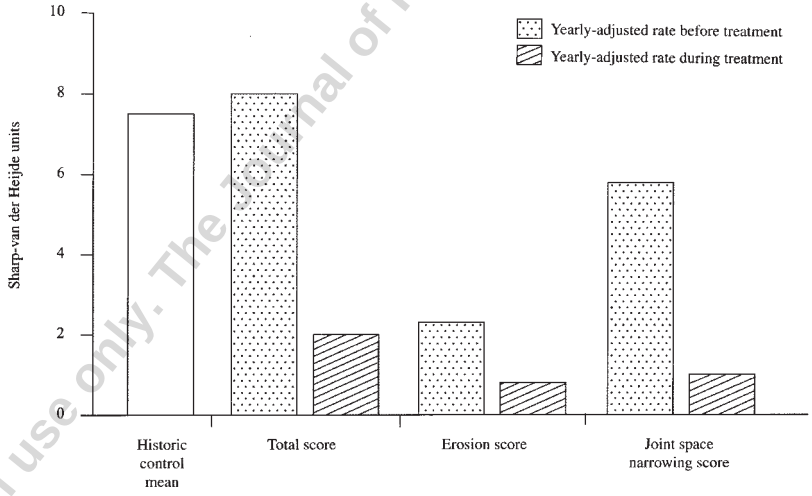

Figure 6. Rate of disease progression in patients (n = 128) before and during leflunomide treatment compared with historic controls[17].

daily. At the same maintenance dose, a loading dose of 100 mg for 3 days would allow all individuals to attain the therapeutic threshold within 3 days. Moreover, some experiences from clinical practice, for instance Chokkalingham's study on a national cohort of 3325 patients, have shown that there is an increased risk of discontinuation of leflunomide following use of a 3-day 100 mg loading dose[28]. The authors suggested that the standard loading dose of leflunomide should be lower than 100 mg daily for 3 days.

Eighty-six percent of the Expert Panel reported they most frequently used a loading dose of 100 mg daily for 3 days. There is no evidence that longterm RA evolution, in terms of disease activity, radiological progression, disability index, or quality of life, is better when a loading dose is prescribed than when it is not. The experts, therefore, recommended that the physician determine, for each patient, the desired balance between tolerability and rapid efficacy; moreover, for those receiving a

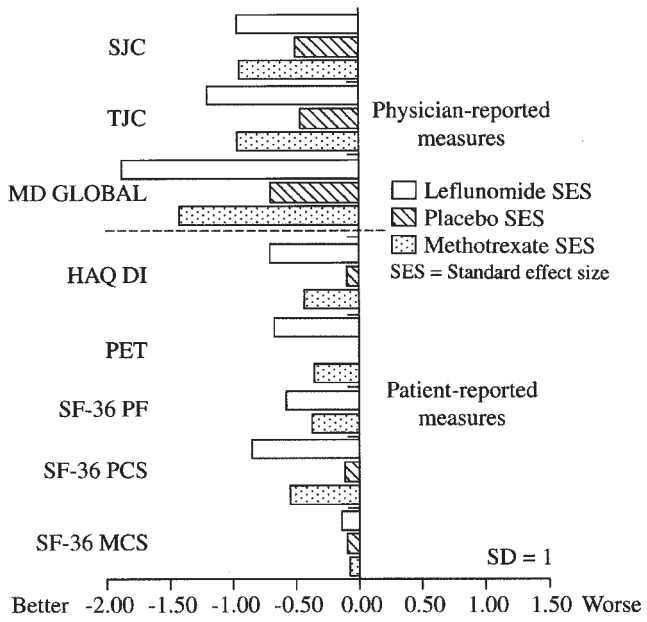

Figure 7. Physician versus patient-reported measures. Adapted with permission from Cohen, et al. *Arthritis Rheum 2001*;44:1984-92[1].

Table 2. Patient-rated measures of minimum clinically important differences (MCID)[19-25].

	Score Range	Direction of Improvement	MCID
HAQ-DI	0–3	↓	–0.22
PET top 5	0–49	↓	–5
SF-36 domains	0–100 (mean)	↑	5–10
SF-36 PCS/MCS	50 ± 10	↑	2.5–5

HAQ-DI: Health Assessment Questionnaire Disibility Index; PET: Problem Elicitation Technique; SF-36: Medical Outcome Study Short Form-36.

loading dose it would be important to ensure efficient monitoring. Without such monitoring the experts consider it preferable to omit a loading dose and to use adjunctive corticosteroids until therapeutic plasma levels have been reached. Thus, as with the maintenance dose, a loading dose should be used flexibly according to patient circumstances.

HOW TO IMPROVE PATIENT COMPLIANCE

There was emphasis on the need to use patient-rated measures of efficacy and tolerability to determine, from the patient's perspective, whether improvement is sufficiently meaningful for them to want to continue treatment.

It is important to convince patients to allow sufficient time for the development of a full response to leflunomide. In the RELIEF study, for example, the proportion of responders increased from 56% to 70% during months 4 to 6[29]. Approximately one-half of the experts reported the need to wait 6 months before deciding whether to change therapy.

Several clear recommendations were produced to avoid or minimize adverse effects, thereby helping patient compliance. These were: informing the patient; reducing the dose; the use of low-dose prednisolone in combination with leflunomide for the first month rather than a loading dose; a good infrastructure to support patients experiencing adverse events from a loading dose; the use of a single dose of cholestyramine for those with adverse reactions to determine whether they would benefit from a dose reduction.

Further information on adverse event management is discussed elsewhere in these proceedings[30].

WHEN AND HOW TO STOP LEFLUNOMIDE MONOTHERAPY

Assessment of disease activity in clinical practice

The panel agreed that the DAS is the most appropriate instrument to assess disease activity in clinical practice. There was also some discussion of the Simplified Disease Activity Index (SDAI), which is the simple linear sum of the tender and swollen joint count (based on a 28-joint assessment), the patient and physician global assessment, and the C-reactive protein level. The SDAI is proven to be a valid and sensitive measure of disease activity and treatment response and is comparable with the DAS 28 and ACR response criteria[31]. Some experts also use a patient-based tool for assessment of disease activity, such as the HAQ.

Switching or combining DMARD

The majority (86%) of the experts report their patients continue leflunomide therapy for at least one year and many for more than 2 years.

Approximately half the Expert Panel assess response to treatment at 1–3 months, and a similar number at 4–6 months; few physicians delay more than 12 months. Fifty-two percent of the Expert Panel agreed that switching from leflunomide is more often due to gastrointestinal side effects, and 39% stated it is due to lack of efficacy. The Expert Panel concluded that switching should be considered after patients had failed to respond to at least 3–4 months of leflunomide monotherapy. If the patient responded to leflunomide originally, another agent should be added; otherwise, leflunomide should be withdrawn and the patient switched to another treatment. A minority (11%) of the expert panel would use a washout with either charcoal or cholestyramine, as described elsewhere in these proceedings[30], when switching from leflunomide to another DMARD.

LEFLUNOMIDE IN MONOTHERAPY: CONCLUSIONS

This expert review of the results from the leflunomide phase II and III clinical trials database, one of the largest resources for RA patients studied in a clinical trial setting, demonstrates that leflunomide meets all 3 goals desired of DMARD therapy: reducing the signs and symptoms of the

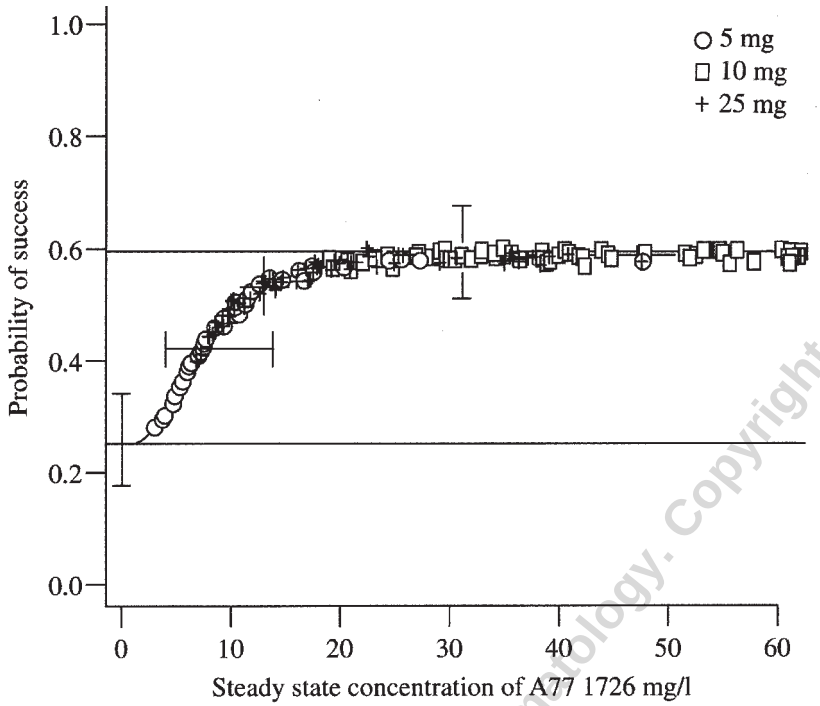

Figure 8. Relationship between concentration of active metabolite at steady state and probability of clinical success following 6 months of treatment with leflunomide[27].

disease; inhibiting structural damage; and improving physical function. Further, leflunomide has a rapid onset of action and sustained efficacy, and is effective in early and late disease, regardless of whether patients have previously received other DMARD. The consistent efficacy of leflunomide across the phase III clinical trials is confirmed by the findings of the RELIEF study in clinical practice. Leflunomide also has a satisfactory and predictable safety profile.

The meeting presentations, and particularly the pharmacokinetic data, questionnaire results, and workshop discussions, resolved several important issues in the management of RA patients with leflunomide monotherapy.

When deciding whether or not to switch a patient to leflunomide, it is important to determine whether failure of the previous DMARD is due to inefficacy or poor tolerability. Patients switched to leflunomide monotherapy should then be observed for at least 3–4 months before assessing efficacy. It is possible to start maintenance therapy either with a daily dose of 10 mg, subsequently changing to 20 mg, or the reverse. The decision to use a loading dose when initiating leflunomide therapy depends primarily on the balance between the tolerability and rapid efficacy associated with a loading dose and the balance desired for an individual patient. In general, therefore, the use of both maintenance and loading doses requires a flexible approach to the treatment of RA. During the first few weeks of leflunomide therapy, patient dropout can be avoided by using prednisolone rather than a loading dose. Patients who receive a loading dose need adequate information and support while experiencing adverse effects.

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