Leflunomide in Combination Therapy

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

ABSTRACT. In most studies of disease modifying antirheumatic drug therapy, in combination with either leflunomide or biological agents, patients are given an additional agent after they have failed treatment with methotrexate (MTX). This review of clinical studies shows that leflunomide is clinically efficacious and well tolerated when added to either sulfasalazine or MTX, as both an initial and ongoing treatment for rheumatoid arthritis (RA). Experience in combining leflunomide with biological agents is limited to a small number of open-label studies with infliximab. According to the opinion obtained at an International Expert Panel Meeting held in Paris in May 2003, leflunomide can be used in combination therapy: 61% of the Expert Panel would use leflunomide with MTX, 71% with sulfasalazine, 43% with infliximab, 33% with adalimumab, 19% with etanercept, and 38% with anakinra. The Expert Panel stated that the combination of leflunomide and infliximab warrants a prospective, randomized, controlled trial in patients with incomplete clinical responses to leflunomide monotherapy, provided leflunomide is started first, without a loading dose, and infliximab is added after good tolerability to leflunomide has been established. The Expert Panel concluded that combination therapy with leflunomide has a place in the treatment of RA. Caution is advised, however, when using combination treatments and, therefore, the patient's safety should be carefully monitored. (J Rheumatol 2004;31:Suppl 71:25–30)

Key Indexing Terms:
COMBINATION DRUG THERAPY RHEUMATOID ARTHRITIS LEFLUNOMIDE
DISEASE MODIFYING ANTIRHEUMATIC DRUGS BIOLOGICS

INTRODUCTION

Antirheumatic drugs used in combination therapy should have complementary biological effects, non-additive toxicity, an acceptable dosing schedule, and a rapid onset of action, and should be cost-effective.

There are 4 different issues to consider when using drug combinations to treat rheumatoid arthritis (RA): the combination of 2 or more disease modifying antirheumatic drugs (DMARD), the addition of a second drug to an existing monotherapy, the combination of DMARD and biological agents, and the combination of different biological agents.

According to the opinion of an International Expert Panel who met in Paris in May 2003, leflunomide can be used in combination therapy: 61% of the Expert Panel would use leflunomide with methotrexate (MTX), 71% with sulfasalazine, 43% with infliximab, 33% with adalimumab, 19% with etanercept, and 38% with anakinra.

Most studies of DMARD therapy in combination with leflunomide, as well as with biological agents, have been conducted in patients who have failed treatment with MTX and who then receive an additional new agent. Leflunomide inhibits pyrimidine biosynthesis, whereas MTX primarily inhibits purine biosynthesis. Therefore the rationale of the combination of the 2 drugs is based on their complementary mechanisms of action[1].

Experience in combining leflunomide with biological agents is limited to a few small, open-label studies with infliximab. The rationale for this combination lies in the complementary mechanisms of action of the 2 agents. Leflunomide modulates T cell responses, and induces a shift from the Th1 to Th2 subpopulation[2]. This process results in a beneficial effect in RA patients, in which there is good evidence of a major role for T cells in both the initiation and perpetuation of the disease[3].

Infliximab blocks the action of the proinflammatory cytokine tumor necrosis factor-α, which also leads to a downregulation of other proinflammatory cytokines interferon, interleukin 1, and interleukin 6[4]. Thus the combination of the 2 agents addresses 2 different targets in the disease pathogenesis.

The primary objective of this review is to define recommendations for the optimal use of leflunomide, based on the review of key studies by the international experts in rheumatology at the Panel Meeting. The following section summa-

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

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

Address reprint requests to Dr. J.R. Kalden, Medizinische Klinik III, Krankenhausstrasse 12, University of Erlangen-Nuremberg, D-91054 Erlangen, Germany. E-mail: joachim.kalden@med3.med.uni-erlangen.de

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rizes the data from leflunomide combination studies that were presented at the Expert Panel Meeting.

LEFLUNOMIDE COMBINED WITH ANOTHER DMARD

Leflunomide added to ongoing MTX treatment

Open-label pilot study. A one-year open-label pilot study was conducted in 30 patients with active RA despite at least 6 months' MTX treatment (at least 15 mg/week or 10–15 mg/week if this was the maximum tolerated dose)[5]. MTX was continued at a dose of 15–25 mg/week, and leflunomide added with a loading dose of 100 mg/day for 2 days and a maintenance dose of 10 mg/day that was increased, if needed, to 20 mg/day. An American College of Rheumatology (ACR) 20% response at year one was achieved in 53% of patients, with 2 patients entering remission. Seven patients withdrew from the study, 3 for adverse events. The study also confirmed the lack of pharmacokinetic interactions between leflunomide and MTX and the good tolerability of the combination treatment.

Double-blind, randomized, placebo-controlled, multicenter study with open-label extension. This multicenter study was conducted in 263 patients, mean disease duration of 11.6 years, with active RA despite MTX treatment (at least 15 mg/week or 10–15 mg/week if this was the maximum tolerated dose) for ≥ 6 months[6]. Patients continued MTX and were randomized to 24 weeks of treatment with either leflunomide (leflunomide + MTX, n = 130) 10 mg daily, increased to 20 mg at week 8 if necessary, or matching placebo (placebo + MTX, n = 133). Leflunomide therapy was started with a loading dose of 100 mg daily for 2 days. At week 24, superior efficacy was shown for the leflunomide + MTX combination [ACR 20% response at endpoint achieved in 46.2% (60/130) of the patients vs 19.5% (26/133) in the placebo group; $p < 0.001$].

Patients already receiving this combination continued therapy and those in the placebo + MTX group were switched to leflunomide + MTX (without a loading dose of leflunomide) for a further 24 weeks of open-label therapy.

Patients achieving an ACR response at 6 months on leflunomide + MTX maintained it for the subsequent 6 months, while those who were switched at this point from placebo + MTX to leflunomide + MTX had, by 12 months, achieved a response comparable to that of those who had been taking leflunomide + MTX since the start of the study (Figure 1)[7]. Health Assessment Questionnaire Disability Index (HAQ-DI) and Medical Outcome Study Short Form (SF)-36 physical component scores showed the same pattern (Figure 2).

The overall frequency of adverse events and liver function test (LFT) elevations was similar between the treatment groups at 6 months and decreased over the subsequent 6 months.

Leflunomide as initial treatment with MTX added

In a 40-week, open-label study, 103 patients with active RA and who were leflunomide- and MTX-naïve received leflunomide with a loading dose of 100 mg daily for 3 days and a maintenance dose of 20 mg/day. At week 16, patients with active disease received additional MTX (7.5–20 mg/week) for a further 24 weeks[8].

Patients who had responded to leflunomide monotherapy at week 16 maintained their response at week 40 — a response that was similar, at week 40, to that of the patients who had received additional MTX (Figure 3). Similarly, from week 16 to 40 the mean improvement in HAQ-DI score was maintained in the leflunomide monotherapy group and increased in the patients receiving combination therapy, albeit to a somewhat lower level (Figure 4). SF-36 physical component scores showed a similar pattern, although those of the combination group remained somewhat lower than those of the patients receiving leflunomide monotherapy throughout, possibly as a result of their slower improvement.

The combination was generally well tolerated, although LFT elevations occurred in more patients with combination therapy than with leflunomide alone.

Sulfasalazine added to ongoing leflunomide treatment

The second double-blind phase of the **R**heumatoid Arthritis **E**valuation of **L**eflunomide: Further **I**nsights into its **EF**ficacy (RELIEF) study[9], described previously, compared the benefits of adding versus switching therapies. At week 24, the patients who had failed to respond (according to the Disease Activity Score-28, DAS-28) were randomized either to receive additional sulfasalazine therapy or to switch from leflunomide to sulfasalazine with a leflunomide placebo. The number of patients who failed to respond to leflunomide monotherapy was much lower than had been expected; thus only a small number of patients (106 in total: 50 sulfasalazine + placebo, and 56 leflunomide + sulfasalazine) entered the double-blind phase, therefore limiting the power of the study. There was, however, a trend in the combination group to a higher response, whether determined by DAS-28 (Figure 5)[9].

There were no unexpected adverse events in patients receiving leflunomide plus sulfasalazine, and the incidence of serious adverse events was comparable between the combination and sulfasalazine monotherapy groups.

Conclusion

This review of clinical studies shows that leflunomide is clinically efficacious and well tolerated when added to either sulfasalazine or MTX treatment, as both an initial and ongoing treatment for RA.

LEFLUNOMIDE COMBINED WITH INFLIXIMAB

The use of combination treatment with leflunomide and biologic agents warrants further investigation in larger studies. Current data are limited as they are from studies with small sample sizes.

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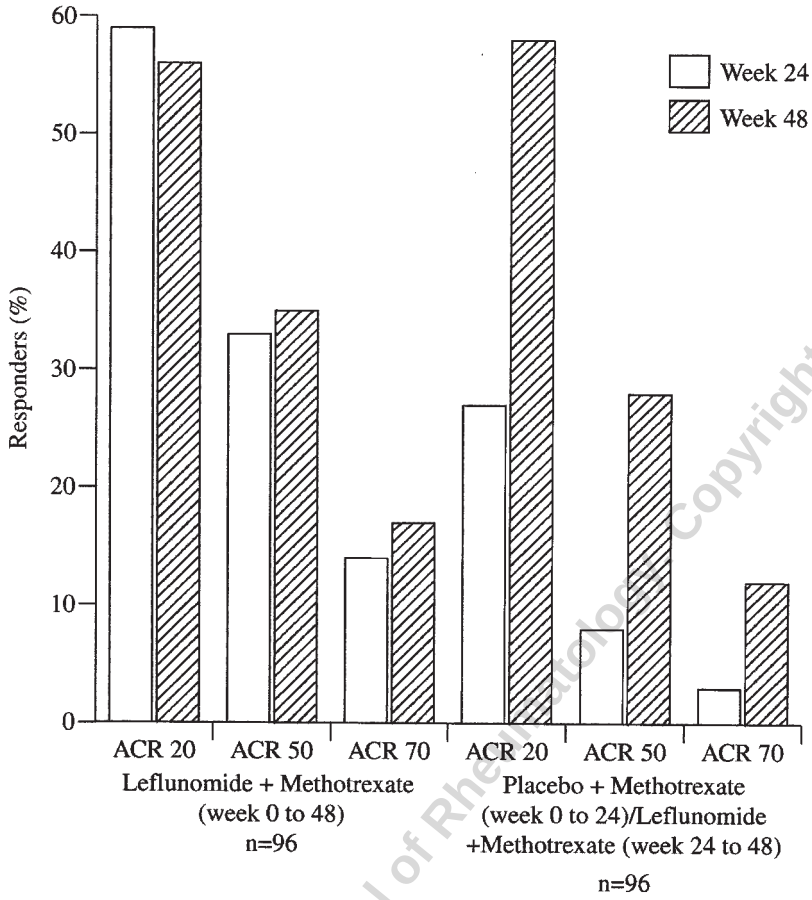

Figure 1. ACR responses at week 24 and 48 in patients receiving double blind leflunomide + methotrexate from week 0 to 48 versus patients receiving placebo + methotrexate from week 0 to 24 followed by open-label leflunomide + methotrexate from week 24 to 48[7].

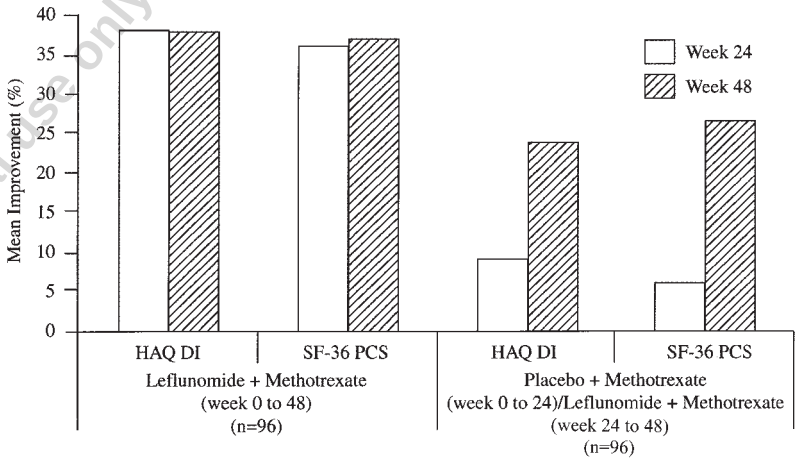

Figure 2. Mean improvement in Health Assessment Questionnaire Disability Index (HAQ-DI) and Medical Outcomes Study Short Form physical component scores (SF-36 PCS) in patients receiving leflunomide + methotrexate from week 0 to 48 versus patients receiving placebo + methotrexate from week 24 to 48[7].

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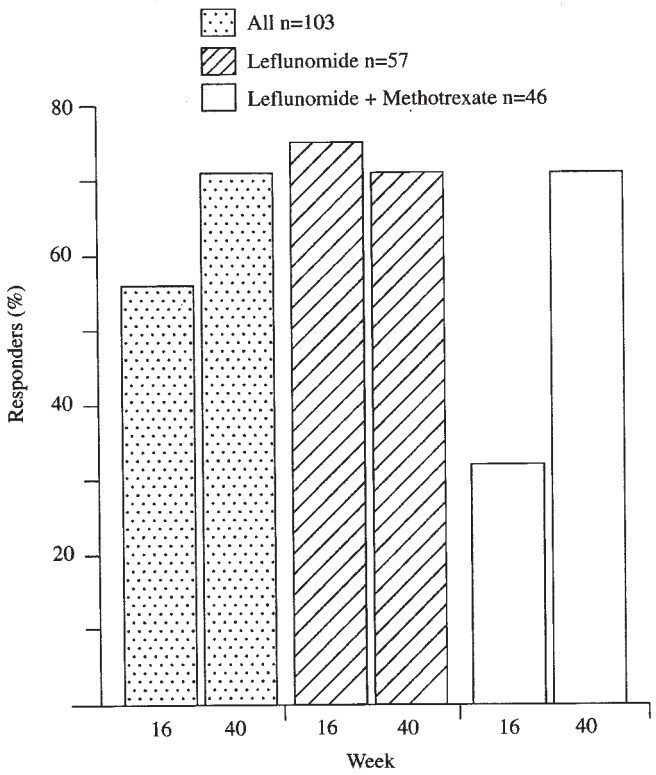

Figure 3. ACR 20% responses at 16 and 40 weeks (last observation carried forward) in patients receiving ongoing leflunomide monotherapy from weeks 0 to 40 and with methotrexate added from weeks 16 to 48 in patients with active RA at week 16[8].

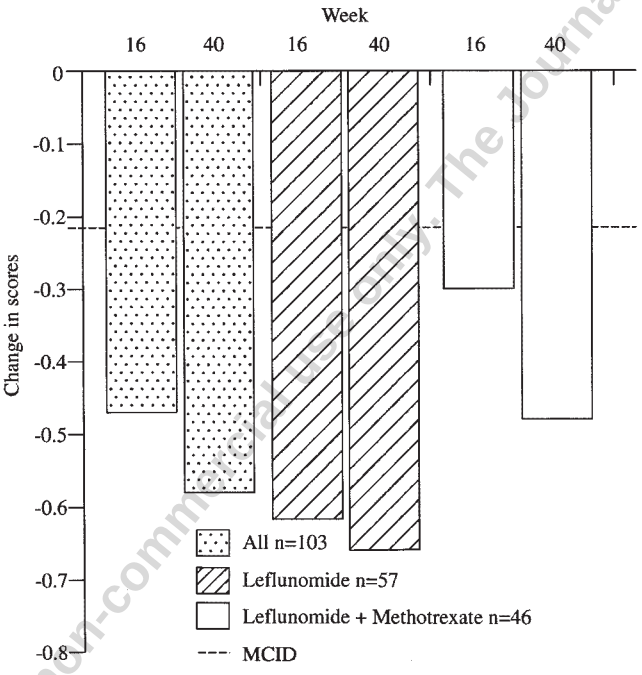

Figure 4. Mean change in HAQ-DI scores from baseline to weeks 16 and 40 (intention to treat) in patients receiving ongoing leflunomide monotherapy from weeks 0 to 40 and with methotrexate added from weeks 16 to 48 in patients with active RA at week 16[8]. MCID: minimum clinically important difference.

Four prospectively collected cohorts[10,11] (C. Antoni, manuscript in preparation; P. Emery, personal communication) and 2 retrospective case collections[12,13] were presented.

Prospective cohorts

UK open-label study. In this prospective, 32-week study, 20 patients with active RA who had failed to respond to treatment with a median (range) of 4 (2–8) DMARD received leflunomide 100 mg once daily for 3 days and then 20 mg once daily[10]. Infliximab (3 mg/kg) was administered at 2, 4, 8, and 16 weeks after the start of concomitant leflunomide treatment. Two patients had already been receiving leflunomide before the start of the study. All patients reported adverse events, often serious, on the combination therapy and only 8 patients completed the study. No patient withdrew because of lack of efficacy of the combination, and all showed improved symptoms and physical function: mean DAS-28 significantly diminished ($p < 0.0001$) and, in patients who completed the trial, an ACR 20% response was achieved in > 80% of patients continuing treatment. The authors believed that simultaneous initiation of leflunomide with a loading dose of 100 mg over 3 days and infliximab contributed to the intolerability.

European combination study

This prospective study was conducted in 6 female patients who were intolerant of, or had failed to respond to, MTX[11]. They received 22 weeks' treatment in which infliximab (3 mg/kg) was added after leflunomide (20 mg/day). DAS-28 improved by 1.3 points, tender and swollen joint counts improved by 8.2 and 6.8 points, respectively, and the patients' and physicians' global assessment improved by 14 and 22 points, respectively.

The investigators concluded that the combination of leflunomide and infliximab was well tolerated, with comparable efficacy to the combination of MTX and infliximab. Further, this combination is considered to be a therapeutic option in patients failing to respond to or intolerant of MTX.

German combination study

This multicenter, 6-month study was conducted in 72 patients who had moderate to severe RA and an inadequate response to at least 4 months' treatment with leflunomide (C. Antoni, manuscript in preparation). Infliximab (3 mg/kg) was added to ongoing leflunomide (20 mg daily reduced to 10 mg daily in the event of toxicity). Efficacy outcomes were DAS-28, ACR core set, C-reactive protein, and HAQ. The study ended recently and is currently being analyzed. So far, 36 patients have completed and 19 have withdrawn, 8 patients because of adverse reactions. There have been a number of serious adverse events, but most were considered to be unrelated to the study treatment.

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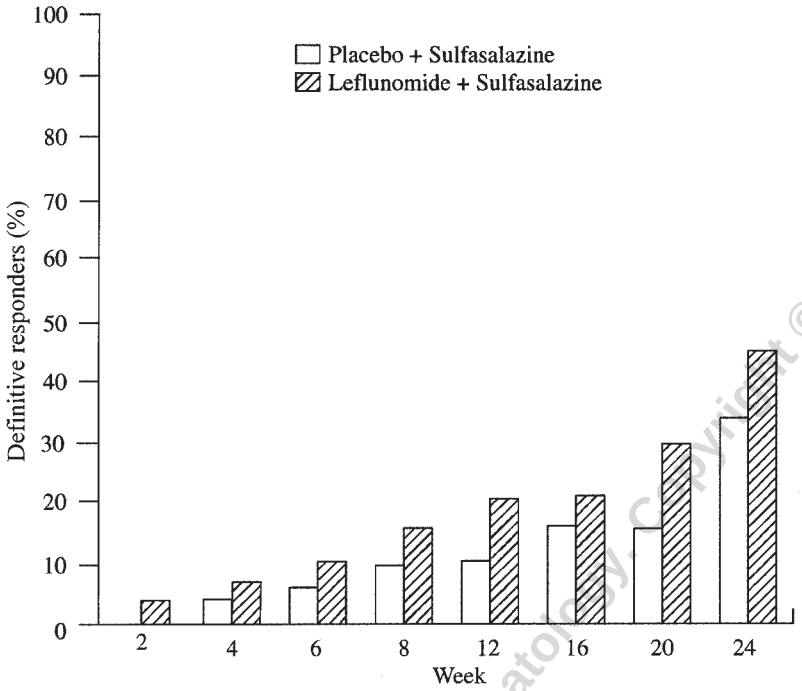

Figure 5. Cumulative definitive responder rate (Disease Activity Score 28 criteria). Progressive increase in population classified as responders[9].

UK combination study

In this prospective series, 40 patients already established on leflunomide, in 2 separate studies, received infliximab plus leflunomide; a further 100 patients received leflunomide monotherapy (P. Emery, personal communication). Patients receiving leflunomide + infliximab showed rashes combined with small vessel vasculitis. The 17/40 patients remaining on, and responding to, therapy showed a progressive increase in antinuclear antibodies and anti-double stranded DNA antibodies; and 6 months after the start of therapy, 55% had developed serological systemic lupus erythematosus.

Retrospective cohorts

US retrospective dataset. In this retrospective dataset, 93 patients received infliximab added to existing leflunomide therapy[12,14]. The mean duration of exposure to the combination was 7.5 months (range 0.5–28.8). Previous DMARD use included MTX (91%), sulfasalazine (40%), hydroxychloroquine (54%), gold (47%), and etanercept (23%). The mean tender and swollen joint counts decreased by 44% and 64%, respectively, compared with baseline. In addition, the average duration of morning stiffness was reduced by 59% and the mean pain level decreased by 56% compared with baseline. There were 32 adverse events (34%), 6 of them (6.5%) serious. Fifteen patients withdrew, 6 due to lack of efficacy and 9 due to adverse events. Overall, the combination was well tolerated. The investigators concluded that the efficacy of the combination appeared comparable to that of infliximab combined with MTX, and that the infliximab and leflunomide combination was therefore a reasonable alternative for patients failing to respond to, or intolerant of, MTX.

US community practices survey

Seventy-seven patients with RA were treated with leflunomide (20 mg/day) in combination with infliximab (3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter)[13]. Concomitant medication included MTX and prednisone. Mean tender and swollen joint counts improved by 45% and 55%, respectively. A 16% improvement in functional class and a 33% reduction in mean prednisone dose was observed. Six percent of patients experienced nausea and vomiting, and 2% had alopecia after 4–5 doses of infliximab plus leflunomide. Other adverse events included anaphylactoid reaction (3 patients), headache (2 patients), unrelated myelodysplasia (2 patients), and arthralgia/myalgia, diarrhea and flu in one patient. Overall, both the efficacy and safety of leflunomide + infliximab were judged to be comparable to those of MTX + infliximab. The investigators stated that the combination of leflunomide and infliximab was a therapeutic option in patients failing and/or intolerant to MTX. Ongoing clinical experience will be carefully evaluated.

The Expert Panel concluded that the combination of leflunomide and infliximab warrants a prospective, randomized, controlled trial in patients with incomplete clinical responses to leflunomide monotherapy, provided leflunomide is started first, without a loading dose, and infliximab is added after good tolerability to leflunomide has been established. Safety must be carefully monitored.

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OPTIMAL WAYS TO COMBINE LEFLUNOMIDE WITH ANOTHER DMARD OR BIOLOGICAL AGENT

Dosing regimens

In their questionnaire responses, only 33% of the Expert Panel indicated they use a loading dose when prescribing leflunomide with another DMARD; 24% and 43% of the Panel, respectively, reported they rarely or never use a loading dose, usually because of concern about side effects. Of those who do use a loading dose, 62% use 100 mg daily for 3 days, 23% 100 mg daily for 2 days; 16% reported using doses of 40–60 mg daily for 4–6 days or 100 mg twice weekly for 3 doses, with 20 mg on other days. The most frequent maintenance dose, reported by 79% of the Panel, was 20 mg daily. Of those changing the initial maintenance dose, 28% would start with 10 mg, increasing it to 20 mg, and 72% would do the reverse. Three-quarters of the Panel reduced the maintenance dose because of an adverse event listed in the product insert, 13% because of an unlisted adverse event, and 13% at the patient's request. The maintenance dose was increased by 44% because of lack of efficacy and by 48% because of a partial, or less than expected, response. For combination therapy, however, none of the Panel experts increases the leflunomide dose above 20 mg/day. In patients not responding to this dose, the experts would add MTX 7.5–10 mg per week.

Choosing the appropriate combination treatment

Following the workshop discussions it was suggested that in MTX partial responders, leflunomide might be added before using a biological agent. In patients with a partial response to MTX plus leflunomide, treatment with leflunomide should be stopped and a biological agent substituted. It was agreed, however, that more data are needed on leflunomide + biological agent combinations, and that currently there is more experience to support the use of MTX in such combinations. Although in principle any biological agent can be combined with leflunomide, experience is minimal and the Panel recommended caution when using such combinations.

Patient monitoring

All the experts reported in their questionnaire that they always carefully monitor patients receiving combinations of leflunomide and another DMARD. The Panel recommended that all patients receiving leflunomide in combination with MTX should have regular blood pressure measurements and laboratory tests. Detailed recommendations, particularly on the intervals for, and interpretation of, LFT, are under further discussion.

CONCLUSION

Leflunomide is effective and well tolerated when added to either MTX treatment or another DMARD. Experience with leflunomide plus infliximab is limited, but the Expert Panel believe the results are encouraging. Combination therapy with leflunomide therefore has a place in the treatment of RA. Caution is advised, however, when using combination treatment: the patient's safety should be carefully monitored.

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