Use of Combination of Leflunomide with Biological Agents in Treatment of Rheumatoid Arthritis

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ABSTRACT. An Expert Panel Meeting was held in May 2004 to assess experience with combination therapy with leflunomide and biological agents in the treatment of rheumatoid arthritis (RA), to identify both optimal use of such combinations and precautions for use. Eleven published prospective or retrospective studies were reviewed, principally evaluating combination of leflunomide with infliximab, as well as patient registry data. Available data suggest that combination therapies are more efficacious than monotherapies, reflecting the complementarity of mechanisms of action. Information on side effects remains contradictory, and tolerability of these combinations may vary between different patient groups. In some studies, tolerability is equivalent to that seen with monotherapy; in others a high rate of adverse events has led to frequent treatment discontinuation. Dermatological reactions may be a specific side effect of these combination therapies. Combination therapy is considered justified for treatment of patients diagnosed early who are at risk for rapid progression and for patients who fail to respond to monotherapy. The majority of participants favored adding biological agents to a previously established leflunomide monotherapy rather than starting both treatments simultaneously. On the other hand, combination therapy should be considered with caution in patients with a history of treatment failure, with hepatic comorbidity, or with other autoimmune disease, and in immunocompromised patients. When considering initiation of combination therapy, it is important to provide full information to the patient on the potential benefits and risks of such treatment and to integrate patients as far as possible into the decision-making process. (J Rheumatol 2005;32:1620–31)

Key Indexing Terms:
LEFLUNOMIDE TUMOR NECROSIS FACTOR-α RHEUMATOID ARTHRITIS
EFFICACY TOLERABILITY COMBINATION TREATMENT

Leflunomide is an immunomodulatory drug that has demonstrated its efficacy as a disease modifying antirheumatic drug (DMARD) for the treatment of rheumatoid arthritis (RA) across several large randomized controlled clinical trials[1-3]. The clinical data on this drug have recently been reviewed by Osiri, *et al*[4] and by Li, *et al*[5]. Efficacy has also been shown in related conditions such as psoriatic arthritis[6]. As with all DMARD, leflunomide needs to be used carefully to ensure a rapid, sustained, and optimal antiinflammatory response without emergence of side effects that could compromise adherence of patients to longterm treatment.

Five years after introduction of leflunomide into rheumatology practice, an expert panel meeting was held in May 2003[7] to discuss experience in the treatment of RA with this drug and to define the optimal way leflunomide should be used and adverse events managed. Recommendations were published in *The Journal of Rheumatology*[8-10].

At the time of the meeting, however, published data on combinations with biological agents were limited to a single, prospective study of combined leflunomide and infliximab in 20 patients with RA[11]. The combination of leflunomide and anti-tumor necrosis factor-α (TNF-α) agents represents a promising treatment in severe and/or refractory RA and, as such, has been investigated widely in rheumatology centers. Over the last year, there have been a number of publications and congress presentations on the usefulness of such combinations. For this reason, it seemed timely to organize a second expert panel meeting to consolidate experience with the combined therapy of leflunomide and biological agents and to identify the optimal way to use such combinations. This review presents an overview of the outcome from this expert panel meeting.

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Rationale for Using Combinations of Leflunomide and Biological Agents

Although monotherapy with DMARD provides important treatment benefits to many patients with RA, in a significant number of patients treatment response is inadequate. In such patients, treatment options for the physician are to switch to, or add, another DMARD. Adding a second DMARD is a particularly attractive option when patients respond partially to monotherapy, and the physician does not wish to risk losing this partial response by switching, but needs to reinforce the effect with a second agent. Combination therapy is based on the concept that different agents with complementary mechanisms of action may produce a synergistic effect on the underlying biological mechanisms of disease progression (Table 1). For example, the potential for synergy between leflunomide and biological anticytokine drugs is of special interest, since these agents block the actions of proinflammatory cytokines released by activated lymphocytes and thereby prevent the activation and proliferation of disease-specific T cells in an apparently antigen-specific manner, thus potentially reinforcing the antiproliferative and antiinflammatory effects of leflunomide.

A potential concern in the use of combination therapy is the emergence of adverse events that would necessitate interruption of treatment. In the case of combinations of leflunomide and biological agents, there is less reason to fear the emergence of combination-specific side effects since the biological mechanisms of action of the drugs are quite different. The principal adverse events described with biological agents are injection site reactions, impaired resistance to infections, headache, and fatigue. Nonetheless, dermatological reactions, notably rash and pruritus, are common with anti-TNF-α drugs and also with leflunomide. Such reactions are a potential cause of concern when combining leflunomide and biological agents, and these have been a focus of attention in the various studies of combination therapy that have been performed (see below).

US PATIENT REGISTRY DATA

In the USA, 2 large databases of patients with RA have made it possible to assess prescription patterns: the CORRONA (Consortium of Research Rheumatologists of North America), which consists mainly of academic practice data, and the National Data Bank for Rheumatic Diseases, a patient database. Based on data from the CORRONA, prescriptions were analyzed for 5436 patients receiving DMARD between October 2001 and March 2004, of whom 4781 (88.0%) were receiving at least one DMARD. Of the 587 patients taking leflunomide, around one-third received the drug as monotherapy and the remainder in combination. When combination treatment was used, biological agents were the most frequently combined drugs. Over one-half of all combinations included infliximab. Biological agents (35% of combinations) and methotrexate (MTX; 31% of combinations) accounted for the majority of all combinations with leflunomide. The drugs taken in combination with leflunomide are MTX (127 subjects, 31%), another DMARD (39 subjects, 9%), and biological agents (143 subjects, 35%). In 103 subjects, leflunomide was combined with 2 or more DMARD/biological agents. Because of the size of the CORRONA database, types of patients in whom different therapies were prescribed could be compared. With

Table 1. Mechanism of action of DMARD for the treatment of RA.

Molecule	Principal Mechanism of Action	References
Leflunomide	Blocks *de novo* pyrimidine nucleotide synthesis by inhibiting dihydroorotate dehydrogenase	Cherwinski[12] Greene[13]
	Preferentially inhibits activated lymphocyte proliferation	Rückemann[14]
	Inhibits proliferation of activated monocytes/macrophages by similar mechanism	Cutolo[15]
Infliximab	Recombinant anti-TNF-α antibody	Feldmann[16]
	Neutralizes circulating TNF-α	Paleolog[17]
	Inhibits functional activity of TNF-α	
Etanercept	Recombinant TNF-α receptor fusion protein	Goffe and Cather[18]
	Competitive inhibition of binding of TNF-α to target cells	
	Inhibits functional activity of TNF-α	
Adalimumab	Recombinant anti TNF-α antibody	Feldmann[16]
	Neutralizes circulating TNF-α	den Broeder[19]
	Inhibits functional activity of TNF-α	
	Prevents regulation of adhesion molecules responsible for leukocyte migration	
Anakinra	Recombinant IL-1 analog	Schiff[20]
	Blocks activation of cell-surface receptors by IL-1	Dayer[21]
	Inhibits responses elicited by IL-1, including induction of NO, PGE_2 and collagenase by joint cells	

TNF-α: tumor necrosis factor-α; IL-1: interleukin 1; NO: nitric oxide; PGE_2: prostaglandin E_2.

respect to leflunomide monotherapy, patients taking combination with biological agents tended to have more severe disease, as measured by the Health Assessment Questionnaire (HAQ), and more previous experience with other DMARD. Patients taking leflunomide in combination with biological agents more frequently used a low (10 mg) dose of leflunomide than patients taking leflunomide monotherapy (24% vs 15%).

The National Data Bank for Rheumatic Diseases contains records on 20,346 patients with RA receiving treatment for at least 2 months. Combination of biological agents and leflunomide accounts for about 17% of all leflunomide use and 9% of all use of biological agents. As in the CORRONA database, patients with more severe disease as measured by the HAQ (as well as by global severity) were more likely to be receiving this combination therapy than leflunomide monotherapy.

PUBLISHED DATA ON LEFLUNOMIDE IN COMBINATION WITH BIOLOGICAL AGENTS

There have been no large-scale investigations on the safety and efficacy of leflunomide in combination therapy with biological agents, and in particular no randomized controlled trials. Nonetheless, numerous retrospective and prospective studies have been performed, with somewhat diverse findings, particulatly with regard to incidence of adverse events. These studies are listed in Table 2 and are briefly summarized below.

Retrospective Studies

In an open, multicenter retrospective study, Hansen, *et al*[22] investigated 88 patients (63 women, average age 53 yrs, disease duration 10.3 yrs), most of whom had mild to moderate disease. MTX and sulfasalazine had been discontinued in 81 (92%) and 35 (40%), respectively, principally for lack of efficacy and/or adverse events. Patients received combination leflunomide and infliximab for a mean duration of 6.6 months, with a total exposure of 581 patient-months. The mean maintenance dose of leflunomide was 17.8 mg/day and the average number of infliximab infusions was 4.8 at a mean dose of 3.3 mg/kg. In all but 3 patients, infliximab was added after initiation of leflunomide treatment.

Thirty-four percent of patients experienced adverse events, which were deemed serious in 6 cases; this is in keeping with the known risks of each individual drug. Of the 10 patients who developed infection, 9 recovered fully and one died of bacterial pneumonia. Both leflunomide and infliximab were discontinued in 4 subjects (diffuse rash; lung cancer in a lifetime smoker; pneumonia and acute respiratory distress syndrome; and cellulitis, leg edema, and newly diagnosed colon cancer), leflunomide alone was discontinued in 3 subjects (lack of efficacy in 1, rash in 2 subjects), and infliximab alone was discontinued in 6 subjects (lack of efficacy in 4, rash in 1, and rash and arthralgia in 1 subject). Leflunomide was discontinued temporarily in 7 subjects: due to diarrhea in 3, rash in 2, pruritus in 1, and herpes zoster in 1 subject. Infusion reactions occurred in 3 subjects (0.7% of all infusions).

Efficacy was shown by improvement in swollen and tender joint counts of 64% and 67%, respectively, and pain levels improved by 57%. C-reactive protein (CRP) levels decreased by 45% and erythrocyte sedimentation rate (ESR) decreased by 39%. There was also a 41% decrease in corticosteroid use. The authors concluded that leflunomide is an alternative DMARD to MTX in subjects receiving infliximab therapy and that with appropriate monitoring the combination appears to be safe.

In the US Community Practices Survey, Patel, *et al*[23] looked at 77 patients (51 women, mean age 56.7 yrs, mean disease duration 9.6 yrs) who were treated with 20 mg/day leflunomide and infliximab (3 mg/kg at Weeks 0, 2, and 6; then every eighth week). Nausea and vomiting were experienced by 6% of this group and alopecia by 2%. Other adverse events included anaphylactoid reaction (3 subjects), headache (2 subjects), unrelated myelodysplasia (2 subjects), and arthralgia/myalgia, diarrhea and influenza-like syndrome in one subject each. Efficacy was shown by mean tender and swollen joint counts that improved by 45% and 55%, respectively, as well as a 16% improvement in functional class and a 33% reduction in mean prednisone dose.

Godinho, *et al*[25] studied 17 patients (7 women; median age 57.6 yrs) with active RA and previous DMARD failures, 13 of whom had been treated for a minimum of 3 months with leflunomide before start of infliximab treatment and had tolerated this well. In the remaining 4 patients, the 2 drugs were started simultaneously. Out of the 17 patients, 13 experienced adverse events, and treatment was stopped in 8 cases due to congestive heart failure (1 subject), hypertension with thoracic pain (2 subjects), eczematous skin patches (2 subjects), and neutropenia (3 subjects). It was concluded that these adverse events were not very different from those seen with either treatment alone. Efficacy, considered similar to that observed with MTX and infliximab, was shown by the decrease in mean Disease Activity Score (DAS) from 5.94 ± 0.88 to 4.34 ± 1.25; and 65% of subjects were rated as being good or moderate responders.

Perdriger, *et al*[24] performed a pharmacoepidemiological survey of infliximab use in France. Data were collected with a standard questionnaire sent to hospital rheumatology and internal medicine departments inviting them to submit data on all patients prescribed a combination treatment using infliximab and any DMARD other than MTX. The study included 262 patients from 48 hospital departments. Patients were diagnosed principally with RA (230 patients), spondyloarthropathy (23 patients), and other diseases (9 patients). Leflunomide was used in combination with infliximab in 178 patients (67.9%). MTX had been used previously in 219 patients and stopped for either intolerance (66%) or lack of

Table 2. Published studies on combination treatment with leflunomide and biological agents in RA.

N	Treatment	Duration	Efficacy	Withdrawals	Conclusions	Reference
Retrospective studies						
88	LEF + INF	6.6 mo	SJC↓ 64%; TJC↓ 67%	13 due to AE (15%)	General improvement in disease control. AE in keeping with the known risks of each drug.	Hansen[22]
77	LEF + INF	Not specified	SJC↓ 55%; TJC↓ 45%	None reported	Combination is safe and effective	Patel[23]
262	DMARD (not MTX) + INF (178 LEF +INF)	8.9 mo	Very good/good, 67.5% Medium, 24% Poor, 9%	77 (29%) due to: AE (61), lack of efficacy (11), risk of pregnancy (3) and disease stabilization (2)	All combinations were efficient and well tolerated Safety for LEF+ INF good to very good in 75.3%	Perdriger[24]
17	LEF + INF	22 wks (median)	DAS28↓ 26.9% Good/moderate responders 68%	8 due to AE (47%)	AE similar to those seen with either treatment alone	Godhino[25]
45	LEF + INF/ LEF + INF + MTX	18.0 mo	DAS28 and HAQ significantly improved	7 due to AE (16%) 2 deaths due to infection	Combination was efficacious AE comparable in all treatment groups	Ortíz[26]
Prospective studies						
20	LEF + INF	32 wks	DAS28↓ ($p < 0.0001$)	11 due to AE (55%)	Combination is efficacious but use may be limited by adverse events, particularly rash	Kiely & Johnson[11]
6	LEF + INF	22 weeks	DAS28↓ 20.3% SJC↓ 6.8 TJC↓ 8.2	None	Good efficacy and safety, comparable to MTX + INF	Strupple[27]
40	LEF + INF	60 wks	ACR20%: 49% at 24mo ACR20%: 42% at 48mo	17 due to AE (43%) 10 due to inefficacy (25%)	Combination is efficacious in most patients but AE are frequent	Bingham[28]
160	LEF + INF (n = 65) vs INF alone (n = 95)	≤ 46 mo	Decrease in DAS28 equivalent in both groups	Identical in both groups 52% due to AE 21% due to inefficacy	Combination of LEF and INF is as efficacious as INF monotherapy. Tolerability mediocre in both groups	Flendrie[29]
72	LEF + INF	30 wks	DAS28↓ 29.4% $p<0.0001$ HAQ↓ 36.4%	13 due to AE (18%)	Clinical benefit shown. AE and withdrawal rate similar to those seen with either treatment alone	Antoni[30]
11	LEF + ETN	Not specified	DAS Good response 73% ACR20% 73%	2 due to AE (20%) 1 death	Clinical efficacy and safety comparable to other studies	Antoni[30]

LEF : leflunomide ; INF : infliximab ; SJC : swollen joint count ; DAS : Disease Activity Score; AE: adverse event; HAQ : Health Assessment Questionnaire; ACR20: American College of Rheumatology 20% response.

efficacy (34%). The average dose of infliximab and leflunomide was 3.2 mg/kg and 19.1 mg/kg, respectively. The mean duration of combination therapy was 8.9 ± 6.2 months. Efficacy and safety were evaluated on a 4-point scale of very good, good, medium, or poor.

Tolerance was rated as very good or good for 78.2% of

cases (75.3% of cases for leflunomide) and medium or poor for 11.0% and 10.7% of cases, respectively. Premature withdrawals from treatment occurred for 23.3% of the patients due to adverse events and for 4.2% of the patients due to lack of efficacy. Efficacy was rated very good or good for 68.4% of cases analyzed, and medium or poor for 24.7% and 7.5% of cases, respectively. No difference in efficacy was found between the various combinations and diseases.

A retrospective study of 45 patients was performed in Spain by Ortíz, *et al* in 2004[26]. Patients were predominantly female (78%) with mean age of 57 ± 14 years and mean disease duration of 141 ± 123 months; all had previously failed a mean of 3.8 ± 1.6 other DMARD treatment regimens. In 28 patients (62%), infliximab was added to previous treatment with leflunomide, and in the remaining 38% of cases leflunomide was added to ongoing infliximab. The originality of this study was that it compared infliximab and leflunomide combinations with triple therapy with infliximab, leflunomide, and MTX.

A total of 64 adverse events were recorded in 29 patients (64.4%) that led to discontinuation in 7 cases. A total of 23 infections occurred in 16 patients and there were 2 deaths due to widespread infection, both in the infliximab and leflunomide group. Elevations of liver enzymes were similar in the dual therapy and triple therapy groups. All efficacy variables improved significantly at last visit compared to first visit (median followup 7 mo, range 3–28 mo). No difference in discontinuation rates for adverse events was observed between the patients on bi-therapy or tri-therapy, or between those in whom leflunomide was added to previous infliximab and those in whom infliximab was added to previous leflunomide. It was concluded that infliximab plus leflunomide may be an alternative for treatment of patients who are not able to take MTX or where disease control is inadequate despite use of infliximab plus MTX.

Prospective Studies

Kiely and Johnson[11] treated 20 patients (18 women, median age 55 yrs) with active RA (median disease duration 10 yrs) who had failed multiple DMARD (median 4 different drugs) with 100 mg leflunomide for 3 days, followed by 20 mg/day for 32 weeks. At Week 2, all patients started infliximab and received 4 further infusions at Weeks 4, 8, 16, and 24. All patients experienced adverse events, the commonest being skin reactions (14 subjects, 70%). Eleven patients withdrew before end of study due to adverse events, including: skin reaction (5 subjects), infusion reactions (3 subjects), Stevens-Johnson syndrome (1 subject), diarrhea (1 subject), and preexisting melanoma (1 subject). The mean DAS28 score fell from 7.18 at the start of the study to 5.18 at Week 4 ($p < 0.0001$) and from Week 8 to Week 32 it varied between 3.85 and 4.85 ($p < 0.0001$ vs baseline). Eighty percent of patients continuing treatment achieved an American College of Rheumatology 20% (ACR20) response from Week 8 to Week 28, with up to 46% achieving an ACR70 response. It should be pointed out that in this study, treatment with the 2 drugs began at the same time, unlike other combination studies, where a second drug was added to an ongoing established treatment.

Struppler, *et al*[27] studied 6 female patients with longstanding RA and insufficient response or intolerance to MTX; they received 20 mg/day leflunomide and infliximab (3 mg/kg) for 22 weeks. In this study, the combination was found to be well tolerated, and no subject withdrew from the treatment. Over the study period, the average DAS28 decreased from 6.4 to 5.1 and ESR from 48 to 40 mm; the number of tender joints was reduced by 8.2, number of swollen joints by 6.8, and average CRP declined from 3.9 mg/dl to 2.8 mg/dl. Patient global assessment (range 0–100) decreased from 76 to 62 and the physician global assessment from 68 to 46. Efficacy and safety were considered comparable to combination of MTX and infliximab.

A prospective open-label study performed in the United Kingdom followed 40 RA patients who had failed to respond to leflunomide monotherapy (no improvement for at least 3 mo) for up to 60 days following addition of infliximab[28]. There was a high rate of treatment discontinuation in this study, with 10 patients (25%) stopping for inefficacy and 17 (42.5%) due to adverse events. ACR20 response rates were 49% at 24 weeks and 42% at 48 weeks. Of adverse events leading to treatment discontinuation, 11 were considered to be immune mediated (3 cases of vasculitic rash, 2 infusion reactions, 2 lupus, and 1 each of cerebral vasculitis and Stevens-Johnson syndrome). These events all resolved upon treatment discontinuation. An important original finding of this study was the appearance of antinuclear antibodies and anti-dsDNA antibodies over the course of the study, with an apparently linear relationship to the duration of infliximab exposure. Such antibodies were not observed in a parallel cohort of subjects receiving leflunomide monotherapy. A cohort study in The Netherlands[29] has followed all patients starting infliximab at a center in Nijmegen since 2000. These patients had failed MTX and at least one other DMARD and had a mean DAS28 score of 5.8 at inclusion. A total of 160 patients have been followed for a maximum of 46 months, including 95 patients who were not taking leflunomide, and 65 taking both infliximab and leflunomide or having used this drug in the previous year. Disease activity, length of time on treatment, and adverse events were compared between the 2 other groups. No statistically significant differences in baseline characteristics between the leflunomide and the non-leflunomide group were observed. Median length of time on treatment was 21 months in the non-leflunomide group and 26 months in the combination group. Reasons for discontinuation were similar between the 2 groups: inefficacy in 21% of subjects, adverse events in 52%, and both inefficacy and adverse events in 19%. Adverse events were reported in 96 patients,

without differences between the 2 treatment groups. The most frequent adverse events reported were infections, allergic reactions, and skin reactions. The extent of formation of antinuclear antibodies was similar between the 2 groups and did not influence the occurrence of adverse events. There was no inter-group difference in reduction in disease activity as measured by evolution of DAS28 scores over time.

In a German open-label 30-week trial[30], 72 subjects with moderate to severe disease and at least 16 weeks' inadequate response to leflunomide monotherapy received 20 mg/day leflunomide and 3 mg/kg infliximab at Weeks 0, 2, 6, 14, and 22. The commonest adverse events observed were upper respiratory tract infections (n = 10, 13.9%), pruritus (9.7%), fatigue (6.9%), diarrhea (5.6%), and exanthema (5.6%). Thirteen of the 72 subjects (15.3%) withdrew due to adverse events considered possibly related to the treatment: these were (in one subject each) angina pectoris, swelling and pain in the knee, skin reaction, skin dryness, exanthema, increased liver enzymes, RA flare, spotted skin and redness on extremities, suspected pneumonia/cardiac insufficiency, and repeated syncope; and infusion reaction in 3 subjects.

A statistically significant improvement in efficacy measures was observed after only 2 weeks and persisted until study end. From baseline to Week 30 mean DAS28 score decreased from 6.8 to 4.8 ($p < 0.0001$), and 19.4% and 46.3% of subjects were rated as good or moderate responders, respectively. The mean HAQ score also decreased over the study period from 1.65 to 1.21 ($p < 0.0001$) and there were significant improvements in patient global assessment score (–31.1 mm; $p = 0.0001$) and the physician global assessment score (–34.8 mm; $p = 0.0001$).

The same group also performed a similar study in 11 patients with moderate to severe disease and at least 16 weeks' inadequate response to leflunomide monotherapy, after which etanercept (25 mg sc twice a week) was added. Eight patients demonstrated a good treatment response as measured by the DAS, with moderate response in 2. Eight patients attained ACR20 response. Serious adverse events were reported in 2 patients, a worsening of RA and erysipelas in one patient, and fatal colitis in one other. Three patients discontinued study prematurely. Upper respiratory tract infections were observed in 5 patients, local skin reactions in 4, and diarrhea in 4 subjects.

Overall, the published studies show that combination therapy with leflunomide and infliximab is efficient and well tolerated, provided leflunomide treatment is established before the addition of the biological agent.

General Safety Data on DMARD and Biological Agent Combination Treatments

Two large placebo controlled studies have investigated the safety of concomitant treatment with biological agents and other DMARD in general. The STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis) study evaluated the safety and efficacy of adalimumab, a fully human monoclonal TNF-α antibody, when given with standard DMARD therapy in patients with active RA[31]. In a 24-week trial, 636 patients (79.4% women, mean age 55.4 yrs, mean disease duration 10.4 yrs), received either 40 mg adalimumab subcutaneously every 2 weeks (n = 318) or placebo (n = 318), while continuing their standard DMARD therapy. Overall, 56.0% of the patients used one traditional DMARD, 23.6% used 2, and 3.9% used 3 or more DMARD. The most frequently used DMARD were MTX (53.9%), antimalarial drugs (24.7%), leflunomide (13.8%), sulfasalazine (9.8%), and parenteral gold (5.8%). After 24 weeks, there were no statistically significant differences between the DMARD/adalimumab and DMARD/placebo groups in terms of adverse events, serious adverse events, or treatment withdrawal.

Although in the published analysis of the STAR study no breakdown of efficacy and safety according to concomitant DMARD use was provided, this was assessed in a secondary analysis performed for the US Food and Drug Administration (http://www.fda.gov/cder/biologics/products/adalabb123102.htm). A higher rate of adverse events leading to treatment interruption (8 cases for leflunomide alone and 1 case for combination) or withdrawal (7 and 3 cases, respectively) was observed in patients receiving adalimumab and leflunomide compared to leflunomide and placebo. In addition, possibly treatment-related adverse events were more frequent in the combination group. There was no difference in the incidence of infection, the most frequently reported adverse event, whereas rash was more frequently encountered in the combination group. There was no difference in ACR20 response rates observed at Week 24 between leflunomide monotherapy and combination groups, possibly due to the higher rate of withdrawals in the combination group or to higher use of rescue steroids.

In a similar study, Tesser, *et al*[32] evaluated the safety of anakinra, a recombinant interleukin 1 receptor antagonist, as a concomitant treatment in 1399 subjects with a mean age of 55 years and mean disease duration of 10 years, 1090 (77.9%) of whom were receiving one or more DMARD at study entry. Around one-half of all subjects (747, 53%) were receiving MTX, taken as monotherapy in 466 (31.9%) cases, and 76 (5.4%) subjects were taking leflunomide as monotherapy.

The subjects were randomized to receive either anakinra (n = 1116) or placebo (n = 283) for 6 months, and safety was assessed by comparing the incidence of infection, adverse events, and injection site reactions in the 2 groups. The data were analyzed according to DMARD group. In the 76 subjects receiving leflunomide, the incidence of upper respiratory infections (12.5% in the anakinra group; 41.7% in the placebo group) and serious adverse events (7.8% in the anakinra group; 8.3% in the placebo group) was no higher in subjects receiving combination therapy than in those receiv-

ing leflunomide and placebo. No serious infectious episodes occurred in either group. Injection site reactions, the most common side effect of anakinra treatment, occurred in 70.3% of the anakinra group and 50.0% of the placebo group. No obvious differences in safety outcome were observed between the different DMARD medication subgroups.

CURRENT PRACTICE

The information on combination leflunomide and biological agents obtained from published studies described above was complemented by a survey of expert practice with combination therapy as used by the participants in the expert panel, representing 12 countries. This information was recorded in a systematic way using a standard questionnaire that was completed before the meeting. It is important to recognize that use of combination therapy in certain countries is strictly limited by regulatory or reimbursement policies of health authorities and may not reflect exactly how the drugs would be used in the absence of such constraints.

Of patients with RA treated in the participants' centers, 92% were treated with DMARD, of which one-third were receiving a combination treatment involving a biological agent (Figure 1). Thirteen percent of these represented combinations with leflunomide. This corresponds to 4% of all patients, a proportion considered rather high for routine care in Europe, although it matches the frequency of reported use in the North American patient registries (see above). The biological agent most frequently used in combination with leflunomide was infliximab, a combination used regularly by one-third of participants. Combination with etanercept and adalimumab was only used occasionally. All participants used MTX in combination with leflunomide and most used MTX with biological agents. On the other hand, most never used sulfasalazine with biological agents, and combination of this drug with leflunomide was occasional.

The situations in which leflunomide combination with biological agents would be regularly prescribed by most participants were nonresponse to DMARD, multiple treatment failure, and rapidly progressing disease (Table 3). The most common situations in which such combinations would be prescribed with precaution were patients with hepatic disease (for 9 participants), arterial hypertension (7 participants), and cardiovascular disease (6 participants).

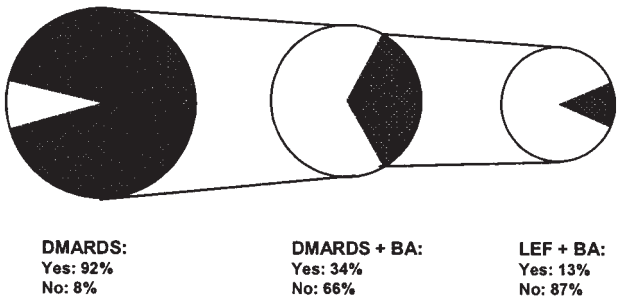

Figure 1. DMARD prescription practice as identified in an Expert Panel Meeting survey. BA: biological agent, LEF: leflunomide.

Table 3. Situations in which combination therapy of leflunomide and biological agents (BA) would be considered, as surveyed at the Expert Panel Meeting.

Situation	Regularly	Occasionally	Never
Early severe disease	5	8	5
Rapidly progressing disease	14	4	—
Poor prognosis	4	10	4
DMARD nonresponder	18	—	—
BA nonresponder	11	7	—
Multiple treatment failure	14	2	2

The majority of participants (16/18) favored adding biological agents to a previously established leflunomide monotherapy and only 5 would consider starting both treatments simultaneously. The most frequently used strategy (11 of 18 participants) was to continue leflunomide at the maintenance dose of 20 mg when the biological agent was introduced and to decrease the dose to 10 mg in case of emergence of side effects. Similarly, once the combination treatment had been established successfully, most of the participants used a maintenance dose of 20 mg leflunomide. Combination therapy was envisaged as a longterm treatment option by 16 out of 18 respondents. The most frequently used variables that were monitored to assess efficacy were the DAS28 and radiographic progression (Table 4).

All participants who had used combinations of leflunomide with infliximab or etanercept considered the efficacy of the combination to be superior to leflunomide monotherapy, as did all but one user of combined leflunomide and adalimumab (Table 5). All users of combined leflunomide and etanercept, and most users of leflunomide and infliximab or adalimumab, considered the combination to be tolerated as well as leflunomide monotherapy; however, 2 users of leflunomide and infliximab and one user of leflunomide and adalimumab considered tolerability of the combination to be worse than leflunomide monotherapy. Ten participants (out of 18) would increase the frequency of moni-

Table 4. Outcome measures considered as most important for monitoring the effectiveness of combination therapy, as surveyed at the Expert Panel Meeting.

Technique	Regularly
Disease Activity Score 28	16/18
American College of Rheumatology 20% response	1/18
Global assessment	8/18
Health Assessment Questionnaire/quality of life	8/18
Radiographic progression	12/18
Erythrocyte sedimentation rate/C-reactive protein	8/18
Swollen joint count	6/18

Table 5. Overall rating by meeting participants of efficacy and tolerability of combining leflunomide with a biological agent compared to leflunomide monotherapy.

	Efficacy			Tolerability		
	Better	Equivalent	No opinion	Equivalent	Worse	No opinion
Biological agent						
Infliximab	16	0	2	12	2	4
Etanercept	14	0	4	11	0	7
Adalimumab	11	1	6	9	1	8

toring of hepatic function, whereas 9 would increase the frequency of monitoring hematology.

PRACTICAL ISSUES IN COMBINING LEFLUNOMIDE WITH BIOLOGICAL AGENTS

Patient Information

When considering initiation of combination therapy, it is important to provide full information to the patient on the potential benefits and risks of such treatment and to integrate patients as far as possible into the decision-making process. This is particularly important given the lack of clear evidence from randomized clinical trials that would allow expected outcome to be predicted with any degree of certainty, and the contradictory information available on the risk of side effects. In particular, the generally favorable evolution of clinical status observed in the open-label studies should be highlighted, as well as the potential for adverse events such as rash. Individual patients may differ in their expectations for satisfactory clinical improvement and the extent to which side effects may be acceptable, and this needs to be taken into account in the decision to initiate combination treatment.

Use of Combination Therapy in Patients with Early Disease (< 6 months)

Combination therapy is considered justified for the treatment of patients with early diagnosis and a prognosis of rapid progression. It was considered that for each newly diagnosed patient, every effort should be made to establish prognosis early as a basis for classifying according to risk. Rapidly progressing patients at high risk for developing severe RA who show rapid erosion need to be identified early so that an appropriate and aggressive therapy can be initiated. Treatment strategies could then be stratified according to the level of risk, with an aggressive approach used in high-risk patients that involves combinations, high dose DMARD monotherapies, or early initiation of biological agents (Table 6). These more intensive treatments should be initiated early and monitored closely in order to adapt treatment if necessary. In particular, in these patients it is recommended not to wait 3 months before modifying treatment, often considered the appropriate timeframe for assessing nonresponse, in order not to lose a window of opportunity. On the other hand, in low-risk patients, a more conservative approach can be used, starting treatment with standard dose DMARD monotherapy with routine monitoring of outcome every 3 months. In case of inadequate response, increasing dose or switching between DMARD monotherapies should be considered before initiating combination treatments with biological agents.

Table 6. Risk assessment and use of combination therapy in RA, as surveyed at the Expert Panel Meeting.

	Radiological Progression	
	Absent	Present
DAS28 score		
Low (< 3.2)	Low risk	High risk
	DMARD monotherapy	LEF/BA combination
Moderate (3.2–5.1)	Low risk	High risk
	DMARD monotherapy	LEF/BA combination
High (> 5.1)	High risk	High risk
	LEF/BA combination	LEF/BA combination

LEF: leflunomide; BA: biological agent.

Risk can be determined by radiographic assessment of disease progression, or other imaging technique such as magnetic resonance imaging or echographic/Doppler evidence for vascular involvement. Certain biochemical markers such as presence of rheumatoid factor, shared epitope, or acute phase reactant may also be useful; indeed, presence of rheumatoid factor or anticyclic citrullinated peptide antibodies may be robust prognostic determinants of rapid progression and poor outcome[33]. The usefulness of risk-based prognostic algorithms in stratifying treatment has been illustrated by the COBRA study, in which patients were directed to sulfasalazine monotherapy or sulfasalazine combination with MTX on the basis of such an algorithm[34]. More recently, the BEST study[35] showed that combination therapy in patients presenting signs and symptoms of RA for less than 2 years resulted in significantly greater and faster reduction in HAQ score and a significant reduction in radiological damage compared to sequential monotherapy or step-up strategy.

Use of Combination Therapy in Patients Who Fail Standard DMARD Therapy

Failure to respond to monotherapy is also a justified indication for initiating combination therapy. Most patients are

currently started on monotherapy with MTX and this should be considered to have failed in patients who respond inadequately to an adequate dose of this drug using concomitant corticosteroids or nonsteroidal antiinflammatory drugs (NSAID) for over 3 months. It should be pointed out that most cases of treatment failure correspond to an unsatisfactory response rather than the absence of any treatment response. The ultimate treatment goal should be stopping progression and remission of symptoms. However, in practice a threshold of 3.2 on the DAS28 is often considered a satisfactory treatment response, although individual treatment targets need to be established for each patient, taking into account pretreatment clinical status. Unacceptable progression of disease according to radiographic criteria or unacceptable symptoms experienced by the patients should also be considered treatment failure. In low-risk patients, a switch to another DMARD should be considered initially, whereas in high-risk patients, adding another drug (leflunomide or a biological agent) may be more appropriate. In many countries, standard practice is to initiate combination therapy with biological agents only when at least 2 DMARD have failed as monotherapy.

When there is marked radiographic progression, addition of biological agents should be considered. The rate of onset of treatment response is generally believed to be faster with biological agents than with classical DMARD. Moreover, combination of a DMARD with a biological agent is likely to be more efficacious than a biological agent alone[36]. Combination therapy with a biological agent should thus be considered a recommended treatment option in patients with quickly progressing disease in whom there is need for a rapid therapeutic response.

In patients already using a combination of 2 classical DMARD who fail to respond adequately, addition of a biological agent may be preferable to a switch. Although patient numbers were small, and caution should thus be excercised in interpreting the results, a Spanish study that compared the tolerability of triple therapy with MTX, leflunomide, and infliximab to that of standard leflunomide and infliximab combination did not demonstrate any specific safety issue associated with use of triple therapy.

Patients in Whom Combination Therapy Should Be Used with Precaution

A number of factors should be taken into consideration before prescribing a combination of leflunomide and a biological agent. These are generally not specific to the combination, but should also be considered when prescribing these drugs in monotherapy.

The history of previous treatments should be considered. A varied and unsatisfactory treatment history is not in itself an issue for expected efficacy, except that such patients may be inherently difficult to treat. However, if treatment history reveals the interruption of 3 or more DMARD for adverse events, then these patients should be considered at particular risk for potential safety issues and be followed more closely.

It has also been suggested that a high HAQ score before treatment initiation may indicate higher probability of adverse events and increased mortality risk[37], and that closer monitoring would be appropriate in such patients.

Age is not an issue for prescription of combination therapy, except for young women of reproductive age who should not be prescribed potentially teratogenic drugs. This is specified in the prescription guidelines for MTX and leflunomide, and these drugs are contraindicated in women who wish to become pregnant. In the elderly, the prevalence of comorbidities may be higher and these need to be assessed carefully before initiating treatment, and appropriate monitoring put in place if necessary.

Comorbidities should be taken into account. Hepatic impairment is a known side effect of leflunomide (and MTX) and these drugs are contraindicated in patients with hepatic disease. Leflunomide is also contraindicated in patients with bone marrow depression or immunodeficiency states and in those with severe renal insufficiency. Similarly, anti-TNF-α drugs should not be used in patients with a recent or chronic history of infectious disease, cancer, or immunodeficiency. In addition, infliximab and adalimumab are contraindicated in patients with moderate to severe heart failure, and anakinra in patients with severe renal failure. Combination therapies should be avoided in subjects with other autoimmune diseases such as systemic lupus erythematosus (SLE) and demyelinating disease. Rare cases of vasculitis and extraarticular manifestations such as nodulosis have been described in patients treated with leflunomide or certain biological agents[38-40], and the use of combination treatment in such patients should be approached with caution.

Contraindications and precautions for use related to concomitant treatments should be considered according to prescribing guidelines for each treatment. Nonetheless, the initiation of combination therapy with leflunomide and a biological agent may permit a reduction in the dose of concomitant corticosteroids or NSAID (see below).

Choice of Leflunomide Dose

Three separate situations could be envisaged for combining leflunomide and a biological agent: adding a biological agent to established leflunomide, adding leflunomide to an established biological agent, and starting both drugs simultaneously.

Adding a biological agent to an existing DMARD treatment is the commonest situation found in clinical practice. Two different strategies could be considered. The first involves keeping the patients on their maintenance dose of leflunomide (usually 20 mg) when the biological agent is introduced. In the event of emergence of side effects con-

sidered to be related to leflunomide, the dose can be reduced to 10 mg. Nonetheless, in patients considered to be at high risk for adverse events (history of adverse effects with leflunomide, history of poor tolerability to DMARD in general, risk due to age or coexisting morbidity the leflunomide dose should be reduced to 10 mg before introduction of the biological agent. The dose of leflunomide can subsequently be increased again to 20 mg after 2 to 3 months if combination therapy is well tolerated. The second strategy involves reducing the dose of leflunomide to 10 mg for all patients during the first 2 to 3 months and subsequently increasing it to 20 mg if the treatment is well tolerated. The difference between these 2 strategies lies essentially in the patient profile in terms of risk of developing adverse events. When leflunomide is added to preexisting therapy with biological agents, step-wise introduction is the most prudent strategy to minimize risk of side effects. No loading dose should be employed, and the starting dose of leflunomide should be 10 mg, with a step-up to a maintenance dose of 20 mg after 2 to 3 months if the treatment is well tolerated.

Simultaneous introduction of leflunomide and a biological agent is not recommended, due to attendant difficulty managing adverse events: If side effects emerge in such treatment regimens, it will not be clear to which medication it should be attributed; thus the only option available would be to stop both drugs, leaving the patient without effective treatment. In patients who are treatment-naive or unresponsive to a third DMARD, it is advisable to start leflunomide treatment first and add the biological agent after 2 or 3 months of good tolerance.

Use of Concomitant Antiinflammatory Medications

There are no specific regimens for the use of concomitant corticosteroids when using combination therapy. As in any treatment regimen, symptomatic medication should be adjusted on an ad hoc basis according to the status of the patient. Nonetheless, if leflunomide is being administered at a low dose of 10 mg in the early stages of combination therapy to reduce risk of emergence of side effects, consideration should be given to the use of a bridging regimen with corticosteroids. A short corticosteroid treatment regimen to cover the period of suboptimal leflunomide dose will help maintain symptom control and prevent deterioration of the clinical or functional status of the patient.

Several open-label studies with leflunomide and infliximab have demonstrated that initiation of combination treatment allows the dose of corticosteroids to be reduced without aggravation of symptoms. This could be an important treatment objective in itself, particularly in patients in whom corticosteroids are poorly tolerated. The same arguments may apply to the use of NSAID. It has been suggested that NSAID use is an important determinant in the (rare) incidence of Stevens-Johnson syndrome in RA[41].

Monitoring Combination Therapy

For monitoring efficacy, validated measures should be used, such as composite indices, DAS28, and radiographic evaluations. There is no reason to believe that combination therapy has a more incisive effect on one disease variable rather than another, and thus in routine followup the same validated outcome measures for monotherapy should be used.

Similarly, there do not appear to be any safety issues that are specific to combination therapy with leflunomide and a biological agent, with the possible exception of rash, which was reported relatively frequently in certain studies, particularly in patients with a history of intolerance to DMARD. Monitoring for safety variables, notably hepatic function and white blood cell count, should follow appropriate regulatory guidelines for monotherapy. When adding a biological agent to leflunomide, standard safety monitoring should be pursued, although increasing the frequency of monitoring may be considered in patients particularly at risk. Such patients include multiple DMARD failure due to adverse events, high HAQ score, vasculitis, extraarticular manifestations, and comorbidity (in particular SLE and demyelinating disease). As noted above, in patients at risk for these adverse events, combination should be avoided. Any monitoring procedures recommended for the biological agent should be initiated. When leflunomide is added to a biological agent, the more intense monitoring recommended for initiation of leflunomide treatment should be followed.

CONCLUSIONS

The combination of leflunomide with biological agents is now widely used in the treatment of RA, notably in patients who fail to respond adequately to previous DMARD treatment regimens. The available data show that these combinations are efficacious, and response rates may even be higher than those obtained with leflunomide and MTX combinations. This may reflect the good complementarity in mechanism of action between anti-TNF-α drugs and leflunomide.

The available data on the safety of combining leflunomide and biological agents are diverse. Some studies have shown that the tolerability of combination therapy is similar to that of the drugs used alone in monotherapy, whereas others have indicated a high incidence of adverse events leading to interruption of treatment, notably severe skin reactions. The reason for this heterogeneity is unknown, but may relate to differences between patients; for example, patients who have failed to tolerate a number of DMARD treatment regimens may be more likely to experience adverse events. This issue is important to resolve before a clear statement can be made about the safety of combinations of leflunomide and anti-TNF-α drugs. Due to the risk of side effects, sequential implementation of combination therapy rather than concomitant introduction of drugs should be preferred in order to manage any emergent side effects in the most expedient manner.

A limitation on the available information, and the conclusions that can be drawn therefrom, is that most experience involves the use of leflunomide in combination with infliximab. The assumption is being made that the data available can be extrapolated to other biological agents such as etanercept, adalimumab, or anakinra, but the extent to which this is valid is unknown. This aspect will need to be reevaluated as more data become available.

The expert panel nevertheless identified a number of recommendations on the practical use of combination therapy with leflunomide and biological agents. It should be underlined that, in the absence of more robust data from randomized studies, these recommendations are preliminary, and will have to be updated as more data become available. Although this is the case for all treatments, patients need to be informed clearly and fully of the potential risks and benefits associated with combination treatment. The establishment of reliable lines of communication between the patient and rheumatology department to facilitate rapid support for emergent adverse events is considered to be very important in maintaining adherence to therapy.

The use of combinations of leflunomide with biological agents was considered appropriate in patients with early disease (< 6 months) in whom prognosis was poor in terms of rate of disease progression and risk factors. Combination therapy should also be considered in patients who have failed DMARD therapy. It was recommended to introduce biological agents in patients in whom treatment with leflunomide was already stabilized in order to optimize management of any emergent side effects. It may be necessary to adjust the dose of leflunomide in patients considered at high risk for adverse events. There are no specific safety concerns associated with the use of combination therapies, but the monitoring recommended for the individual drugs used as monotherapy should be strictly followed. In patients considered at high risk for side effects, more stringent monitoring may be warranted should the combination be prescribed.

APPENDIX

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