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ORIGINAL ARTICLE

The Safety and Efficacy of Leflunomide in Combination With Infliximab in Rheumatoid Arthritis

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Objective. **To report the safety and efficacy of leflunomide (LEF) in combination with infliximab (INF) for the treatment of rheumatoid arthritis.**

Methods. **In an open, multicenter, retrospective study, data were collected on the safety and efficacy of LEF and INF.**

Results. **Eighty-eight patients received the combination of LEF and INF for an average of 6.6 months and a total exposure of 581 patient-months. The mean duration of LEF was 17 ± 9 months (range 3–32 months; median 18.5 months) with an average of 4.8 INF infusions per patient. In all but 3 subjects, LEF was used initially and INF was added later. Infusion reactions occurred in 3 patients (0.7% of all infusions). A total of 34% of subjects experienced adverse events and in 6 (6.8% of the group) these were deemed serious. Ten infections occurred when patients were taking the combination; 9 patients recovered fully and 1 died of bacterial pneumonia. A lifetime smoker developed lung cancer and another patient was found to have colon cancer.**

Conclusions. **The adverse events noted within the combination therapy group were in keeping with the known risks of each drug when used individually. Limited data were available on efficacy, but a general improvement in disease control was noted with the combination of drugs, which for most patients involved the addition of INF to previous use of LEF.**

KEY WORDS. Rheumatoid arthritis; Combination therapy; Leflunomide; Infliximab.

INTRODUCTION

Over the past several years, the treatment of rheumatoid arthritis (RA) has changed dramatically. We have seen the introduction of several new disease-modifying antirheumatic drugs (DMARDs), the entry of which has led to improved control of RA and other forms of inflammatory arthritis. Many rheumatologists now use novel combinations of DMARDs to better control the disease process, yet the safety and efficacy of these new combinations is unknown. Although infliximab (INF) is usually given with methotrexate, lack of efficacy or an adverse reaction to methotrexate may prompt a switch from methotrexate to leflunomide (LEF). Because the combination of LEF and INF has not been formally studied or approved by the Food and Drug Administration, insurance companies may deny coverage of the combination of drugs. We report here a retrospective study on the safety and efficacy of LEF and INF in patients with RA (1).

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PATIENTS AND METHODS

Six centers were invited to participate in this study. All patients with RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (2), who had taken the combination of LEF and INF for at least 1 month were eligible. Subjects were excluded if they took concomitant methotrexate. A standardized chart review form was created to collect information on demographics, disease severity, markers of disease activity before and after the combination therapy, and incidence of adverse events. Demographic data included sex, rheumatoid factor results, radiographic evi-

dence of erosions, periarticular osteopenia or joint space narrowing, functional class, and disease duration. Prior DMARD use and reason for discontinuation were recorded (lack of efficacy, adverse event, or other reason). Onset of LEF therapy was recorded along with initial and current dosages of the drug. Likewise, the onset of INF therapy was recorded with the current dosage and total number of infusions. The frequency and indication for dose reduction, and temporary or permanent discontinuation of either drug was recorded.

Efficacy measures included tender and swollen joint counts (maximum count of 28), pain level, morning stiffness (minutes), dosage of prednisone or prednisolone, erythrocyte sedimentation rate (ESR), C-reactive protein level, ability to work, and the presence of fever, weight loss, or fatigue before and after combination therapy. Safety measures included laboratory data (complete blood count, aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and creatinine before and after the combination therapy), number and severity of infusion reactions, infections, neurologic symptoms, new malignancies, hospitalizations, life-threatening illness, pregnancy, congenital abnormalities, and death. For all infections, the type of infection (viral, bacterial, fungal, or tuberculous) was recorded along with the form of therapy, need for hospitalization, need to withhold immunosuppressive drugs, and final outcome. Hospital records were requested for all admissions related to infection. All side effects resulting in temporary or permanent discontinuation of medication were also recorded.

RESULTS

Demographics. Eighty-eight RA patients had received at least 1 month of therapy with the combination of LEF and INF. A total of 38 subjects had received ≥6 months of the combination of LEF and INF, 24 had received ≥3 months but <6 months, and 26 had received <3 months of the combination with a total of 581 patient-months exposure to the combination of LEF and INF among the group. We report safety data here for all 88 patients to allow reporting of early or serious adverse events. Efficacy data is reported for the entire group, as well as the subgroup that received >3 months of combination therapy.

For the whole group, the mean maintenance dosage of LEF was 17.8 mg/day (median dosage 20 mg/day) with an average duration of 17 ± 9 months of therapy (median 18.5 months, range 3–32 months). The average number of INF infusions was 4.8 at a mean dosage of 3.3 mg/kg. The mean duration of combination therapy was 6.6 months (range 1–27 months). In all but 3 patients, LEF had been used for several months or longer, and INF was later added to better control disease parameters.

The patients in this study were predominantly female (n = 63; 72%) with an average age of 53 years (range 25–82 years) and average disease duration of 124 months (range 12.5–532.5 months). Sixty-nine of 85 subjects (81%) with recorded data were seropositive; in the 71 with radiographic data, 47 (66%) had erosive disease, 47 (66%) had periarticular osteopenia, and 54 (76%) had joint space narrowing on hand or foot radiographs. Most patients had mild to moderate disease (3): Of 81 patients with recorded data, 24% were in functional class I, 39% in functional class II, 25% in functional class III, and 5% in functional class IV.

Table 1. Indication for discontinuation of prior DMARDs*

DMARD	n (%)	Lack of efficacy no. (%)	Adverse event no. (%)
Methotrexate	81 (92)	44 (54)	30 (37)
Sulfasalazine	35 (40)	19 (54)	6 (17)
Gold compounds	40 (45)	24 (60)	10 (25)
Hydroxychloroquine	46 (52)	32 (70)	6 (13)
Etanercept	19 (22)	14 (74)	3 (16)

* The sum of lack of efficacy plus adverse event does not equal 100% due to missing data or other indications for stopping therapy. DMARD = disease-modifying antirheumatic drug.

The vast majority of patients (92%) had previously used methotrexate. Other DMARDs used by this population included sulfasalazine (40%), hydroxychloroquine (52%), oral or intramuscular gold (45%), and etanercept (22%). Table 1 summarizes the indication for discontinuation of these DMARDs.

Safety measures. In 73 subjects with recorded information, none experienced a white cell count ≤3,000/mm^3 or a platelet count <100,000 mm^3 while taking combination therapy. There were no significant changes in hemoglobin or hematocrit levels. Two subjects (2.6%) experienced elevated liver enzymes out of 73 patients with available information. In 1 case, the ALT was 63 U/liter before combination therapy, and 65 U/liter after. Another subject had a new increase in AST and ALT (16 U/liter and 26 U/liter before; and 122 U/liter and 251 U/liter after combination therapy, respectively). The LEF dosage was reduced to 10 mg and liver enzyme levels returned to normal. Serum albumin was recorded in 55 subjects; only 2 had a decrease in albumin below 3 gm/liter. The decrease in albumin was 0.3 gm/liter in both subjects with a final serum albumin of 2.8 and 2.9 gm/liter, respectively. There were no significant changes in serum creatinine.

Dose reduction, suspension, or discontinuation. Both LEF and INF were discontinued in 4 patients: 1 patient had diffuse rash, 1 had lung cancer, 1 pneumonia and acute respiratory distress syndrome, and 1 had cellulitis, leg edema, and newly diagnosed colon cancer. LEF was discontinued in 1 patient for lack of efficacy, 1 patient with hypertension, and 1 with rash. INF was discontinued in 4 patients for lack of efficacy and in 2 patients for rash (1 of whom reported increased arthralgia while on INF). Table 2 summarizes these data, including the number of months exposure to combination therapy before discontinuation of medication.

Temporary discontinuation of LEF occurred in 7 subjects due to diarrhea (3 subjects), rash (2 subjects), pruritis (1 subject), and herpes zoster (1 subject). INF was tempo-

Table 2. Cause for permanent discontinuation of leflunomide or infliximab*

	Leflunomide	Infliximab	Both
Lack of efficacy, no.	1	4	0
Adverse event, no. and event	2	2	4
	Hypertension (16.5 m)	Rash (3.5 m)	Rash (3.5 m)
	Rash (1.25 m)	Rash and arthralgia (4.75 m)	Lung cancer (4.5 m)
			Pneumonia/ARDS/death (1.5 m)
			Cellulitis/edema/colon cancer (1 m)

* m = months of exposure to combination therapy before the adverse event occurred; ARDS = adult respiratory distress syndrome.

rarily held in the subject with herpes zoster infection. Five patients had a decrease in dosage of LEF due to diarrhea (2 patients), elevated liver enzyme levels (1 patient), nausea (1 patient), and elevated blood pressure (1 patient).

Three patients (3 of 426 infusions; 0.7%) experienced infusion reactions, including headache and dizziness (1 subject) and rash (2 subjects). There were no serious infusion reactions leading to a change in cardiovascular or respiratory status.

Infections and hospitalizations. A total of 5 viral and 5 bacterial infections occurred while patients were taking combination therapy (11.4% of the group, Table 3). The onset of infection ranged from 1 to 16 months exposure to combination therapy (median 4.1 months, mean 5.8 months for the group). One case of herpes zoster occurred, prompting a 1-week suspension of INF and LEF and therapy with prednisone and famciclovir. The patient fully recovered. Three upper respiratory infections occurred and all subjects recovered without suspension of INF or LEF therapy. One subject experienced flu-like symptoms and likewise recovered with no change in therapy.

Five bacterial infections occurred during combination therapy. All subjects were hospitalized and treated with antibiotics. Full recovery occurred in all but 1 subject, who had underlying rheumatoid lung disease and died of acute respiratory distress syndrome and bacterial pneumonia. No fungal, tuberculous, or opportunistic infections occurred in this study. There were no congenital abnormalities, pregnancies, or neurologic events in the group.

Summary of adverse events. All forms of adverse events occurred in 30 subjects (34%), including 6 serious adverse events (6.8% of the group). Serious adverse events included the 5 bacterial infections described above; 1 of these subjects was diagnosed with colon cancer during hospitalization for the infection, which occurred after 1-month exposure to combination therapy. The sixth serious adverse event involved a lifetime smoker who developed lung cancer after 4.5 months of combination therapy.

Efficacy. Measurements of efficacy were recorded before and after use of the combination of medications for the whole group (Table 4). When we analyzed the data separately for those receiving >3 months of the combination of

Table 3. Viral and bacterial infections during combination therapy*

Infection	Treatment	Duration of exposure, months	Immunosuppressives	Outcome
Viral				
Shingles	Prednisone, famciclovir	13.75	LEF suspended for 1 week	Resolved
Flu-like symptoms	None	1	Continued	Resolved
Upper respiratory infection	None	1.25	Continued	Resolved
Upper respiratory infection	None	2.75	Continued	Resolved
Upper respiratory infection	None	9.5	Continued	Resolved
Bacterial				
Septic arthritis of left ankle	Hospitalization, IV levofloxacin, arthrocentesis	5.5	Continued	Resolved
Toe cellulitis, leg edema†	Hospitalization, cephalexin	1	LEF and INF permanently withdrawn	Resolved
Postoperative foot infection	Hospitalization, ceftriaxone, oxacillin, ceftazidime	6	Continued	Resolved
Pneumonia	Hospitalization, IV antibiotics, high-dose steroids, bronchoalveloar lavage	16	Continued	Resolved
Pneumonia, ARDS	Hospitalization, IV antibiotics, high-dose steroids, bronchoalveolar lavage	1.5	LEF and INF permanently withdrawn	Death

* Duration of exposure indicates the months of exposure to combination therapy before the adverse event occurred. LEF = leflunomide; IV = intravenous; INF = infliximab; ARDS = adult respiratory distress syndrome.
† This subject was diagnosed with colon cancer during hospitalization.

Table 4. Efficacy measures of combination therapy with LEF and INF*

Efficacy variable	Before LEF + INF	After LEF + INF	Change	Percent improvement
Tender joint count, n = 67	15	5	−10	67
Swollen joint count, n = 67	14	5	−9	64
Pain, n = 36	7.0	3.0	−4.0	57
Corticosteroid dosage, mg/day, n = 82	5.4	3.2	−2.2	41
ESR, mm/hour, n = 48	52	32	−20	39
C-reactive protein, mg/liter, n = 36	10.7	5.9	−4.8	45

* Pain as measured on a 10-cm visual analog scale. LEF = leflunomide; INF = infliximab; ESR = erythrocyte sedimentation rate.

INF and LEF (n = 62), efficacy parameters were very similar (Table 5). Because of the retrospective nature of this study, data for every efficacy variable were not available for the whole group.

For all 88 subjects, the swollen joint count improved by 64% with combination therapy (mean of 14 before and 5 after combination therapy). The tender joint count improved by 67% with combination therapy (mean of 15 before and 5 after the combination). Pain levels improved from a level of 7.0 to 3.0 on a 10-point scale (57% improvement). C-reactive protein levels improved by 45% (10.7 mg/liter before and 5.9 mg/liter after the combination). The baseline ESR of 52 mm/hour decreased by 20 mm/hour. Combination therapy resulted in a decrease in mean prednisone or prednisolone dosage by 41% (5.4 mg/day down to 3.2 mg/day).

Of 74 subjects who provided information on work status, 71 (96%) had no change in work status, 2 (2.7%) became unable to work, and 1 (1.3%) became able to work. Information was recorded on fatigue in 75 subjects; 21 (28%) reported resolution, 52 (65%) were unchanged, and 1 (1.3%) noted new fatigue with combination therapy. Body weight was available for 85 subjects; 3 (3.5%) noted resolution of weight loss, 4 (5%) had new weight loss, and the remainder experienced no change in weight with combination therapy. No subject reported fever related to rheumatoid arthritis or medications. Data on patient global assessment was not available in this retrospective format.

DISCUSSION

The current era of therapy for RA has been described in the recently published RA management guidelines (4). Early diagnosis and initiation of DMARD therapy is thought to be pivotal (5). Active synovitis and progression of radiographic damage can be arrested in the majority of patients responding to therapy, and quality of life and disability may improve significantly. Combination therapy, where monotherapy has had an incomplete response, has become the standard of care for RA.

Although methotrexate is the most commonly used DMARD in the United States for treatment of RA, some patients experience lack of efficacy or an adverse event (6). For those who do respond, remission of the disease is rare and another DMARD is often needed for better disease control. When using INF therapy, the development of human antichimeric antibodies (HACA) may neutralize the benefit of INF. Methotrexate therapy decreases HACA and is associated with improved disease control when used with INF (7). For subjects receiving INF who cannot take methotrexate, an alternative DMARD is often necessary to minimize development of HACA and improve efficacy. We propose that LEF is an alternative to methotrexate in patients taking INF. However, the study was not designed to compare the safety and efficacy of INF–LEF combination to INF–methotrexate combination.

Two major weaknesses of this study were its retrospective nature and the absence of a control group. The retrospective design of the study resulted in incomplete data collection and would tend to inflate the overall efficacy results, because subjects are more likely to be identified and their data recorded if they responded well to therapy and continued to take the combination of drugs. The lack of a control group and missing data prevented the authors from reporting anything other than descriptive improve-

Table 5. Efficacy measures for 62 subjects taking LEF and INF for ≥3 months*

Efficacy variable	Before LEF + INF	After LEF + INF	Change	Percent improvement
Tender joint count, n = 51	15	6	−9	60
Swollen joint count, n = 52	13	5	−8	62
Pain, n = 26	7.2	3.3	−3.9	54
Corticosteroid dosage, mg/day, n = 58	6.2	3.5	−2.7	44
ESR, mm/hour, n = 40	50	32	−18	36
C-reactive protein, mg/liter, n = 26	17.7	7.6	−10.1	57

* Pain as measured on a 10-cm visual analog scale. LEF = leflunomide; INF = infliximab; ESR = erythrocyte sedimentation rate.

ment in efficacy. ACR improvements cannot be calculated on the incomplete dataset.

Another weakness of the current study (and topic for future study) is the absence of data regarding HACA. It would be of clinical interest to demonstrate in a prospective study whether LEF diminishes HACA production in patients receiving INF. In our retrospective study, patients received an average of 6.6 months combination therapy and the dosage of INF remained at an average of 3.3 mg/kg, giving indirect support that LEF is effective at decreasing HACA.

In this article, we have explored the novel combination of LEF and INF. LEF has been shown to improve ACR scores, quality of life, Health Assessment Questionnaire disability index, and radiographic progression (8,9). The combination of INF and methotrexate has also been demonstrated to improve these parameters (10). This observational analysis shows that in 88 patients with RA, the combination of LEF and INF shows a reasonable safety and efficacy profile. The adverse events noted during this study were in keeping with the known risks of each drug when used individually. Efficacy parameters showed improvement when the combination was used. Laboratory data demonstrated no additional toxicity when patients took the combination of INF and LEF. Bacterial infections requiring hospitalization did occur on the combination and all but 1 subject recovered fully. The subject who died had underlying rheumatoid lung disease, developed pneumonia 1 month into combination therapy, and succumbed to adult respiratory distress syndrome. A heightened awareness of infections and low threshold for treatment is recommended to minimize the potential risks of immunosuppression.

We conclude that LEF is an alternative DMARD to methotrexate in subjects receiving INF therapy, and with appropriate monitoring appears safe. For RA patients receiving INF who report lack of efficacy or a side effect of methotrexate mandating cessation of the drug, LEF is an alternative DMARD to consider. Further controlled studies should be pursued to establish if there are efficacy or side effect differences between the LEF–INF combination and the methotrexate–INF combination.

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