Safety of Infliximab Used in Combination with Leflunomide or Azathioprine in Daily Clinical Practice

ALETH PERDRIGER, XAVIER MARIETTE, JEAN-LOUIS KUNTZ, OLIVIER BROCQ, RYM KARA-TERKI, XAVIER LE LOET, ALAIN CANTAGREL, STEPHAN PAVY, CHANTAL JOB DESLANDRE, FRANÇOISE DEBIAIS, BERNARD COMBE, and the Club Rhumatismes et Inflammation

ABSTRACT. ***Objective.*** To investigate the safety of infliximab (INF) combination therapy with leflunomide (LEF) or azathioprine (AZA) in patients with rheumatoid arthritis (RA).

Method. A standardized questionnaire on the use of INF in combination with LEF or AZA was mailed to hospital physicians and collected over a 2 month period. Adverse events (AE) and the reasons for withdrawal of combination therapy were analyzed.

Results. Data on 225 patients with RA were collected retrospectively. INF was used in combination with LEF in 171 patients and with AZA in 54. The duration of INF exposure was similar in both groups (mean 8.8 mo). AE were reported in 75 patients (33.3%), 60 LEF/INF (35%) and 15 AZA/INF combinations (27.8%) (p = nonsignificant). No unexpected AE were observed. The main AE were infections (6.2%), cytopenia (5.8%), hepatotoxicity (5.8%), reactions to infusion (5.3%), and skin reactions (4%). At the time the questionnaires were sent out, 161 patients were continuing combination therapies. The main reasons for drug withdrawal were AE (53 patients, 23.5%), inefficacy (10 patients, 4%), and one temporary discontinuation for surgery.

Conclusion. Our study suggests that INF used in combination with LEF or AZA could be an alternative to methotrexate/INF combinations. (J Rheumatol 2006;33:865–9)

Key Indexing Terms:
INFLIXIMAB RHEUMATOID ARTHRITIS LEFLUNOMIDE AZATHIOPRINE

Many studies have shown that biological agents targeting tumor necrosis factor-α (TNF-α) offer a sustained improvement in symptoms and signs in patients with rheumatoid arthritis (RA). Three anti-TNF agents have been approved for the treatment of RA, namely, infliximab, a chimeric monoclonal anti-TNF-α antibody; adalimumab, a fully human anti-TNF-α antibody; and etanercept, an engineered p75 TNFR dimer[1,2].

Etanercept and adalimumab can be prescribed alone for RA, while infliximab (INF) is only approved for use in combination with methotrexate (MTX). The immunosuppressive properties of MTX markedly reduce the incidence of antibodies to INF in patients with RA. In the first multicenter trial of repeated INF infusions, it was shown that human antibody responses to INF were diminished in patients who concomitantly received low-dose oral MTX[3]. In Crohn's disease, concomitant use of immunosuppressive drugs [mainly azathioprine (AZA)] and INF significantly reduces the level of antibodies to INF and the risk of reactions to the infusions[4]. Combination of MTX with anti-TNF agents improves the efficacy of the latter in patients with RA[5,6]. Disease modifying antirheumatic drugs (DMARD) other than MTX may also be used in combination with biological therapies. Adalimumab has been combined with standard DMARD in treatment of refractory RA with no increase in adverse events[7]. Combination therapy with standard DMARD and the interleukin 1 receptor antagonist anakinra proved synergistic in patients with RA[8]. However, little is known regarding combinations of standard DMARD with INF in patients with inflammatory diseases. The safety of leflunomide (LEF) combined with INF is controversial[9-13].

We carried out a retrospective multicenter study of the safety of INF combination therapy with LEF or AZA, as rou-

From the Department of Rheumatology, Medical University, Rennes; Department of Rheumatology, Paris-sud University, AP-HP, le Kremlin Bicètre; Department of Rheumatology, Medical University, Strasbourg; Department of Rheumatology, Medical University, Nice; Department of Rheumatology, Medical University, Grenoble; Department of Rheumatology, Medical University, Rouen; Department of Rheumatology, Medical University, Toulouse; Department of Rheumatology A, Cochin University, Paris; Department of Rheumatology, Medical University, Poitiers; and Department of Rheumatology, Medical University, Montpellier, France.

A. Perdriger, MD, PhD, Department of Rheumatology, Medical University, Rennes; X. Mariette, MD, PhD, Department of Rheumatology, Paris-sud University; J-L. Kuntz, MD, Department of Rheumatology, Medical University, Strasbourg; O. Brocq, MD, Department of Rheumatology, Medical University, Nice; R. Kara-Terki, MD, Department of Rheumatology, Medical University, Grenoble; X. Le Loet, MD, Department of Rheumatology, Medical University, Rouen; A. Cantagrel, MD, PhD, Department of Rheumatology, Medical University, Toulouse; S. Pavy, MD, Department of Rheumatology A, Cochin University; C. Job Deslandre, MD, Department of Rheumatology A, Cochin University; F. Debiais, MD, PhD, Department of Rheumatology, Medical University, Poitiers; B. Combe, MD, PhD, Department of Rheumatology, Medical University, Montpellier.

Address reprint requests to Prof. A. Perdriger, Service de Rhumatologie, Hôpital Sud, CHU de Rennes, 16 Boulevard de Bulgarie, 35056 Rennes Cedex, France. E-mail: aleth.perdriger@chu-rennes.fr

Accepted for publication December 29, 2005.

tinely used by French rheumatologists to treat inflammatory arthritis refractory to MTX.

MATERIALS AND METHODS

Retrospective data on combination therapy with INF and LEF or AZA were collected with a standardized questionnaire. The questionnaire was sent to all the French hospital rheumatologists and specialists in internal medicine in March 2003 by standard mail and was also made available on the website of the Club Rhumatismes et Inflammation (CRI, a section of the French Society of Rheumatology). All the data were collected over a 2 month period. In September 2003, additional data on the outcome of adverse events were requested.

Demographic characteristics included age, sex, diagnosis, and disease duration. Information on the previous use of MTX and reasons for MTX discontinuation was also collected.

The efficacy and tolerability of the combination therapies were evaluated by the physicians, using a 4-grade scale (very good, good, medium, poor). Reported adverse events and the reasons for withdrawal of the combination therapy were analyzed.

Statistical analysis. Descriptive statistics were obtained using SAS software version 8.2 (SAS Institute, Cary, NC, USA). The different combinations were compared by chi-square analysis and the Mann-Whitney U test, as appropriate. Withdrawal of the combination therapies over time was estimated using Kaplan-Meier curves and differences between groups were assessed using the log-rank test. All the tests were 2-tailed, and a probability value below 0.05 was considered significant.

RESULTS

Patients' characteristics. Data were collected on 225 patients with RA in 48 hospitals. Three-quarters of the patients were women, with a mean age of 56.8 ± 12.4 years (range 25–81). The mean disease duration was 13.4 ± 8.1 years (range 2–42). MTX had previously been used by 203 patients (90.2%). The reasons for MTX discontinuation were inefficacy in 33.2% or adverse events in 66.8% of the cases.

LEF combination therapy was prescribed to 171 patients (76%), at a mean dosage of 20 ± 2.7 mg/day, while AZA combination therapy was prescribed to 54 patients (24%) at a mean dosage of 99 ± 49.95 mg/day. The characteristics of the patients are reported in Table 1 according to the DMARD combinations.

DMARD were introduced before the onset of INF therapy in 164 patients (72.8%). The mean duration of DMARD monotherapy, before INF was added, was 12.9 ± 13 months. The DMARD was inadequately effective in these patients, but was well tolerated. LEF was started before INF for 144 patients (84.2%). In 61 cases (27 patients receiving LEF and 34 patients receiving AZA; 27%), the DMARD was started concomitantly with or after INF.

The average dose of INF during DMARD combination therapy was 3.09 ± 0.38 mg/kg per infusion. The mean duration of combination therapies was 8.8 ± 6 months (range 0.5–30 mo), equivalent to 164.6 patient-years. In 2 patients, the dates when the combination therapy began were not reported precisely. A total of 209 patients (92.8%) received at least 3 infusions of INF in combination with the DMARD that were studied.

Global efficacy and tolerability of the combinations. Only the 209 patients who received 3 or more INF infusions were analyzed for efficacy. Overall, efficacy was considered very good in 29.7%, good in 38.8%, medium in 23%, and poor in 8.6% of the cases. No significant difference in efficacy was observed according to the use of DMARD (Figure 1).

Tolerability of the 225 combination therapies was considered very good in 41.7%, good in 35.6%, medium in 11.6%, and poor in 11.1% of the cases. Tolerability did not differ according to the DMARD (Figure 2).

Adverse events. Seventy-five patients (33.3%) experienced

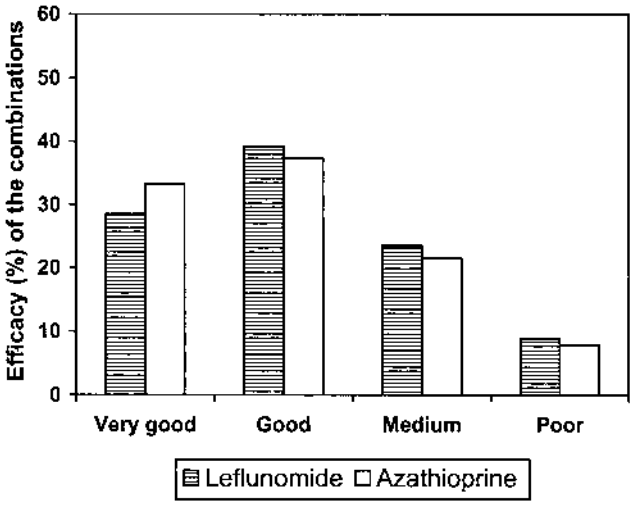

Figure 1. Comparative efficacy of LEF/INF and AZA/INF as evaluated by physicians using a 4-level score. Only the 209 patients who received 3 or more INF infusions were analyzed for efficacy.

Table 1. Characteristics of patients receiving LEF/INF and AZA/INF combinations.

	All Combinations, n = 225	INF/LEF Combinations, n = 171	INF/AZA Combinations, n = 54
Sex ratio F/M (%)	170/55 (75/25)	125/46 (73/27)	44/10 (81/19)
Age, mean ± SD yrs	56.8 ± 12.4	56.6 ± 12	57.5 ± 13.4
Previous use of MTX, n (%)	203 (90.2)	152 (88.8)	51 (94.4)
Disease duration, mean ± SD yrs	13.4 ± 8.1	12.8 ± 7.8	15.3 ± 8.8
Duration of combination therapy, mean ± SD months	8.8 ± 6	8.7 ± 6.2	9 ± 5.4

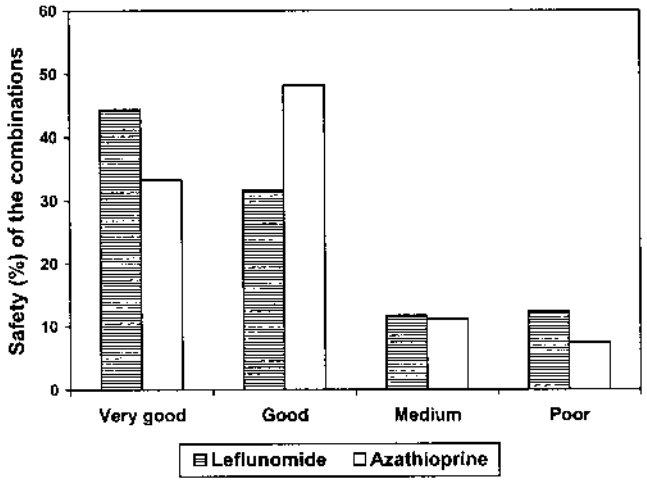

Figure 2. Comparative tolerability of LEF/INF and AZA/INF, evaluated by physicians using a 4-level score.

one (n = 66) or 2 (n = 9) adverse events. Frequencies of adverse events were similar for patients receiving INF/LEF (n = 60, 35%, 48/100 patient-yrs) or INF/AZA (n = 15, 27%, 37/100 patient-yrs) (p = nonsignificant). Adverse events tended to be more frequent in the group who added LEF or AZA to INF (25 with adverse events in the group of 61 patients, 41%) in contrast to adding INF to the DMARD (50 with adverse events in the group of 164 patients, 30.5%) (p = 0.13). This difference only reached statistical significance in patients receiving LEF/INF: 14 of the 27 patients who began LEF concomitantly with or after INF had adverse events, compared to 46 of the 144 patients who began LEF before INF (51.8% vs 32%; p < 0.047).

All the 84 adverse events observed in this study are described, by DMARD status, in Table 2. Infections occurred in 14 patients (6.2%). The main site of involvement was the lungs (6 patients). A 53-year-old man died of joint infection 8 months after starting the INF/LEF combination. Cytopenia occurred in 13 patients (5.8%), but was never associated with severe complications, including infections. Reactions related to the infusions were reported in 12 patients (5.3%). Elevated liver enzyme activities were reported in 12 patients (5.3%) and were rated as mild to moderate. Skin reactions were observed in 9 patients (4%). No severe cutaneous reactions, including Stevens-Johnson syndrome, were reported.

Two patients receiving INF/LEF were diagnosed with ovarian and skin cancer after 3 months and 1 month, respectively, of treatment. Pulmonary embolism occurred after 4 infusions in a 45-year-old woman with RA who also had cardiovascular risk factors (combined oral contraception, smoking, and steroid therapy). Three cases of heart failure were reported, all taking the INF/LEF combination (3.3%, 2.3/100 patient-yrs). One of these cases was associated with renal failure in a woman with RA and amylosis. Two other cases of heart failure occurred at the outset of combination therapy (after the first infusion in one case and the second infusion in the other). Unexplained abrupt-onset peripheral neuropathy occurred after 8 months of INF/LEF combination therapy in a patient with RA. A case of histologically-proven rheumatoid pneumonia deteriorated after 3 months of INF/LEF combination therapy.

Table 2. Description of the 84 adverse events observed in patients receiving infliximab combined with leflunomide (LEF) or azathioprine (AZA). No significant difference in the frequency of adverse events between the 2 combinations was observed.

	All Combinations, n = 225	INF and LEF, n = 171	INF and AZA, n = 54
Adverse events, n (%)			
Infections	14 (6.2)	8 (4.7)	6 (11)
Septic arthritis	1 (0.44)	1 (0.6)	0 (0)
After joint replacement	1 (0.44)	0 (0)	1 (1.8)
Urinary tract	1 (0.44)	0 (0)	1 (1.8)
Pulmonary	4 (1.8)	1 (0.6)	3 (5.6)
Skin	1 (0.44)	1 (0.6)	0 (0)
Pyelonephritis	2 (0.88)	1 (0.6)	1 (1.8)
Septicemia	1 (0.44)	1 (0.6)	0 (0)
Pulmonary aspergillosis	1 (0.44)	1 (0.6)	0 (0)
Pulmonary tuberculosis	1 (0.44)	1 (0.6)	0 (0)
Diverticulitis	1 (0.44)	1 (0.6)	0 (0)
Cytopenia	13 (5.8)	10 (5.8)	3 (5.6)
Hepatotoxicity	13 (5.8)	11 (6.4)	2 (3.7)
Reactions to infusion	12 (5.3)	11 (6.4)	1 (1.8)
Skin reactions	9 (4)	8 (4.6)	1 (1.8)
Diarrhea	4 (1.8)	4 (2.3)	0 (0)
Alopecia	4 (1.8)	2 (1.2)	2 (3.7)
Hypertension	4 (1.8)	4 (2.3)	0 (0)
Heart failure	3 (1.3)	3 (1.7)	0 (0)
Asthenia/vertigo	2 (0.88)	1 (0.6)	1 (1.8)
Malignancy	2 (0.88)	2 (1.2)	0 (0)
Pulmonary embolism	1 (0.44)	1 (0.6)	0 (0)
Peripheral neuropathy	1 (0.44)	1 (0.6)	0 (0)
Rheumatoid pneumonia	1 (0.44)	1 (0.6)	0 (0)
Renal failure	1 (0.44)	1 (0.6)	0 (0)

Withdrawal of combination therapy. Overall, 161 (71.5%) of the 225 combination therapies were continuing at the time of this analysis. The reasons for drug withdrawal were adverse events in 53 cases (23.5%) and inefficacy in 10 cases (4%). In one case, the combination was stopped for surgery (joint replacement) and had not been resumed at the time of this analysis. Distribution of the 2 combination therapies over time is reported in Figure 3. No difference between LEF/INF and AZA/INF combinations was observed.

The management of the 61 adverse events observed in the 53 patients who stopped the treatment is reported in Table 3. The DMARD and the INF treatments were not always both withdrawn. INF, alone or together with the DMARD, was stopped in 40 patients (17.7%, 24.3/100 patient-yrs) after 46 adverse events. Infections (n = 10, 4.4%) and reactions related to the infusions (n = 11, 4.8%) were the main reason for permanent INF withdrawal. The DMARD alone was stopped in 13 patients (5.7%, 7.9/100 patient-yrs) after 15 adverse

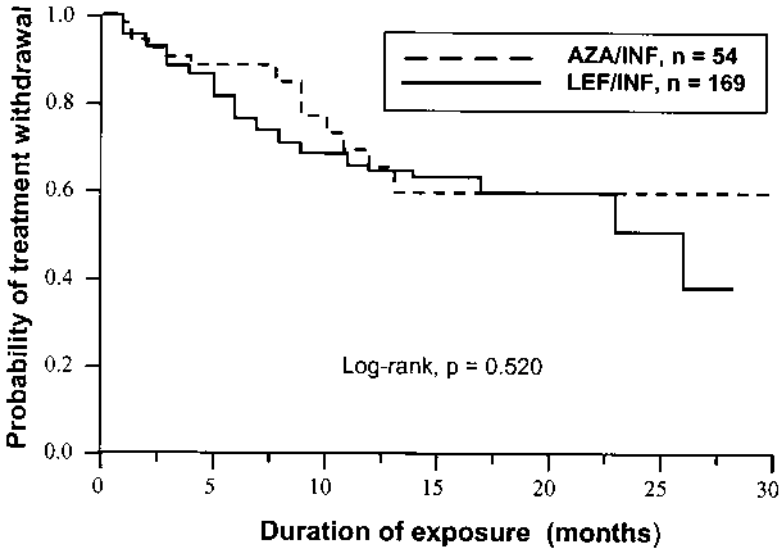

Figure 3. Distribution of the 2 combination therapies over time. Only data from 223 patients were included in the analysis; 2 patients were excluded because the dates the LEF/INF combination was started were not reported precisely.

Table 3. Description of the 61 adverse events observed in 53 patients who were withdrawn from treatment (total 225 patients).

	n (%)
Infections*	12 (5.3)
Cytopenia	7 (3.2)
Hepatotoxicity	11 (4.8)
Reactions to infusion	11 (4.8)
Skin reactions	7 (3.2)
Diarrhea	1 (0.4)
Hypertension	3 (1.3)
Heart failure	3 (1.3)
Malignancy	2 (0.8)
Pulmonary embolism	1 (0.4)
Peripheral neuropathy	1 (0.4)
Pneumonia	1 (0.4)
Renal failure	1 (0.4)

* For 2 infections, the combinations were temporarily suspended.

events. The main reason for discontinuing the DMARD alone was hepatotoxicity (n = 6, 2.7%).

DISCUSSION

In this retrospective study, we used a standardized questionnaire to question French physicians about their use of infliximab with a DMARD different from MTX in patients with RA. Data on 225 RA patients treated with INF plus LEF (76%) or AZA (24%) were collected in March 2003. The demographic characteristics of the patients in the INF/LEF and INF/AZA groups were very similar, notably in terms of age (mean 56.8 yrs), disease duration (mean 12.3 yrs), and the length of exposure to INF at the cutoff date for the study (mean 8.8 mo). Most of the patients (90.2%) were refractory to or intolerant of MTX. Interestingly, these patients' characteristics were similar to those of the ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) trials of INF in RA[14].

When our questionnaire was sent out, 161 cases undergoing combination therapy (71.5%) were still continuing, and 53 patients (23.5%) had stopped the combination because of adverse events. This withdrawal rate is high, but it should be borne in mind that the combinations were used to treat MTX-refractory patients with a long disease duration. Moreover, the DMARD and INF treatments were not always both withdrawn. INF was stopped because of adverse events in 40 patients (17.7%), a frequency similar to the rate of serious adverse events (17%) observed in the ATTRACT study[14].

Seventy-five patients (33.3%, 48.6/100 patient-yrs) had one or 2 adverse events, with no significant difference between the LEF/INF and AZA/INF groups and with no unexpected adverse events. As reported with INF therapy, infection was the main adverse event, occurring in 14 patients (5.7%)[15]. The frequency and the sites of the infections were similar to those observed in RA patients receiving traditional therapies[16]. Reactions related to the infusions were observed in 12 patients (5.3%). The frequency of such reactions was compatible with that described in the infliximab summary of product characteristics (up to 8% during the first infusions)[17]. The frequencies of cytopenia (5.8%), hepatotoxicity (5.8%), and skin reactions (4%) were similar to those reported with DMARD monotherapy[18]. Hepatotoxicity and skin reactions have previously been observed in about 10% of RA patients treated with LEF. Cytopenia has also been reported during both LEF and AZA therapy[2,18]. Peripheral neuropathy was observed in one of our patients, and has also been reported with LEF monotherapy[19]. Our results showed an acceptable efficacy/tolerability ratio: only 10 patients stopped the combi-

nation therapy for inefficacy, and tolerability was graded by physicians as very good or good in 77.3% of the patients.

The efficacy and the safety of the INF/LEF combination have recently been analyzed in small studies, with controversial results[9-13]. The first report involved 20 patients with active RA studied prospectively[9]. LEF treatment was started after washout of all other DMARD in 18 patients and INF was added 2 weeks later. All the patients had adverse events, including a high frequency of cutaneous reactions (70%). Rash and vasculitis were also reported among 40 patients prospectively treated with INF/LEF[10]. Although the efficacy of the combination was good, these studies suggested that the concomitant use of LEF and INF increases the risk of adverse events. In contrast, no increase in the frequency of adverse events was observed in another prospective study of INF/LEF combination therapy in 72 patients with LEF-refractory RA[11]. Good tolerability has been reported in 2 other studies[12,13]. In 88 RA patients treated with the LEF/INF combination and analyzed retrospectively[12], adverse events were observed in 34% of cases, a frequency similar to that observed in our study. No clear explanation is evident for the discrepancies between these studies. In some predisposed patients, the LEF/INF combination could be associated with immune-mediated adverse events, with the appearance of autoantibodies, as observed by Bingham, *et al*[10]. However, in 88 patients with RA studied by Hansen, *et al*[12], as in the 225 patients analyzed retrospectively in our study, no case of cutaneous vasculitis was observed. We also found that adverse events tended to be more frequent when LEF was introduced concomitantly with or after INF. These results are consistent with a report that adverse events from LEF were more frequent at the outset of treatment[20]. The simultaneous introduction of LEF and INF therapy might contribute to the appearance of intolerance reactions.

There are no published data on the use of AZA in combination with INF in patients with rheumatic diseases. However, the safety of the INF/AZA combination is well established in patients with Crohn's disease, in which responses are more long-lasting when INF is used with immunosuppressive agents[4,21].

Overall, our retrospective study on routine use of infliximab combined with leflunomide or azathioprine in 225 patients with RA suggests no increase in the frequency of adverse effects relative to the INF/MTX combination. Infliximab combination with a DMARD such as leflunomide or azathioprine could be an alternative for patients who do not qualify for methotrexate therapy.

ACKNOWLEDGMENT

We thank members of the Club Rhumatismes et Inflammmation for their active participation in this study.

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