

Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis

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ABSTRACT

Objective. To analyse the safety of leflunomide plus infliximab combination therapy, in adult rheumatoid arthritis (RA) patients.

Patients. A retrospective study of 17 adult patients with active RA (DAS 28 = 5.94 ± 0.88 at baseline) who were treated with a combination of leflunomide plus infliximab after failure of treatment with other DMARDs. 13 patients were treated for a minimum of 3 months with leflunomide without toxicity before beginning infliximab. Treatment was begun simultaneously with both drugs in 4 patients. Side effects (clinical and biological) and efficacy (DAS 28) were evaluated at each infliximab infusion (3 mg/kg at week 0, 2, 6 and then every 8 weeks).

Results. Thirteen patients experienced 20 types of side effects and 8 of them stopped the combination therapy. The causes of discontinuation were congestive heart failure (1 case), hypertension with thoracic pain (2 cases), eczematous skin patches (2 cases) and neutropenia (3 cases). No death was registered. Nine RA patients continued the therapy with a median follow-up of 22 weeks. Only 4 of them experienced no side effects.

Eight patients were positive for antinuclear antibodies (ANA) and 1 for double-stranded DNA (dsDNA) antibodies at study entry. After treatment, 13 and 5 patients tested positive respectively for ANAs and dsDNA antibodies. There was no relationship between discontinuation and ANA/dsDNA positivity.

Conclusion. In this cohort, adverse events were not very different from those seen in patients on either treatment alone and the combination of leflunomide plus infliximab did not appear to be as badly tolerated as described in a previous study.

Introduction

With the introduction of biological therapies for the treatment of rheumatoid arthritis (RA), the association of infliximab with methotrexate is now widely used. Efficacy and a prolonged duration of response are the main reasons for this combination therapy (1, 2). It has been demonstrated that add-

ing methotrexate reduced the formation of anti-idiotypic antibodies that may develop during treatment with a chimeric monoclonal antibody such as infliximab (1,3). In some cases these antibodies have been shown to neutralize the biological effectiveness of a therapeutic antibody (4), but the potential immunogenicity of chronic infliximab treatment remains a subject of investigation, and thus far has not been clearly shown to impact clinical efficacy in a significant way (5).

Because some patients cannot tolerate MTX, leflunomide has been proposed as an alternative in the combination therapy and the association leflunomide plus infliximab could provide a synergistic effect (6). However, Kiely and colleagues (7) studied the safety and efficacy of infliximab plus leflunomide in 20 patients and concluded that, although highly efficacious, the applicability of this combination may be limited because of common, and in some cases, severe adverse events. A similar observation has been reported in patients who cannot tolerate or in whom MTX was ineffective or contraindicated (8). A frequent increase in titres of antinuclear antibodies (ANA) and dsDNA antibodies has also been shown, suggesting that this combination therapy may have an effect on their production (9).

In the present work, we described our experience with 17 RA patients treated with the combination leflunomide plus infliximab, including a discussion of the adverse events and efficacy.

Patients

Seventeen adult patients (10 males; 7 females) with active RA (DAS 28 > 3.2) treated with a combination of leflunomide plus infliximab were retrospectively studied. Their median age was 57.6 years (range 30-80) at the time of the first infusion of infliximab. The median duration of RA was 144.7 months. At the beginning of the study, ANA were positive in 8 patients and dsDNA antibodies were positive in one of them. Thirteen tested positive for rheumatoid factor (RF) and 11 for anti-keratin antibodies (AKA). All patients had been previously treated with other

DMARDs (median = 4.8 different drugs, range 2 to 7) that were stopped because of inefficacy or adverse events.

Fifteen patients were taking oral prednisolone (median dose 12.6 mg/daily) at the beginning of the study protocol. Thirteen patients were treated with leflunomide (100 mg/daily for 3 days, and then 20 mg/day orally) for at least 3 months without toxicity before adding infliximab. Four patients started both drugs simultaneously. All patients received infliximab at the dose of 3 mg/kg intravenously, and infusions were repeated at 2, 6 and then every 8 weeks. At each visit side effects (clinical and biological) and efficacy (DAS 28) were evaluated.

Results

Thirteen patients experienced twenty different types of adverse events (Table I). Skin reactions included eczematous patches in 3 cases and pruritic rash in 2

cases. Three non-severe infections were observed: cystitis, respiratory infection and sinusitis. All resolved after oral antibiotic therapy. In 8 patients adverse events led to discontinuation of treatment. Causes of discontinuation were cardiac failure in one patient after the first infusion of infliximab, toxiderma in 2 patients (one after the second, and the other after the fourth infusion), hypertension and thoracic pain in 2 patients (at the second and sixth infusions) and neutropenia (neutrophil polynuclears $< 2,000/\text{mm}^3$) in 3 cases, two after the third and one after the fourth infusion. No death was registered and all of the adverse events reversed after discontinuation. Nine patients continued the treatment with a median follow-up of 22 weeks. Four patients experienced no side effects.

After treatment, 13 of 16 patients tested positive for ANA, and 5 for dsDNA autoantibodies. ANA became positive

quite rapidly, after 1 infusion in one patient and after 2 infusions in 4 patients. Three of the 9 patients who initially tested positive for RF became negative and the other 6 showed a decrease in the titres. The antikeratin antibodies titres, detected by immunoblotting and immunofluorescence, remained stable. Efficacy was evaluated according to the DAS 28 response at each perfusion of infliximab. Patients were grouped as good, median or bad responders, using the EULAR criteria (Table II). The mean DAS score was 5.94 ± 0.88 before treatment, 4.34 ± 1.25 at the end of our follow-up. Patients were grouped in Table II according to their outcome as good ($n=1$), moderate ($n=10$) or bad responders ($n=5$). There was no relationship between the response and adverse events, or between adverse events and ANA or dsDNA antibody positivity.

Discussion

In this retrospective study, leflunomide plus infliximab combination treatment for active RA was associated with a high number of adverse events: 20 in 17 patients. These side effects were serious enough to justify an early stoppage of the treatment in 8 patients, which was followed by a total recovery in all cases. Adverse events observed in 5 other patients were benign and compatible with the continuation of treatment.

The most frequent events observed in our patients were skin reactions (35.2%). In previous studies reporting on the safety of leflunomide, the frequency of adverse cutaneous events was lower, between 7.4% and 18.9% (10-13). However, we did not confirm the very high incidence of skin reactions (70%) reported in the only currently published work evaluating the same association (7). Moderate alopecia was observed in only one of our patients, in agreement with the incidence of 8-16.6% reported in the literature (11-13).

Hypertension was more frequently found in our cohort than in studies with each drug alone (2,10, 11), but it was mild and disappeared in all cases (after the discontinuation of therapy in 2 cases). Non-severe infections were ob-

Table I. Description, number of adverse events and cause of discontinuation observed in a cohort of 17 patients treated for active RA with the combination of leflunomide plus infliximab.

Type of adverse events	Number of observed adverse events	Number of discontinuations
Heart failure	1	1
Hypertension with thoracic pain	3	2
Eczematous patches	2	2
Rash	4	0
Alopecia	1	0
Non-severe infection	3	0
Elevated liver enzymes	2	0
Neutropenia	3	3
Paresthesias	1	0

Table II. Efficacy and relationship between efficacy, adverse events and antibody positivity observed in a cohort of 17 patients treated for active RA with the combination leflunomide plus infliximab. Efficacy has been assessed according to variations of the Disease Activity Score and using EULAR criteria.

	Patients with adverse events (N)	Patients with ANA positivity (N)	Patients with dsDNA positivity (N)
Good response	1	1	0
Moderate response	10	7	4
No response	5	4	1
Non-assessable response	1	1	-

In one patient treatment was stopped after the first injection because of heart failure and efficacy was not assessable.

served in only 3 patients (17.6%). In previous studies with infliximab, alone or in association with leflunomide, non-severe infections were more frequently reported (2,7).

The incidence of elevated liver enzymes (2 to 3 times the upper limit of normal) was approximately the same as shown in other studies. It is worth noting that 3 cases of neutropenia, which is not frequently found in treatment with each drug alone, were also registered in this small cohort. In each case neutropenia disappeared after stopping leflunomide.

ANA and dsDNA titres have been described to rise with infliximab therapy (2,14,15), and RFs have been described to decrease (2,15). Previous studies of the association leflunomide plus infliximab also showed an increase in ANA and dsDNA titres (7,9). Our study confirms these results and also shows that there is a significant decrease in RFs titres, whereas AKA titres remain stable.

In terms of efficacy, the mean DAS score decreased with the treatment and the rate of good or moderate responders (68%) was in agreement with the response observed with MTX plus infliximab. We did not find any relationship between the response and adverse events or between adverse events and ANA or dsDNA antibody positivity.

In conclusion, the association lefluno-

mid plus infliximab may offer an alternative to the classical association methotrexate plus infliximab. The incidence of adverse events in our series was not as high as in previous reports (especially skin reactions). Further studies are necessary to confirm the place of leflunomide in association with infliximab for active RA.

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