Letters to the Editor

Effectiveness and safety of infliximab combined with leflunomide in chronic polyarthritis

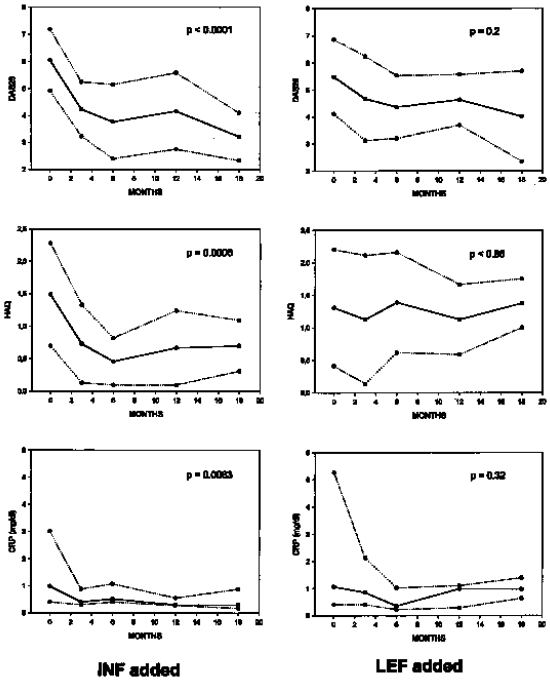

Fig. 1. Evolution of DAS28, HAQ and CRPdepending on the agent added in patients treated with the combination of infliximab and leflunomide. Data are shown as the mean (continuous line) and standard deviation (dotted line) for continuous variables (DAS28, HAQ) and as the median (continuous line) and interquartilic range for non-parametric variable (CRP). **INF added**: patients on leflunomide who receive infliximab as the added agent. **LEF added**: patients on infliximab therapy who receive leflunomide as the second agent. **DAS28**: 4 variables disease activity score with 28 joint counts; **CRP**: C-reactive protein; **HAQ**: health assessment questionnaire.

Sirs,

We have read with interest the paper that Godinho *et al.* recently published in your journal (1). Other two articles have been previously published describing the use of combination therapy of leflunomide (LEF) and infliximab (INF) for rheumatoid arthritis (RA) (2, 3). The results of all these studies are controversial in some aspects. Here, we describe our experience with this combination, in order to provide further information about this topic.

Data from 45 patients who received concomitant INF+LEF from May 2000 to October 2002 in 5 Spanish hospitals were retrospectively obtained. INF administration in Spain is clinically protocolized and adverse events (AE) and disease activity parameters systematically recorded in each drug infusion.

INF was added to LEF in 28 patients (62.2%; INF added) and LEF to INF in the remaining 37.8% (17 patients; LEF added). In addition, 27 patients were also treated with concomitant MTX (18 patients in the INF added group and 9 in the LEF added group). No differences between groups were observed in demographic features or dose regimens at baseline.

The clinical response after a mean follow-up of 8.5± 6.4 months was analyzed by subgroups. As shown in Figure 1, a statistically significant decrease in DAS28 and HAQ scores and CRP levels was observed in the INF added group. However, in the LEF added group some variables improved without statistical significance from baseline, probably because in most of those patients LEF was added to achieve a greater improvement without increasing the INF dose or decreasing the INF infusion interval. In this regard, DAS28 and HAQ were significantly reduced independently of concomitant MTX. However, although the initial INF dose was similar independently of concomitant MTX (3.5±0.7 vs 3.6±0.5 mg/ kg), at 6 months follow-up the INF dose was lower in the group with concomitant MTX than in patients without this drug (3.9 ± 0.8 vs 4.5 ± 0.7 mg/kg respectively; p = 0.022). The total exposure to the combination was 385 months and the discontinuation rate was 0.03 patients/month (9 patients due to AE and 3 to inefficacy). Withdrawal mainly occurred within the first 6 months. Our therapy survival data (73.3% at 18 months) are much higher than that previously reported by Kiely's group (2), probably because in our study both drugs were not started at the same time and the LEF loading dose was never prescribed.

Two patients belonging to the LEF added group died; neither of them was on concomitant MTX and both suffered severe long-term RA and several comorbidities. Patient 1 died due to septic endocarditis involving a previously damaged rheumatic valve, and patient 2 as a consequence of bronchiolitis obliterans organizing pneumonia complicated by cardiogenic shock. The mortality rate (4.4%) was clearly higher than that in clinical trials of INF (4). However, the patients included in clinical trials usually have fewer comorbidities than patients treated in daily clinical practice.

In addition, 64 AE were reported in 29 patients during the follow-up. Twenty-three infections were reported in 16 patients, only 6 of them were considered severe (intravenous treatment, hospitalization or sequelae). Eleven infusion-related reactions were reported in 6 patients. An increase in liver enzymes was observed in 3 patients with concomitant MTX (11%) and in the other 3 patients without MTX (16%). Four patients showed mild skin reactions.

In summary, our results support the idea that patients who cannot tolerate MTX could be candidates for INF and LEF combination therapy. However, a strict selection of the patients to receive this combination should be performed and all means should be exercised to establish a thorough follow-up to detect infections early, especially in patients with comorbidities, who seem to be more susceptible to suffer serious AE.

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*The Infliximab and Leflunomide Study Group, in alphabetical order: Bascones Ilundain, Miriam. Hospital Gregorio Marañón, Madrid, Spain. Caro Fernández, Natividad. Hospital Gregorio Marañón, Madrid, Spain. Castillo Montalvo, Rosa del. Hospital Gregorio Marañón, Madrid, Spain. García-Vicuña, Rosario. Hospital Universitario de la Princesa, Madrid, Spain. Juan Mas, Antonio. Hospital Son Llatzer, Palma de Mallorca, Spain. Rivera Redondo, Javier. Instituto Provincial de Rehabilitación, Madrid, Spain. Tomero Muriel, Eva. Hospital General, Segovia, Spain.

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A.M. ORTIZ GARCÍA[1], *MD*
I. GONZÁLEZ-ÁLVARO[1], *MD, PhD*
R. ROSELLÓ PARDO[2], *MD*
L. CARMONA[3], *MD, PhD*
M.D. FÁBREGAS CANALES[2], *MD*
I. MONTEAGUDO SAEZ[4], *MD, PhD*
*on behalf of the Infliximab and Leflunomide Study Group**

[1]Rheumatology Dept., Hospital Universitario de la Princesa, Madrid; [2]Rheumatology Dept., Hospital General San Jorge, Huesca; [3]Research Unit, Sociedad Española de Reumatologia; [4]Rheumatology Dept., Hospital Gregorio Marañón, Madrid, Spain.

Address correspondence to: Ana M Ortiz Garcia, Servicio de Reumatología, Hospital Universitario de la Princesa, Cl Diego de Leon no. 62, 28006 Madrid, Spain.
E-mail: lanult©yahoo.es

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