Effectiveness and safety of leflunomide in the clinical practice. A different experience

Sirs,

It is true that prescription patterns, effectiveness and safety of a drug in clinical practice often differ from those expected from clinical trials. We read with interest the article of Martin *et al*. (1). The authors described the effectiveness and safety profile of leflunomide (LEF) in 116 patients (mean age 55 years, 70% women). At one year of follow-up, the discontinuation rate was 70% in the French cohort compared to 28-47% in clinical trials. In the postmarketing surveillance study published by Geborek *et al*. (2), the discontinuation rate was 78% after 20 months of follow-up which is also consistent with the results of the French study.

We would like to illustrate our experience which is more positive than that of these two studies. The characteristics of our patients are similar to those of the French cohort for the severity and duration of the disease, the use of concomitant drugs (NSAID, steroid) and the follow-up (Table I). We reviewed the records of 140 patients with rheumatoid arthritis treated with LEF from January 2000 to May 2004 in the Department of Rheumatology of the Gaetano Pini Institute of Milan, Italy.

The mean age was 59.6 ± 12.63 years (range 31–84). The M/F sex ratio was 0.16. The mean duration of the disease was 14.74 ± 10.32 years. The average number of prior disease modifyng antirheumatic drugs (DMARDs) treatment was 2.3 ± 1.08 (range 1–5). Concomitant prescriptions were corticosteroid (67.1%), with a daily dose equal to 10 mg of prednisone-equivalent in 2%, and NSAIDs (79.3%). Rheumatoid factor was positive in 82.8% of the patients.

Ninety-one patients (65%) were treated with LEF in monotherapy. 35% of the patients was being concomitantly treated with another DMARDs (methotrexate 12.1%, antimalarial 18.6%, gold salts 7.9%). There were no naive patients. 25 patients (17.9%) had previously received a 100 mg loading dose over 3 days; patients with combination therapy started LEF at 20 mg every other day for the first month and then 20 mg/day. In cases of minor side effects (diarrhoea, pruritus or rise of aminotransferases) the dosage of LEF was reduced. The mean daily dose of LEF was 15.92 mg ± 6.75. Mean duration of treatment with LEF was 16 ± 10.88 months.

The most frequent adverse events (AEs) were hypertension, diarrhoea, skin involvement and increased liver tests function. AEs were more frequent in patients treated with a loading dose (80% vs 46.1%). During the study period, treatment was stopped in 23 patients (16.4%): for lack of efficacy in 2.8% and for the occurence of an AE in 13.6%. At 30 months, the global discontinuation rate was 26% (Fig. 1) close to the data of clinical trials (28-47%) (3-5), the experience of a large national cohort study of veterans (6) (discontinuation rate of 42% after 33 months of follow-up) and also of the observational study of Alehata (55% after two years of follow-up) (7).

Table I. Differences in leflunomide use between clinical trials and clinical practice.

	Clinical trials (3-5) n = 482	French study (1) n = 116	Our cohort n = 140
Maximal duration of follow-up (mos.)	6 to 12	31	52
Mean age (years)	54 to 58.3	55.5	59.6
Women (%)	71 to 76	71	86.4
Rheumatoid arthritis duration (years)	3.7 to 7.6	10.2	14.74
Positive rheumatoid factor (%)	65 to 79	88	82.8
Prior treatment with DMARDs (%)	55 to 66	99	100
Average number of prior DMARDs	0.8 to 1.2	3.4	2.3
Naïve patients (%)	34 to 44	1	0
Loading dose (%)	**100**	**100**	**17.9**
Mean daily dose of leflunomide (mg)	**20**	**20**	**15.9**
Concomitant NSAIDs (%)	75 to 85	77.6	79.3
Concomitant corticosteroids (%)	29 to 54	83	67.1
Concomitant disease (%)			
Hypertension	21.4 to 25.7	35	-
Hypothyroidism	4.6 to 8.9	4.3	-
Lipid disorders	2.8 to 6	-	-
Diabetes mellitus	5.1 to 5.2	6	-
Reason for withdrawal			
Adverse event	14.3 to 22	32	12.9
Lack or loss of efficacy	7 to 17	38	2.8
Adverse events leading to withdrawal (%)			
Skin rash	10.8 to 12.4	17.7	2.9
Diarrhoea	22.2 to 33.5	12.6	2.1
Rise of aminotransferases	5.8 to 10.2	3.4	2.1
Arterial hypertension	8.9 to 11	3.4	2.9
Peripheral neuropathy or paresthesia	3.2 to 3.6	9.5	0
Haematologic alterations	0 to 1	?	1.4

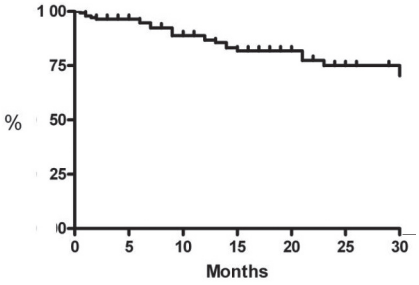

Fig. 1. Discontinuation of leflunomide in our cohort according to duration of treatment in months (time): Kaplan-Meier survival analysis.

Discrepancies between the French study and our study could reflect some differences in therapeutic management or in patient characteristics. In our cohort only 25 patients (17.9%) had previously received a loading dose. The dose of LEF was adjustable as occasion may require. Patients with combination therapy started LEF at half dose for the first month and then 20 mg/day. In cases of minor side effects, the dosage of LEF was reduced. Many patients did well with dosage of 20 mg 3 or 4 days a week.

As long as the above points are taken into consideration, many patients could continue the treatment with persistent advantage. In conclusion ,we confirm that LEF is an effective and relatively safe DMARD. To obtain the best results from this drug, it is important to adopt a to go low go slow treatment modality and modulate the dosage according to the effects and tolerability in the individual patients.

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