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The effectiveness of leflunomide in psoriatic arthritis

A. Asiri[1,2], A. Thavaneswaran[2], G. Kalman-Lamb[2], V. Chandran[2], D.D. Gladman[2]

[1]Aseer Central Hospital, King Khalid University, Abha, Saudi Arabia;
[2]Psoriatic Arthritis Program, Centre for Prognosis Studies in the Rheumatic Diseases, University Health Network, Toronto Western Hospital, Toronto, Ontario, Canada.

Alhussain Asiri, MD, FACP, FACR
Arane Thavaneswaran, MMath
Gideon Kalman-Lamb, BA
Vinod Chandran, MBBS, MD, DM, PhD
Dafna D. Gladman, MD, FRCPC

Please address correspondence to:
Dr Dafna D. Gladman,
Toronto Western Hospital,
399 Bathurst Street,
1E-410B Toronto,
Ontario M5T 2S8, Canada.
E-mail: dafna.gladman@utoronto.ca

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ABSTRACT

Objective. *This study aimed to evaluate the effectiveness and safety of leflunomide alone and in combination with methotrexate in the treatment of psoriatic arthritis (PsA).*

Methods. *Patients were followed at the University of Toronto PsA Clinic. PsA patients who received leflunomide alone or in combination with methotrexate were identified from the PsA clinic database. Effectiveness was defined by drug persistence, a ≥40% reduction in actively inflamed joints, a ≥40% reduction in swollen joint count, and PASI50 and PASI75 response following treatment with leflunomide. Descriptive statistics and logistic regression analyses with stepwise selection were used for data analysis.*

Results. *85 patients were identified. 43 patients (50.6%) were on leflunomide alone and 42 (49.4%) patients were on combined leflunomide and methotrexate therapy. 30 patients discontinued leflunomide mainly due to toxicity.*
Of the 55 patients who continued the drug, 38%, 48% and 56% achieved a ≥40% reduction of actively inflamed joint count at 3, 6 and 12 months, respectively. PASI50 was achieved by 27%, 28% and 38% at 3, 6 and 12 months, whereas PASI75 was achieved by 19% at 3 and 6 months and 32% at 12 months.
Longer duration of PsA and higher swollen joint count at baseline were predictive for improvement of the swollen joint count at 3 months. The use of concomitant MTX was predictive of achieving PASI50 at 12 months.

Conclusion. *Leflunomide led to improvement in almost 50% of the patients by 1 year. Those also taking methotrexate were more likely to achieve a PASI50 response.*

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting skin and joints (1) and it is a potentially disabling inflammatory condition that affects 5–30% of patients with psoriasis (2, 3). Pathophysiologically, PsA is characterised by the presence of activated T cells, particularly in joint fluids and synovial tissues (4, 5). T cell activation has also been implicated in psoriasis (6) and rheumatoid arthritis (RA) (7) suggesting a common pathway linking these disorders. Although recent advances in biologic therapies have improved the treatment options for patients with PsA, many do not respond to these therapies, or cannot afford these expensive medications (8). Effective treatment options for patients with PsA are limited. Most disease modifying anti-rheumatic drugs (DMARDs) used to treat PsA have been employed because of evidence supporting their use in RA; very few controlled studies have demonstrated their efficacy and safety in PsA (9). In a meta-analysis of PsA clinical studies, only high-dose parenteral methotrexate (MTX; 1–3 mg/kg every 10 days) (10) and sulfasalazine were found to be significantly more efficacious than placebo (11). These agents, as well as other treatment options such as low-dose oral MTX (15 mg/week), cyclosporine, and intramuscular gold, often fail to improve joint and skin symptoms or are poorly tolerated (12, 13).

Leflunomide is a DMARD that inhibits *de novo* pyrimidine synthesis. Because activated lymphocytes require a large pyrimidine pool, leflunomide preferentially inhibits T cell activation and proliferation (14) and thus has the potential to address underlying pathophysiologic events in RA, PsA, and psoriasis. Leflunomide has been approved for the treatment of RA in the United States, several countries of the European Union, and numerous other countries for several years (8). In patients with RA, controlled clinical trials have demonstrated that leflunomide reduces symptoms and radiographic progression (15-17). Follow-up studies indicate that safety and efficacy have been maintained for up to 5 years (18-20).

Short term efficacy and safety of leflunomide has been demonstrated in PsA and psoriasis in small open-label studies and case reports (21-23). In addition, the data from the Treatment of Psoriatic Arthritis Study (TOPAS), a multinational, double blind, randomised, placebo-controlled clinical trial examining the safety and efficacy of leflunomide in the treatment of PsA and psoriasis showed that it is an effec-

tive treatment for PsA and psoriasis, providing a safe and convenient alternative to current therapies in short term (9). In a "real life" study of leflunomide in a multinational European study it was demonstrated that the drug was effective over 24 weeks (24). However, the long-term effect and safety of leflunomide in clinical situations is not known. Our aim in this study was to evaluate the effectiveness of leflunomide alone and in combination with methotrexate in "real life" situation, as well as assess their adverse effects.

Patients and methods

Setting

An observational cohort study of patients with PsA was initiated at the University of Toronto in 1978. Patients have been followed prospectively according to a standard protocol at 6–12-month intervals (25). At each visit, symptoms, physical examination (including complete musculoskeletal examination and assessment of psoriasis severity), detailed medication history and laboratory findings were recorded. The data were entered and stored in a computerised database. Written consent was obtained according to the Declaration of Helsinki from all subjects. The study has been approved by the University Health Network Ethics Board. The majority of the patients (98%) fulfill CASPAR criteria for the classification of PsA (26).

Patient selection

Leflunomide became available in 2002. PsA patients who received leflunomide alone or in combination with methotrexate were identified from the PsA clinic database.

Clinical assessment

In each patient the number of actively inflamed (tender [of 68] and/or swollen joints [of 66]) was recorded as well as the Psoriasis Area Severity Index (PASI) score (27). Effectiveness was defined by: persistence on the medication, a ≥40% reduction in the total number of actively inflamed joints (AJC40), a ≥40% reduction in swollen joint count (SJC40), and a reduction in PASI score by 50% (PASI50) and 75% (PASI75) following treatment with leflunomide.

Statistical analysis

Descriptive statistics were used to determine the frequency (%) of patients who achieved the 4 outcomes (AJC40, SJC40, PASI50, PASI75) at 3, 6 and 12 months**.** Logistic regression with stepwise selection was also used to determine the baseline covariates associated with these outcomes at 3, 6 and 12 months. Covariates included sex, age, duration of PsA, active joint count, swollen joint count, clinically damaged joint count, PASI, and MTX use.

Results

Eighty five patients who were taking leflunomide were identified in our cohort and their demographics are presented in Table I. Of these, 43 patients (50.6%) were on leflunomide alone and 42 (49.4%) patients were on leflunomide in combination with methotrexate (MTX). There were 38 females and 47 males with a mean age of 51.6 (12.6) and mean disease duration of 12.3 (9.1). The mean number (sd) of actively inflamed joints count was 16 (12.9), swollen joint count was 5.4 (5.8), damaged joint count was 12.3 (13.0) and the mean PASI score was 4.7 (6.5).

Thirty patients discontinued leflunomide, 16 in the leflunomide alone group and 14 in those taking leflunomide and MTX. The main reason for discontinuing the drug was toxicity, including diarrhea, alopecia, and renal toxicity. For patients treated with leflunomide only, 8 (15.1%) had side effects and for those treated with leflunomide and MTX, 12 (25.0%) had side effects at some point over their course of treatment. Of the 55 (64.7%) patients who continued the drug, 38% achieved a ≥40% reduction of actively inflamed joint count at 3 months, 48% at 6 months and 56% at 12 months. PASI50 was achieved by 27%, 28% and 38% at 3, 6 and 12 months, whereas PASI75 was achieved by 19% at 3 and 6 months and 32% at 12 months. Similar numbers were observed among those treated with leflunomide alone and those treated with leflunomide and methotrexate. These results are based on the patients who were actually taking the drug at each time point. However, if we calculate the response based on intention to treat, the response rate would be much lower. No predictors were identified for the improvement in actively inflamed joint count. However, duration of PsA (OR 1.09 95% CI 1.00, 1.18, p=0.03) and the number of swollen joints (OR 1.35, 95% CI 1.00, 1.83, p=0.003) at baseline were predictive for improvement of the swollen joint count at 3 months. The number of swollen joints at baseline was also predictive for improvement at 12 months (OR 2.01 95% CI 1.23, 3.27, p=0.005). The use of concomitant MTX was predictive for achieving a PASI50 (OR 6.19 95% CI 0.20, 31.97) at 12 months.

Table I. Demographics and clinical characteristics of study population.

Variable	Mean (SD) or Frequency (%)
Sex (Male / Female)	47 (55.3%)/ 38 (44.7%)
Age	51.6 (12.6)
Age at diagnosis of Ps	30.6 (14.1)
Age at diagnosis of PsA	39.2 (13.8)
Duration of Ps	20.9 (12.9)
Duration of PsA	12.3 (9.1)
Active joint Count	16.0 (12.9)
Swollen Joints	56 (65.9%)
Swollen Joint Count	5.4 (5.8)
Damaged Joints	51 (60.7%)
Damage Joint Count	12.3 (13.0)
PASI	4.7 (6.5)
Use of Methotrexate	42 (49.4%)
Prior DMARDs used	
Gold	16 (18.0%)
Azathioprine	14 (16.5%)
Sulfasalazine	42 (49.4%)
Cyclosporine	5 (5.9%)
Oral steroids	21 (24.7%)
Antimalarials	31 (36.8%)
Retinoids	5 (5.9%)
Other DMARD	7 (8.2%)

Discussion

In this study it was found that leflunomide eventually led to ≥40% reduction in tender and swollen joint counts in almost 50% of the patients by 1 year which is consistent with the results of the TOPAS where 56 of 95 leflunomide-treated patient (58.9%; 95% confidence interval [95% CI]48.4–68.9) were classified as responders according to the psoriatic arthritis response criteria (PsARC) (9).

Our patients were similar to those reported by Behrens *et al*. (24) in terms of age and gender, but our patients had a longer disease duration at start of the study. Our patients also had a lower number of tender and swollen joints at baseline, but this is possibly related to the fact that we used the 68/66 joint count whereas in the study by Behrens they used a 78/76 joint count. Berhens *et al*. used the PsARC response as the primary end point. We used the joint count and PASI score as those are recorded in our clinic on a regular basis at each visit, and the patient reported outcomes are done only yearly. Nonetheless, both studies demonstrated a response to leflunomide. Our study further demonstrates that there is almost a 65% retention of the drug at 12 months. The Behrens study also demonstrated a positive effect on other manifestations of PsA including dactylitis, pain and fatigue.

We found that while MTX did not modify the response of the arthritis, it did help the response of the skin. Patients taking MTX in combination with leflunomide were more likely to achieve a PASI50 response than patients taking leflunomide alone.

Behrens *et al*. reported that 12% of their patients discontinued leflunomide in the 24 week period. The discontinuation rate was higher in our study where 35% of the patients prescribed leflunomide discontinued it, while the remainder continued on it for at least 1 year. The main reason for discontinuation in our study were adverse events, including diarrhoea, alopecia, and renal toxicity, consistent with those reported in previous studies (28-30). Importantly the addition of MTX did not add significantly to the toxicity of leflunomide.

Thus leflunomide is effective for the treatment of PsA and psoriasis and is reasonably well tolerated over 1 year of treatment in clinical practice. Whether leflunomide has any beneficial effect for preventing joint damage remains to be determined. There is interest in developing treat to target strategies in psoriatic arthritis (31). Psoriatic arthritis leads to a significant economic burden, and anti-TNF agents costs contribute to this burden (32). Leflunomide may therefore provide an option towards achieving a therapeutic target while reducing the cost of treating psoriatic arthritis.

Table II. Change in features of disease activity over time.

Outcome	n.	3 months*	n.	6 months*	n.	12 months*
40% reduction in AJC 95% CI	55	21 (38.2%) 25.4%, 51.0%	48	23 (47.9%) 33.8%, 62.0%	36	20 (55.6%) 39.4%, 71.8%
40% reduction in SJC 95% CI	55	14 (25.5%) 14.0%, 37.0%	48	15 (31.3%) 18.2%, 44.4%	36	15 (41.7%) 25.6%, 57.8%
50% reduction in PASI 95% CI	52	14 (26.9%) 14.9%, 39.0%	43	12 (27.9%) 14.5%, 41.3%	34	13 (38.2%) 21.9%, 54.5%
75% reduction in PASI 95% CI	52	10 (19.2%) 8.5%, 29.9%	43	8 (18.6%) 7.0%, 30.2%	34	11 (32.4%) 16.7%, 48.1%

Number (%) (95% confidence interval. The number of patients changes since between the various time points patients discontinued drug for side effects or personal preference.

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