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Original Article

Efficacy and safety of leflunomide in psoriatic arthritis

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Abstract

Objective To compare the effectiveness and safety of leflunomide with methotrexate (MTX) in the treatment of psoriatic arthritis.

Methods An open, randomized clinical trial was conducted in 32 patients of psoriatic arthritis at the department of Dermatology and Venereology and Rheumatology wing of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from June 2002 to December 2003. 17 patients of leflunomide group were treated with oral leflunomide l00 mg for first three days followed by 20 mg daily. 15 patients of MTX group were treated with methotrexate 10 mg weekly. Both groups were allowed to take ibuprofen, maximum 1400 mg daily. For both groups hematological and biochemical tests were done at baseline and at every follow-up. All patients were assessed clinically for articular features, psoriasis area and severity index (PASI) for effectiveness and for side effects of drugs was listed for safety measure.

Results Sixteen patients of leflunomide group and 14 of MTX group completed 24 weeks follow-up. Male: female ratio was 14:2, in leflunomide and 13:1 in MTX group. Significant improvement was observed in tender joint count, swollen joint count, joint tenderness index, NSAIDs score and PASI score in both groups. Adverse effects in both groups were tolerable and did not require any withdrawal or dose reduction. Asthenia, alopecia, nausea and vomiting were common side effects noticed by patients but overall there was no significant difference in between two groups.

Conclusion Leflunomide appears to be as effective and safe as methotrexate in psoriatic arthritis.

Key words
Psoriasis, psoriatic arthritis, leflunomide, methotrexate.

Introduction

Psoriatic arthritis (PsA) is a potentially disabling inflammatory condition that affects 5-30% of patients with psoriasis.[1] It is associated with significant disability, increased mortality, and reduced quality of life.[2] Pathophysiologically, PsA is characterized by the presence of activated T cells, particularly in joint fluids and synovial tissues. T cell activation has also been implicated in psoriasis and rheumatoid arthritis (RA), suggesting a common pathway linking these disorders.[3,4] Effective treatment options for patients with PsA survey found that 25% of patients are dissatisfied with the treatment they receive for PsA.[4] A number of disease modifying antirheumatic drugs (DMARDs) used to treat rheumatoid arthritis have been employed

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for PsA. Methotrexate (MTX), sulfasalazine, cyclosporin, intramuscular gold and few other DMADRs were tried for PsA with variable outcome and tolerability.[5] High-dose parenteral MTX (1-3 mg/kg every 10 days) and sulfasalazine were found to be more effective than placebo.[6]

Recently biologics are the main option of treatment in developed world. Infliximab and etanercept, tumor necrosis factor (TNF) inhibitors, have demonstrated significant efficacy in the treatment of PsA and psoriasis.[7,8] Another biologic agent, alefacept, a lymphocyte function-associated antigen 3 fusion protein that blocks T cell activation, is available for the treatment of psoriasis and may also be useful in PsA.[9]

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 and thus has the potential to address underlying pathophysiologic events in RA, PsA, and psoriasis.[10] Leflunomide has been approved for the treatment of RA in the US, countries of the European Union, and numerous other countries for several years. In patients with RA, controlled clinical trials have demonstrated that leflunomide reduces symptoms and radiographic progression.[11] Follow-up studies indicate that safety and efficacy have been maintained for up to 5 years.[12]

In developing countries like Bangladesh, majority of the people are of poor socioeconomic condition. Available, effective and cheap agents are essential for managing our patients. Both, leflunomide and MTX, are such agents. Leflunomide can be an effective alternative in the management of active psoriasis and psoriatic arthritis patients. To our knowledge no such study was undertaken to see the efficacy and safety of leflunomide compared with MTX in our active psoriasis and psoriatic arthritis patients.

Methods

This open, randomized clinical trial was carried out with 32 cases of psoriatic arthritis at the Department of Dermatology and Venereology and Rheumatology wing of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from June 2002 to December 2003. Randomization was done with using a random number table. Sample size was calculated with the following formula $n=Z^2PQ/d^2$. Out of them 17 were in the leflunomide group and 15 in the MTX group. 32 patients of psoriatic arthritis were taken consecutively and grouped into two by card test. Patient fulfilling the following criteria was selected for the study, a) active psoriatic arthritis (≥3 swollen and 3 tender joints); b) age ≥18 years; c) both sexes (females only if they agreed to practice appropriate contraceptive measure); d) patients should have serum ALT, serum creatinine, WBC count and platelet count within defined range: serum ALT: 0-40 U/L, serum creatinine: <130 μmol/L, leucocyte count: $\geq 3.5\times10^9$/L, platelet count: $\geq 150\times10^9$/L. Exclusion criteria were: a) axial joint involvement; b) compromised immune function including bone marrow dysplasia; c) severe uncontrolled infection; d) concurrent vaccination with live vaccine; and e) patients who received retinoids, PUVA, cyclosporin within last two weeks. Patients of leflunomide group were treated with leflunomide 100 mg daily orally for three days followed by 20mg daily for 6 months and MTX group treated with methotrexate 10 mg orally in two divided doses (12 hours apart) weekly for 6 months. Both

groups were allowed to take ibuprofen orally with a maximum allocated dose 1400 mg. A score of 10 was assigned to a daily dose of 1400 mg. A patient was withdrawn from the study; a) if WBC count $<3.5\times10^9$/L or platelet count $<150\times10^9$/L; b) serum ALT exceeded three times of the upper limit of normal in single measurement; c) serum creatinine >160 μmol/L. Clinical assessment was done at baseline, after first month and then monthly for 5 months. Laboratory assessment was done at baseline, after 2 weeks, end of first month and then monthly for 5 months. Clinical assessment covered detail medical history, physical examination, measures of disease activity (arthritis and psoriasis).

Monitoring of adverse effects was done after two weeks, at the end of first month and then monthly by query of symptoms of different systems, physical examination and hematological and biochemical laboratory tests, NSAID score and different measures of arthritis disease activity were assessed at one month and then monthly.

The measures of arthritis disease activity

1. Tender joint count (68 joints)
2. Joint tenderness index (0=none, l= describe pain, 2= grimace, 3= withdrawal)
3. Swollen joint count (66 joints)
4. Joint swelling index (0= none, l= mild (detectable synovial thickening with normal joint contour), 2= moderate (loss of normal joint contour), 3= severe (bulging synovial proliferation with cystic characteristics).
5. Duration of morning stiffness until maximum improvement (0= absent, 1= up to 30 minutes, 2= 30-60 minutes, 3= more than 60 minutes).
6. Patient assessment of pain (visual analogue scale - graded on a scale of 1-10 cm).
7. Physician's global assessment of disease activity. On a scale of 1 to 5 (1= asymptomatic, 2= mild, 3= moderate, 4= severe, 5= very severe).
8. Patient's global assessment of disease activity, on a scale of 1 to 5.
9. Health assessment questionnaire score.
10. NSAID score.
11. Psoriasis area and severity index (PASI)

The primary endpoint with respect to efficacy in psoriatic arthritis was the proportion of patients who met the psoriatic arthritis response criteria at 6 months.[13] A secondary endpoint for the assessment of psoriatic arthritis was the proportion of patients meeting the American College of Rheumatology (ACR) preliminary criteria for improvement as ACR 20, ACR 50 and ACR 70.[14]

Results

Out of total 32 patients, one patient from each group was excluded from analysis due to lack of follow-up. Sixteen in the leflunomide group and 14 in the MTX group completed 24 weeks follow-up.

Table 1 shows the comparative baseline characteristics of patients about personal information, duration, activity and laboratory investigations and **Table 2** reflects the outcome of two groups after 24 weeks of therapy. Within each group, there was significant improvement of disease activity; however, the outcome of disease activity and laboratory reports between two groups was not different.

Adverse effects of drugs are listed with percent distribution in **Table 3**. Asthenia and alopecia

Table 1 Baseline characteristics of patients (n=30).

Characteristics	*Leflunomide group (n=16)*	*Methotrexate group (n=14)*	p^a
Age (Years)	41.81±13.43	37.93±9.34	0.372
Sex (Male/Female)	14/2	13/1	0.552
Duration of psoriasis(Years)	7.56±5.29	7.00 ±4.24	0.753
Duration of arthritis(Years)	3.22±2.43	2.82 ±2.22	0.645
Tender joint count	7.75±1.81	9.64 ±2.34	0.019*
Swollen joint count	5.24±1.48	6.36 ±1.34	0.042*
Joint tenderness index	11.50±3.08	14.64 ±3.23	0.011*
Joint swelling index	6.72±3.19	8.29 ±2.97	0.186
Morning stiffness score	2.06±0.57	2.07 ±0.62	0.968
Patient's assessment of joint pain	5.06±0.68	4.93 ±0.27	0.496
Patient's global assessment of disease activity	3.06±0.25	3.00 ±0.00	0.359
Psoriasis area and severity index (PASI)	9.75±5.49	7.67 ±3.71	0.242†
NSAID score	6.96±1.95	8.88 ±0.61	0.001*
HAQ score	0.88±0.20	0.87 ±0.16	0.811
Physician's global assessment of disease activity	3.06±0.25	3.00 ±0.00	0.359
ESR (mm/1st Hour)	65.44±18.95	66.36 ±13.28	0.880
Hemoglobin (gm/dl)	12.05±1.14	12.17 ±1.31	0.783
Platelet count (10^9/L)	277.25±78.94	248.93 ±42.80	0.242†
Serum ALT (U/L)	26.88±8.28	28.93 ±7.83	0.493
Serum creatinine (µmol/L)	98.19±14.90	99.29 ±10.31	0.819†

*Variables are expressed as mean ± SD, Sex expressed in ratio, P^a = p value obtained from ANOVA test, † =p value obtained from Mann- Whitney U-test, *Significant*

Table 2 Comparison of outcome of treatment.

Variables	*Leflunomide group (n=16)*	*Methotrexate group (n=14)*	p^a
Tender joint count	1.0± 0.97	1.33±0.96	1
Swollen joint count	0.50±0.63	0.64±0.74	0.574
Joint tenderness index	1.00±0.97	1.00±0.96	1
Joint swelling index	0.50± 0.63	0.64±0.74	0.574
Morning stiffness score	0.50±0.52	0.50±0.52	1
Patient's assessment of joint pain	1.00±1.03	0.93±0.83	0.886†
Patient's global assessment of disease activity	2.00±0.00	2.00±0.00	1
Psoriasis area and severity index (PASI)	2.69±1.60	2.68±1.67	0.998
NSAIDS score	1.51±1.22	2.14 ±1.34	0.192
Physician's global assessment of disease activity	2.00±0.00	2.00±0.00	1
HAQ score	23.25±7.05	26.71±5.44	0.147†
ESR (mm/Hr)	23.25±7.05	26.71±5.44	0.147
Hemoglobin (gm/dl)	11.81±2.34	12.34 ±1.06	0.442
Total count of WBC	7.73±1.56	8.21±1.24	0.361
Platelet count	232.69±53.35	236.00±29.75	0.838
Serum ALT (U/L)	31.63±6.26	31.07±5.64	0.802
Serum creatinine (µmol/L)	102.56±10.83	103.86±11.80	0.756

p^a =p value obtained from ANOVA test., †Mann Whitney U test

was more in the leflunomide group but nausea and vomiting in MTX group (p>0.05).

Discussion

Disease modifying antirheumatic drugs such as sulfasalazine, gold, penicillamine, azathioprine, MTX, cyclosporine etc. are well studied in psoriatic arthritis. Safety, efficacy, and cost of these agents are erratic thus keeping dermatologists and rheumatologists in search of new, safe, as well as cost-effective treatment

Table 3 Psoriatic arthritis endpoints study.

	Group		*Difference*	p^a
	Leflunomide (n=16)	*MTX (n=14)*		
Primary endpoint-achieved at 6 months				
PsARC	16 (100.00%)	14 (100.00%)	0%	
Secondary endpoint- achieved at 6 months				
ACR20	16 (100.00%)	14 (100.00%)	0%	
ACR50	13 (81.30%)	12 (85.70%)	4.40%	0.342
ACR70	05 (31.30%)	02 (14.20%)	17.10%	0.004*

[a]*Chi-Square Test, *Significant*, PsARC=Psoriatic Arthritis Response Criteria.

Table 4 PASI improvement at 6 months.

PASI (Improvement)	*Group*		*Difference*	p^a
	Leflunomide (n=16)	*MTX(n=14)*		
25%	16 (100.00%)	14 (100.00%)	0%	
50%	11 (86.80%)	09 (64.30%)	4.50%	0.455
75%	06 (31.70%)	02 (28.60%)	3.10%	0.646

p^a *=p value achieved from Chi- Square Test,* PASI=Psoriasis area and severity index.

Table 5 Adverse effects of drugs.

Adverse effects	*Leflunomide group (n=16) N (%)*	*Methotrexate group (n=14) N (%)*	p^a
Dyspepsia	9 (56.2)	9(64.30)	0.312
Asthenia	12 (75.0)	0 (0)	0.001
Alopecia	2 (12.5)	0 (0)	0.001
Nausea	1 (6.2)	11 (78.6)	0.001
Vomiting	0 (0)	5 (35.7)	0.001
Headache	1 (6.2)	1 (7.1)	0.774
Dizziness	0 (0)	1 (7.1)	0.007

p^a *=p value obtained from Chi-squire test.*

option. Recent discovery of targeted molecules such as infliximab, etanercept etc. has opened new avenues and hope in the management of this illness but cost remained big barrier of their use in 3rd world. Statistically significant improvement was observed in leflunomide group in all clinical parameters i.e. tender joint count, swollen joint count, joint swelling index, joint tenderness index, morning stiffness score, patient's assessment of joint pain, patient's global assessment of disease activity, physician's global assessment of disease activity, health assessment questionnaire score and ESR. The results were consistent with the findings of other study with leflunomide in rheumatoid arthritis.[15] In MTX group statistically significant improvement was noted in all clinical parameters including PASI and ESR. The results were also consistent with the results of other studies.[16,17] All patients of two groups achieved the primary end point but for secondary end point there was significant difference in ACR 70 in favour of leflunomide.

Common adverse effects were asthenia (75%) and dyspepsia (56.2%) in leflunomide group and other side effects were alopecia (12.5%), nausea (6.2%) and headache (6.2%). Similar pattern of adverse effects were reported by Schiff et al. in rheumatoid arthritis with leflunomide.[15]

The most common adverse effects in MTX group were nausea (78.6%) and dyspepsia (64.3%) and other side effects were vomiting (35.7%), headache (7.1%) and dizziness (7.1%).

Dyspepsia, nausea, headache were observed in both groups. Statistically significant differences

were observed in adverse events of two groups except dyspepsia and headache (p>0.05). Adverse events were mild and improved with time that required no withdrawal or dose reduction of drugs.

Conclusion

Oral leflunomide is an effective and safe drug for psoriatic arthritis when compared with methotrexate. It has some adverse effects but they were well-tolerable and self-manageable. Chances of nausea and vomiting are less in leflunomide. In the light of our study, we suggest leflunomide as a treatment option for psoriatic arthritis before trying any other conventional hazardous drug.

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