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Original Article

Efficacy and safety of leflunomide in the treatment of plaque type psoriasis

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Abstract

Background Psoriasis is universal in occurrence, representing a lifelong burden for affected patients. Various modalities of treatment are available and new drugs are coming up but toxicity and cost of the drug is very important. Leflunomide is an immunomodulatory and anti- inflammatory drug effective in chronic plaque type Psoriasis.

Objectives To assess the efficacy and safety of leflunomide in the treatment of chronic plaque type psoriasis.

Patients and methods The prospective controlled randomized study was carried out in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2005 to June 2006 over a period of one and half years. Forty patients with moderate to severe plaque-type psoriasis patients were treated in two groups (A & B). In group A, 20 patients were treated with leflunomide 100mg daily for 3 days, then 20mg daily for 12 weeks and in group B 7.5mg methotrexate was given in 3 divided doses 12 hourly for 12 weeks. The effectiveness and side effects were assessed at 4th week and 12th week of the study on the basis of psoriasis area and severity index (PASI).

Result At the final follow up mean percentage of improvement of psoriasis was observed based on PASI score reduction. It was 52.14% in group A and 42.11% in group B.

Conclusion From the current study it may be suggested that leflunomide is effective and well tolerated agent and has some advantages over methotrexate in the treatment of psoriasis

Key words
Leflunomide, methotrexate, plaque psoriasis

Introduction

Psoriasis is a common, chronic, recurrent inflammatory disease of skin characterized by circumscribed erythematous, dry, scaling plaques of various sizes, covered by silvery white lamellar scales.[1] The prevalence of the disease is 2-3% in general population.[2] The exact pathogenesis is unknown. The accelerated proliferation and abnormal differentiation of epidermal keratinocytes is a reaction to the activation of the immune system in focal skin regions, which in turn is mediated by activated CD8+ and CD4+ T lymphocytes that accumulate in affected skin.[3]

UVB phototherapy, psoralen plus UVA (PUVA), methotrexate (MTX), acetretin, cyclosporine and biologics are used for

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treatment of moderate to severe plaque type psoriasis.[4]

Leflunomide is an isoxazole derivative. Its primary mode of action is the specific inhibition of the dihydro-orotate dehydrogenase, a key enzyme in the *de novo* synthesis of pyrimidines, and subsequent inhibition of RNA and DNA synthesis.[5] Activated T lymphocytes, which predominantly synthesize pyrimidines via the *de novo* pathway, may be especially susceptible to leflunomide. The immunomodulatory and anti-inflammatory effects of leflunomide have been also reviewed.

In a developing country like Bangladesh, the majority of people are in poor socioeconomic condition. Both methotrexate and leflunomide are cheap and available in this country. Although the toxicity of MTX is known, that of leflunomide has not yet been explored in psoriasis. To the best of knowledge, there is no recorded study in this field in Bangladesh

So, this study was undertaken to see the efficacy and safety of leflunomide in the treatment of plaque type psoriasis.

Patients and methods

A prospective controlled randomized study was done to compare the efficacy and safety of leflunomide and methotrexate in the treatment of chronic moderate to severe plaque type psoriasis. The study was conducted in 40 patients of age ranging from 18-55 years of both sexes attending the Department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, during the period of January, 2005 to June, 2006. Diagnosis of the patients were based on history, clinical findings and confirmed by histopathology examination. Pustular, guttate or erythrodermic psoriasis, pregnant women and lactating mothers, immunosuppressive conditions, extreme of ages, those taking other immunosuppressive drugs and those having severe systemic disorders were excluded from the study.

Group A (n=20) was treated with oral leflunomide 100 mg daily for 1 to 3 days then 20 mg daily for 12 weeks. group B (n=20) was given tab MTX 7.5 mg in 3 divided doses 12 hours apart weekly as control for the same period. Emollients were used in both groups during the study period.

The patients were assessed at baseline and at the 4^{th} week and at 12^{th} week of study. In order to measure the clinical severity of psoriasis in each patient psoriasis area and severity index (PASI) scoring system (0- 72 points) was used. Clinical assessment covered detailed medical history, physical examination and measurement of disease severity by PASI. Adverse events were monitored by query, physical examination and laboratory tests. Laboratory investigations including complete blood counts, urine R/E, chest X ray, serum alanine transferase (ALT) and creatinine were done at baseline, at 4^{th} week and at 12^{th} week.

Results

Mean age of the respondents of both groups was 36.9±9.97 years. **Table 1** summarizes the demographic features of the study population. Maximum respondents were service holders (27.5%) followed by housewives and others. Among respondents middle class people were more in both groups followed by the lower class. 5 (12.5%) respondents had positive family history of psoriasis.

It was observed in both group A and B that

Table 1 Distribution of respondent's demographic characteristics group A & group B

Characteristics	*n (%)*
Sex	
Male	31(77.5
Female	9(22.5
Occupations	
Service	11 (27.5
House wife	9(22.5
Business	7(17.5
Student	4(10
Others	9(22.5
Economic status	
Upper	3 (7.5
Middle	32(80
Lower	5(12.5
Family history of psoriasis	
Present	5 (12.5
Absent	35 (87.5

Table 2 Mean PASI score group A (leflunomide) and group B (methotrexate)

	Group A n=20	*Group B* n=20*
At base line	16.29 (±4.31)	14.13 (±2.74)
At week 4	13.46 (±4.52)	12.24 (±2.03)
At week 12	7.94 (±3.84)	8.08 (±2.51)

**p* value >0.05 as calculated by ANOVA insignificant.

Table 3 Distribution of respondents of both groups by range of PASI reduction group A & group B

Reduction in PASI	*Group A (n=20)*	*Group (n=20)*
<50% (good)	7 (35.0%)	14 (70.0%)
≥50% (excellent)	13 (65.0%)	6 (30.0%)

mean PASI scores declined gradually after treatment of leflunomide and MTX. In group A (leflunomide), the mean PASI score at the base line was 16.29±4.31 which declined to 7.94±3.84 on the final follow up (week 12). On the other hand, the mean PASI score of group B at baseline was 14.13±2.74 which reduced to 8.08±2.51 on the final follow up (**Table 2**). ANOVA test revealed no significant difference in terms of PASI scores between two groups on follow up.

Table 4 Combined side effects of both group A (leflunomide) and group B (MTX) in the treatment of psoriasis.

Adverse events	*Leflunomide*	*MTX*
Diarrhea	6 (30.0%)	4 (20.0%)
Headache	3 (15.0%)	5 (25.0%)
Nausea	3 (15.0%)	4 (20.0%)
Rash	3 (15.0%)	2 (10.0%)
Dyspepsia	3 (15.0%)	3 (15.0%)
Alopecia	2 (10.0%)	3 (15.0%)
Asthenia	2 (10.0%)	3 (15.0%)
Back pain	1 (5.0%)	2 (10.0%)
Abdominal pain	2 (10.0%)	0 (.0%)
Vomiting	1 (5.0%)	0 (.0%)
Dizziness	0 (.0%)	2 (10.0%)
Pruritus	0(.0%)	1 (5.0%)

**p* value >0.05

After 4 weeks of treatment, the mean percentage improvement in PASI with leflunomide was 17.50±12.61 in contrast to 12.88±6.59 with MTX. It further improved to 52.14±15.40 and 42.11±17.92 at week 12 in the respective groups. 13 (65%) respondents of group A and 6(30%) of group B had reduction ≥50% (excellent). It is statistically significant ($p<0.05$) (**Table 3**) whereas 7 (35%) respondents of group A and 14 (70%) of group B had reduction of PASI less than 50% (good).

Table 4 enlists the side effects observed in both treatment groups ($p>0.05$). Headache was the most common side effect seen following treatment with both drugs.

Discussion

This study was done to see the efficacy and safety of leflunomide in plaque type of psoriasis. As there is no recorded study in this field, it happens to be the first one in Bangladesh. MTX has been in use to treat psoriasis and psoriatic arthritis for the last 45 to 55 years. Since 1950s, MTX has become the gold standard for treatment of psoriasis.[5] Drugs like retinoids,

cyclosporine, PUVA are well studied in the treatment of psoriatic arthritis. Dermatologists have been always looking for new safe as well as cost effective drugs. Recent discovery of targeted molecules i.e. infliximab, etanercept, efalizumab etc. has opened a new avenue and hope in the management of this disease but cost remained big barrier of their use in the third world. Psoriasis is a chronic disease and may need life long treatment. During this time many drugs may show side effects and resistance. So after 1 to 2 years it is wise to switch over to another drug.[3]

Statistical analysis revealed that 31 (77.5%) respondents of present study were males and 9 (22.5%) were females. This is in accordance with Shupack *et al.*[7] but largely differs from Christophers and Mrowitetz,[6] where they found equal prevalence rate of psoriasis in males and females. Mean age of this study group was 36.90±9.97 years with a range from 18 to 55 years. This finding is almost similar to that of Shupack *et al*.[7]

Present study also showed that maximum respondents were service holders 11 (27.5%) followed by housewives 9 (22.5%). Among respondents, middle class people there were 32 (80%) in both groups followed by lower class 5 (12.5%). Due to scarcity of literature these findings can not be correlated with other studies. Five (12.5%) psoriatics had family history. This study is similar to the study done by Christophers *et al*.[6]

The mean PASI scores declined on both group A and B gradually after treatment with leflunomide and MTX, respectively. Mean PASI scores were calculated 16.29± 4.31 in group A at the baseline which declined to 7.94±3.84 on the final follow up. On the other hand, 14.13±2.74 were the mean PASI score of group B at baseline which declined to 8.08±2.51 on the final follow up. A 50% reduction in the psoriasis area and severity index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis as described by Carlin *et al*.[8]

The most common side effects following treatment with leflunomide were diarrhea 6 (30%), headache 3 (15%), nausea 3 (15%), rash 3 (15%), dyspepsia 3 (15%), alopecia 2 (10%), asthenia 2 (10%), abdominal pain 2 (10%) and back pain 1 (5%). Similarly most common side effects observed following treatment with MTX were headache 5 (25%), diarrhea 4 (20%), nausea 4 (20%), dyspepsia 3 (15%), alopecia 3 (15%), asthenia 3 (15%), rash 2 (10%), back pain 2 (10%), dizziness 2 (10%) and pruritus 1 (5%). No significant difference was observed during these 12 weeks period of study (p>0.05). Similar side effects with leflunomide were recorded by Schiff *et al*.[9] in a trial study of 24 weeks in the treatment of rheumatoid arthritis.

Conclusion

From the present study it may be suggested that leflunomide is a useful and well tolerated agent for the treatment of plaque type psoriasis. Leflunomide has some advantages over MTX in the treatment of psoriasis. In majority of patients it is well tolerated, convenient and effective in reducing or remitting skin lesions. In addition, orally administered leflunomide is cost effective. Since biologics are costly and not easily available, leflunomide may be one of the alternative treatment options of plaque type of psoriasis.

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