Dermatology Practical & Conceptual

Efficacy of Leflunomide Compared to Methotrexate in the Treatment of Moderate to Severe Plaques Psoriasis: A Randomized Controlled Clinical Trial

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory autoimmune skin disease. Several treatment options are available including topical and systemic options. Methotrexate was the main systemic medication in treating severe psoriasis, yet adverse events can limit its use. Leflunomide is an isoxazole derivative that inhibits the synthesis of pyrimidines, and subsequently inhibits RNA and DNA synthesis.

Objectives: As available data directly comparing MTX to leflunomide in psoriasis are lacking, this double blinded study was designed to compare the efficacy of methotrexate versus leflunomide in the treatment of moderate to severe psoriasis.

Methods: The study included 40 patients (25 males and 15 females) with chronic plaque psoriasis. s. Patients were randomly assigned to one of two equal groups, group A for subcutaneous methotrexate injections and group B for leflunomide (loading dose 100mg daily for the first 3 days, then 20 mg daily for 3 months. Disease severity was determined by psoriasis area and severity index (PASI) score before and at the end of treatment The treatment response was evaluated at the baseline and weeks 4, 8 and 12 PASI score.

Results: Both groups were matching at the baseline in aspects of gender, age, disease duration and PASI scores Both medications yielded comparable results with no significant difference between both groups in PASI score neither in side effects.

Conclusions: Leflunomide can be as effective as methotrexate in treatment of moderate to severe psoriasis

Introduction

Psoriasis is a chronic proliferative and inflammatory skin disease. Clinically, the disease is characterized by erythematous plaques covered by silvery scales mainly on the extensor surfaces, scalp, and lumbosacral region. Joints and eyes can be affected. Several types are described, but the plaque type is the commonest [1,2]. Disease affects 0.2% to 4.8% of the population. It is of unknown etiology. However, it is considered an autoimmune disease mediated by T lymphocytes, with genetic predisposition as it runs in families. Any skin injury (eg mechanical, chemical, radiation) seems to induce the psoriatic lesions. Additionally, the disease is worsened by certain drugs (eg chloroquine, lithium, and beta-blockers). But it improved in summer. Other triggering factors include infections, stress, smoking, obesity, alcoholism, and hypoglycemia [3].

The main pathophysiological changes include stimulating keratinocyte proliferation by infiltration of the skin by activated T-cells, with subsequent formation of thick plaques. Other features include epidermal hyperplasia and parakeratosis. The epidermal cells also fail to secrete lipids which results in flaky and scaly skin, which is typical of psoriasis [4]. Psoriasis can present with different morphological patterns (eg plaque, guttate, rupioid, erythrodermic, pustular, inverse, elephantine, and psoriatic arthritis) [5,6].

The Psoriasis Area Severity Index (PASI) is the most widely used assessment tool to estimate the severity of the condition and permits treatment evaluation. Topical therapy is used for mild to moderate psoriasis (eg coal tar, dithranol, corticosteroids, vitamin D analog, and retinoids) [7].

Systemic drugs are used in severe cases. Methotrexate, retinoids, cyclosporine, and fumarates are possible treatment options. Routine blood, liver and renal functions should be assessed in patients during systemic therapy. Biological agents (eg infliximab, adalimumab, etanercept, and interleukin antagonists) work by interrupting the immune process. However, there is a serious risk of infections in these patients (on biological treatment) and all precautions should be taken to prevent severe immunosuppression in such patients [8,9].

Methotrexate (MTX) is a folate antagonist initially used to treat hematological malignancies. It has been used as an anti-inflammatory drug in psoriasis for more than 50 years. It is the first-line systemic treatment agent in the United States and Europe. It is used for moderate-to severe psoriasis when topical treatments are ineffective, impractical, or contraindicated [10]. It was suggested to exert its action by its antiproliferative effects, increasing susceptibility of T-lymphocytes and monocytes to the inhibition of the purine and pyrimidine synthesis, anti-inflammatory and immunosuppressant effects [11,12].

Leflunomide is an isoxazole derivative. It is primarily inhibiting the dihydro-orotate dehydrogenase, a key enzyme in the de novo synthesis of pyrimidines, and subsequently inhibit RNA and DNA synthesis. Activated T-lymphocytes may be especially susceptible to leflunomide. It also has immunomodulatory and anti-inflammatory effects [13]. Leflunomide is a useful and well tolerated treatment option for plaque psoriasis. It has some advantages over MTX in the treatment of psoriasis (eg it is well tolerated, convenient and effective). 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 [14,15].

Objectives

As available data directly comparing MTX to leflunomide in psoriasis are lacking, this double blinded study was designed to compare the efficacy of methotrexate versus leflunomide in the treatment of moderate to severe psoriasis.

Methods

Recruitment of Participants

This comparative clinical study included 40 patients with chronic plaque psoriasis that were diagnosed clinically. Patients were recruited from the Dermatology outpatient clinic of **Al-Azhar**University Hospital (**New Damietta**) between October 2022 and September 2023. The study was approved by the Research Ethical Committee, **Damietta** Faculty of Medicine, **Al-Azhar** University (IRB 00012367-22-06-002), and fulfilled all the ethical aspects required in human research. All patients received full information about both medications used, the study design and all the possible side effects. All recruits provided an informed consent to participate in the study. We excluded patients younger than 18 years or older than 60, pregnant and lactating women, patients with any autoimmune disease (eg rheumatoid arthritis, systemic lupus) patients with any dermatological disease other than psoriasis, patients with hematologic disorders (eg thrombocytopenia, anemia), patients with systemic chronic diseases (eg liver, kidney or heart diseases), patients who received systemic anti-psoriatic treatment for the last 3 months before inclusion in the study and those receiving any topical treatment for 4 weeks prior to enrollment. Patients with history of allergy to any of the medications used were also excluded.

Randomization and Assigning Treatment Groups

Patients were randomly assigned to one of the two groups using closed envelop technique. Group A included 20 patients

who received subcutaneous methotrexate injection treatment once per week for 3 months. Group B of 20 patients who received oral leflunomide regimen loading dose 100 mg daily for the first 3 days then 20 mg daily for 3 months. Randomization was performed by generation of random numbers by computer and each number indicate one treatment and sealed in an enclosed envelope which opened before starting treatment by a nurse who was blinded to the other parts of the study.

All patients were subjected to full history taking, thorough general and dermatological examination. The disease severity as well as treatment response were determined by (PASI) score at the baseline and at weeks 4, 8 and 12. The documentation of the lesion was performed using digital photography (using iPhone 12 camera) at the baseline and week 12. The laboratory investigations were performed at the baseline and at 4, 8 and 12 weeks after treatment. These included complete blood picture (CBC), liver and kidney function tests. In the methotrexate group, all patients received folic acid 5mg daily except on the day of injection.

Every patient received a printed checklist of the possible side effects of the treatment and was instructed to report any of the mentioned manifestations on every visit. The manifestations included in the checklist were nausea, vomiting, diarrhea, abdominal pain, dyspepsia, headache, dizziness, asthenia, back pain, any skin rash, pruritus and alopecia.

Statistical Analysis

The statistical package for social science (SPSS), version 20 (IBM® SPSS® Inc.) was used to perform all analysis. The data were originally anonymized by coding and fed to the personal computer. Categorical variables were summarized by their relative frequency and percentages. However, the quantitative variables were represented by the arithmetic mean and standard deviation (SD), minimum and maximum when appropriate. Groups were compared by Student T test when quantitative and compared by Pearson chi-square or Fisher exact test (when appropriate). P value ≤ 0.05 was considered statistically significant, at confidence intervals (CI) of 95.0%.

Results

Forty patients completed the study and were included in the analysis. Demographic and clinical characteristics of the studied patients are listed in Table 1. Both groups showed matching characteristics in aspects of gender, age, disease duration and presence of positive family history.

Among the methotrexate group (Figures 1-3); the mean PASI score at the baseline was 33 ± 11.68, by the end of the fourth week it improved to 14.66 ± 7.35 and at the end of the study at week 12 it improved to 1.95 ± 1.33. While among the leflunamide group (Figures 4-8); the mean PASI score at the baseline was 31.75 ± 7.71 and improved at the end of the 4th week to 17.46 and by the end of the study at week 12 to 1.94 ± 1.28. Both groups showed comparable improvement at all the 3 visits (P = 0.693, 0.141, 0.99, respectively).

The laboratory investigations after 12 weeks of treatment were comparable between both methotrexate and leflunomide groups, except for significant increase in red blood cell count, hemoglobin concentrations, and total protein in the methotrexate group, while albumin was significantly lower in methotrexate than the leflunomide group side effects: No

Table 1. Demographic and Clinical Characteristics Among Study Groups

Variables		Methotrexate Group (n=20)	Leflunomide Group (n=20)	P value
Sex (N, %)	Male Female	11 (55.0%) 9 (45.0%)	14 (70.0%) 6 (30.0%)	0.327
Age (years)	Mean±SD	38.9 ± 12.88	37.6 ± 13.6	0.758
	Range (Min. – Max.)	42 (18 - 60)	33 (26 - 59)	
Occupation (N, %)	Housewife	4 (20%)	6 (30%)	0.902
	Employee	8 (40%)	7 (35%)	
	Student	3 (15%)	3 (15%)	
	Other	5 (25%)	4 (20%)	
Economic status (n, %)	High	2 (10%)	2 (10%)	0.891
	Intermediate	16 (80%)	15 (75%)	
	Low	2 (10%)	3 (15%)	
FH of psoriasis		2 (10%)	3 (15%)	0.663
Duration of the disease	Mean±SD	11.2 ± 8.69	10.75 ± 8.06	0.866
	Range (Min. – Max.)	28 (2 - 30)	27 (3 - 30)	

FH = positive family history…; SD = standard deviation.

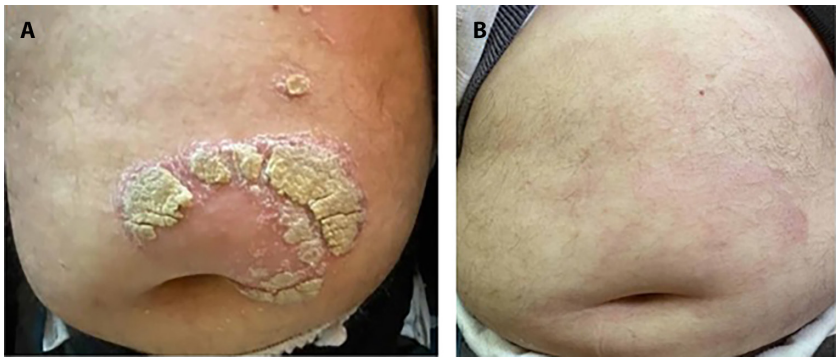

Figure 1. Male patient, 60 years old, with psoriasis vulgaris his Psoriasis Area Severity Index (A) before metotrexate was 34.1 that decreased to 0 (B) after 12 weeks of treatment.

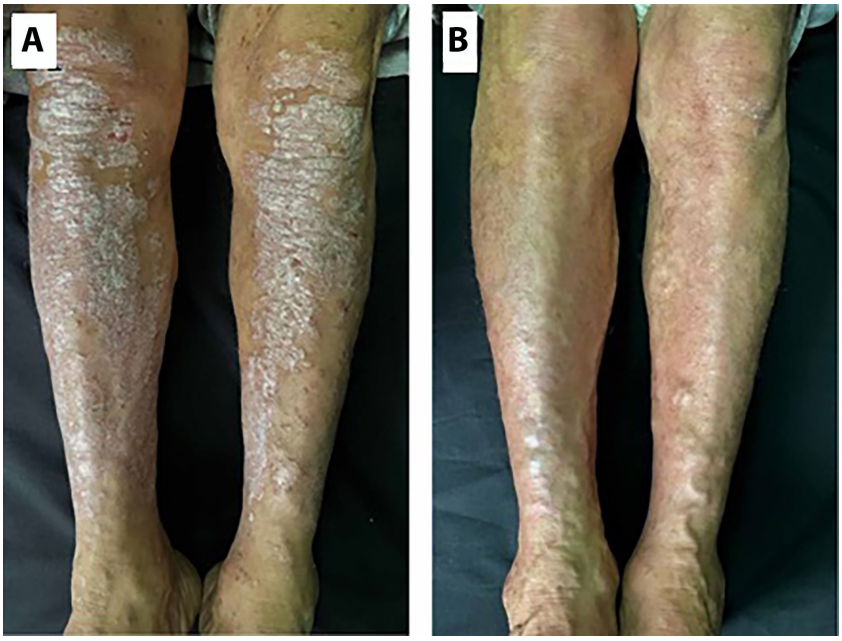

Figure 2. Male patient, 55 years old, with psoriasis vulgaris his Psoriasis Area Severity Index (A) before metotrexate was 43.1 that decreased to 0 (B) after 12 weeks of treatment.

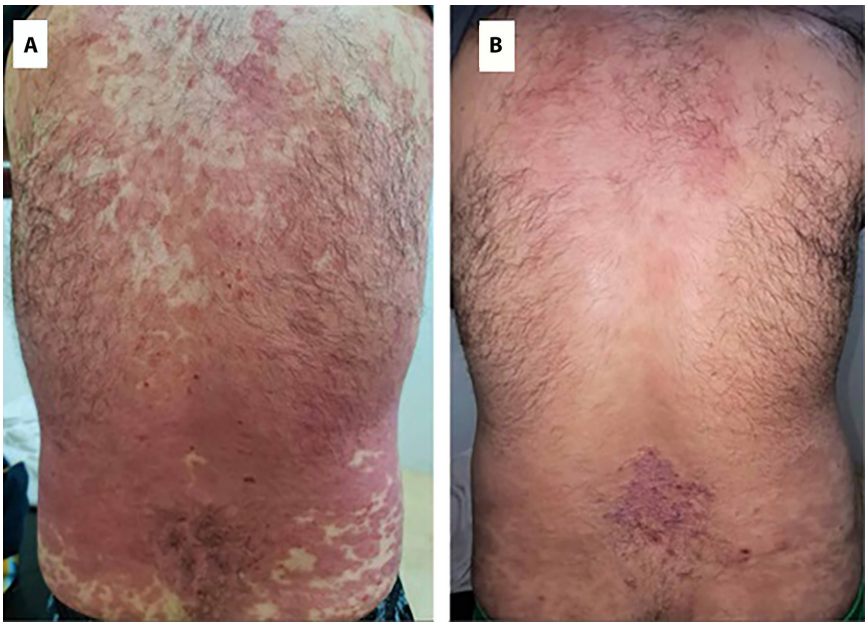

Figure 3. Male patient, 40 years old, with psoriasis vulgaris his Psoriasis Area Severity Index (A) before metotrexate was 34.2 that decreased to 2.3 (B) after 12 weeks of treatment.

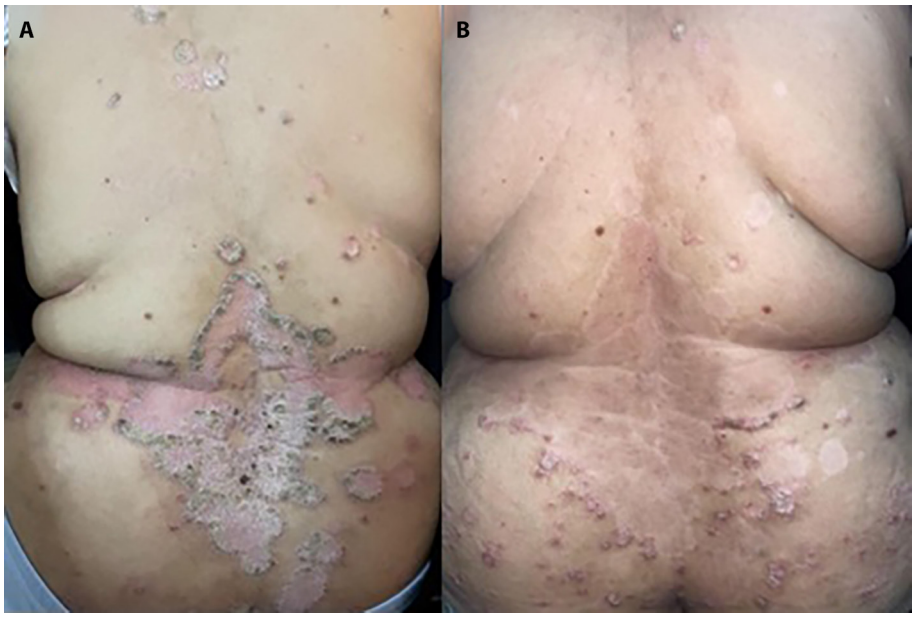

Figure 4. Female patient 60 years old with psoriasis vulgaris her Psoriasis Area Severity Index (A) before oral leflunomide was 36.3 that decreased to 2.5 (B) after 12 weeks of treatment.

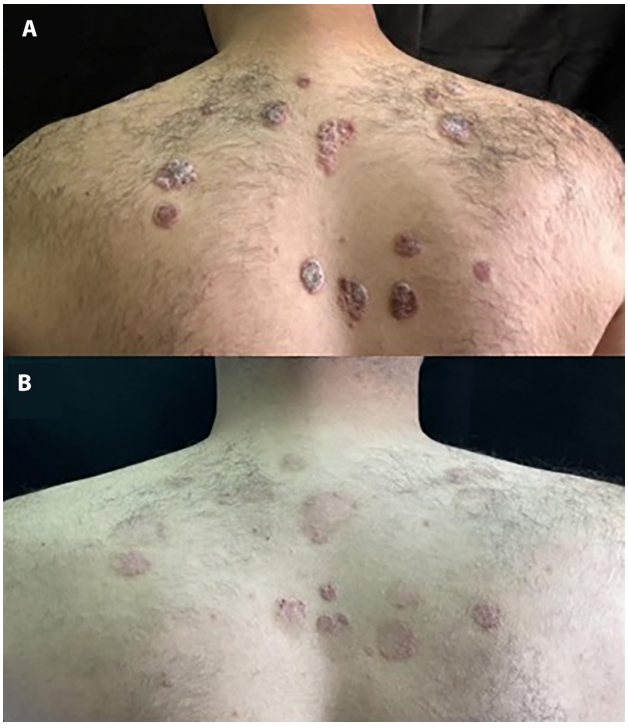

Figure 5. Male patient 27 years old with psoriasis vulgaris his Psoriasis Area Severity Index (A) before oral leflunomide was 21.6 that decreased to 2.4 (B) after 12 weeks of treatment.

significant difference was found between both groups in any of the reported side effects.

None of the patients among both groups discontinued the treatment because of the side effects, nausea and vomiting were the most frequent side effect among patients within the leflunamide group, this was similar to the methotrexate group (P = 677 and 465 respectively). Gastrointestinal manifestation, general and dermatological side effects were comparable between both groups (Table 2).

Conclusions

Methotrexate has been the treatment of choice for severe psoriasis for decades the main objective of the current study was to compare the efficacy and safety of the anti-arthritic medication leflunamide versus methotrexate in treating moderate to severe cases with psoriasis [16]. Leflunomide, a disease-modifying antirheumatic drug, was initially licensed for the treatment of psoriatic arthritis. Patients treated with leflunamide for psoriatic arthritis showed promising short and long-term improvement of cutaneous psoriasis lesions suggesting that it can be a good potential for treating psoriasis [17].

Our results were in accordance with previous double blinded trials studied leflunomide as a monotherapy for psoriasis compared to placebo [18-20]. Compared to placebo; these studies showed significant reduction of PASI among treated patients. We suggest that the effect of leflunomide on psoriasis could be attributed to prevention of pyrimidine synthesis pathway by inhibiting the enzyme dihydroorotate dehydrogenase

On the other side, Thami and Garg included 10 patients with different severity and types of psoriasis and showed no clinically significant improvement after 6 to 8 months of treatment with leflunomide, 20 mg/d [21]. In another study, 8 of 12 patients with psoriatic arthritis had moderate to marked clinical improvement in their psoriasis after 2 to 3 months of treatment with leflunomide alone or in combination with another disease-modifying antirheumatic drug [20]. Other case-series of 8 patients receiving leflunomide, 20mg/d, over 12 weeks showed a reduction in PASI score and improvement in quality of life in 6 patients [19].

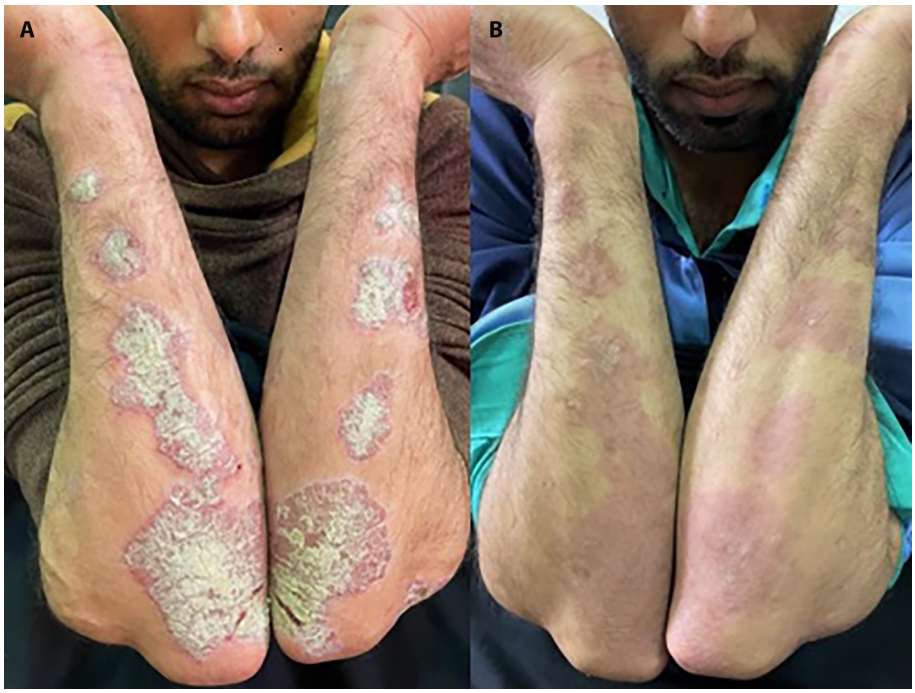

Figure 6. Male patient, 27 years old, with psoriasis vulgaris his Psoriasis Area Severity Index (A) before oral leflunomide was 59.92 that decreased to 2.2 (B) after 12 weeks of treatment.

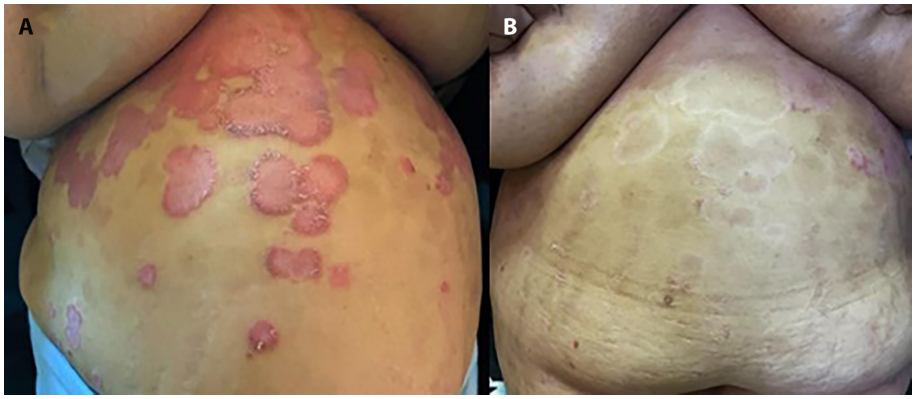

Figure 7. Female patient, 58 years old, with psoriasis vulgaris her Psoriasis Area Severity Index (A) before oral leflunomide was 25.2 that decreased to 2.4 (B) after 12 weeks of treatment.

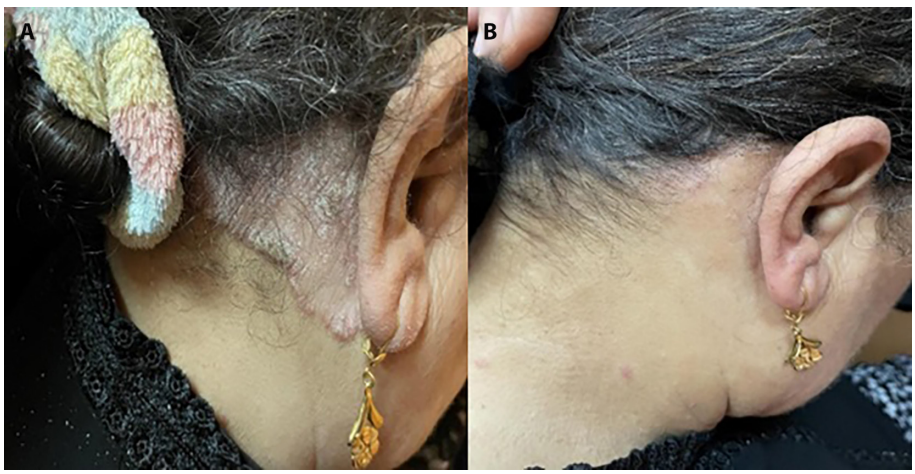

Figure 8. Female patient ,56 years old, with psoriasis vulgaris her Psoriasis Area Severity Index (A) before oral leflunomide was 25 that decreased to 0 (B) after 12 weeks of treatment.

Table 2. Gastrointestinal, General and Dermatological Manifestations Among the Study Groups

	Methotrexate Group (N = 20)	Leflunomide Group (N = 20)	Test	P Value
Nausea	4 (20%)	3 (15%)	0.173	0.677
Vomiting	0 (0%)	1 (5%)	1.026	0.311
Diarrhea	4 (20%)	6 (30%)	0.533	0.465
Abdominal pain	0 (0%)	2 (10%)	2.105	0.147
Dyspepsia	3 (15%)	3 (15%)	0.001	1.0
Headache	5 (25%)	3 (15%)	0.625	0.429
Dizziness	2 (10%)	0 (0%)	2.105	0.147
Asthenia	3 (15%)	2 (10%)	0.229	0.633
Back pain	2 (10%)	1 (5%)	0.36	0.548
Rash	2 (10%)	3 (15%)	0.229	0.633
Pruritus	1 (5%)	0 (0%)	1.026	0.311
Alopecia	3 (15%)	2 (10%)	0.229	0.633

In a prospective observational study, Behrens et al investigated the effectiveness and tolerability of leflunomide in treatment of psoriatic arthritis [23]. They reached the conclusion that leflunomide is an effective, safe (well-tolerated) treatment option for psoriatic arthritis on a clinical basis. It affects peripheral arthritis, and other constitutional manifestations of arthritis (eg pain, fatigue) and it was associated with significant reduction of skin manifestations.

All the previous studies indicate the efficacy and safety of leflounomide in treatment of psoriasis or psoriatic arthritis when compared to placebo or without comparison to placebo. However, the efficacy and safety of leflunomide are in need to be confirmed in comparison to a standard treatment option. Hence, the current work was designed, carried out and yielded the reported results.

Mulder et al compared methotrexate monotherapy (25 mg once weekly) to methotrexate (as the previous dose) plus leflunomide (20 mg once daily) in patients with psoriatic arthritis [15]. They concluded that combination therapy is more effective but less tolerated than monotherapy. This confirms the need for the current work.

In a more recent systematic review, Hsieh and Tsai investigated the combination therapy of methotrexate with other disease modifying drugs for treatment of psoriasis [24]. They reported a better effect with combination therapy. However, they need stronger evidence to recommend such combinations, as their studies were small-scaled and retrospective in nature. This finding regains the treatment options again to monotherapy. Thus, research much be continued for the most effective and well-tolerated treatment option.

Mazhar et al) conducted an observational study on 6294 adult patients with psoriasis with or without psoriatic arthritis, who started the treatment by methotrexate or other biologics between 2006 and 2021 [25]. They aimed to address side effects between different therapeutic drugs. They reported that patients on methotrexate had higher risk of mild to moderate anemias, mild to moderate liver adverse events. However, chronic kidney injury did not differ between drugs. In addition, acute kidney injury, serious infections and major gastrointestinal adverse effects had no clinically significant difference between therapies. These results confirm the value of the current study, where leflunomide was associated with better profile of side effects regardless of the insignificant difference between groups. This could be explained by the small number of included subjects in each group.

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Although our study had several methodological and scientific strengths as the double blinded design, the computer assisted randomization as well as the new research question comparing two medications that were not compared in psoriasis before, it is still important to consider certain limitations when reading our results, we did not perform a sample size calculation, we only could study a limited number of participants and we did not follow up for long term effects and recurrences.

In conclusion, leflunamide is an anti-arthritic and low-cost drug that can effectively treat moderate to severe psoriasis as effective as MTX.

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