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Treatment of Chronic Plaque Psoriasis with Etanercept and Methotrexate

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Abstract
Objectives: The aim of study is to assess the efficacy of methotrexate and etanercept in the treatment of chronic plaque psoriasis.
Methods: This therapeutic, interventional comparative single center study was carried out at the Center of Dermatology and Venereology, Baghdad Teaching Hospital, from January 2015–July 2017. A total of 62 patients were enrolled; divided in to two groups. Group I: Thirty three patients (23 males and 10 females), their ages ranged between15 and 65 years mean ± SD 33.13 ± 13.07, received etanercept 50 mg twice weekly for 3 months then once weekly thereafter. Group II: Twenty nine patients (19 males and 10 females), their ages ranged between 15 and 62 years mean ± SD 38.16 ± 15.2, received methotrexate 15 mg per week for six months then tapered. Both groups were followed up monthly for 6 months and their PASI score, DLQI, side effect and pictures were recorded.
Results: Seven patients defaulted from the study for unknown reason, 30 patients completed in etanercept group, while 25 patients completed in methotrexate group. After 12 weeks the PASI score decrease from base line 19.13 ± 10.67 to 6.38 ± 4.96 and then to 3.34 ± 5.38 after 24 weeks treatment with Etanercept compaired to reduction in PASI score from base line 18.97 ± 10.54 to 5.72 ± 4.8 to 2.95 ± –6.01 after 12 weeks and 24 weeks respectively. There is significant statistical effect in the two groups.
Conclusion: Both are effective monotherapy for patients with moderate to severe plaque psoriasis with tolerable side effects.
Keywords: Etanercept, methotexate, psoriasis

Introduction

Psoriasis is chronic potentially life ruining multisystem disease with worldwide distribution and multifactorial disease as both polygenic predisposition combined with environmental factors participate in its development, in addition to its physical impact, it has psychosocial impacts on the affected individuals.[1] Psoriasis is worldwide disease. According to published reports, its prevalence in different populations varies from 0.1% to 11.8%.[2] Iraq, a study shows psoriasis frequency in the outpatient clinic was 2.3%.[3] Psoriatic arthritis found to affect 5–30% of patients with cutaneous psoriasis.[4] There are two peak ages of incidence, the first occurring between 20 and 30 years and the second between 50 and 60 years of age. This has led to proposing the notion of type I and type II psoriasis.[5] Studies reported that 35% to 90% of patients with psoriasis had Positive family history.[6] External triggering factors: The Koebner phenomenon (isomorphic response), i.e. the provocation of psoriatic lesions by injury to the skin, is observed 7–14 days after injury in approximately 25% of psoriatic patients. Other forms of cutaneous injury, e.g. sunburn, morbilliform drug eruption, viral exanthema can also induce Psoriasis.[7] Systemic triggering factors: infection (pharyngitis),[7] Endocrine factors (Hypocalcaemia),[8] Psychogenic stress,[9] lithium, IFNs, β-blockers,[9] alcohol consumption, smoking, and obesity.[10] Different variants may coexist in a particular individual, but all skin lesions share the same important hallmarks: erythema (salmon pink), thickening and scale. Although the size of a lesion may vary, the outline of the lesion is usually circular, oval, ora pale blanching ring, which is referred to as (Woronoff's ring), sometimes surrounds polycyclic, psoriatic lesions. Superficial silvery white scales are removed via curettage characteristic coherence is observed, as if one has scratched on a wax candle.[11] Methotrexate (MTX) is an antimetabolite analog of folic acid considered first-line systemic therapy for chronic plaque psoriasis, initial improvement is observed between 1 and 7 weeks and maximum improvement can be expected after 8–12 weeks of treatment.[12] Oral administration 10–15 mg weekly dose followed by complete blood count with differential (CBC), platelet count and hepatic profile after two weeks from initial of treatment to 3 months.[13] Pregnancy and lactation are contraindication of (MTX).[13] Etanercept (Enbrel): received FDA approval on April 2004 to treat moderate to severe plaque psoriasis and psoriatic arthritis,[14] recommended dose is 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg subcutaneously per week. It should discontinue if patient do not reach PASI score of 50 by week 12,[15] side effects of Etanercept are; injection site reactions, risk of demyelinating disease, viral hepatitis, paradoxical response of immune mediated disease to TNF_α inhibitors.[15] The aim of study is to assess the efficacy of methotrexate and etanercept in the treatment of chronic plaque psoriasis.

Methods

This was therapeutic, interventional comparative single center study carried out at the Center of Dermatology and Venereology, Baghdad teaching hospital, from January 2015–July 2017. A 62 patients included in the study aged 15–65 years. All patients have chronic moderate to severe plaque psoriasis. The baseline PASI score >10, body surface area involved >10% and DLQI >10) and patients with palmoplantar psoriasis were included in the study. Pregnant and lactating women, those with severe hepatic, renal, hematological or other systemic disorders, immunosuppressed patients, and moderate to severe infection, lymphoproliferative, demyelinating disease, active or latent tuberculosis, positive virology for hepatitis

or HIV infection, all excluded from the study. Selection of patients as the following; patients with chronic, moderate to severe plaque psoriasis who fail to respond to topical treatment, PUVA, acitritene, or previously used metotrexate with good response were selected for methotrexate group if not having a contraindication to it and Patients with chronic, moderate to severe plaque psoriasis who fail to respond to topical treatment, PUVA, acitriten, methotrexate, cyclosporine or had contraindication for them were selected for etanercept group. The patients divided into two groups; **Group A:** 33 patients treated with Etanercept (50) mg subcutaneous injection twice weekly for first 3 months then once weekly thereafter for a total of 6 months. **Group B:** 29 patients treated with methotrexate (5) mg test dose then 15 mg weekly either oral (in three divided doses 12 hours apart) or intramuscular (single weekly injection) with the use of folic acid tablet (5 mg per day) in days free of treatment, for 6 months then the dose had been tapered according to response to treatment. Before starting the treatment all patient were interrogated and full history was taken regarding the age, gender, occupation, residence, age of onset, duration of disease, seasonal variation, association with itching, history of previous therapy and family history. Careful physical examination regarding the size, site, erythema, scale, thickness of the plaque was carried out. Each patient in MTX group was sent for CBC with PLT count, AST, ALT, renal function test, serology for viral hepatitis and HIV and Pregnancy test for women of child bearing age as initial screening, then CBC with PLT count and AST, ALT after initial 5–10 mg test dose, CBC and PLT count and AST/ALT monthly for 4 months and then every 3–4 month if stable, as follow up monitoring. Each patient in Etanercept group sent for TST, CBC, serology for viral hepatitis and HIV, chest x ray prior to treatment then CBC every 3 months and chest x ray or TST annually or as clinically indicated. The severity and the extent of psoriasis were assessed by using PASI score and DLQI.[16,17]

Statistical Analysis

For determination of statistical significance among different variables, descriptive statistics (mean and standard deviation) were used together with analytic statistics (*t*-test, *F*-test). *P* values <0.05 were considered to indicate statistical significance.

Results

Group A: Treated with Etanercept; 33 patients, their ages range from 15–65 with mean ± SD of 33.13 ± 13.07 years were recruited in this group, 23 (69.69%) male and 10 (30.30%) females.

Group B: Treated with methotrexate; 29 patients their ages range from 15–62 with mean ± SD of 38.16 ± 15.2 years were recruited in this group, 19 (65.52%) male and 10 (34.48%) female. As described in Table 1.

Group I (Etanercept Group)

A total of 33 patients were enrolled in this group. Only 30 patients complete 6 months of treatment. Regarding PASI score: After 4 weeks of treatment mean ± SD PASI score reduced from baseline 19.13 ± 10.67 to 13.94 ± 10.732 with *P*-value = 0.0655. After 12 weeks of treatment, their mean ± SD PASI score reduced to 6.38 ± 4.96 with significant *P*-value <0.0001. After 24 weeks of treatment mean ± SD PASI score reaches 3.34 ± 5.38 with significant *P*-value <0.0001. As shown in Table 2.

After 4 weeks of treatment with etanercept; 2 (6.66%) patients achieved 50–75%, 4 (13.33%) patients achieved 75–90%, 1 (3.33%) patient achieved >90%, 3 (10%) patients achieved 25-50%, 20 (66%) patients achieved 0–25% reduction in their PASI score. After 12 weeks of treatment; 8 (26.33%) patients achieved 50–75%, 13 (43.33%) patients achieved 75–90%, 2 (6.66%) patients achieved >90%, reduction in PASI score and considered as good responders, and 3 (10%) patients achieved 25–50% and 4 (13.33) patients achieved 0–25%, reduction in PASI score. After 24 weeks of treatment; 1 (3.33%) patients achieved 50–75%, 5 (16.66%) patients achieved 75–90%, 11 (36.66%) patients achieved >90%, reduction in PASI score, while 8 (26.66%) patients achieved complete clearance, 3 (10%) patients achieved 25–50% reduction in their PASI score and received MTX in addition to etanercept, two of them have palmoplanter psoriasis, while the last two (6.66%) patients developed 0–25% reduction after initial mild response and considered as non-responders and stopped treatment Table 3.

Table 1. **Demographic characteristics of group (I) and group (II)**

Groups Patients characteristics		Group I: (Etanercept) No = 30	Group II: (MTX) No 25
Age (years)	Range	15–65	15–62
	Mean ± SD	33.13 ± 13.07	38.16 ± 15.2
Gender	Male	23	19
	Female	10	10
PASI score at baseline mean ± SD		19.13 ± 10.67	18.97 ± 10.54

Table 2. **PASI score mean ± SD with *P* value during treatment with etanercept**

Weeks	PASI mean ± SD	*P*-value
Baseline visit after 4 weeks	19.13 ± 10.67 13.94 ± 10.732	0.0655
Baseline visit after 12 weeks	19.13 ± 10.67 6.38 ± 4.96	**<0.0001**
Baseline visit after 24 weeks	19.13 ± 10.67 3.34 ± 5.38	**<0.0001**

F-test = 21.86, *P*-value ≤0.05 (significant).

Table 3. **Reduction rate in PASI score during treatment with etanercept**

Reduction rate	No. of patients after 4 weeks	No. of patients after 12 weeks	No. of patients after 24 weeks
Complete clearance	–	–	8 (26.33%)
>90%	1 (3.33%)	2 (6.66%)	11 (36.66%)
75–90%	4 (13.33%)	13 (43.33%)	5 (16.66%)
50–5%	2 (6.66%)	8 (26.33%)	1(3.33%)
25–50%	3 (10%)	3 (10 %)	3 (10%)
0–25%	20 (66%)	4 (13.33%)	2 (6.66%)

A total of 29 patients were enrolled in this group. Only 25 completed the study. The results of treatment with MTX were as the following: Regarding PASI score: after 4 weeks of treatment mean ± SD PASI score reduced from baseline 18.97 ± 10.54 to 12.276 ± 8.131 with *P*-value = 0.01, after 12 weeks of treatment mean ± SD PASI score reduced to 5.72 ± 4.8 with significant *P*-value <0.0001, after 24 weeks of treatment mean ± SD PASI score reduced to 2.95 ± 6.01 with significant *P*-value <0.0001 Table 4.

After 4 weeks of treatment; 8 (32%) patients achieved 50–75%, 7 (28%) patients achieved 25–50%, 10 (40%) patients developed 0–25%, reduction in their PASI score. After 12 weeks treatment; 8 (32%) patients achieved 50–75%, 5 (20%) patients achieved 75–90%, 4 (16%) patients achieved >90%, reduction in PASI score, 2 (8%) patients achieved complete clearance, while 5 (20%) patients achieved 25–50%, and 1 (4%) achieved 0–25%, reduction in PASI score. After 24 weeks treatment; 5 (20%) patients achieved 75–90%, 6 (24%) patients achieved >90% reduction in PASI score, 10 (40%) patients achieved complete clearance, 1 (4%) patient achieved 25–50% reduction in PASI score, 3 (12%) patients achieved 0–25% reduction and shifted to other modalities of treatment as in Table 5.

Discussion

Psoriasis is a common, chronic, relapsing, inflammatory, skin disease. Its severity may be mild that can be treated with topical modalities to moderate-severe that need different systemic modalities for treatment such as methotrexate, cyclosporine, acitriten and biological agents. All of these agents have serious systemic side effect starting from systemic immunosuppressant, renal, liver and bone marrow toxicity ending with carcinogenic and teratogenic effect which make them not suitable for selected patients.[18] Since psoriasis is hyperprolifferative disorder in which both adaptive and innate immunity play important roles and greater understanding of the immunopathology of psoriasis was developed more targeted therapy have emerged with apparently fewer side effects.[19] Biologics are new therapeutic agents. Among them is etanercept which has been FDA approved for treatment of rheumatoid arthritis,[15] and is FDA approved on April 2004 for treatment of moderate to severe plaque psoriasis and psoriatic arthritis.[14] In this study both etanerecpt and methotrexate were effective; apart from its cost, patients on etanercept where comfortable and more complianed to treatment as it is a new therapeutic agents and being free of side effects they complained previously with other modalities; while patients treated with methotrexate were afraid of infertility, hair loss and hepatotoxicity. Tournier A et al. noted the fast clearing of psoriatic skin lesions in patients with psoriatic arthriris who were managed with antimetabolic drug aminopterin. Later on this drug was replaced by less toxic derivative methotrexate.[20] Despite its wide spread use in the treatment of psoriasis there is little evidence on safety of using methotrexate in patient with psoriasis. Although it has had a long history of use, there is no significant data on cumulative doses of MTX that result in early hepatic toxicity.[21] In study which was conducted by Babino G et al., he demonstrated that using etanercept at dose of 50 mg subcutaneously twice per week has been shown to induce PASI 75 response to treatment in 49% of patients after 12 weeks,[15] this was consistent with our study. In study, which was conducted by Kim A Papp, they reduced the dose to 25 mg twice per week for additional 12 weeks and they found that the patient percentage exhibiting PASI 75 response was increased to 54%.[22] Pharmacogenitics represent the new frontier for discovery of potential genetic marker of biological response to etanercept. Clinical study showed that TNF-α-308G\G, IL-17F (rs 763780), + 489GG favor response to etanercept. Improvement in the knowledge of pharmacogenomic can make it possible to tailor treatment accordingly and to lower the unnecessary toxicity in patients receiving Etanercept.[23] In study conducted by Gordon KB et al. they found that PASI 25 achievement at week 4 was highly predictive of response to methotrexate at 16 weeks. Patients with a predicted response probability less than 30% were recommended to discontinue therapy. The rate of week 16 PASI 75 response were 65.8% and 21% (*P* <0.001) for patients whom were recommended to continue and discontinue to MTX therapy, respectively.[24] In study conducted by Gordon KB et al. they found that low dose of MTX (<15–20 mg per week) is an effective therapy for extensive and severe form of psoriasis if patient were selected carefully and monitored regularly, they observe that the effect was good in 76%, moderate in 18% and poor in 6% of subjects.[24] MTX has been associated with significant gastrointestinal side effect, one method of reducing of these side effect is by devided the dose. Rodríguez-Zúñiga et al., were first proposed to devide the dose of methotrexate for psoriasis. They showed small dose of 2.5–7.5 mg given at interval of 12 hours for total three doses every week had an improvement from 75–100% in 26 patients with gastrointestinal side effect (nausea, oral ulcer and herpes).[25] In our study, we had 2 patients with palmoplantar psoriasis on etanercept who fail to respond adequately to treatment and need additional treatment with methotrexate after 6 months as shown in Figures 1 and 2. This may suggest the poor response of this type of psoriasis to etanercept compared to a very good response in one patient with palmoplantar psoriasis in MTX group.

Table 4. PASI score mean ± SD with *P* value during treatment with MTX

Weeks	PASI mean ± SD	*P*-value
Baseline visit after 4 weeks	18.97 ± 10.54 12.276 ± 8.131	**0.01**
Baseline visit after 12 weeks	18.97 ± 10.54 5.72 ± 4.8	**<0.0001**
Baseline visit after 24 weeks	18.97 ±10.54 2.95 ± 6.01	**<0.0001**

F-test = 21.67, *P*-value ≤0.05 (significant).

Table 5. **Reduction rate in PASI score during treatment with MTX**

Reduction rate	No. of patients after 4 weeks	No. of patients after 12 weeks	No. of patients after 24 weeks
Complete clearance	–	2 (8%)	10 (40%)
>90%	–	4 (16%)	6 (24%)
75–90%	–	5 (20%)	5 (20%)
50–75%	8 (32%)	8 (32%)	–
25–50%	7 (28%)	5 (20%)	1 (4%)
0–25%	10 (40%)	1 (4%)	3 (12%)

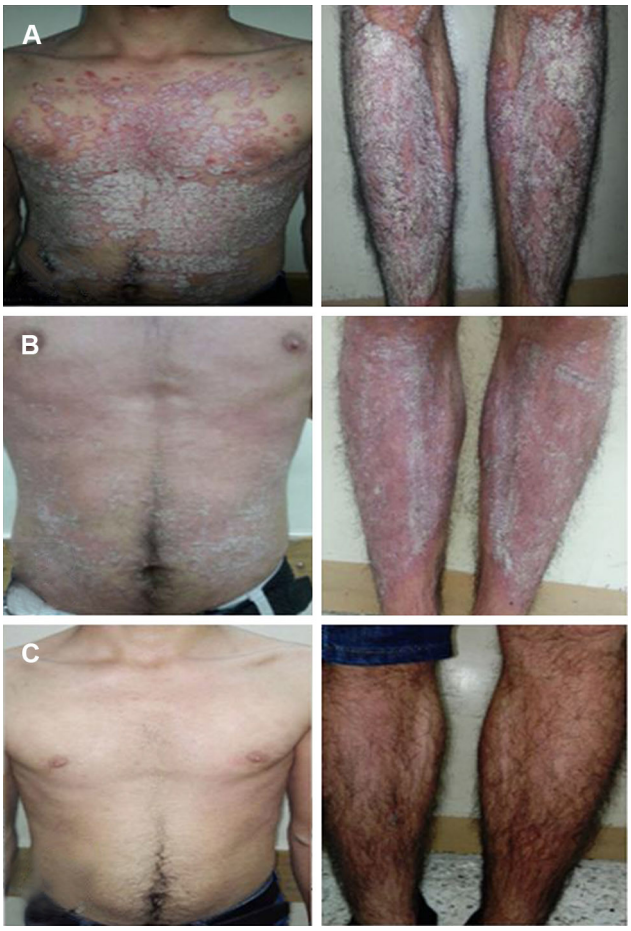

Fig. 1 **24 years old male with plaque psoriasis treated with Etanercept. (A): Before treatment. (B): After 12 weeks. (C): After 24 weeks.**

This is inconsistente with a case report published by Weinberg JM who reported a successful treatment of recalcitrant palmoplanter psoriasis with etanercept in 59 years old woman unresponsive to other treatment modalities.[26]

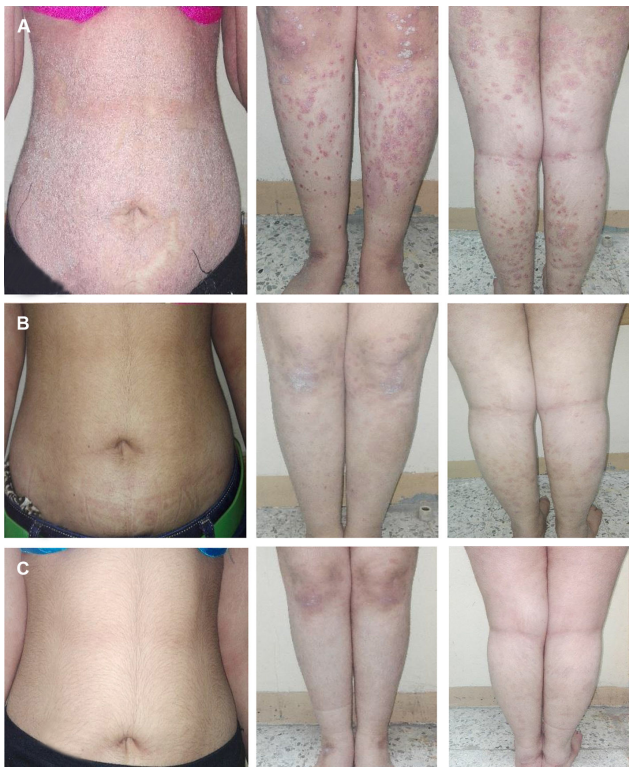

Fig. 2 **18 years old male with plaque psoriasis treated with MTX. (A): Before treatment (B): After 12 weeks (C): After 24 weeks.**

Conclusion

Both are effective monotherapy to treat patients with moderate to severe plaque psoriasis with tolerable side effects.

Conflicts of Interest

None.

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