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Etanercept versus Methotrexate in the Treatment of Psoriasis and Associated Metabolic Syndrome: 12-Month Open-Label Comparative Study

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Keywords
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Abstract

Introduction: Psoriasis is a chronic inflammatory systemic disease accompanied by systemic damage that leads to the development of multiple comorbidities including metabolic syndrome. Conventional systemic therapies for psoriasis are associated with toxicity and have a greater burden on the patients. The study aimed to assess the effectiveness of etanercept (ETN) monotherapy in comparison with methotrexate (MTX) monotherapy. ***Methods:*** In this prospective interventional comparative open-label study, 117 patients with psoriasis were randomized to 2 groups; 1 group of 42 patients; 32 (67.2%) males and 10 (23.8%) females treated with MTX, and the second group of 75 patients; 54 (72%) males and 21 (28%) females treated with ETN. Full laboratory investigations, body mass index (BMI), measurement of skin disease severity which was performed using Psoriasis Area Severity Index (PASI), and the reduction of 75% of the skin lesions (PASI 75) were calculated for all participants. ***Results:*** In the MTX group, there were no significant differences in BMI, or blood pressure after 12 weeks of the study. There is a reduction in the values of FBS, TSC, LDL, TRIG, ESR, CRP, and PASI, but this reduction was statistically not significant. Ten (23.8%) patients achieved PASI 75. In the ETN group, except for BMI, systolic and diastolic blood pressure, all other metabolic syndrome components, inflammatory markers, and PASI were decreased; the reduction was statistically significant. Sixty (80%) patients achieved PASI 75. ***Conclusion:*** Etanercept monotherapy showed greater efficacy than MTX monotherapy in the treatment of moderate to severe plaque-type psoriasis as it achieved greater reductions in PASI score and greater achievement of PASI 75 after 12 weeks. Etanercept monotherapy showed greater efficacy than MTX monotherapy in the improvement of all components of the associated metabolic syndrome except for BMI, which was increased in etanercept-treated patients.

Introduction

Psoriasis is a common chronic immune-mediated inflammatory skin disorder that affects approximately 1%–3% of the general population [1, 2]. Chronic plaque psoriasis is the most prevalent form of the disease. The most characteristic lesion consists of chronic, sharply demarcated, dull red, scaly plaques,

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particularly on the extensor aspects of the body and scalp. The pathogenesis of psoriasis is complicated and involves the interplay between keratinocytes, immune cells, and other skin-resident cells. Psoriasis is an immune cell-driven disease, and keratinocytes are just executors that perform the immune function [3]. IL-23/IL-17 pathogenic axis is the pivotal axis to promote the disease. The activation of plasmacytoid dendritic cells promotes the maturation of myeloid dendritic cells leading to the production of tumor necrosis factor-α (TNF-α), IL-12, and IL-23, which promote the activation of Th1 and Th17 and subsequent secretion of inflammatory cytokines, such as TNF-α, IL-17, IL-21, and IL-22 [4]. Previously, psoriasis was considered a disease that mainly affects the skin and joints, but its obvious impact on cardiovascular and metabolic disorders has been widely established recently [5, 6]. Psoriatic patients are associated with an increased risk of cardiovascular risk factors like metabolic syndrome (MetS) as well as its components such as obesity, dyslipidemia, hypertension, and insulin resistance compared to the general population [5, 7]. Psoriasis is associated with increased comorbidities and increased mortality rates compared to the general population [8, 9]. A meta-analysis including 12 other studies showed that patients with psoriasis were 2.2 times more likely to have MetS than the general population [10], and some authors found that there is a positive correlation between the severity of psoriasis and the presence of MetS [11]. The exact mechanism for this interaction remains uncertain but the link between them may be the effects of proinflammatory cytokines and adipocytes on glucose regulation, lipid status, and endothelial function [12]. TNF-α which is derived from activated dendritic cells, keratinocytes, T helper 1 cells, and T helper 17 cells has been identified as a key cytokine mediating cutaneous inflammation found to increase in psoriatic skin versus healthy controls [13]. It has therefore become an important target for the treatment of psoriasis. MetS is a cluster of several interrelated cardiometabolic risk factors, which include central obesity, atherogenic dyslipidemia, hypertension, and impaired glucose tolerance [14, 15]. Although several expert groups have proposed different diagnostic criteria for MS, they all include the same core components. MetS according to the WHO comprised of obesity which is defined by the presence of waist-to-hip ratio >0.90 in men and >0.85 in women and/or BMI >30 kg/m^2, triglycerides ≥150 mg/dL, HDL cholesterol <35 mg/dL in men and <39 mg/dL in women, blood pressure ≥140/90 mm Hg, fasting plasma glucose IGT, IFG, or Type 2 DM, microalbuminuria >30 mg albumin/g creatinine [15, 16]. Numerous epidemiological and cross-sectional studies have linked MS and its components with immune-mediated conditions, such as psoriasis, and psoriatic arthritis [17, 18]. Because of the interindividual differences in the pharmacokinetics of drugs that are linked to race, ethnicity, and ancestry [19], as well as the very few studies report prospective data on methotrexate (MTX) which is still considered the ideal therapy for moderate to severe psoriasis [20, 21], and Scanty studies comparing the efficacy of MTX and the novel drug (ETN) in patients with psoriasis in particular in our country, therefore we undertook the current open-label study to examine the comparative efficacy of MTX monotherapy relative to TNF inhibitor monotherapy in MTX-naïve patients with psoriasis and associated MetS.

Patients and Methods

This prospective interventional comparative open-label study was conducted at the Dermatology Outpatient and Basrah Biologic Center in Basrah Teaching Hospital from May 2021 to May 2022. A total of 117 (86 male and 31 female) patients with moderate to severe chronic plaque-type psoriasis vulgaris made by a certified dermatologist were enrolled in the study and randomly allocated into 2 groups. All participants were naive to any prior systemic medication for at least 3 months before the study with 42 patients treated with MTX (15 mg/w), and 75 patients were treated with subcutaneous etanercept 50 mg twice weekly for 3 successive months followed by 50 mg weekly. The Inclusion criteria for the study were patients above 18 years and below 60 years of age, both sexes, moderate to severe plaque, type of psoriasis, and patients willing to follow-up and continue the study. The exclusion criteria were children below 18 years and elderly patients more than 60 years, pregnant and lactating women, any serious systemic illness and infections, concurrent immunodeficiency state, patients with impaired renal function or renal disease, severe anemia, leukopenia, or thrombocytopenia. A detailed history was obtained from patients concerning family history, prior treatment, clinical history, physical activity, and other lifestyle factors, including cigarette smoking. Data also included weight, height, body mass index (BMI), blood pressure, disease duration, type, and severity of psoriasis. BMI was calculated as weight (kg)/[height (mt)^2]. Blood was drawn for fasting glucose (by automated enzymatic method); total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (by enzymatic/colorimetric methods); ESR (erythrocyte sedimentation rate by the Westergren method); and CRP (C reactive protein by immunoturbidimetry). All participants were screened for tuberculosis, hepatitis B, hepatitis C, and HIV infection. Measurement of skin disease severity was performed using the Psoriasis

Table 1. Demographic and clinical characteristics of the MTX group and ETN group

Characteristic	MTX group	ETN group	*p* value
Total, *n* (%)	42 (100)	75 (100)	
Male, *n* (%)	32 (67.2)	54 (72)	0.09
Female, *n* (%)	10 (23.8)	21 (28)	0.06
Age, years, mean±SD	47±4.5	46±4.5	0.12
Disease duration, years, mean±SD	8±5.4	9±1.6	0.11
BMI, mean±SD	25±2.3	24±2.1	0.11
Normal weight, *n* (%)	12 (28.57)	23 (30.66)	0.12
Overweight, *n* (%)	20 (47.6)	35 (46.66)	0.12
Obese, *n* (%)	10 (23.83)	17 (22.68)	0.11
PASI (mean±SD)	27±1.4	26±1.5	0.12

BMI, body mass index; PASI, Psoriasis Area Severity Index.

Area Severity Index (PASI) [22]. A PASI score below three, between 3 and 10, and above 10 was defined as mild, moderate, and severe disease, respectively. PASI 75 was calculated for all participants.

Statistical Analysis

SPSS software version 25.0 was used for data analysis. Percentages and mean were used to present the data in tables. In addition, a comparison of study groups was carried out using a χ^2 test for categorical data and Student's *t* test for continuous data. A *p* value of <0.05 was considered statistically significant.

Results

Of the 42 patients in the MTX group, there were 32 (67.2%) males and 10 (23.8%) females with mean age, disease duration, BMI, and PASI were 47 ± 4.5, 8 ± 5.4, 25 ± 2.3 and 27 ± 1.4, respectively. Of the 75 patients in the ETN group, there were 54 (72%) males and 21 (28%) females with mean age, disease duration, BMI, and PASI were 46 ± 4.5, 9 ± 1.6, 24 ± 2.1, and 26 ± 1.5, respectively, as shown in Table 1. Table 2 shows the differences in MetS components, inflammatory markers, PASI, and PASI 75 in the MTX group at baseline and after 12 weeks. There were no significant differences in BMI, systolic and diastolic blood pressures after 12 weeks of the study ($p > 0.05$). There is a reduction in the levels of FBS, TSC, LDL, TRIG, ESR, CRP, and PASI, but this reduction was statistically not significant ($p > 0.05$). HDL was increased after 12 weeks, but this increment was also insignificant ($p = 0.11$). Ten patients (23.8%) achieved PASI 75 in the MTX-treated group. In the ETN-treated group, except for BMI, systolic and diastolic blood pressure, all MetS components, inflammatory markers, and PASI were decreased; the reduction was statistically significant ($p < 0.05$ for all), while the HDL was significantly increased ($p = 0.03$). Sixty patients (80%) in the ETN group achieved PASI 75, as shown in Table 3. GIT symptoms were the prevalent adverse reaction in the MTX group, while injection site reaction was the prevalent adverse reaction in the ETN group, as shown in Table 4.

Discussion

It is estimated that 47 million Americans have MetS according to the 2000 US Census data [23], while the prevalence of MetS in Iraq was 39.4% in a study conducted in 2015 [24]. MetS is a comprehensive term for a cluster of interrelated metabolic disorders such as abdominal obesity, hypertension, insulin resistance, dysglycemia, and dyslipidemia [23]. It is associated with a higher risk of cardiometabolic diseases, including coronary artery diseases, type 2 diabetes mellitus, and all-cause mortality [25]. A clear association between psoriasis and obesity, which is an important parameter of the MetS, was established recently, and there is a growing awareness that both diseases are chronic inflammatory processes that have significant consequences on the individual's health; however, the findings of other studies appear to indicate that obesity may be a consequence of psoriasis rather than a risk factor for the condition [26]. In this study, there is a high percentage of overweight and obesity in the study population. Obesity has been shown by Shapiro et al. [27] to be more prevalent in psoriasis patients than in patients without psoriasis. The relationship between obesity and psoriasis is estimated to be interrelated in that obesity correlates with an increased risk of psoriasis and psoriasis might conversely lead to the occurrence of obesity [28]. Our study showed an increase in BMI after 12 weeks of treatment with ETN compared

Table 2. Differences in MetS components, inflammatory markers, PASI, and PASI 75 in the MTX group at baseline and after 12 weeks

Parameter	At baseline	After 12 weeks	*p* value
BMI, mean±SD	25±2.3	25±1.2	>0.05
Blood pressure (systolic), mean±SD	128±2.6	128±3.4	>0.05
Blood pressure (diastolic), mean±SD	80±2.4	79±4.5	>0.05
FBS, mean±SD	154±3.5	150±5.3	0.09
TSC, mean±SD	168±2.6	162±2.4	0.10
LDL, mean±SD	140±4.4	140±4.1	0.11
HDL, mean±SD	53±3.5	59±3.5	0.11
TRIG, mean±SD	160±5.6	163±4.4	0.12
ESR, mean±SD	30±3.6	29±2.2	0.12
CRP, mean±SD	7±3.5	6±4.3	0.19
PASI, mean±SD	27±1.4	19±4.5	0.06
PASI 75, *n* (%)	0	10 (23.8)	

FBS, fasting blood sugar; TSC, total serum cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TRIG, triglycerides; ESR, erythrocyte sedimentation rate; CRP, C- reactive protein.

Table 3. Differences in MetS components, inflammatory markers, PASI, and PASI 75 in the ETN group at baseline and 12 weeks

Parameter	At baseline	After 12 weeks	*p* value
BMI, mean±SD	24±1.2	26±3.2	0.07
Blood pressure (systolic), mean±SD	128±3.4	112±2.1	>0.05
Blood pressure (diastolic), mean±SD	88±2.4	70±2.2	>0.05
FBS, mean±SD	148±3.5	110±1.3	0.04
TSC, mean±SD	188±4.6	102±1.2	0.04
LDL, mean±SD	154±7.4	100±2.3	0.04
HDL, mean±SD	48±1.3	69±4.5	0.03
TRIG, mean±SD	180±5.6	110±1.2	0.03
ESR, mean±SD	28±5.5	10±3.2	0.01
CRP, mean±SD	7±2.5	2±1.2	0.01
PASI, mean±SD	26±1.5	4±2.5	0.002
PASI 75, *n* (%)	0	60 (80)	

FBS, fasting blood sugar; TSC, total serum cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TRIG, triglycerides; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Table 4. Adverse effects in the MTX group compared with the ETN group

Adverse effect	MTX group (*n* = 42)	ETN group (*n* = 75)	*p* value
Injection site reaction, *n* (%)	0	4 (5.33)	0.011
URTI, *n* (%)	1 (2.38)	2 (2.66)	0.122
GIT symptoms, *n* (%)	10 (23.80)	1 (1.33)	0.011
Allergic skin reaction, *n* (%)	1 (2.38)	2 (2.66)	0.122
Headache, *n* (%)	1 (2.38)	2 (2.66)	0.122
Skin infection, *n* (%)	0	0	0.122
Fever, *n* (%)	1 (2.38)	2 (2.66)	>0.05
UTI, *n* (%)	1 (2.38)	2 (2.66)	0.122
Tuberculosis, *n* (%)	0	0	0.122

GIT, gastrointestinal tract; UTI, Urinary tract infection; URTI, upper respiratory tract infection.

to treatment with MTX, this finding is consistent with a study on patients with spondyloarthropathy ($n = 19$, $n = 4$ for PsA), 2 patients were treated with ETN for up to 1 year. Results from treatment with either infliximab or ETN showed a significant increase in body weight and lean mass from 6 months to 1 year of therapy with an increase in body weight by 1.77 kg ($p = 0.0012$) and in lean mass by 0.8 kg ($p = 0.03$) [29]. Association between treatment with TNF-a inhibitors and weight gain was apparent in several observational studies [30, 31], and a 2020 meta-analysis confirmed that psoriasis patients treated with TNF-α inhibitors had a significant increase in body weight compared with patients receiving conventional systemic therapy (mean difference, 1.4 kg–1.93 kg) [32]. The same meta-analysis detected no significant increase in weight or BMI in psoriasis patients treated with anti-IL-12/23 or anti-IL-17 antibodies [32]. Studies revealed that TNF-α induces weight loss through two different mechanisms; one of them is the central weight regulation in the brain by inducing appetite loss by hypothalamic anorexigenic signaling and the second is the induction of carbolic process in the periphery; therefore, TNF-α inhibition might affect both mechanisms resulting in weight gain [33, 34]. Improvements in the levels of FBS, TSC, LDL, and TRIG were obvious findings in this study in both MTX and ETN-treated groups; this improvement was more marked in the ETN-treated group, a result consistent with another study that has shown that antitumor necrosis factor improved insulin sensitivity and alters lipid profile in psoriasis patients [35]. Other studies show conflicting results in the effects on insulin resistance with etanercept in psoriatic patients, and Boulton and Bonilla et al. [36, 37] showed a decrease in serum glucose level in response to ETN. The effects of short-term ETN in 12 psoriatic patients were examined in a 2-week randomized, double-blind clinical trial. No changes in insulin secretion and sensitivity were observed after 2 weeks [38]. Contrary to our findings, Gisondi et al. [39] ($n = 58$) and Marra et al. [40] ($n = 9$) revealed no significant differences in TG and TC after 24 weeks of ETN. Another study found no change in TC, LDL, HDL, and TG after 48 weeks of etanercept ($n = 50$) [41]. Among patients with MetS, inflammatory risk markers, including CRP, are elevated and associated with cardiovascular and other components of MetS [42]. In this study, inflammatory markers like CRP were decreased at the endpoint in both MTX-treated and ETN-treated groups, but it is more marked and significant in the ETN-treated group, this result is consistent with other studies on patients with known inflammatory conditions, including ankylosing spondylitis, and psoriatic arthritis in which etanercept has been shown to decrease CRP levels and improve endothelial function [43–45]. In this study, the subjects who received ETN had a mean PASI score at baseline of 26 ± 1.5 and 4 ± 2.5 after 12 weeks ($p = 0.002$), while subjects who received MTX had baseline PASI of 27 ± 1.4 and 19 ± 4.5 after 12 weeks ($p = 0.06$). After 12 weeks, 60 patients (80%) of the ETN group achieved PASI 75 compared to 10 patients (23.8%) of the MTX group who achieved PASI 75, this finding is consistent with the findings of other previous 2 studies. The first one was conducted on 652 subjects who received a placebo, 25 mg once weekly, 25 mg twice weekly, or 50 mg twice weekly for 3 months. At 3 months, 47% of the 50-mg-twice-weekly group, 32% of the 25-mg-twice-weekly group, and 14% of the 25-mg weekly groups achieved PASI 75 compared to placebo (4%) [46]. The second study conducted on 583 patients yielded similar results. Subjects were randomized to receive 25 mg twice weekly, 50 mg twice weekly, or placebo for 3 months. Then, all groups received open-label etanercept 25 mg twice weekly for 9 months. Forty-six percent of the 50-mg twice-weekly and 32% of the 25-mg twice-weekly groups achieved PASI 75 in 3 months compared with placebo (3%) [47]. In a study from Iraq, Abbas tested etanercept monotherapy for 6 months on patients with psoriasis regardless of the associated MetS and was recorded with obvious PASI score reduction (60%) [48]. In another study from Iraq, Obeed [49] compared the efficacy of etanercept and MTX treatment for psoriasis. After 6 months of treatment, he found no statistical differences between the two groups. In psoriasis skin, IL-12 and IL-23 induce the differentiation of naive CD4 + T-cells which produce pro-inflammatory cytokines in particular TNF-α, which is heavily involved in the pathogenesis of psoriasis and plays an important role in metabolic regulation and induction of MetS and its components [50, 51]. Improvement of MetS components after treatment with anti-TNF-α may be linked to the induction of adiponectin which is an adipocyte-derived cytokine, that has anti-inflammatory and antiatherosclerotic properties and is decreased in obese populations [52]. Systemic agents such as anti-TNF-α have the potential to positively impact both psoriatic skin lesions and metabolic health due to the shared activation of systemic immune pathways between psoriasis and MetS [53]. In this study, apart from injection site reaction and GIT symptoms in ETN and MTX-treated patients, respectively, there were no serious adverse events. Even though tuberculosis is an endemic disease with an estimated incidence of 27 per 100,000 in Iraq [54], we reported no tuberculosis infection or reactivation. An important limitation of this study is that it is a one-center study.

Conclusion

Etanercept monotherapy showed greater efficacy than MTX monotherapy in the treatment of moderate to severe plaque-type psoriasis as it achieved greater reductions in PASI score and greater achievement of PASI 75 after 12 weeks. Etanercept monotherapy showed greater efficacy than MTX monotherapy in the improvement of all components of the associated MetS except for BMI, which was increased in etanercept-treated patients.

Key Message

Because psoriasis is associated with metabolic alterations, treatment with novel drugs is essential.

Statement of Ethics

Written informed consent was obtained from all participants before their involvement. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was conducted after obtaining the approval by Basrah Directorate of Health, the Center of Training and Human Resources, Approval No. 02/2021.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Samer A. Dhaher and Jinan Q. Mohammed participated equally in the concept and design, as well as in the final drafting of the manuscript. Samer A. Dhaher provided significant contributions to the conception and design, the analysis and interpretation of the data, and to the drafting of the final article and revising it critically for important intellectual content and on the final approval of the version to be published. Jinan Q. Mohammed critically revised the intellectual content and approved the final version to be published.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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