ORIGINAL ARTICLE

Etanercept monotherapy in the treatment of severe psoriasis: An experience from Amiri hospital, Kuwait

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ABSTRACT

Background: Psoriasis is a chronic, relapsing inflammatory skin disease that can seriously affect patient quality of life. Although many psoriatic patients may in the short term benefited from traditional therapies including the systemic, the lack of long-term remissions and the potential of developing toxic effects limited their use. There is obvious need for treatment options that have favourable safety and efficacy profiles. Biological treatments, such as etanercept, a tumor necrosis factor antagonist, have been recently used to treat psoriasis with encouraging outcomes.

Objective: To assess efficacy and safety of the recommended high dose 24 weeks course of etanercept in the treatment of severe plaque psoriasis in Kuwaiti population and to determine the relapse time after completion of therapy course. Additionally, to evaluate the long-term effectiveness and safety of continuous and interrupted maintenance regimens using both recommended and lower doses.

Methods: Sixteen patients with severe psoriasis were started on the recommended high dose of etanercept i.e. 50 mg subcutaneously twice weekly (BIW) for 12 weeks, followed by either 50 mg once weekly (QW) or 25 mg BIW for another 12 weeks. During follow-up period, relapsed patients received either a repeated course of high dose etanercept (50 mg subcutaneously twice weekly (BIW) for 12 weeks then 50 mg once weekly (QW) for another 12 weeks) (option I) or 50 mg and 25 mg of etanercept once weekly for 12 weeks then 50 mg once weekly for another 12 weeks (option II). A group of the cohort (8 patients) continued maintenance therapy with etanercept (50 mg / 10 days) without interruption till the end of the study (option III).

Results: All 16 patients tolerated and completed the recommended high dose etanercept therapy (24 weeks). Fifteen patients (93.8%) achieved 75% reduction in the PASI at the first primary end point (12 weeks). Whereas one patient (6.3%) achieved only 26% reductions in PASI score. Among the 15 patients, eight (50%) were also able to achieve 90% reduction in PASI. By the end of 24 weeks of therapy 15 patients (93.8%) were sustained on achieving 75% reduction in PASI while one patient achieved only PASI 71.

Limitations: This was a preliminary retrospective uncontrolled analysis at a single practice site. This report includes a very small number of patients, which reflects the relatively small scale of Kuwait population.

Conclusion: Etanercept provided clinically significant benefit to our patients with severe psoriasis. It was generally well tolerated with expected controllable safety profile that allows an expedient flexible option to manage patients with psoriasis.

KEYWORDS:Etanercept, psoriasis

INTRODUCTION

Psoriasis is a common chronic immune-mediated skin disease that affects approximately 2-3% of the population worldwide.[1, 2] Psoriasis can be classified based on its severity into mild, moderate or severe. Psoriasis has substantial morbidity and psychological impact which eventually lead to profound negative outcomes on patient quality of life.[3] The conventional therapies traditionally used to treat psoriasis include topical agents, phototherapy and systemic agents.[4,5] Such treatment modalities can reduce the extent and severity of

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the disease and therefore improve quality of life. However, they do not provide permanent cure.[6, 7] Moreover, the unrestricted long-term administration of the systemic agents, namely methotrexate, cyclosporine, retinoids, phototherapy and fumaric acid esters is limited by their potential side effects, particularly organ-targeted toxicity.[3,8] In addition, there is increasing evidence on patient dissatisfaction with the effectiveness of available therapies and the desire for more aggressive forms of therapies that may offer more extended long-term remission periods.[3] A number of biologic agents with selective mechanisms of action are currently approved for the treatment of adults with moderate to severe plaque psoriasis as well as other immune-mediated diseases.[9,10] Two groups of biologics are available for the treatment of psoriasis: (I) agents targeting the cytokine tumor necrosis factor (TNF-α) (e.g. etaneracept, infliximab, adalimumab) and (II) agents targeting T-cells or antigen-presenting cells (e.g. efalizumab, alefacept). Etanercept, an inhibitor of TNF- α, is a fully human soluble recombinant p75 TNF receptor which blocks the binding of TNF to cell surface receptors and consequently neutralizing its biological activity. Etanercept has been extensively used in rheumatology to treat patient with rheumatoid arthritis.[11] ankylosing spondylitis.[12] and also in patient with psoriatic arthritis who showed simultaneous improvement of their psoriatic cutaneous lesions.[13] The efficacy and safety of etanercept have been demonstrated in randomized placebo-controlled clinical trials in patients with moderate to severe psoriasis.[14, 15, 16]

PATIENTS AND METHODS

Patients

This retrospective study was conducted on 16 patients with severe plaque psoriasis who were treated with etanercept during the period March 2005 March 2007 at the out-patient clinics of dermatology department, Amiri hospital in Kuwait.

Adult patients with severe plaque psoriasis who meet inclusion criteria were selected and enrolled in the study. Eligible patients were males and females aged at least 18 years with clinically stable plaque psoriasis that rated at least 10 on the Psoriasis Area and Severity Index (PASI) at the baseline screening. Additional entry criteria also required that the patients had received at least two previous systemic psoriasis therapy (such as methotrexate, oral retinoids, or cyclosporine) or phototherapy (8-methoxy psoralen plus UVA-PUVA; UVB (broad-band or narrow-band)) with history of failure, or intolerance or contraindication to these systemic therapies. Patients had terminated such therapies at least 4 weeks before starting the present drug administration. Patients should have adequate hematological, renal and hepatic function at the screening visit.

Patients were excluded if they had guttate, erytherodermic, or pustular psoriasis, renal insufficiency, hepatic disorders, history cancer or other lymphoproliferative disorders, demyelinating diseases, tuberculosis, pregnancy, lactation.
Written informed consents were obtained from all patients before starting any study-related procedures. No other concomitant therapy was allowed during drug administration apart from emollients and low to moderate corticosteroid preparations. None of our patients had been treated with etanercept or any other biological agents.

The following data were collected: age, sex, duration of psoriasis, family history, body weight, previous treatments, and joint involvement. A detailed personal and family history of tuberculosis was taken. The severity of psoriasis was assessed by Psoriasis Area and Severity Index (PASI) at baseline i.e. before starting treatment, then at 12 weeks (primary end point) and at 24 weeks (secondary end point). All patients included in the study were followed up over two years of treat-

ment with etanercept for clinical response, adverse events, relapse times and adjustment of the etanercept dose.

All patients were fully investigated prior to treatment. The screening tests included a full blood count, urea and electrolytes, liver function profiles, antinuclear antibodies (ANA), hepatitis B virus, HIV, and tuberculin test (Mantoux, <10 mm of induration, 48-72 hours after placement) and chest X-ray.

Assessment of etanercept efficacy in controlling our patients was attained via estimations of PASI scores, scheduled at week 0, week 12 (primary efficacy end point), week 24 (secondary efficacy end point) then every 4 weeks during follow-up period. A 75% improvement in the PASI score (PASI-75) at the end of week 24 relative to baseline score was used to document the effectiveness of the drug in the present study.[17, 18] Relapse was defined as loss of 50% of PASI improvement from baseline in patients who achieve a clinically meaningful response.[19]

All patients were followed up over a period of two years of treatment with etanercept for clinical response, adverse events, relapse times and adjustment of the etanercept dose. Follow-up visits were scheduled as twice weekly for the first three months, every two weeks for the second three months and then monthly.

Our patients were assessed for any possible side effect including acute adverse events, such as headache, fever, chills, nausea, vomiting, or myalgia, injection site reactions ect. Laboratory tests were monitored every four weeks or required as deemed necessary and tuberculin skin test was evaluated yearly. A temporary cessation of etanercept was required in patients who developed infection during the course of therapy until they were fully recovered.

Study drug

Etanercept (Enbrel, Wyeth Europa Ltd., Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH, United Kingdom) was supplied through the Ministry of health, State of Kuwait and was available in syringes, each containing the contents of one constituted vial of etanercept. Etanercept was administered by subcutaneous injection (SC), initially at the clinic by a professional nurse who then trained all the patients to self-inject the drug.

Etanercept was the first biological agent to be introduced in our dermatology department, Amiri Hospital, Ministry of health, Kuwait.

Study design

The study protocol was to use etanercept as monotherapy to qualified psoriatic patients on two phases as outlined in Figure 1. The objectives in the first treatment phase were to assess its efficacy and safety when using the recommended high dose and to determine the relapse time after termination of such therapy. In the follow-up treatment phase, the use of different starting dose of etanercept (lower vs. higher) during first 12 weeks of therapy was explored. Also, the efficacy and safety of etanercept as a maintenance therapy was assessed.

The first phase or the recommended treatment phase in which all the patients were started on the recommended higher dose of etanercept i.e. 50 mg subcutaneously twice weekly (BIW), in order to produce a more rapid response[14, 15, 16] and to ensure maximal benefit to patients during the initial 12 weeks of therapy period. This was followed by

either 50 mg once weekly or 25 mg twice weekly (BIW) of etanercept for another 12 weeks.

The second phase or the follow-up treatment phase entitled patients who completed their initial full course and allowed to relapse (to assess the relapse time for each of them) then restarted etanercept therapy with either:

i. a repeated second course of etanercept (50 mg subcutaneously twice weekly (BIW) for 12 weeks then 50 mg once weekly for another 12 weeks (Option I) or

ii. both 50 mg and 25 mg etanercept once weekly for 12 weeks then 50 mg once weekly for another 12 weeks (Option II).

Whereas those who completed their initial full course but given no chance to relapse:

iii. receive 50 mg of etanercept every 10 days directly following last dose of the recommended treatment phase (24 weeks) without interruption as a continuous maintenance dose (Option III).

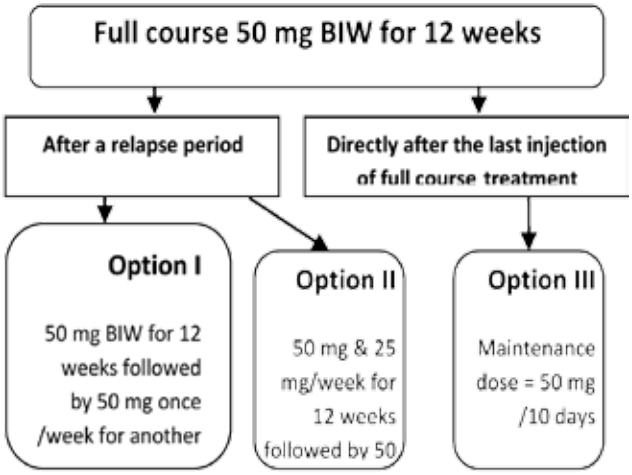

Fig 1. Study design and dosing regimens of etanercept monotherapy in severe plaque psoriasis.

RESULTS

Patients

All patients were referred to our outpatient clinics from our local recruitment areas. All the selected patients fulfilled the inclusion criteria for the use of etanercept therapy and were on the drug for a minimum of 24 weeks. Demographic data and clinical characteristics of these patients are summarized in Table 1 and include: 16 adult patients 10 males and 6 females with age range of 20-58

Table 1 Demographic and clinical characteristics at baseline.

Characteristic	
Total number of patients	16
Age: mean (range-years)	39 (20-58)
Male: Female	10:6
Weight: mean (range in kg)	85.5 (58-113)
Duration of psoriasis: mean (range years)	16 (7-25)
Patients with psoriatic arthritis (No.)	5
PASI (Psoriasis Area Severity Index) score: mean (range)	31.5 (20-53.3)
Prior systemic therapy (no. of patients): - Methotrexate - Oral Retinoids - Corticosteroids	 4 3 3
Prior phototherapy (No. of patients): - PUVA - UVB	 8 4

years (mean 39). All have severe chronic plaque psoriasis as indicated by patients' disease history and clinical presentation, duration of the disease (range 7-25; mean 16 years), extent of body involvement (PASI score: range 20-53; mean 31.5) and history of previous treatment for their psoriasis with systemic therapy or phototherapy (Table 1). Five of our patients (31.3%) suffered from psoriatic arthritis. All laboratory tests remained within normal limits during treatment with etanercept.

The first treatment phase:

Efficacy

All 16 patients complete the initial 24 weeks therapy with etanercept on the recommended high dose of 50 mg SC injection (BIW) for 12 weeks, followed by 25 mg (BIW) or 50 mg once weekly for another 12 weeks. One patient developed adverse effects on last injection of the full course.

PASI score was determined in all the 16 patients (Fig 2). Fifteen patients (93.8%) achieved 75% reduction in the PASI at the first primary end point (12 weeks). Among the 15 patients, eight (50%) were also able to achieve 90% reduction in PASI. only one patient (NO. 6) (6.3%), achieved 26% reduction in PASI score. By the end of 24 weeks of therapy the fifteen patients (93.8%) were sustained on achieving 75% reduction in PASI. Furthermore, five of them (31.3%) attained PASI-100 with clinical clearance, while one patient (NO. 6) achieved only PASI 71, and was therefore considered a nonresponder and exempted from follow-up phase (Fig. 2). None of our patient needed concomitant systemic treatment beside the etanercept therapy as concomitant topical treatment was sufficient. Figure 3 illustrates an example of clinical improvement obtained at end of 24 weeks of etanercept therapy as compared to baseline in a representative patient.

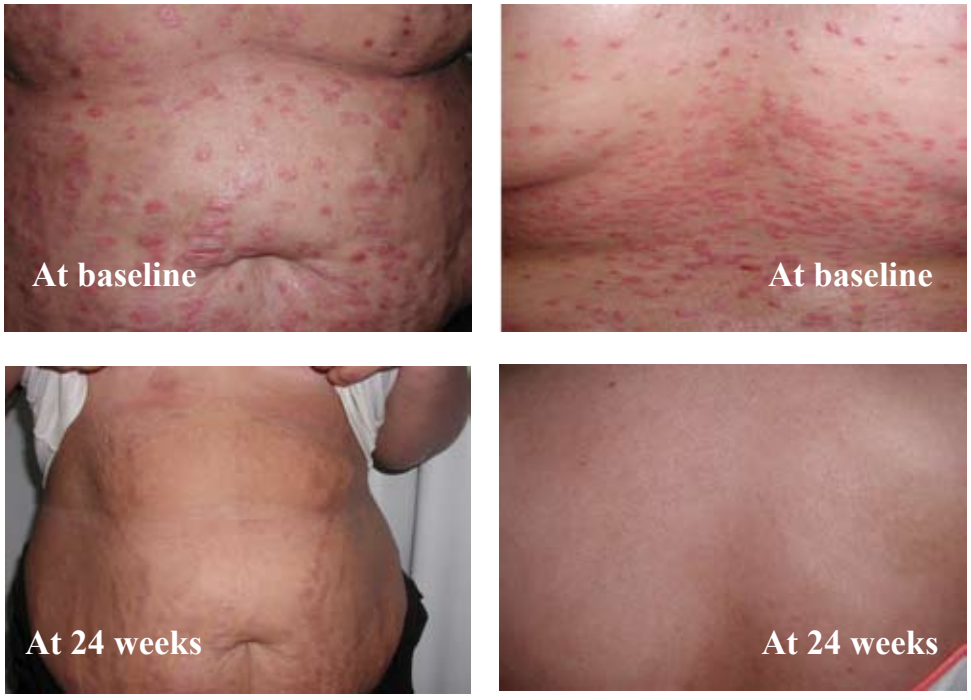

Fig. 3 Comparison of clinical improvement achieved at 24 weeks versus at baseline in a representative patient.

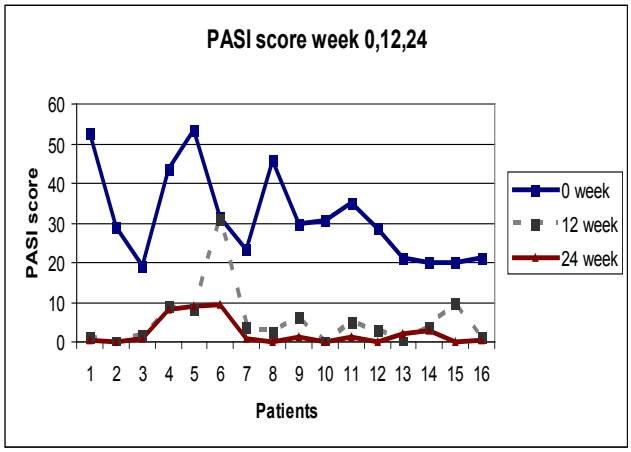

Fig. 2 PASI score of the 16 patients at 0 (baseline), 12, and 24 weeks.

Relapsed time after completion of the first treatment phase:

The first 8 patients who completed their first course of the recommended high dose etanercept at 24 weeks, relapsed after a mean remission period of 7.3 weeks (range 4-12 weeks) (Fig. 4).

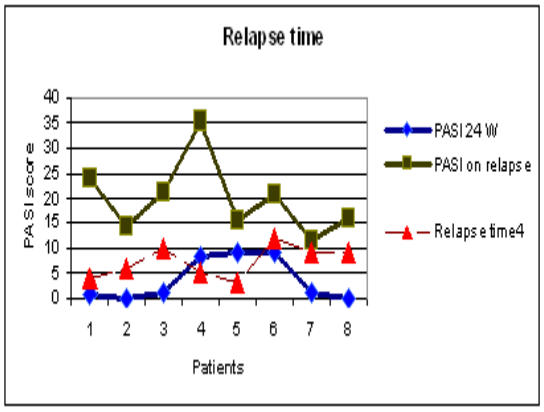

Fig. 4 Relapse time for 8 patients following completion of full etanercept therapy course (24 weeks).

The second phase or follow-up treatment phase with different etanercept dosing:

Patients on the first follow-up treatment option (Option I):

Three patients, who already completed the recommended high dose etanercept treatment course and relapsed, were chosen for the first follow-up treatment option i.e. to receive a second course of etanercept on the same recommended high dose

Table 2 PASI score at end of the first and second full etanercept course

Patient No.	PASI at end of 1st course	PASI at end of 2nd course	Dose
3	0.9	0.0	50/50 – 50/QW
7	0.9	0.0	50/50 – 50/QW
8	0.0	0.0	50/50 – 50/QW

Table 3 PASI score at end of first full course and at end of second course (with 50/25 mg etanercept dose followed by 50 mg/week dose)

Patient No.	PASI at end of 1st course (full etanercept therapy)	PASI at end of 2nd course (with dose 25/50mg for 12 weeks - 50/week for 12 weeks)
1	0.6	6.3
2	0.0	0.0
4	8.3	9
5	8	8

of 50 mg (BIW) for 12 weeks followed by 50 mg once weekly (QW) or 25 mg twice weekly (BIW) for another 12 weeks. There was no difference in the response compared with the results obtained following the first course as all the three patients not only achieved a PASI 75 improvement at the end of the second full course of etanercept but also a complete clearance with PASI 0 (Table 2).

Patients on the second follow-up treatment option (Option II):

Four patients, who also completed the recommended high dose etanercept treatment course and relapsed, were given a second etanercept course but with a lower dose of 25 mg and 50 mg once weekly for 12 weeks then a 50 mg once weekly for another 12 weeks.

Three of them attained similar improvement in PASI score on this treatment option as compared with their improvement on full etanercept therapy. However, one patient (No. 1) achieved only PASI 6.3 as compared to PASI 0.6 which was achieved with the full etanercept therapy (Table 3) (Fig. 5).

Table 4 PASI score and maintenance period in patient on follow-up treatment option III.

Patient No	PASI before maintenance dose	Period of maintenance (weeks)	PASI during maintenance dose
3	0	32	1.2
9	0	32	1.6
7	1.5	25	1.5
5	2.4	18	10
8	0.3	12	1.2
10	0	12	3.5
14	2.8	10	1.8
11	2.8	8	11.7

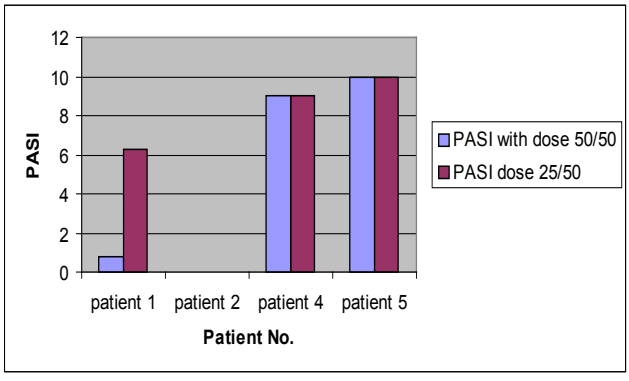

Fig. 5 PASI score comparison between etanercept dose 50 mg (BIW) & 25/50 mg once/week.

Patients on the third follow-up treatment option (Option III):

Eight patients were kept on a maintenance dose of etanercept (50 mg/10 days) directly after completion the recommended high dose etanercept course without any interruption i.e. no chance of relapse was given.

The maintenance period extended between 8 and 32 weeks following the end of a full high dose course of etanercept (24 week) (Table 4). Only two patients (No. 5 and No. 11) lost their PASI 75 improvement with a clinical relapse rating 10 and 11.7 respectively. They were consequently shifted again to the full dose etanercept therapy, while the other 6 patients attained their PASI 75 improvement as they continued on the maintenance dose (Fig. 6).

Table 5 Summary of adverse events.

Patient No.	Adverse events
1	---
2	Herpes simplex, body ache, acute tonsillitis
3	Injection site reaction, joint pain
4	---
5	Joint pain
6	---
7	Sore throat, Fever
8	---
9	---
10	---
11	---
12	---
13	---
14	Palmo-planter pustules
15	Fatigue
16	Acne-form eruption (face), calesion (right upper eyelid)

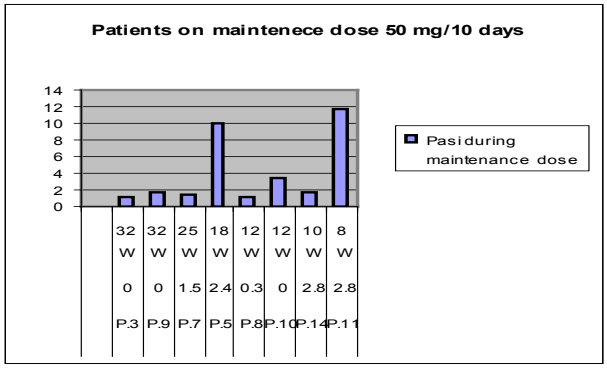

Fig. 6 PASI score during maintenance in patients on follow-up treatment of 50 mg/10 days (option III).

Adverse effects

There were no serious adverse events reported during treatment with etanercept in our psoriatic patients. Etanercept was generally safe, well tolerated and acceptable by all the patients. The adverse events reported by our patients are summarized in Table V. These were mild and included: injection site reaction, fever, fatigue, myalgia, herpes simplex, acute tonsillitis, joint pain (Table 5). Treatment was discontinued in only one patient, No. 14, who developed a palmo-planter pustular eruption just following last dose of etanercept course (at week 24). While Patient (No.6) has an acne-form eruption on face (Started in the fourth week of therapy and cleared after 4 weeks) associated with a clesion (on right upper eye-lid).

DISCUSSION

Biologic therapies have been studied rigorously in well-designed controlled trials treating significant numbers of patients with psoriasis.[14, 15, 16] TNF-α has been shown to be a key proinflammatory cytokine in the pathogenesis of psoriasis and psoriatic arthritis. Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human TNF-α receptor linked to the Fc portion of human immunoglobulin G1. In 2004, etanercept has been approved by US FDA and European Union for the

treatment of adult patients with chronic moderate to severe plaque psoriasis.[20]

This report summarized our local Kuwaiti clinical experience in treating 16 patients with severe psoriasis with etanercept in a daily clinical practice set-up. Here we share our standard procedures for patient selection, screening and treatment initiation, treatment dosing and report the efficacy and safety of etanercept in our patients. Our patients appreciated the convenience of using etanercept compared with other therapy interventions.

At the first phase, all 16 patients completed the recommended high dose etanercept course i.e. 50 mg subcutaneously twice weekly (BIW) for 12 weeks, then stepping down to either 50 mg once weekly (QW) or 25 mg twice weekly (BIW) for another 12 weeks. Compared to other studies,[14, 15, 16, 21] our inclusion/exclusion criteria were more restricted to patients with severe psoriasis, as indicated by their baseline PASI score (mean 31.5), who were already resistant to at least two other systemic therapies but were not on other concomitant therapies. We have, therefore, chosen to start all our patients on this recommended high dose regimen of etanercept in order to attain the maximum benefit of having rapid response during their initial treatment period.[14, 15, 16, 21]

Regarding efficacy assessment, a 75% improvement in the PASI score (PASI 75) is predominantly used to document the effectiveness of individual therapies in clinical trials of patients with extensive psoriasis.[17,18] Accordingly, fifteen of our patients (93.8%) achieved 75% reduction in the PASI at the first primary end point (12 weeks). In addition, eight (56%) of them were also able to achieve 90% reduction in PASI. By the end of the 24 weeks of therapy (second end point) 15 of the sixteen patients (93.8%) were sustained on achieving 75% reduction in PASI. A 100 % reduction in PASI (complete clearance) (PASI 100) was achieved in 5 patients (31.3%). One patient (6.3%), however, failed to show similar improvement in PASI 75 and achieved only PASI 26 and PASI 71 at 12 weeks and 24 weeks of therapy respectively and was excluded from follow-up phase. The percentage of our patients attaining both PASI 75 and PASI 90 is apparently better than that reported in other etanercept clinical studies[14, 15, 16, 21] documented in the literature. However, the number of our patients is far well blew that included in those studies to allow for a real comparison. At the secondary end point, 13 out of 16 patients (81.2%) achieved PASI 90, two patients (12.5%) achieved PASI 75 and one patient (6.2%) achieved only 71%. Such high level of improvement in patients attaining PASI 90 may be attributed to the using of the maximum recommended dose of etanercept (50 mg BIW) from the start.

Majority of patients on treatment options I and II, who were allowed to relapse following initial high dose of etanercept, attained improvement in PASI 75 comparable with that achieved following first high dose etaneracept course without any reported serious side effects.

In comparison to our relapsed patients, Ahmed and Rogers (2007)[22] reported a longer mean remission time of 13.4 weeks in their patients. This might be attributed to the concomitant use of other systemic agents, namely methotrexate, cyclosporine, and hydroxycarbamide for their patients either during an overlap period at the start therapy or on continuous basis. None of our patients experienced rebound or flare of his psoriasis on discontinuation of etanercept therapy. Their response to subsequent treatment courses of etanercept was equally good in most but not all of them. In agreement with our finding, several published reports suggested that etanercept therapy can be interrupted and then resumed with successful retreatment without potential safety risks.[23, 24]

Rheumatologists, compared to dermatologists, traditionally used etanercept in a continuous ap-

proach in a number of immunological diseases such as rheumatoid arthritis [11] and psoriatic arthritis.[13] Therefore, accumulated rheumatologic experience suggests psoriasis should be treated with etanercept in a similar manner. However, the major concerns in continuous etanercept treatment for psoriasis are efficacy and long-term safety as well as the proper dosing to be used. These were explored in our patients on option III, who continue on a maintenance dosing of 50 mg/10 days directly following initial high etanercept course. Majority of them (75%) were also able to maintain their improvement in PASI 75 throughout maintenance period (up to 32 weeks) again with favorable safety profile. The biological half-life of a drug is defined as the time taken by this drug to lose half of its pharmacologic activity. The biological half-life of etanercept ranges from 70-132 hours.[25] This could explain the clinical response in our patients maintained on etanercept dosing of 50 mg/10 days.

An overview of the different etanercept dosing regimen that were used in the present study, lead to the conclusion that the recommended full course of high dose, 50 mg/twice weekly for 12 weeks, followed by 50 mg once weekly for another period of 12 weeks, gave the best results for improving the PASI score in our patients. However, all the three follow-up treatment options were generally effective in maintaining good response parallel to that obtained following initial high dose etanercept course. This may underline the need to continue using etanercept treatment regardless of the type of dosing regimen. Furthermore, a recent report from Korea confirmed the effectiveness of a low-dose etanercept for moderate to severe psoriasis in Asian patients.[26]

Although further studies that clearly include broad cohort of psoriatic patients and in a more controlled fashion, are needed to establish the proper dosing regimen and long-term safety profile of etanercept therapy, our observations confirm the effectiveness and safety of etanercept in our population with severe psoriasis through the period of study and suggest the need for some sort of follow-up with etanercept as a maintenance therapy.

CONCLUSION

Etanercept was effective and generally well tolerated in our psoriasis patients. Etanercept has demonstrated consistent efficacy and excellent safety profile in the treatment of psoriasis both in clinical trials as well as in real practice. The easily self-administered etanercept injections provide an obvious advantage over traditional therapies and other biological agents. Furthermore, etanercept treatment dosing may offer a more flexible regimen, both as continuous or intermittent therapy, to achieve and maintain favorable results for individual patients if properly adjusted during follow-up period.

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