ORIGINAL ARTICLE

The treatment of psoriasis with etanercept: An experience from South Kuwait

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ABSTRACT

Background: Etanercept, a tumor necrosis factor antagonist, is an approved biologic agent for treatment of chronic plaque psoriasis in the United States and Europe.

Objective: To observe the efficacy and safety profile of etanercept in patients with moderate to severe plaque psoriasis.

Methods: In this retrospective study, 56 patients were treated with etanercept between May 2005 and May 2008. All patients were screened for tuberculosis. They were started on etanercept 50 mg twice a week (BIW) for 12 weeks followed by 25 mg BIW for another 12 weeks. Response to treatment was assessed by Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI). Patients were reviewed at 4-week intervals, when clinical response and adverse effects were noted and photographs taken.

Results: Forty-nine patients (87.5%) had chronic plaque psoriasis, three (5.35%) were erythrodermic and four (7.15%) had palmoplantar psoriasis. At least 75% reduction in PASI was achieved in 52% of patients at week 12 and 64% at week 24. Mean percentage of improvement from baseline in DLQI at week 12 was 47.6%, reaching 79% at week 24. The percentage of patients in the DLQI category correlating with 'no effect' on quality of life increased from 3.6% at baseline to 66% at week24, while the percentage in the category correlating with 'extremely large effect' decreased from 16% at baseline to 1.8% at week 24. In our study, a correlation was noted between DLQI and PASI score before treatment as well as at week 12 and 24. The adverse effects and laboratory abnormalities were minor.

Conclusions: Etanercept was effective and well tolerated for moderate to severe psoriasis. It can be used intermittently without rebound, with psoriasis responding again on reintroduction.

KEYWORDS: psoriasis, etanercept, bologics

INTRODUCTION

Psoriasis is a multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. The major manifestation of psoriasis is chronic inflammation of the skin. It is characterized by disfiguring, scaling, and erythematous plaques that may be painful or often severely pruritic and may cause significant quality of life issues.[1] The disease is associated with many physical and mental disabilities, including work-related discrimination, financial distress, depression, and suicidal ideation.[2-6] The pathogenesis of psoriasis is quite complex, but there is compelling evidence that overproduction of proinflammatory cytokines by T cells and keratinocytes, including tumor necrosis factor (TNF), plays a very important role.[7-10] TNF-α is found in increased concentrations in the joints and skin of patients with rheumatoid arthritis, psoriatic arthritis and psoriasis.[11] It plays an active role in Langerhans cell migration, maturation, and in leukocyte recruitment.[12] Serum and lesional TNF levels decrease after effective psoriasis therapy, correlating with clinical improvement in the dis-

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ease.[13] These observations suggest that interfering with the proinflammatory effects of TNF may reduce the characteristic inflammation seen in psoriatic lesions.

Until recently, psoriasis treatment options ranged from topical products for mild to moderate forms of psoriasis to phototherapy and systemic therapies such as methotrextae (MTX) and cyclosporine, for moderate to severe disease.[14-16] They reduce the symptoms of this chronic disease,[18] but many well-established systemic drugs for patients with moderate to severe psoriasis are associated with substantial safety and tolerability issues, which include cutaneous malignancies (psoralen plus ultraviolet A therapy),[18] hepatic disease, teratogenicity, myelosuppression (methotrexate),[19] and nephrotoxicity (cyclosporine).[20] Patient surveys have shown that only 25% of psoriasis patients are highly satisfied with the outcome of their treatment, another 50% indicate moderate satisfaction, and approximately 20% report low treatment satisfaction.[21] In addition, phototherapy or topical therapies are inconvenient, time consuming, or have limited effect in moderate to severe psoriasis and there is a high non-compliance rate in the intake of medication of up to 40%.[22] Such issues have spurred efforts to develop psoriasis therapies with a better combination of long-term effectiveness and safety.[23]

Etanercept is a fully human, soluble, TNF receptor-IgG1 fusion protein that binds to both soluble and membrane bound TNF, inhibiting its interaction with cell-surface receptors and preventing TNF-mediated cellular responses.[24] The safety and efficacy of etanercept have been demonstrated in patients with rheumatoid arthritis,[25,26] juvenile rheumatoid arthritis,[27,28] psoriatic arthritis,[29,30] and ankylosing spondylitis.[31] In studies of patients with psoriasis and psoriatic arthritis, etanercept as monotherapy provided clinically significant benefit and had a favorable safety profile.[29,30,32-34] The Food and Drug Administration has approved the use of etanercept for the treatment of moderate to severe plaque psoriasis.[35] Here we describe our 3-year experience in treating patients with moderate to severe plaque psoriasis with etanercept.

PATIENTS AND METHODS

Patients

We conducted a retrospective study evaluating patients treated with etanercept in the Department of Dermatology, Adan Hospital - Kuwait, between May 2005 and May 2008. Data were recorded, using a standard proforma at each visit for all patients treated with etanercept during this period. It included: age, sex, duration of psoriasis, initial and maintenance dose of etanercept, PASI score at 0, 4, 8, 12, 16, 20 and 24 weeks, DLQI at 0, 12 and 24 weeks, laboratory analyses as well as adverse effects.

All these patients started etanercept therapy after it had been approved by the Food and Drug Administration and they were on etanercept for a minimum of 24 weeks. All the patients received verbal and written information about the drug and written consent was obtained. They were treated according to protocols approved by local ethics committees.

Inclusion criteria were age between 18-80 years and moderate to severe plaque psoriasis defined as Psoriatic Area Severity Index (PASI) > 10 or body surface area (BSA) > 10 or Dermatology Life Quality Index (DLQI) > 10, or involvement of sensitive areas (e.g. face, palms, soles, nails and genitals), alongside a lack of response, intolerance, or contraindication to standard systemic

therapies.

Exclusion criteria were: (1) age less than 18 years or more than 80 years; (2) active infection, especially tuberculosis; (3) significant concurrent medical disease, including heart failure, hepatitis and HIV; (4) demyelinating neurological disease; (5) pregnancy or breast-feeding in female patients; or (6) a history of psychiatric disease or substance abuse that would interfere with the patient's ability to comply with the study protocol.

Protocol

Pretreatment screening included complete blood count (CBC), full biochemical profile, antinuclear antibodies (ANA) as well as HIV and hepatitis screening. A personal and family history of tuberculosis was taken and patients were screened for tuberculosis with the purified protein derivative test, (two tuberculin units) and a chest X-ray. Those with a positive PPD test (defined as > 15 mm palpable induration evaluated 72 hours after inoculation) and/or an abnormal chest X-ray were examined by a respiratory physician and treated with isoniazid and vitamin B6 for 9 months for a minimum of 2 months before etanercept as a prophylaxis. Pregnancy was excluded by history and pregnancy test when relevant. A reliable contraception was advised for women of child-bearing age. The PPD was checked yearly, and the CBC and liver function tests were repeated periodically.

Patients were treated with etanercept 50 mg subcutaneously (s.c.) twice weekly for 12 weeks, followed by 25 mg s.c. twice weekly for 12 weeks. After 24 weeks, etanercept was stopped if psoriasis was clear and resumed on relapse defined as return of psoriasis to 50% of the area or extent of rash before treatment or patient demand for further treatment.[36]

The patients viewed a video on the administration of etanercept which was also demonstrated to them on several occasions by a dermatology nurse. Afterwards, it was self-administered by subcutaneous injection under supervision of the nurse, before administering it at home by the patient.

Patients were reviewed at 4-week intervals when clinical response and adverse effects were noted and photographs taken.

At each visit, presence of infection was excluded and patients who developed infection required temporary cessation of etanercept until they recovered.

Assessments

The severity of psoriasis as well as treatment efficacy was assessed by calculation of the PASI score and DLQI.

The PASI is an index that incorporates measures of erythema, desquamation, induration, and affected BSA. It is expressed as a score between 0 and 72, with 0=no psoriasis and 72= severe disease.[37] Treatment efficacy was analyzed by calculation of the percentage improvement in PASI from baseline of at least 50%, 75% or 90% (PASI-50, PASI-75 and PASI-90, respectively). Patients' PASI scores were calculated at baseline and every 4 weeks thereafter. Due to logistical reasons the individual visits were not always fixed at these time points. If so, the interpolated PASI between most nearby visits was included in the analysis.

The DLQI is a validated patient-reported outcomes measure that has been used exhaustively in clinical trials of psoriasis and is widely accepted by dermatologists.[38] The quality-of-life index is calculated from an equal-weighted summary of

10 items that measure 6 subclasses: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment satisfaction. Each item is graded on a 0-3 scale for a maximum score of 30, with higher DLQI scores indicative of poorer outcomes. Hongbo et al. have recently developed a set of DLQI cutpoints which categorize patient health related quality of life status as follows: DLQI score 0-1, no effect on patient's life; 2-5, small effect, 6-10 moderate effect, 11-20, very large effect; 21-30, extremely large effect.[39] An improvement in DLQI of at least five points was considered to be clinically meaningful, with a total DLQI score of 0 as an important endpoint which indicates that patient's quality of life is not impacted by either psoriasis or its therapy.[40] Patients' DLQI scores were calculated at baseline, week 12 and 24.

Statistical analysis

All patients who completed at least 24 weeks of treatment with etanercept in the out patient clinic were included for analysis. Descriptive statistics were used to reproduce study results as percentage, mean, range, SD and SEM. All statistical tests were two-sided with a significance (α) level of 0.05. The correlation between PASI score and DLQI at baseline, week 12 and 24 was evaluated using the Spearman rank correlation test. Baseline, week 12 and 24 DLQI data were also evaluated using the set of DLQI cutpoints advocated by Hongbo et al. In addition, PASI scores at week 24 were categorized into ranges of: PASI = 0; 0 to 2.5; 2.5 to 5; or more than 5. Their association with a DLQI score of 0 was evaluated using the Mantel-Haenszel row mean score test.

RESULTS

Demographics

A total of 56 patients were treated with etanercept. Forty-four (78.6%) were male and 12 (21.4%) were female, with a mean age of 36.6 years (SEM = 1.8, range 16-72). Forty-nine patients (87.5%) had chronic plaque psoriasis, three (5.35%) had erythrodermic psoriasis and four (7.15%) had palmoplantar psoriasis. The mean duration of psoriasis was 15 years (SEM= 1.4, range 1-40). The mean PASI at baseline was 19 (SEM = 1.2, range 5.9-43.8). The mean DLQI at baseline was 12.8 (SEM = 0.97, range 1-29). The results are summarized in Table 1.

Table 1 Demographic and clinical characteristics of patients

Total number of patients	56
Male, n (%)	44 (76.8%)
Age (years), mean ± SD (range)	36.7 ± 13.2 (18-72)
Duration of psoriasis (years), mean ± SD (range)	15 ± 10.2 (1-40)
Baseline PASI, mean ± SD (range)	19 ± 9.3 (5.9-43.8)
Baseline DLQI, mean ± SD (range)	12.8 ± 7.2 (1-29)

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index

Efficacy

Psoriasis Area and Severity Index

The percentage of improvement of PASI from baseline continuously increased over the course of 24-week period. Forty-one patients (73%) achieved PASI-50, twenty nine (52%) achieved PASI-75 and sixteen (29%) achieved PASI-90 at week 12. Fifty-three patients (95%) achieved PASI-50, thirty six (64%) achieved PASI-75 and twenty six (46%) achieved PASI-90 at week 24 (Fig. 1). The mean period of recurrence was 5.4 months (range 1-15) with a mean PASI score 6.7 (range 3.2-17.4).

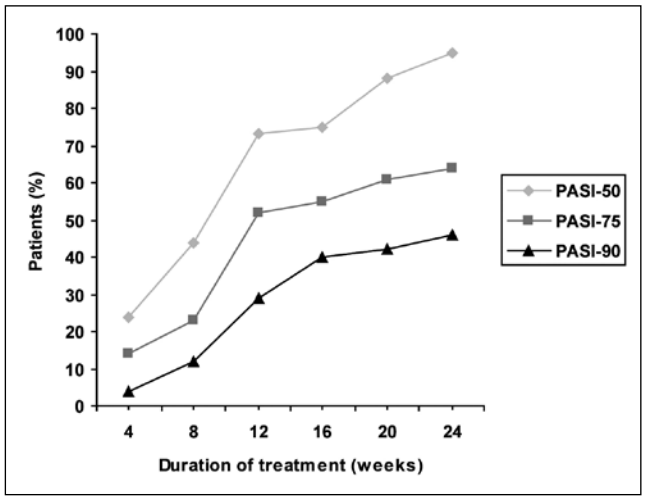

Fig. 1 Percentage of patients achieving at least 50%, 75% and 90% reduction in PASI score (PASI-50, PASI-75, PASI-90) at 4-week intervals.

Dermatology Life Quality Index

At baseline, the mean DLQI score for all patients was 12.8 (SEM = 0.97). Mean percentage of improvement from baseline in DLQI at week 12 was 47.6%, reaching 79% at week 24. When DLQI was categorized based on cutpoints,[39] the percentage of patients in the DLQI category correlating with 'no effect' on quality of life increased from 3.6% at baseline to 39.3% and 66% at week 12 and 24 respectively. At the same time, the percentage in the category correlating with 'extremely large effect' decreased from 16% at baseline to 5.3% and 1.8% at weeks 12 and 24 respectively (Fig. 2).

In our study, a significant correlation was noted between DLQI and PASI score before treatment as well as at week 12 and 24 (Fig. 3-5). Furthermore, we categorized the patients according to their PASI score at week 24 into four categories: PASI = 0; 0 to 2.5; 2.5 to 5; or more than 5 (Fig.6). The proportion of patients having a DLQI score of 0 was significantly higher in patients with a PASI score of 0 (71%), compared with those with higher PASI scores (P< 0.001). None of the patients with a PASI score >5 had a DLQI score of 0.

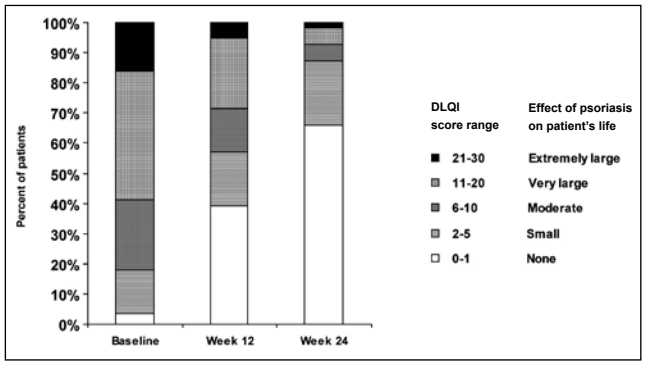

Fig. 2 Dermatology Life Quality Index (DLQI) response ranges at baseline, week 12 and week 24.

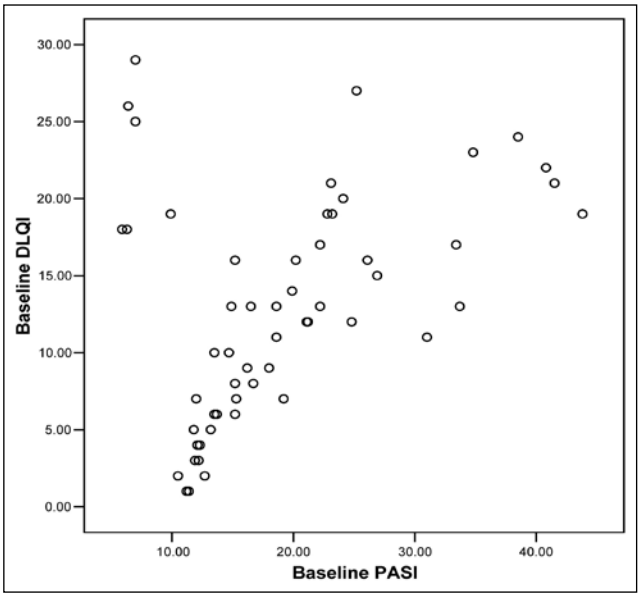

Fig. 3 Baseline Psoriasis Area and Severity Index (PASI) plotted against baseline Dermatology Life Quality Index (DLQI). P<0.01

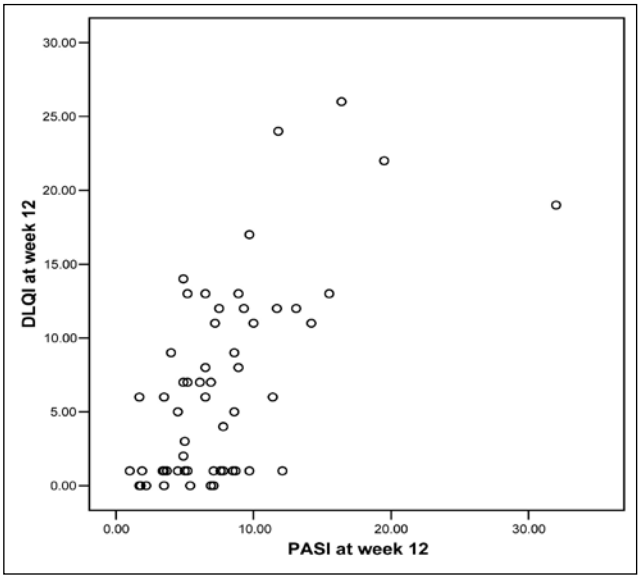

Fig. 4 Psoriasis Area and Severity Index (PASI) at week 12 plotted against Dermatology Life Quality Index (DLQI) at week 12 (P<0.001).

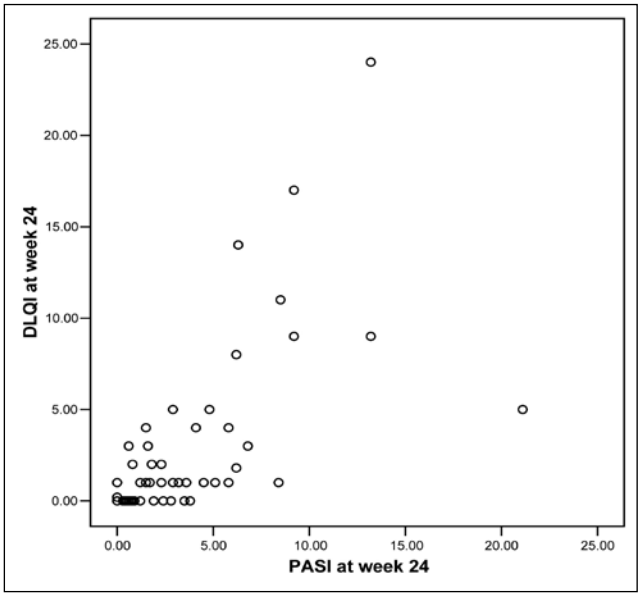

Fig. 5 Psoriasis Area and Severity Index (PASI) at week 24 plotted against Dermatology Life Quality Index (DLQI) at week 24 (P<0.001).

Intermittent treatment

Nineteen patients (34%) fully cleared of psoriasis and etanercept was stopped after 24 weeks. Sixteen of these (84.2%) relapsed and were recommenced on etanercept after a mean remission period of 5.4 months (range 1-15), with a mean relapse PASI of 5.9 (range 1.9-16.4). The response was equally good on the second cycle of treatment. Rebound did not occur in any of these patients. Three patients remain in remission (mean 45 weeks). Thirty-seven patients (66%) have been on etanercept with a mean of 67 weeks (range 24-128) at the time of submission of this study.

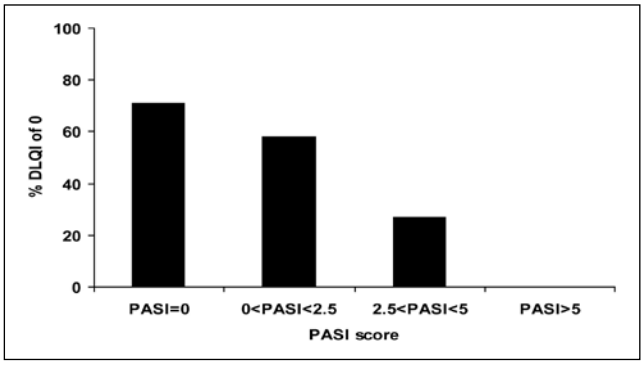

Fig. 6 Proportion of patients with a Dermatology Life Quality Index (DLQI) score of 0 by Psoriasis Area and Severity Index (PASI) core at week 24.

Adverse effects

Etanercept was generally well tolerated. Four patients (7%) developed injection site reactions including erythema, ecchymosis, pruritic reaction, and pain. Nasopharyngitis was observed in 3 patients (5%), chest infection in 2 (4%), flu syndrome in 3 (5%), arthralgia in 2 (4%) and myalgia in another. One patient (2%) reported nausea and another one informed of feeling hungry after every injection of etanercept. Other minor adverse effects included headache in 3 (5%) and lethargy in 4 (7%) patients. In those who developed infection, the treatment was temporarily stopped until recovery. No serious adverse events were reported or observed.

Routine laboratory monitoring revealed newly developed leukocytosis in 3 (5%) patients. In these cases, a concurrent increase in C-reactive protein was monitored in one patient. One patient developed a positive ANA of homogeneous pattern with a titer of 1 : 40 at 24 week. The baseline ANA was negative. One patient exhibited increased laboratory value of alanine aminotransferase that tested in the normal range 4 weeks later. Etanercept was not discontinued in any of the patients because of laboratory abnormalities.

Discussion

Psoriasis is debilitating disease associated with major morbidity and negative impact on patients' lives. Etanercept, a tumor necrosis factor antagonist, is an approved treatment in the United States and Europe for plaque psoriasis.[24] Etanercept therapy has been shown to significantly improve the physical and psychological burdens of the disease, as well as to improve the quality of life of affected individuals.41 PASI 75 is the most frequently used measure of psoriasis treatment outcome. In

previous studies the percentage of patients who achieved PASI 75 at week 12 ranged from 30% to 49%.[32,33,41,42] The studies which reported a lower percentage were using 25 mg etanercept biweekly versus 50 mg in the studies which reported a higher percentage. Fifty-two percent of our patients achieved PASI 75 at week 12, 55% at week 16, 61% at week 20 and 64% at week 24 (Fig. 1).

Measures such as the PASI may not always agree with patient quality-of-life assessments because patients have more concern over more visible areas of the body, while the PASI rigidly weighs each body part strictly by the area covered.[43] These findings suggest that the DLQI and the PASI measure aspects of treatment outcomes in psoriasis, which correlate and are complementarry (Fig. 3-6), but differ in very important ways.[41] In our study the mean percentage of improvement from baseline in DLQI at week 12 was 47.6%, which improved to 79% at week 24. Moreover, when the DLQI was categorized based on cutpoints, an obvious shift from the baseline DLQI was demonstrated, reflecting a marked increase in the proportion of patients reporting 'no effect' of disease on quality of life, and a marked decrease in those reporting 'extremely large effect' (Fig. 2).

We found a correlation between DLQI and PASI score before treatment as well as at week 12 and 24 (Fig. 3-5). Considering a total DLQI score of 0 as an important endpoint which indicates that patient's quality of life is not impacted by either psoriasis or its therapy,[40] we found that the proportion of patients having a DLQI score of 0 was significantly higher in patients with a PASI score of 0 (71%), compared with those with higher PASI scores (Fig. 6). This signifies a correlation between the absence of skin symptoms and a lack of measurable impact of psoriasis or its treatment on quality of life.

As TNF plays a role in mounting an immune response, concerns have arisen that such therapies may predispose patients to an increased risk of infections.[44,45] Although adverse events were noted in 24 (42.86%) of our patients, they were mainly mild and overall etanercept was well tolerated. Common adverse events were injection site reactions, lethargy, nasopharyngitis, flu-like symptoms, headache, arthralgia, myalgia, chest infection and nausea. The overall laboratory abnormalities were transient. One patient developed a positive ANA but it did not rise beyond 1 : 40. In clinical trials 11% of patients on etanercept developed a positive ANA titer of 1 : 40 or greater, compared with 5% of patients in the placebo group.[46]

Rebound did not occur in any of our patients when etanercept was discontinued. This was in accordance with other previous studies.[41,42,47,48]

In conclusion, our experience confirms the efficacy and safety of etanercept in the treatment of moderate to severe plaque psoriasis. Furthermore, our results suggest that etanercept can be used intermittently without rebound, with psoriasis responding again on reintroduction. Randomized controlled trials are needed to establish the intermittent use of etanercept and for its long-term safety.

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