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Original Article

An 11-year single centre experience with etanercept use in the treatment of moderate-to-severe psoriasis: a retrospective report

單一中心依那西普治療中至重度銀屑病的11年經驗：回顧性報告

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Introduction: Biologics have significantly improved patient outcomes in psoriasis. This study describes our clinical experience using etanercept for the treatment of moderate-to-severe psoriasis. ***Methods:*** We conducted a retrospective analysis of patients with moderate-to-severe psoriasis started on etanercept from December 2004 to May 2016 at the National Skin Centre, Singapore. The primary measure of clinical response was 75% or greater improvement in percentage of affected body surface area (BSA) following 12 weeks of treatment. ***Results:*** Twelve out of twenty-three patients (52%) achieved at least 75% improvement in the percentage of BSA after 12 weeks of treatment. Etanercept was generally well tolerated. ***Conclusion:*** Etanercept for the treatment of psoriasis showed improvement in disease severity after 12 weeks in a substantial number of patients.

簡介：生物製劑可顯著改善銀屑病患者的病情。這項研究描述了我們使用依那西普治療中至重度銀屑病的臨床經驗。**方法**：我們對從 2004 年 12 月至 2016 年 5 月在新加坡國家皮膚中心開始使用依那西普治療的中至重度銀屑病患者進行了回顧性分析。臨床療效的主要衡量指標是治療 12 週後受影響的體表面積達百分之 75 或更高的改善。**結果**：在 12 週治療後，23 名患者中有 12 名（52％）的體表面積百分比改善了至少 75％。依那西普的耐受性一般良好。**結論**：依那西普治療銀屑病個案中，可見 12 週後許多患者的病情嚴重程度都有改善。

Keywords: Efficacy, etanercept, psoriasis, safety

關鍵詞：功效、依那西普、銀屑病、安全

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory disorder that results from a polygenic predisposition, provoked by various environmental factors. It carries significant physical and socio-economic burden, with indication of rising

impact over the past two decades. Based on the 2010 Global Burden of Disease study, the global average disability-adjusted life years (DALYs) for psoriasis was estimated at 1,050,900, a 42.8% increase since 1999.[1] Limited data is available on the incidence of psoriasis in Asian countries. Data collected from population-based surveys show that the prevalence ranges between 0.24% in Taiwan,[2] and 0.34% in Japan.[3] In Singapore, it is estimated that at least 1% of the population are affected.

Cutaneous lesions of psoriasis are characterised by hyperproliferation of keratinocytes and epidermal T-cell infiltration, with evidence of increased tumour necrosis factor-alpha (TNF-α) activity in lesional skin.[4] A parallel decrease in circulating TNF-α was observed with clinical improvement.[5] These findings suggest that TNF-α is a key cytokine driving the pathogenesis of psoriasis.

Etanercept (Enbrel®) is a human recombinant fusion protein consisting of the extracellular ligand-binding domain of TNF receptor and Fc portion of human IgG1. It binds soluble TNF-α with high specificity and affinity, preventing its interaction with cell surface receptors and thus inhibiting its pro-inflammatory effects. Etanercept is approved by the US Food and Drug Administration for the treatment of moderate to severe psoriasis and psoriatic arthritis. To date, its safety and efficacy has been demonstrated in many controlled studies,[6-7] however there is paucity of data available in the Asia-Pacific region. Herein we describe our experience with the use of etanercept for the treatment of psoriasis in Asian skin, over 11 years in our institution.

Patients and methods

The study was a retrospective chart review from the subspecialty psoriasis clinic of the National Skin Centre (NSC), a tertiary dermatological referral centre in Singapore.

Audit department approval was granted for this retrospective review. The pharmacy database was searched for patients with psoriasis who were started on etanercept from December 2004 to May 2016. Data on baseline demographics, disease characteristics, past and concurrent therapies, dosage regimen and duration of etanercept treatment was collected from the physician records. Real world efficacy and safety evaluations were performed. The primary measure of clinical response was 75% or greater improvement in percentage of affected body surface area (BSA) following 12 weeks of etanercept treatment. Significant infectious and non-infectious adverse events were documented.

Results

Twenty-three patients were evaluated. Demographics and disease characteristics are summarised in Table 1. Most of the patients were male (n=16, 70%), of Chinese ethnicity (14, 61%) and had chronic plaque psoriasis (n=19, 83%). The mean age among patients was 46.7 years (range 15-70 years). On average, percentage of BSA affected at baseline was 40.6%. Fourteen patients (61%) had concomitant psoriatic arthritis. Past treatments received include at least one previous phototherapy or systemic therapy (acitretin, methotrexate, cyclosporine, hydroxyurea). Eight patients (35%) had prior exposure to other biologic therapies, which included alefacept, efalizumab, ustekinumab, and adalimumab. All past treatments were discontinued mostly due to inefficacy or intolerance.

The majority of patients were treated with either 25 mg twice weekly (n=7, 30%) or 50 mg once weekly (n=10, 43%) of etanercept. A change in treatment regimen was documented in six patients (26%). Seven patients (30%) received etanercept concomitantly with one other agent, including acitretin (n=2, 9%), methotrexate (n=2,

9%), cyclosporine (n=2, 9%), and narrow-band ultraviolet B (n=1, 4%). One patient received both cyclosporine and acitretin in addition to etanercept. The mean duration of etanercept therapy was 83 weeks (range 4-507 weeks).

Efficacy

Twelve patients (52%) achieved at least 75% improvement in BSA affected by psoriasis after 12 weeks of treatment. Eight patients (35%) were partial responders, defined as having less than 75% improvement in BSA at 12 weeks. Lack of response, defined as having no improvement in BSA involvement at 12 weeks, was observed in two patients (9%). Treatment was discontinued early at four weeks in one patient (4%), due to ineffectiveness.

Overall, etanercept was discontinued in 21 patients (91%). The most common reason for discontinuation was inefficacy, with lack of improvement in both cutaneous and joint disease recorded in seven patients (30%) and two patients (9%) respectively. Other reasons for discontinuation include influenza like symptoms, increased hair loss, blood test abnormalities, difficulty adhering to injectable therapy, and financial issues.

Six patients (26%) were switched to a different biologic agent due to a lack of efficacy; three patients (13%) received ustekinumab and the other three patients (13%) received adalimumab.

Safety

Mild to moderate treatment-related complications were reported in five patients (22%). Adverse events included lethargy (n=1, 4%) and influenza-like symptoms (n=2, 9%). Abnormal blood investigations were observed in two patients (9%); one patient with pre-existing myelodysplastic syndrome developed worsening pancytopenia. Another patient with a history of fatty liver developed worsening transaminitis after 14 weeks of treatment. Four patients (17%) had to discontinue etanercept due to the aforementioned adverse events of blood test abnormalities and influenza-like symptoms. There were no incidences of allergic reactions. No serious adverse events, opportunistic infections or malignancies were observed during the treatment period.

Discussion

Psoriasis is a chronic disease that typically requires lifelong treatment, with the goal of inducing remission or maintaining control. Etanercept has demonstrated significant short and long-term efficacy in both skin and joint symptoms. We observed rapid clinical reduction in disease severity over 12 weeks in more than half of our patients. In an extended open-label study, sustained PASI 75 response rates were achieved with high-dose etanercept therapy (50 mg twice weekly) for up to 96 weeks.[8] No significant immunogenicity has been reported with etanercept, unlike other biologics such as infliximab and adalimumab. Anti-etanercept antibodies detected were non-neutralising, and did not impair efficacy.[8] As such, patients who relapse after withdrawal of treatment can regain rapid and satisfactory response upon retreatment with lower doses of etanercept.[9]

Etanercept was generally well-tolerated in our patient population. This is consistent with the safety profile established in various controlled studies and meta-analyses. No dose-related or cumulative increases in infectious and non-infectious events were demonstrated in both short- and long-term analyses.[10] A 5-year observational surveillance registry of 2510 patients did not identify new safety signals with prolonged therapy.[11] An expert consensus favoured the use of etanercept in elderly patients, in patients planning for pregnancy, and in patients with chronic viral infections.[12]

Based on our experience, etanercept can be safely combined with phototherapy or systemic

agents in patients with plaque psoriasis not responding adequately to these agents alone. The use of conventional systemic therapies concomitantly with biologics is commonly practised to optimise treatment options, improve efficacy and to reduce cumulative toxicity. An additional advantage of this treatment strategy is the use of lower doses of etanercept, translating to improved cost-effectiveness. In a large multicentre cohort study, methotrexate and ciclosporin were the most common systemic therapies used concomitantly with biologics.[13] A combination of etanercept and acitretin was shown in a controlled trial to be synergistic and well-tolerated, and was significantly more effective than treatment with acitretin alone.[14]

Table 1. Patient characteristics

	n (%)
Gender	
Male	16 (70)
Female	7 (30)
Ethnicity	
Chinese	14 (61)
Malay	4 (17)
Indian	3 (13)
Others	2 (9)
Mean age, years (range)	46.7 (15-70)
Psoriasis subtypes	
Chronic plaque psoriasis	19 (83)
Erythrodermic psoriasis	3 (13)
Pustular psoriasis	1 (4)
Diagnosis of psoriatic arthritis	14 (64)
Prior therapies for psoriasis	
Phototherapy (NBUVB, BBUVB, soak/bath PUVA, UVA, excimer)	16 (70)
Acitretin	11 (48)
Methotrexate	17 (74)
Cyclosporine	9 (39)
Hydroxyurea	2 (9)
Other biologics (alefacept, efalizumab, ustekinumab, adalimumab)	8 (35)
Mean BSA before ETN (range)	40.6 (3-90)

Values are n (%) unless stated otherwise. NBUVB, narrow band ultraviolet B. BBUVB, broad band ultraviolet B. PUVA, psoralen-ultraviolet A. ETN, etanercept.

Another key benefit of etanercept is that of flexibility of dosing regimens which allows for individualised therapy.[12] Dose reductions were carried out in six of our patients in line with improving disease activity, whilst maintaining clinical response. The longest treatment period documented in our centre is 507 weeks (ongoing); our patient had sustained efficacy during down-titration from 50 mg twice weekly to 25 mg weekly, and his disease remains well-controlled to date.

In conclusion, we have highlighted the ability of etanercept to achieve efficacy in a Southeast Asian population. We encountered a low risk of adverse events in real world practice, which corroborates with etanercept's well-established safety and tolerability record.

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