Mini Review

TNFα inhibitors treatments for Psoriasis

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Psoriasis is a genetically determined, inflammatory, proliferative disease of the skin, and it is often intractable. The most characteristic lesions consist of chronic, sharply demarcated, red, scaly plaques, particularly on the extensor prominences and scalp. The prognosis is benign, however, patients often feel self-conscious regarding the appearance of the lesions and quality of life (QOL) can hence be lower than that for those with cancer or diabetes. At present, the main therapy for psoriasis in Japan is corticosteroids and activated vitamin D_3 analogs as topical treatment, and cyclosporine, etretinate, and methotrexate as systemic therapy. However, topical treatments themselves can be stressful for patients, and long-term administration of medications can cause adverse reactions. Etanercept, infliximab, and adalimumab are biologic preparations with anti-TNFα activities, and these preparations are more effective than the existing treatments and cause fewer adverse reactions. They can also be effective against psoriasis accompanied by joint symptoms that resist other treatments.

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Introduction

Psoriasis is a genetically determined, inflammatory, proliferative disease of the skin. Although it is a benign condition, it can be intractable. The most characteristic lesions consist of chronic, sharply demarcated, red, scaly plaques, particularly on the extensor prominences and scalp (Fig.1). The prevalence of psoriasis is 0.1-0.2% and there are approximately 100,000 patients in Japan. The etiology and pathogenesis of psoriasis are based on genetic factors, and the lesions are triggered and exacerbated by traumatic, infectious, metabolic, pharmacologic, and psychogenic factors. At present, the main therapy for psoriasis is corticosteroids and activated vitamin D_3 analogs as topical treatment for mild to moderate cases, and cyclosporine, etretinate, and meth-

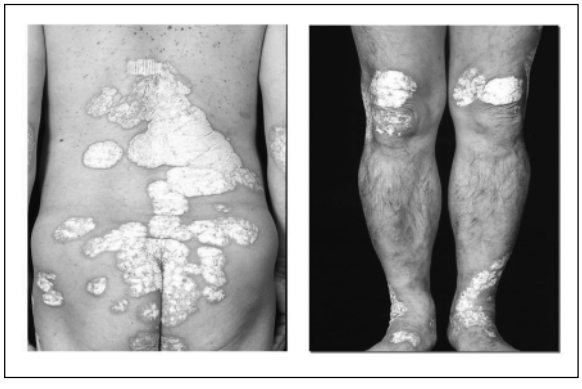

Fig.1 Clinical feature of Psoriasis
The most characteristic psoriasis lesions consist of chronic, sharply demarcated, red, scaly plaques, particularly on the extensor prominences and scalp.

otrexate as systemic therapy for moderate to severe cases. These agents can be highly effective; however, they have well-established risks of major organ toxicities including hepatotoxicity, nephrotoxicity, and bone marrow suppression. Clinicians have recently become aware that patient QOL should be given as much consideration as disease severity. Although psoriasis is a benign condition, sufferers can feel self-conscious due to the appearance of lesions, and QOL is reported to be lower than in patients with cancer or diabetes[1]. While topical approaches account for the majority of treatments for psoriasis, studies have shown that if a large area is affected, topical treatments themselves can be stressful for patients and lower compliance[2]. Therefore, since the vital prognosis of psoriasis is favorable, systemic therapy is not generally actively performed. However, in recent years, from the viewpoint of QOL, it is generally recognized that topical treatments should not be administered aimlessly and that some type of treatment should be actively employed. Subsequently, the use of biologic preparations, mainly anti-TNFα antibodies, has been examined as a therapeutic option that is more effective than the existing treatments[3-5].

Psoriasis pathology and anti-TNFα agents

The local pathological features of psoriasis include: epidermal cell abnormalities, antigen-presenting cell abnormalities, lymphocyte (mainly T lymphocyte) abnormalities, and vascular endothelial cell abnormalities (Fig.2). These cells are thought to interact in a complex manner to cause psoriasis. TNFα is a pro-inflammatory cytokine known to play an important role in the pathogenesis of psoriasis. Inflammation is evidenced by the recruitment and activation of many inflammatory cells, especially macropharges. Elevated levels of TNFα have been demonstrated in psoriatic skin lesions[6]. Moreover, serum concentrations of TNFα have been correlated with psoriatic disease activity[7]. Excessive TNFα has a direct role in the development, proliferation, and maintenance of psoriatic plaques[8], TNFα also promotes activation of T cells and synthesis of other cytokines and inflammatory mediators, leading to further inflammation. Because TNFα is a cytokine that drives inflammatory response of psoriasis, it is a suitable target for selective deactivation to manage these chronic debilitating diseases. Therefore, TNFα plays an important role in cytokine networks, and it is believed that psoriasis can be suppressed by blocking TNFα. At present, Etanercept, Infliximab, and Adalimumab are three anti-TNFα agents being used for the treatment of psoriasis. These anti-TNFα agents are already being used for many patients with psoriasis and psoriasis arthritis in Western countries, such as the United States and the United Kingdom. On the other hand, in Japan, The clinical tests for psoriasis and psoriasis arthritis of Infliximab and Adalimumab have only been started recently. Therefore, there is only one report regarding the effectiveness of Infliximab for psoriasis arthritis[9], and none for Adalimumab in Japan.

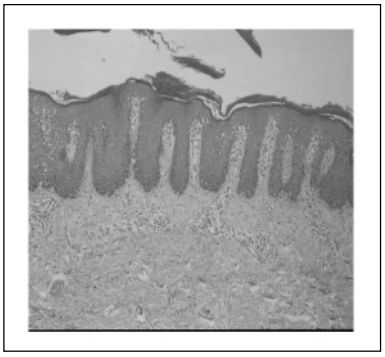

Fig.2 Histopathology of Psoriasis
Irregular epidermal hyperplasia with suprapapillary t hinning. Mononuclear cells and neutrophils infiltrate around the blood vessels in upper dermis.

1)Etanercept

Etanercept is a fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. It was approved by the FDA for psoriasis in 2004 and has been used in more than 210,000 patients over the last 6 years for the treatment of psoriatic arthritis, ankylosing spondylitis, juvenile and adult rheumatoid arthritis, and psoriasis. In terms of efficacy, with 50 mg twice weekly administration, the proportion of patients achieving PASI 75 (improvement of psoriasis area and severity index scores by at least 75%) was 49% after 12 weeks and 59% after 24 weeks[10-11].

2)Infliximab

Infliximab is used in the treatment of rheumatoid arthritis and Crohn's disease in Japan. It is a murine-human chimeric monoclonal antibody that neutralizes TNFα's biologic activity by binding with high affinity to its soluble and transmembrane forms and by inhibiting the binding of TNFα with its receptors. Concerning efficacy of infliximab for psoriasis, 72% of patients achieved PASI 75 when administered 3 mg/kg, and 88% achieved PASI 75 at 5 mg/kg (for 10 weeks for both doses). However,

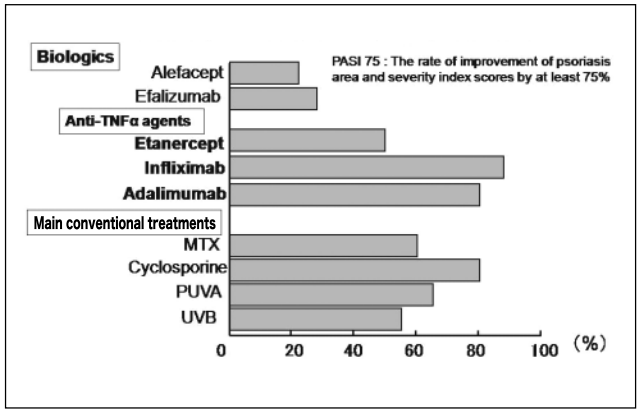

Fig.3 PASI 75 Improvement by 3 Months[3)]

Anti-TNF α agents have a superior effectiveness compare to the main conventional treatments in Japan. (※ This figure is made by changing reference literature 3)

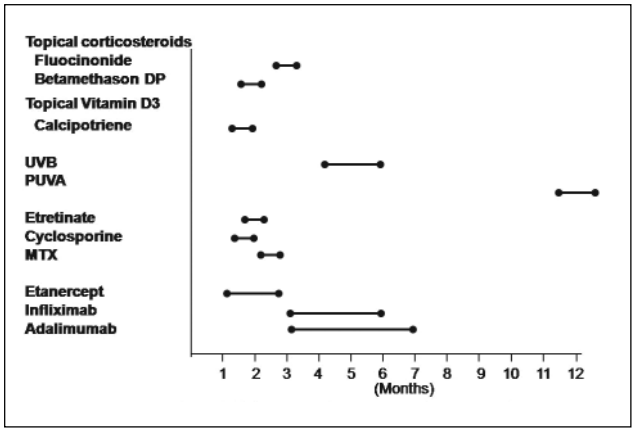

Fig.4 Relative duration of remission for psoriasis therapies

The anti-TNF α agents have produced longer remission when compared to the conventional treatments.

because infliximab is a chimeric antibody, adverse reactions such as allergic reactions during infusion and production of neutralizing antibody have been reported[12-13)].

3)Adalimumab

Adalimumab is a fully human monoclonal antibody that specifically binds to TNF α, blocking its interaction with the p55 and p75 cell surface TNF receptors. It was approved by the FDA for the treatment of rheumatoid arthritis in 2002. Concerning efficacy of psoriasis, PASI 75 was achieved in 80% of patients at 12 weeks, at a 40 mg weekly dose. Adalimumab was well-tolerated in this group of patients, and there were no new safety concerns identified in psoriasis patients when compared to the rheumatoid arthritis population[14-15)].

Significance of anti-TNF α agents for the treatment of psoriasis

Five biologic therapies, alefacept, efalizumab, etanercept, infliximab, and adalimumab are used to treat psoriasis in Western countries. Alefacept is a fusion protein combining a portion of human immunoglobulin (IgG) and the binding site of lymphocyte function-associated antigen-3 (LFA-3). Concerning the efficacy of intramuscular alefacept at 15 mg weekly, 33% of patients achieved PASI 75 at 12 weeks[16)]. Efalizumab is a humanized monoclonal antibody directed against the T-cell surface molecule CD11a. The CD11a and CD18 proteins together (LFA-1) play a critical role in allowing lymphocytes to adhere to intracellular adhesion molecule-1 (ICAM-1). Concerning the efficacy of efalizumab at 2 mg/kg weekly, 28% of patients achieved PASI 75 at 12 weeks[17)]. Hence the efficacy of these latter two biologic agents is lower than that of the three anti-TNF α agents described above.

Figure 3 compares therapeutic effects between the above-mentioned preparations and the main conventional treatments[3)]. When compared to cyclosporin, which is thought to be the most effective of the conventional treatments, the therapeutic effects of the above-mentioned preparations are comparable or better. Moreover, the anti-TNF α agents have produced longer remission when compared to the conventional treatments (Fig.4)[10-15,18)]. Because these biologic preparations are highly effective, they can alleviate the stress associated with topical treatments. Moreover, early therapeutic effects and long remission can reduce the number of patient visits. At present, agents such as cyclosporin, methotrexate, and etretinate, are systemically administered in severe cases, and long-term administration can cause reactions such as nephropathy and hepatopathy. However, these adverse reactions are less frequent with biologic preparations, and a result, biologic preparations are useful in patients with adverse reactions caused by long-term conventional therapy. Furthermore, studies have reported the effectiveness of biologic preparations for arthropathic psoriasis which does not respond favorably to the existing treatments, and these preparations may be effective against types of psoriasis that have resisted conventional treatments.

The advantages of biologic preparations over the conventional treatments include long remission period, efficacy against resistant psoriasis and arthropathic psoriasis, and fewer adverse reac-

tions. However, when compared to the conventional treatments, the biologic preparations are 2-4 times more expensive, and long-term safety has not been established. Because psoriasis is an intractable skin disease, both long-term safety and therapeutic efficacy are important. In the near future, biologic preparations, predominantly anti-TNFα antibodies, will be used in the treatment of psoriasis, and dermatologists will therefore need to use these agents appropriately after clearly understanding their merits and demerits.

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