Psoriasis is recently recognised as a T-cell mediated immunological disease. In the immuno-pathogenetic pathway, unknown antigens are captured by the antigen-presenting cells (APCs) in the epidermis. The activated APCs travel to the lymph nodes where naive T-cells are activated and maturated. Subsequently, the activated T lymphocytes migrate along the blood vessels and traffick back to the skin under chemokine stimulation. Finally, the T cells are reactivated in the skin followed by an intense inflammatory cascade: cytokines production, keratinocyte proliferation, cutaneous hypervascularity and neutrophil chemotaxis.

Biological agents specifically target at different points of the immunological pathway. Up to date, three biological agents, namely efalizumab, alefacept and etanercept have been approved by the United States Food and Drug Administration for the treatment of moderate to severe plaque type psoriasis in adults who are candidates for systemic therapies. Two other biological agents, infliximab and adalimumab, are currently in clinical trials for psoriasis.

**Mechanism of efalizumab in the treatment of psoriasis**

Efalizumab is a recombinant humanised monoclonal antibody that binds to CD11a and blocks at the early stage of the psoriatic pathogenesis. CD11a is the α subunit of leucocyte function associated (LFA) antigen-1 expressed on all leukocytes. Efalizumab blocks the binding of LFA-1 on T-cells to the intercellular adhesion molecule-1 (ICAM-1) on antigen presenting cells, vascular endothelial cells and keratinocytes. The interaction between LFA-1 and ICAM-1 serves as an important co-stimulating signal for T cell activation, reactivation and migration from blood vessel to skin. Therefore, efalizumab specifically blocks the early step in the pathogenetic pathway of psoriasis and inhibits the subsequent inflammatory processes.

**Clinical efficacy of efalizumab in plaque type psoriasis**

Early phase I and phase II trials showed that single, weekly intravenous infusion or weekly subcutaneous injection of efalizumab, from 0.1mg/kg up to 2.0 mg/kg for seven to eight weeks, had clinical and immunobiological benefits on psoriasis. Clinical efficacy is measured by the Psoriasis Area and Severity Index (PASI) score, that measures the redness, thickness and scaliness of psoriasis lesions and the area of the body that is affected. PASI 75 is defined as 75% reduction of PASI score from the baseline.

Two double blind, placebo-controlled, multicentre phase III studies on 1153 patients showed that 22%-27% of patients could achieve PASI 75 after weekly subcutaneous administration of efalizumab at a dose of 1mg/kg for 12 weeks. The improvement was significant when compared to placebo (4%-5%) and could occur as early as four weeks. In the extended-treatment phase of Lebwohl’s study, 77% of patients could maintain their improvement at week 24 if they continued to receive efalizumab, as compared to 20% of those who were switched to placebo ($p<0.001$).

Several phase III studies showed that more patients could achieve PASI 75 when efalizumab was continued after the initial treatment period. In the study by Leonardi et al, 498 patients received an initial efalizumab treatment for 12 weeks. Patients who did not achieve PASI 75 at 12 week would be re-randomised for an extended treatment of another 12 weeks. At week 12, efalizumab-treated patients had significant improvement: PASI 75 was respectively 39% (1mg/kg), 27% (2mg/kg) and 2% (placebo). At week 24, an additional 20% of efalizumab-treated patients could achieve PASI 75. Menter et al also showed a further improvement when efalizumab was continued, with PASI 75 increased from 26.6% at week 12 to 43.8% at week 24.

The long term safety and tolerability of efalizumab were evaluated. When efalizumab was continued as maintenance treatment, the PASI 75 increased from 23.6% at week 12 to 59.5% at week 60. In an ongoing multi-centre open label trial, weekly subcutaneous efalizumab at a dose of 2mg/kg, was given to 339 patients for 12 weeks. At 12 week, 41% of patients respectively achieved PASI 75. Subsequently, 290 responding patients continued to receive 1mg/kg of efalizumab for an additional 33 months. The preliminary results showed that PASI-75 responses were 50% (intention to treat), 58% (maintenance group) and 78% (as-treated group) at month 30. This study suggested that long-term administration of efalizumab...
was effective and safe for treating psoriasis.\textsuperscript{17} The overall PASI 75 ranged from 22\% to 39\% for a 12-week course of efalizumab at 1mg/kg per week and continued to improve with further treatment.\textsuperscript{12-18} There was also a parallel improvement in other assessment scores, including Physician’s Global Assessment, Dermatology Life Quality Index and Psoriasis Symptom Assessment.\textsuperscript{12-18}

**Adverse effects of efalizumab**

Up to date, efalizumab has a satisfactory safety profile, with no additional side effects reported in the extended treatment trials.\textsuperscript{12-17} The most serious adverse effect is the psoriasis flare during the first three months of treatment or rebound after discontinuation of therapy. Some patients experienced an erythroderma, pustular flare up or inflammatory arthritis. Minor side effects occurred mostly during the first two injections, including headache (32\%), infection most commonly upper respiratory infection (29\%), chills (13\%), nausea (11\%), pain (10\%), myalgia (8\%), flu-like symptoms (7\%) and fever (7\%).\textsuperscript{18-20} In order to reduce the first dose reaction, it is recommended to start efalizumab with a single conditioning subcutaneous dose of 0.7mg/kg followed by 1mg/kg weekly.\textsuperscript{20} No significant increase in opportunistic infection or malignancy was reported. Eight out of 2762 efalizumab-treated patients developed thrombocytopenia with platelet count at or below 52,000 cells/\mu L, mostly between eight to 12 weeks after initiation of drug therapy.\textsuperscript{20} It is recommended to check platelet count monthly initially and then three-monthly subsequently.\textsuperscript{20} Efalizumab should be discontinued if thrombocytopenia develops.\textsuperscript{20}

**Clinical use of efalizumab**\textsuperscript{21-22}

Efalizumab can be considered as an effective treatment option for psoriasis. It can be used as one of the agents in rotational, combination or sequential therapies for moderate to severe psoriasis.

However, special care is needed in order to minimise the flare up events in the initial treatment period or rebound effect after discontinuation. It is practical to transition slowly from other agents to efalizumab or vice versa. Patients should be closely monitored during the first three months of therapy. Though improvement may occur as early as four weeks, some may delay up to 12 weeks. Responders can continue the efalizumab therapy and satisfactory safety profile is observed for up to 36-month therapy. On-going studies are continued to investigate the long-term usage of efalizumab. Further evaluation is required to find out the criteria for selecting responders, cost-effectiveness of using efalizumab as compared to other conventional systemic therapies, combination with conventional topical or systemic therapies and long-term adverse reactions for continuous use.

**Conclusion**

The understanding of the pathogenesis of psoriasis has led to the development of specific immuno-modulating agents such as efalizumab. Current information shows that efalizumab has a satisfactory safety profile except the possible flare up and rebound events. Patients should be closely monitored during the first three months of treatment and immediately after discontinuation. Clinicians should be familiar with the potential benefits and risks of efalizumab before they start the treatment.

**References:**