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Review Article

Biological breakthroughs in the treatment of psoriasis

治療銀屑病在生物醫學上的突破

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Psoriasis is recently found to be an immunological disease. This leads to the possibility of developing selectively targeted biological therapeutic agents. These biological agents are designed to block certain points in the pathogenetic pathway and subsequently result in decrease in clinical activity. This review briefly discusses the immunological basis of psoriasis and the underlying mechanisms of four biological agents: efalizumab, alefacept, infliximab and etanercept. Results of updated clinical studies relating the use of these agents in the treatment of moderate to severe psoriasis are also reviewed.

銀屑病最近被證實為一種免疫異常性疾病。由此而出現研製選擇性生物活性治療藥物的楔機。這類生物製劑能阻斷發病過程中的某幾個步驟，從而令病情減輕。本文概述銀屑病的免疫學基礎以及以下四種生物製劑的作用原理：efalizumab, alefacept, infliximab and etanercept 。其在中至重度銀屑病中的臨床研究結果也一併討論。

Keywords: Biologic therapy, psoriasis

關鍵詞：生物活性治療、銀屑病

Introduction

Psoriasis is a common chronic debilitating disease. In moderate to severe cases, patients are often physically disabled with significant psychological burden. The current systemic therapies, including methotrexate, oral retinoids, cyclosporine and phototherapy are non-selective and known to have considerable side effects.[1] The recent concept of immunopathogenesis of psoriasis has led to the development of selective and targeted biological therapeutic agents.

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Immunological pathogenesis of psoriasis[2] (Figure 1)

Psoriasis has recently been recognised as a T cell mediated immune disease. The initial triggering

factors or antigens to the antigen presenting cells remain unknown. However, the critical step is the antigen capture by immature Langerhans' cells in the epidermis. The Langerhans' cells then maturate and migrate into the corresponding draining lymph nodes. Another key pathway is the activation of the T lymphocytes via signal 1 and signal 2 interactions with antigen presenting cells. The activated naïve T cells further activate and proliferate through positive feedback. They undergo TH1 differentiation into effector T lymphocytes and will be selectively trafficking back to skin. The epidermal or dermal activated T lymphocytes are further induced to release inflammatory cytokines. Subsequently an intense inflammatory response is elicited through further cytokine activation on epidermal keratinocytes, dermal vasculature and other inflammatory cells. One important cytokine is the tumour necrosis factor (TNF) alpha. It is synthesised and released by injured keratinocytes. It plays an essential role in antigen presenting cell function and regulates apoptosis. It is shown that the concentration of TNF alpha in skin correlates with the clinical severity in psoriatic patients.

Mechanisms of biological therapies (Figure 1)

The understanding of the pathogenesis in psoriasis has shed lights on designing selective targeted therapy.[3,4] Biologic agents are proteins that are extracted from animal tissue or synthesised through recombinant DNA techniques. It usually aims at blocking molecular activation in one of the cellular pathways in immune activation. In psoriasis, particular biological agents are designed to attack certain point of the pathogenetic pathway. There are four possible interventional sites: (1) to eliminate activated T cells (2) to inhibit T cell activation (3) induction of immune deviation with shift of the TH1 to TH2 differentiation and (4) to inhibit the cytokines.[5]

Biological therapies for psoriasis

A number of biological agents are being investigated for the treatment of psoriasis, based on the four strategies in the immunological pathogenesis.[5] At the time of writing, four biological agents, including efalizumab, alefacept, infliximab and etanercept, have already accumulated substantial data. The results of clinical studies relating the use of these four agents will be discussed below. In these studies, only adult patients with moderate to severe plaque psoriasis were recruited. The objective endpoint clinical efficacy is measured by the percentages of patients achieving at least 75% or 50% reduction of the Psoriasis Area and Severity Index (PASI) score from baseline: PASI 75 and PASI 50.

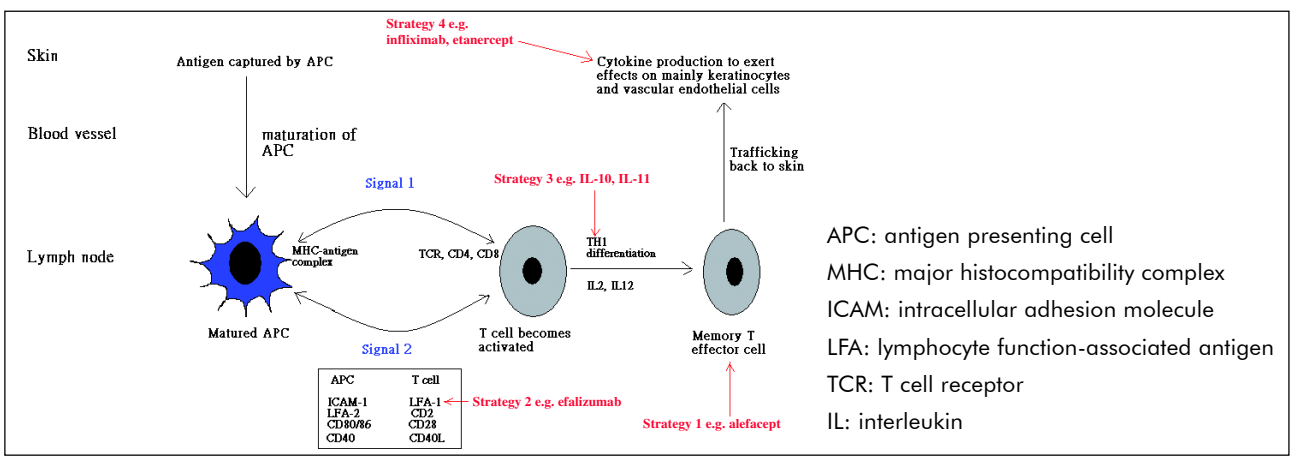

Figure 1. Schematic diagram to illustrate the immunological basis of psoriasis and the different strategy mechanisms targeted by biological agents.

Nomenclature of biological agents

The terms "ximab" and "zumab" respectively refer to chimeric and humanised monoclonal antibodies. Examples are infliximab and efalizumab. Chimeric antibodies are fused segments of mouse and human antibodies. Humanised monoclonal antibodies, in contrast to chimeric monoclonal antibodies, are less likely to form neutralising antibodies.

The term "cept" refers to receptor to the Fc portion of human IgG. It is usually a fusion protein consisting of the receptor domain of a human protein fused to the constant region sequences of human IgG so that the fusion protein can bind specifically to a particular ligand or co-receptor and then become soluble in plasma. Examples are alefacept and etanercept.

Efalizumab

Efalizumab is a recombinant humanised monoclonal antibody to CD11a and targets at the early pathogenetic pathway of psoriasis (strategy 2).[5] CD11a is the α subunit of lymphocyte function associated (LFA) antigen-1 expressed on T lymphocytes. Efalizumab inhibits the interaction between CD11a and intercellular adhesion molecule-1 which are expressed on antigen presenting cells. This particular interaction provides important co-stimulating signal for T cell activation and then subsequent inflammatory events: adhesion of T lymphocyte to endothelial cells and trafficking of lymphocytes back to the skin. In October 2003, the United States Food and Drug Administration (FDA) approved efalizumab to treat moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

It can be administered by intravenous or subcutaneous injection. In early studies, single or weekly intravenous infusion of at least 0.3 mg/kg efalizumab for seven to eight weeks had clinical and immunobiological benefits on psoriasis.[6-8] In another dosing trial, weekly subcutaneous injection of 1-2 mg/kg efalizumab for eight weeks was as effective as intravenous infusion.[9] At the end of the dosing period, 29.2% of patients receiving 1-2 mg/kg efalizumab achieved PASI 75.[9]

The clinical efficacy of subcutaneous efalizumab was further elicited by the double blind, placebo-controlled, multicentre phase III study.[10] Five hundred and ninety-seven moderate to severe psoriatic patients were randomised to receive subcutaneous injection of either placebo, 1 mg/kg or 2 mg/kg of efalizumab weekly for 12 weeks.[10] At week 12, PASI 75 was significantly higher in the efalizumab-treated patients ($p<0.001$): 22% (1 mg/kg); 28% (2 mg/kg) and 5% (placebo).[10] The improvement occurred as early as four weeks ($p<0.001$). In the extended-treatment phase, patients were re-randomised according to their response at week 12, to continue efalizumab or switch to placebo for an additional 12 weeks. Among the good responders who could achieve PASI 75 at week 12, improvement was maintained in 77% of patients who continued to receive efalizumab, as compared with 20% of those who were switched to placebo ($p<0.001$).[10]

The major disadvantage of efalizumab is the frequent clinical relapse or even rebound of the disease (0.7%) upon discontinuation of the drug, suggesting that maintenance therapy is necessary.[11] Therefore, the long term safety and tolerability of continuous administration of subcutaneous efalizumab were evaluated in a multi-centre open label trial.[12] Efalizumab was administered subcutaneously to 339 patients at a dose of 2 mg/kg weekly for 12 weeks.[12] At the end of treatment, 41% and 82% of patients respectively achieved PASI 75 and PASI 50.[12] Subsequently, 290 patients who achieved at least PASI 50 or an overall lesion severity of mild, minimum, or clear were then eligible to enter the continuous treatment phase.[12] From week 13 to 60, subjects continued to receive 1 mg/kg of efalizumab subcutaneously every week.[12] A continual clinical improvement was observed during the maintenance phase. At week 24, 51% and 50% achieved PASI 75 and PASI 50 while at

week 60, 64% and 79% achieved PASI 75 and PASI 50.[12] The study suggested that persistent administration of efalizumab could result in continuous clinical improvement and the regime was well tolerated. However, the tremendous cost relating to continuous treatment remained an important issue regarding to health cost.

Only 37% of patients experienced minor side effects during the first two injections, consisting of flu-like symptoms, fever, headache, chills, nausea, vomiting and myalgia.[9] In order to reduce the first dose reaction, efalizumab should be started with a single conditioning dose at 0.7 mg/kg followed by weekly dose of 1 mg/kg.[11] There was no significant increase in opportunistic infection or malignant disease. However, a total of eight patients out of 2762 efalizumab-treated patients developed thrombocytopenia with platelet count at or below 52,000 cells/uL, as compared with none in the placebo.[11] Five of the eight patients had onset of thrombocytopenia between eight to 12 weeks after initiation of drug therapy.[11] It is recommended that platelet count should be checked monthly initially and then three-monthly during the treatment period. Efalizumab should be discontinued if thrombocytopenia develops.

Alefacept

Alefacept is a recombinant human LFA-3/IgG1 dimeric fusion protein that binds to CD2 receptor expressed on T cell. LFA-3 is a cell surface receptor protein on antigen presenting cells, while CD2 is highly expressed on activated memory cells as compared to naïve T cells. In psoriasis, the LFA-3 and CD2 co-stimulating interaction contributes to T cell activation, and then leads to a cascade of inflammatory events. Alefacept is originally designed to block this co-stimulatory signal. However, alefacept can also bridge between highly expressed CD2 on activated T cells and the immunoglobulin Fc receptors on natural killer cells, then leading to selective elimination of activated T cell through apoptosis (strategy 1) while preserving the naïve T cells.

In January 2003, FDA approved alefacept for the treatment of moderate and severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. It is available in two formulations: 15 mg for intramuscular injection or 7.5 mg for intravenous bolus injection.

In Ellis et al's double-blind placebo-controlled phase II dose-escalating study, 229 patients were randomised to receive placebo, 0.025, 0.075 or 0.150 mg/kg alefacept as a 30 second intravenous bolus injection once weekly for 12 weeks, followed by another 12 week observation.[13] The efficacy of the drug was dose related. At week 14, patients on 0.075 mg/kg or 0.150 mg/kg alefacept achieved 53% reduction in the PASI scores as compared to 21% in placebo ($p<0.001$).[13] At the most effective dose (0.075 mg/kg), 33% and 60% of patients respectively achieved PASI 75 and PASI 50 as compared to 10% ($p=0.02$) and 27% ($p=0.001$) in placebo.[13] Significant clinical response occurred at 60 days after the initiation of therapy. At week 24, 28 patients (24%) still remained clear or almost clear without additional therapy according to the physician's overall assessment score.[13] These good responders subsequently entered into a retreatment study and had a median interval of 10 months (range: 6 to 18) from the last dose of initial alefacept course to subsequent retreatment course.[14] In an ongoing, open-label, multicentre retreatment study, up to two repeated courses of alefacept were well tolerated and at least as effective as previous phase II study.[15]

In a phase III study, 553 patients were randomised to receive two 12-week courses of once-weekly intravenous alefacept 7.5 mg or placebo in a 2:1 ratio.[16] Each course was followed by a 12-week observational period. In the second course, previously placebo patients would be given alefacept whereas previously alefacept-treated patients would be randomised to continue alefacept or receive placebo. At 24 and 48 weeks, PASI 75 results significantly favoured alefacept

over placebo (Course 1: alefacept 28% vs placebo 8%, $p<0.001$; Course 2: alefacept 37% vs placebo 19%, $p<0.001$).[16] A second course of alefacept could enhance clinical efficacy from 28% to 40%.[16] Overall, the clinical efficacy of alefacept was paralleled by an improvement in the physician global index.

Another phase III study investigated the use of giving intramuscular injection of alefacept in the treatment of psoriasis.[17] Placebo or alefacept 10 mg or 15 mg were randomised to 507 patients via weekly intramuscular injections for 12 weeks followed by another 12 weeks observation.[17] Similar to previous studies, the best clinical efficacy appeared in the post-dosing period, approximately six weeks after treatment was stopped. At any time during the study, PASI 75 were achieved by 33% ($p<0.001$) in 15 mg group, 28% ($p<0.001$) in 10 mg group and 13% in placebo.[17] Remission in the responders was long lasting. At week 24, 71% of the 15 mg group maintained at least PASI 50.[17] Therefore, intramuscular administration was a convenient alternative to intravenous dosing.

There is a major concern about the reduction of circulating T cell counts. Weekly CD4 T lymphocyte count monitoring is recommended during alefacept course. Alefacept should be withheld if the CD4 T lymphocyte count is below 250 cells/mL and discontinued if remained below 250 cells/mL for four weeks.[12] In the intravenous phase III study, 10% and 2% of patients discontinued treatment temporarily and permanently due to a low CD4 T lymphocyte count.[16] In the intramuscular study, only 4% of patients temporarily discontinued treatment while none permanently discontinued treatment due to a low CD4 T lymphocyte count.[17] The maximal effect on lymphocytes occurred within six to eight weeks after initiation of therapy. The rate of infection requiring hospitalisation was 0.9% in the alefacept group as compared to 0.2% in placebo group.

Up to date, alefacept has a satisfactory safety profile. No rebound or tachyphylaxis was reported. Laboratory tests showed no consistent chemical abnormalities due to alefacept. The most common adverse events were pharyngitis, headache, rhinitis and dizziness.[13-17] Transient chill during the first day of treatment occurred more often in the intravenous alefacept group while mild injection site reaction occurred more often in the intramuscular alefacept group.[16,17] Approximately 4% of alefacept-treated patients developed low titre (<1:40) of anti-alefacept antibodies which were not clinically important.[17] Out of a total of 1357 alefacept-treated patients, lymphoma was reported in three patients.[12] It was not certain whether these malignancies were incidental. However, alefacept should not be used in patients with concurrent serious infection or with a history of systemic malignancy.

Infliximab

Infliximab targets the later stage of the psoriatic pathogenesis (strategy 4). It is a chimeric monoclonal antibody, reversibly binds to transmembrane and soluble TNF alpha, thus preventing the binding of TNF alpha with its natural receptors. Currently, infliximab is FDA-approved for the treatment of Crohn's disease and rheumatoid arthritis.

Early reports suggested that infliximab might be efficacious in treating psoriasis.[18,19] In a controlled clinical trial, 33 patients were blindly randomised to receive placebo, inflixmab 5 or 10 mg/kg intravenous infusion over 2 hours at week 0, 2 and 6.[20] At week 10, significantly greater proportion of infliximab-treated patients achieved PASI 75 (10 mg/kg: 73%, $p=0.03$; 5 mg/kg: 82%, $p=0.0089$; placebo:18%).[20] The median time to response was 4 weeks for both infliximab groups.[20] In the open-label extension study, 29 responding patients from previous trial were evaluated for relapse and retreated with infliximab 5 or 10 mg/kg as needed.[21] At week 26, PASI 50 response was maintained in 40% and 73% of patients

receiving 5 mg/kg and 10 mg/kg respectively.[21] Only nine patients required one or two retreatment infusions, suggesting that infliximab could produce a rapid, effective and sustainable effect in moderate to severe psoriasis.[21]

In a multicentre, randomised, double-blinded, placebo-controlled phase II trial, 249 patients were randomised to receive intravenous infusion of infliximab at a dose of 3 or 5 mg/kg, or placebo in a 2:2:1 ratio at week 0, 2 and 6.[22] At week 10, 88% of the patients in the 5 mg/kg group while 72% in the 3 mg/kg group achieved PASI 75 as compared to 6% in the placebo.[22] Among the 5 mg/kg group, nearly half achieved PASI 75 as early as 4 weeks and 58% could even achieve PASI 90.[22] Headache, pruritus, fatigue, myalgia and infusion reaction (5%) consisting of hypotension and allergic reactions, occurred more commonly in the infliximab-treated group.[22]

There were reports of low titres of antibodies to infliximab (10%) which is associated with higher risk of infusion reaction, usually during or within two hours of infliximab infusion.[23] The infusion reaction can be in the form of anaphylactic reaction and seizures. Positive ANA (52%) and anti-double stranded DNA (17%) could also be detected during infliximab treatment, though the significance was not known.[23] In the post-marketing period, there were incidences of aggravation of central nervous system demyelinating diseases and serious infections including invasive fungal infections, disseminated or extrapulmonary tuberculosis and other opportunistic infections.[23,24] Most tuberculosis developed within the first three to six months after initiation of infliximab therapy, consistent with reactivation of latent tuberculosis. A prior tuberculin test and treatment for latent tuberculosis are recommended before the commencement of infliximab treatment.[23,24] In addition, higher mortality and increased hospitalisation were reported in a study of using infliximab to treat congestive heart failure.[23] Therefore, infliximab is contraindicated in patients with moderate to severe heart failure. Finally, there was insufficient data to determine the impact of infliximab on developing malignancy.

Etanercept

Etanercept is a dimeric fusion protein consisting of two TNF receptor components linked to the Fc portion of human IgG1. It binds specifically to TNF and blocks its interaction with cell surface receptors (strategy 4). FDA has approved etanercept in treating rheumatoid arthritis and psoriatic arthritis. Most recently, it is also approved for the treatment of chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is administered by subcutaneous injection once or twice per week.

The efficacy and safety of etanercept in treating psoriasis and psoriatic arthritis was evaluated in a double blind, placebo-controlled study.[25] Sixty patients were randomised to 12-week course of etanercept 25 mg twice per week or placebo.[25] Both symptoms of psoriatic arthritis and psoriatic skin lesions improved clinically. The PASI 75 was achieved by 26% for etanercept group as opposed to none in the placebo ($p=0.0154$).[25] A subsequent double-blind placebo controlled phase II study was done consisting of 112 psoriatic patients with same dosing regime, but for a duration of 24 weeks.[26] At week 12, 30% achieved PASI 75 as compared to 2% in placebo group ($p<0.0001$).[26] The clinical improvement is further enhanced with continuing treatment. At week 24, 56% of the etanercept group achieved PASI 75 as compared to 5% in the placebo ($p<0.0001$).[26]

The phase III trial consisted of randomisation of 672 patients into receiving placebo, etanercept at a dose of 25 mg once per week, 25 mg twice per week or 50 mg twice per week for initial 12 weeks followed by another 12-week course.[27] In the second 12-week course, all placebos would be given etanercept. In both periods, the higher dose group responded better. At week 12, the response rates were ($p<0.001$): 49% (50 mg twice per week), 34% (25 mg twice per week), 14%

(25 mg once per week) and 4% (placebo).[27] At week 24, the response rates were: 59% (50 mg twice per week), 44% (25 mg twice per week) and 25% (25 mg once per week).[27] Clinical improvement was observed as early as 2 weeks.

The main adverse effect of etanercept was injection site reactions (20%), which can be managed by rotation of injection sites. Other adverse effects included upper respiratory infections (57%) and headache (13%). The potential risk of developing malignancy is unknown. There were noteworthy reports of induction of antinuclear antibodies (11%), antibodies to double-stranded DNA (15%) and anticardiolipin antibodies, though full cases of systemic lupus erythematosus are rare.[28] Few patients developed reactivation of tuberculosis, aplastic anaemia, exacerbation of pre-existing or recent onset of central nervous system demyelinating disorders and worsening of heart failure.[29,30] It is not a pre-requisite, though advisable, to perform tuberculin test before the commencement of etanercept therapy.

Consideration in the use of biological therapies

It is exciting to see the recent development of effective and selective therapeutic agents in the treatment of moderate to severe psoriasis. Table 1 is a summary to compare the above four biological agents based on current information.

However, we must be cautious in interpreting these clinical results. We are not certain about the risk benefit ratio in using these biological therapies in the treatment of relatively non-life threatening disease such as plaque type psoriasis. Furthermore, there is no efficacy data regarding the use of these biological therapies in treating life-threatening erythrodermic or pustular psoriasis. We are also not sure of the long term and rare serious adverse reactions when these therapies are used in a large number of patients. Serious adverse effects were noted in the post-marketing period, for example, exacerbation of demyelinating diseases associated with the use TNF inhibitors. Another concern is the predisposition to malignancy and opportunistic infections, such as tuberculosis. Especially, disseminated tuberculosis was associated with the use of infliximab therapy. These adverse effects can be life threatening.

Practical issues have to be considered as well. For example, weekly monitoring of CD4 count during alefacept therapy may not be available in local public and private dermatology clinics. In addition, the long infusion hour of infliximab may not be convenient to the patients. The settings of the clinic should include resuscitation facility to tackle serious infliximab-related infusion reaction. In our locality, it is also difficult to interpret accurately the tuberculosis skin test prior to the administration of TNF inhibitors.

Finally, the costs of these therapies, including the drug cost, the cost of laboratory monitoring and the consumption of the health care manpower in the management, will be extremely high. It is advisable to compare the cost-effectiveness of these new biological therapies with the current systemic psoriatic therapies.

Conclusion

The understanding of the pathogenesis of psoriasis has led to the development of specific biological agents that are both effective and selective to alter the immunopathogenesis. Both alefacept and efalizumab have recently been approved in United States for the treatment of moderate to severe psoriasis in adult patients. It can be anticipated that other agents would also be available in the future. However, further evaluation is required in order to justify the use of biological therapies in the treatment of psoriasis. We need more clinical studies to look into the following aspects: selection of the best responders, cost-effectiveness, comparison with existing

Table 1. Summary of the four biological agents in the treatment of psoriasis

Biological agent	**Efalizumab**	**Alefacept**	**Infliximab**	**Etanercept**
Trade name	**Raptiva**	**Amevive**	**Remicade**	**Enbrel**
FDA status	Approved in October 2003 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	Approved in January 2003 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	Approved for the treatment of Crohn's disease and rheumatoid arthritis.	Approved for the treatment of rheumatoid and psoriatic arthritis. Approved in April 2004 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Structure	Humanised monoclonal antibody.	Immunoglobulin/ receptor fusion protein.	Chimeric monoclonal antibody.	Immunoglobulin/ receptor fusion protein.
Mechanism of action	Block LFA-1/ ICAM-1 interaction and inhibits subsequent inflammatory events.	Block LFA-3/CD2 interaction and selective elimination of activated T cells.	Bind to and block activites of TNF alpha.	Bind to and block activities of TNF alpha.
Strategy	2	1	4	4
Administration	Subcutaneous.	Intramuscular or intravenous bolus.	Slow intravenous infusion over 2 hours.	Subcutaneous.
Dosage regime for one course of treatment	Initial single conditioning dose at 0.7 mg/kg sc, then 1 mg/kg sc once a week for a total of 12/52.	15 mg imi or 7.5 mg ivi once a week for 12/52.	3 or 5 mg/kg iv infusion at week 0, 2, 6.	50 mg sc twice a week (administered 3-4 days apart) for 12 week, then step down to 50 mg sc weekly for maintenance.
Time of onset of clinical improvement	4 weeks	8 weeks	4 weeks	2 weeks
Laboratory monitoring during therapy	Platelet count monthly initially and then 3-monthly.	Weekly CD4 T lymphocyte count.	None	None
Advantage	Can be administered by patient.	Long lasting remission.	Highly efficacious. Can be used in combination with methotrexate.	Can be administered by patient. Also effective against psoriatic arthritis and can be used in combination with methotrexate.
Common side effects	Mild transient flu-like symptoms.	Transient chill, injection site reaction.	Infusion reaction, headache.	Injection site reaction, upper respiratory infection, headache.

Table 1. Summary of the four biological agents in the treatment of psoriasis (con't)

Biological agent	**Efalizumab**	**Alefacept**	**Infliximab**	**Etanercept**
Trade name	**Raptiva**	**Amevive**	**Remicade**	**Enbrel**
Disadvantage	Rapid relapse after discontinuation, making long term maintenance therapy necessary.	Weekly CD4 T lymphocyte count monitoring during therapy.	Risk of serious anaphylactic infusion reaction. Time and labour consuming due to slow iv infusion. Inconvenience to patients. Serious opportunistic infections reported, prior tuberculin skin test necessary.	Serious opportunistic infections reported, prior tuberculin skin test advisable in endemic area.
Contraindication	Known hypersensitivity to efalizumab and its components.	Known hypersensitivity to alefacept and its components.	Known hypersensitivity to murine proteins or other components of the product. At a dose of >5 mg/kg, it is contraindicated in patients with moderate to severe congestive heart failure.	Sepsis, known hypersensitivity to etanercept and its components.
Special precautions	Thrombocytopenia. Worsening or rebound of psoriasis during or after treatment period. Should not be given to patients with clinically important infections or who are receiving other immuno-suppressive agents. Should be cautious if used in patients with a chronic infection, history of recurrent infections, at a high risk of malignancy or with past history of malignancy.	Withheld treatment if CD4 T lymphocyte count is <250 cells/µL and discontinued if abnormality persist for >1 month. Should not be given to patients with clinically important infections, who are also receiving other immuno-suppressive agents or with a past history of systemic malignancy. Should be cautious if used in patients at high risk of malignancy, with chronic infections or history of recurrent infection.	Should not be given to patients with clinically important active infection. Should be cautious if used in patients with a chronic infection or a history of recurrent infections. Caution in patients with pre-existing or recent onset of CNS demyelinating disorders or seizure disorders. Resuscitation facility should be available for management of serious infusion-related reactions.	Should not be given to patients with active infection, whether chronic or localised. Should be cautious if used in patients with history of recurring infections or with underlying medical conditions leading to immunosuppression e.g diabetes mellitus Exacerbation of pre-existing or recent onset of CNS demyelinating disorders. Rare reports of pancytopenia. Cautious if used in patients with heart failure.
Estimated Drug Cost (US$)	14,000 per year for continuous treatment.	7,000-10,000 per course depending on dosing.	12,000 per year for use in rheumatoid arthritis patients.	12,000 per year for use in rheumatoid arthritis patients.

FDA: United States Food and Drug Administration; LFA: Lymphocyte function-associated antigen; ICAM: Intercellular adhesion molecule; TNF: Tumour necrosis factor; CNS: Central nervous system

systemic therapies, combination with conventional topical or systemic therapies and long-term adverse reactions. Dermatologists should be familiar with the potential benefits and risks of these therapeutic agents in order to make a rational decision in their patient management.

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