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Review Article

Biologicals in psoriasis

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Abstract During the recent years, a new class of therapeutic agents has been introduced for the treatment of psoriasis and psoriatic arthritis. These agents target different inflammatory mediators involved in the pathogenesis of disease. The focus of this article is on the mechanism of action, side effect profile and dosing of the agents currently in use today for the treatment of psoriasis

Key words
Biologicals, psoriasis

Introduction

Psoriasis is a chronic inflammatory and proliferative skin disorder involving the interplay of both environmental and genetic factors. It is associated with significant morbidity with 20-30% of patients having severe disease.[1,2] Most of the traditional therapies available, aim at producing only clinical improvement of the disease without targeting the factors that cause psoriasis. Hence gaining a basic understanding of the pathogenesis of psoriasis is crucial in developing new strategies to control the inflammatory process. The recent advances in immunology based upon increased understanding of the basic pathophysiology of the disease and the advent of genetic engineering techniques have paved the way for a new group of drugs referred to as "biologicals". Furthermore it is anticipated that such treatment will alleviate the pain and inflammation of psoriatic arthritis that many patients manifest. The advantage of these biological agents is their less toxic systemic side effect profile that improves the quality of life in psoriatic patients.[3] Though several new biologicals are currently undergoing trials, the focus of this article is on the mechanism of action, side effect profile and dosing of the agents currently in use today for the treatment of psoriasis.

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What are biologicals?[4,5]

"Biological therapy or biologics" describe drugs that are proteins produced by living organisms to block specific molecular steps important in the pathogenesis of psoriasis and have emerged over the last 3-5 years as potentially valuable alternative therapeutic options. They represent an important addition to the psoriatic armamentarium and have a great impact on the disease course and the quality of life of those affected with psoriasis. Currently available biologics for psoriasis target either the T cells or antigen presenting cells (APC) or block the inflammatory action of TNF-α. They appear to offer a safe and effective alternative to conventional systemic therapies and phototherapy for the treatment of moderate to severe chronic plaque psoriasis.

Immunopathogenesis of psoriasis[6,7,8,9]

Psoriasis is an immune-mediated disease caused by the activation of T lymphocytes that elaborate a Th1 type of immune response. There is considerable evidence now that activated T cells are the primary modulators in the pathogenesis of psoriasis. This is further supported by the fact that increased levels of activated T lymphocytes are present in psoriatic skin plaques and blood of patients.[10] The activation of T cells is dependant upon its binding with the APCs. The T cells get attached to the APCs through adhesion molecules CD2 and LFA-1 on T cells. The reciprocating cell adhesion molecules on APCs are LFA-3 and ICAM-1 (**Figure 1**). After the T cell-APC binding has occurred through their respective surface adhesion molecules the antigen is presented to the T cells by the APCs. The T cells express the cell receptor which recognizes the peptide antigen being presented by the APC in the groove of the MHC complex. This antigen-stimulated activation leads to the conversion of naïve T cell into a memory T cell that circulates in the body. After the activation of T cells, a cascade of cytokines is secreted by different cells in the local microenvironment. The cytokines involved in the development of psoriasis include granulocyte macrophage colony stimulating factor (GMCSF), epithelial growth factor (EGF), IL-1, IL-6, IL-8, IL-12, TNF-α and interferon-γ. The effects of these cytokines include keratinocyte proliferation and epidermal hyperplasia, neutrophil migration, angiogenesis, upregulation of adhesion molecules and potentiation of Th1 type of response.[11] Out of these cytokines TNF-α plays a critical role in the pathogenesis of psoriasis by causing activation of both innate and acquired immune responses leading to chronic inflammation, tissue damage and keratinocyte proliferation.

Which patients should be considered for biological therapy?

Most patients with moderate to severe disease achieve satisfactory disease control in the short-term with at least one of the systemic agents currently available. Long-term disease control frequently requires some form of continuous therapy and consequent, predictable risks of toxicity. At present the risks and benefits of anti-TNF-α agents or efalizumab, relative to standard systemic therapy are unknown and early widespread use of these agents in uncomplicated moderate to severe psoriasis is inappropriate. To be considered eligible for treatment, patients must have severe disease as defined in **Table 1(a)** and fulfil one of the clinical categories outlined in **Table 1(b)**.[5,12]

Pretreatment assessment

All patients should undergo a full clinical history, physical examination and further investigations as required with particular reference to the known toxicity profile of the agent being considered. Specific exclusion criteria and recommended pretreatment investigations are listed in **Table 2** and **3**.

Monitoring and assessment of disease response

Patient should be seen at 12 weeks to determine whether therapy should be continued, and thereafter at 3-6 monthly ntervals.[13] A favourable response to the

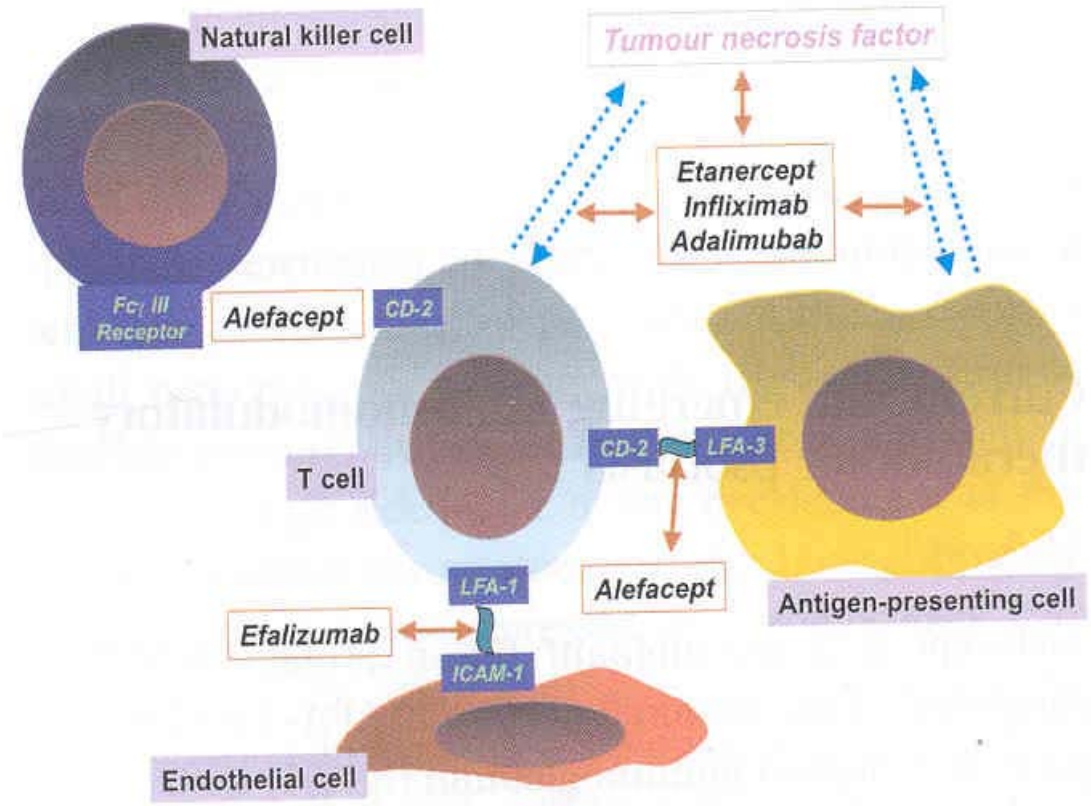

Figure 1 Immunopathogenesis of psoriasis and the site of action of various biologicals

Table 1 Eligibility criteria

a) Severe disease is defined as PASI score of 10 or more (or a BSA of 10% or greater where PASI is not applicable) and a DLQ1 > 10. Disease should have been severe for 6 months; resistant to treatment and the patient should be a candidate for systemic therapy.
AND
b) Fulfill at least one of following clinical categories
1. Have developed or are at higher than average risk of developing clinically important drug related toxicity and where alternative standard therapy (acitretin, methotrexate, narrow-band UVB, PUVA and ciclosporin) cannot be used.
2. Are unresponsive, intolerant to or cannot receive standard systemic therapy.
3. Have disease that requires repeated inpatient management for control.
4. Have significant co-existent unrelated morbidity which precludes the use of systemic agents like ciclosporin and methotrexate.
5. Have severe, unstable, life threatening disease such as erythrodermic or pustular psoriasis.
6. Have psoriatic arthritis

treatment is defined as a 50% or greater reduction in baseline PASI score (or percentage BSA where the PASI is not applicable) and a 5 point or greater improvement in DLQI within 3 months of initiation of treatment. PASI score is based on the severity of erythema, desquamation and plaque induration as well as the extent of involvement in 4 separate body areas. It ranges from 0-72.

PASI75 or a reduction in baseline PASI

Table 2 Exclusion criteria

Absolute contraindications
1. Pregnancy or breast feeding
2. Active infections (chronic leg ulcers, persistent or recurrent chest infections, indwelling urinary catheter)
3. Latent tuberculosis
4. Malignancy or premalignant states
5. Demyelinating disease
6. Congestive cardiac failure
Relative contraindications
1. Psoralen + UVA therapy > 200 treatments, especially when followed by ciclosporin therapy.
2. Human immunodeficiency virus positive or AIDS.
3. Hepatitis B and C positivity

Table 3 Recommended pretreatment and monitoring investigations

Investigations	
Full blood counts	Efalizumab: monthly for 3 months, then every 6 months TNF blockers: 3 months, every 6 months
LFT, RFT, Electrolytes	3 months, every 6 months
Urinalysis, HIV, Hepatitis B & C, chest X-ray, autoantibodies i.e. ANA, anti-ds DNA	At baseline
Disease severity assessment	
PASI, DLQI (for skin & joints)	3 months and 6 months
General health enquiry (with regard to infections, heart failure, demyelination)	3 to 6 months

PASI – Psoriasis area and severity index, DLQI – Dermatology life quality index

score of 50% is the standard used by the FDA to assess the efficacy of a new psoriatic agent. The dermatology life quality index (DLQI) is a simple questionnaire and a DLQI of 10 or more correlates well with severe disease requiring admission, phototherapy or second line therapy. Therapy should be withdrawn after 3 months if these criteria are not fulfilled.

Agents targeting T cells or antigen presenting cells

Alefacept

Alefacept is a bivalent recombinant fusion protein, composed of the terminal portion of LFA-3 and the Fc portion of human immunoglobulin IgG1. Alefacept is manufactured by Biogen (Cambridge, MA, USA) under the trade name Amevive® and was the first biological agent approved by the U.S. Food and Drug Administration (FDA) in January 2003 for the treatment of patients with moderate to severe chronic plaque psoriasis.[14]

LFA-3 is expressed on APCs and is the ligand for CD2 which is expressed on mature T lymphocytes and natural killer (NK) cells. Ligation of CD2 by LFA-3 acts as a costimulatory signal and is important in the proliferation and activation of T lymphocytes. The LFA-3 moiety on alefacept blocks the interaction between LFA-3 on APCs and CD2 on T cells through competitive inhibition and prevents transduction of costimulatory signals between APCs and T lymphocytes. In addition, alefacept acts as a bridging molecule between CD2 receptor on T lymphocytes and the FcϒIII (CD16) receptor on natural killer cells thereby inducing apoptosis of the T lymphocytes. Thus, alefacept inhibits the proliferation and activation of memory T lymphocytes through blockage of LFA-3-CD2 interaction and also induces apoptosis of T lymphocytes through mediation between T lymphocytes and NK cells.[15]

It is given either intramuscularly or intravenously at a dose of 10-15mg IM

weekly or 7.5 mg IV weekly and a 12-week course is recommended.

In a multicentre, randomized, placebo-controlled, double-blind study for the treatment of chronic plaque psoriasis, 229 patients received either alefacept or placebo intravenously for 12 weeks with a follow up for additional 12 weeks. There was a significant reduction in the psoriasis area and severity index (PASI) among the alefacept treated group, with 24% of patients being clear or almost clear after 12 weeks of therapy. The average duration of remission in those who were clear was 8 months, with some lasting up to 17 months. No serious adverse effect or rebound of psoriasis was noted following cessation of therapy.[16,17]

Another multicentre, randomized double-blind, placebo-controlled, phase 3 trial investigated the efficacy of intramuscular alefacept where a total of 507 patients with chronic plaque psoriasis were randomized into three groups: placebo, alefacept 10mg and 15mgs intramuscularly once weekly for 12 weeeks followed by a 12 week observation period. During the study, a higher percentage of patients in the 15mg alefacept group achieved a significant reduction in the PASI as compared to the placebo and 71% maintained 50% improvement in PASI throughout the 12 week follow up. There were no opportunistic infections and no cases of disease rebound seen.[18]

No combination therapy using alefacept and other systemic agents has been reported to date, however there is evidence that narrow-band phototherapy in conjunction with alefacept has a synergistic effect in psoriasis than alefacept alone.[19]

Alefacept is safe and well-tolerated in a broad spectrum of patients including those on concomitant immunosuppressive agents. The incidence of serious adverse events, discontinuations, infections, malignancies and anti alefacept antibodies remain low upto six alefacept courses. Because of its effects on T cells the product labeling recommends CD4 counts to be monitored weekly during therapy and if the CD4 count falls below 250 cell μl^{-1}, the drug must be discontinued until the CD4 count increases above 250 cells μl^{-1}. If the CD4 count remains <250 cells μl^{-1} for 4 continuous weeks, then alefacept treatment must be permanently discontinued.[5]

Efalizumab

Efalizumab is a recombinant human IgG1 monoclonal antibody directed against the CD11a subunit of LFA-1. It disrupts the interaction of LFA-1 and the ICAM-1 (intercellular adhesion molecule), thereby destabilizing the APC-T cell binding. *In vitro* studies indicate that by binding to LFA-1, efalizumab inhibits several key steps in the pathogenesis of psoriasis such as T cell activation, trafficking and adhesion to the keratinocytes.[20]

It is manufactured by the Genetech/Xoma (San Francisco CA, USA) under the trade name Raptiva® and was approved by the FDA in October 2003 for the treatment of moderate to severe chronic plaque psoriasis. Currently, it is the only biological agent approved for continuous administration and can be self-administered as weekly subcutaneous injections. The initial loading dose is 0.7mg/kg followed by weekly continuous doses at 1mg/kg. The initial loading dose is lower in order to minimize

the transient flu like symptoms that were observed in clinical trials at higher doses.

A single vial of efalizumab contains 125mg of the drug as sterile lyophilized powder with preloaded single use syringes containing 1.3ml of sterile water. Patients should be instructed to rotate the injection sites between the thigh, abdomen, buttocks and upper arms with each dose.[21]

The safety and efficacy of efalizumab has been documented in four large phase 3 trials involving over 2700 patients, with moderate to severe plaque psoriasis, most of whom had received previous systemic therapies. Overall the drug appears to be effective at a dose of 1mg/kg weekly with 27% of patients achieving a PASI75 response as compared to 4% of the placebo by week 12. Continuing therapy beyond 12 weeks may increase the response rate further. The duration of remission following discontinuation of therapy is variable and relapse is usually evident at about 2 months of discontinuation.[22,23,24]

Acute flu-like symptoms such as fever, headache, malaise, nausea may occur after the administration of first two doses with a decreasing incidence at each subsequent injection. Discontinuation of therapy may be associated with an exacerbation of the disease including the development of pustular and erythrodermic psoriasis.[5]

Anti-tumour necrosis factor-α agents

Etanercept

Etanercept is a human recombinant fusion protein comprising of the human TNF-α p75 receptor and the Fc portion of human IgG1 fused together. It functions as a TNF-α inhibitor by competitively binding to and in activating the TNF-α thereby preventing its interaction with cell surface receptors and inhibiting it proinflammatory effects.[25]

Etanercept is manufactured by Augen Thors and Oaks, CA, USA under the trade name Enbrel™ and is FDA approved as a subcutaneous monotherapy for patients of moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In addition, it is also indicated for rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile rheumatoid arthritis and ankylosing spondylitis.[26] Etanercept is available in India now (Wyeth Ltd ; Worli, Mumbai), as 25 mg dose per vial as a sterile, white, preservative free lyophilized. powder for parentral administration after reconstitution with 1 ml of supplied sterile bacteriostatic water for injection. The licensed adult dose is 25mg or 50mg/week which can be self administered by the patient subcutaneously over the abdomen, thighs or upper arms. In order to minimize the injection site reactions, patients are instructed to place their injections at least an inch apart from the prior injection sites or inject at contralateral sites.

Several small phase II and two key phase III randomized controlled trials involving over 1000 patients with moderate to severe chronic plaque psoriasis, the majority of whom had received previous systemic treatments or PUVA, indicate that etanercept is an effective treatment for chronic plaque psoriasis. Efficacy is dose-related with 34% and 49% of patients receiving 25mg and 50mg twice weekly, respectively achieving PASI75 response after 12 weeks of therapy. Continued treatment for 24 weeks appears to increase the response rate further.[27,28,29]

Etanercept can safely be added as a combination therapy to phototherapy (PUVA/UVB) and other systemic agents, especially when they are being tapered to prevent any rebound recurrences without any additional toxicity.[5] The current license recommends intermittent courses no longer than 24 weeks with the time to relapse being variable and dose-related ranging from 70-90 days. Of patients achieving PASI75 response at 24 weeks, 11% remained in remission at 1 year.

Infliximab

Infliximab is a human-murine monoclonal antibody that binds to and inhibits the activity of TNF-α thereby inhibiting production of other proinflammatory cytokines. It is manufactured by Centocor, Malvern, PA, U.S.A. under the trade name Remicade™ and is licensed for use in rheumatoid arthritis and Crohn's disease. It is also effective in moderate to severe chronic plaque psoriasis, psoriatic arthritis and may be of value in generalised pustular psoriasis.[30]

Infliximab is given by intravenous infusion over a period of 2 hrs. A standard induction dose of 5mg/kg or 10mg/kg at week 0, 2, 6 is followed by repeat single infusion at 8-12 week intervals. Though studies have established the optimal frequency and dose of repeat infusions required to achieve disease control, once significant disease relapse has occurred, repeat infusions do not achieve the same rate of disease clearance as that seen on the initial three dose induction treatment.[31]

In two randomized placebo-controlled trials conducted in patients with moderate to severe stable chronic plaque psoriasis, 75% improvement in PASI at week 10 was noted in 87% patients receiving standard induction therapy. The time to relapse following successful induction is highly variable between individuals and may depend on the initial dose given.[32] Several case series report infliximab monotherapy to be of benefit in psoriatic patients previously resistant to multiple systemic therapies and it may be given in combination with methotrexate, ciclosporin, acitretin and hydroxyurea.[33,34] Unwanted adverse effects with infliximab include infection, infusion-related effects, headache, vertigo, flushing, gastrointestinal effects, abnormal hepatic functions and fatigue.

Choice of agent to use

There are no studies directly comparing the efficacy of infliximab, etanercept and efalizumab,[5] but extrapolating data from short-term, placebo-controlled trials of each individual drug suggest a possible rank order of efficacy, with infliximab being the most effective and efalizumab the least effective at 12 weeks. Choice of the biological to be used depends on the clinical pattern of psoriasis, pre-existing co-morbidity, patient preference, prescriber preference and local facilities.

- Etanercept should be considered the first choice for patients with significant uncontrolled psoriatic arthritis.
- For patients with stable psoriasis where a decision has been made to treat with an anti-TNF-α agent, etanercept should be used unless there are clear reasons not to do so.
- Infliximab is useful in clinical circumstances requiring rapid disease control e.g. in unstable erythrodermic or

pustular psoriasis due to it very rapid onset of action and high response rate.

- For patients with a high risk of latent tuberculosis or with evidence of demyelinating disease, efalizumab should be considered the first choice.

Side effects of biologics

1. Allergic reactions and antibody development

Injection site reactions comprising of erythema, edema and localized burning are frequently reported with etanercept in 10-20% of patients in the first month of therapy. They resolve spontaneously in 2-3 days and tolerance develops gradually in most patients with continuous use. Antibodies to etanercept may develop in 6% of patients. With infliximab, infusion reactions occur within 1-2 hours of treatment and may affect up to 20% of all patients treated. Rarely an anaphylactic shock occurs. For mild to moderate reactions, the infusion rate may be slowed or interrupted temporarily but for severe cases further infliximab infusion should be discontinued. Acute flu-like symptoms may occur during the first few weeks of treatment with efalizumab, but tend to resolve by 3-4 weeks of therapy.

2. Infections

Reactivation of tuberculosis may occur following treatment with anti-TNF agents as TNF-α plays a key role in host defence against mycobacterial infection, particularly in granuloma formation and inhibition of bacterial dissemination. The risk of TB is estimated to be six times with infliximab than with etanercept in trials of patients with either rheumatoid arthritis or Crohn's disease, however no cases of TB were reported in clinical trials of patients with psoriasis probably reflecting the limited number of patients being treated and possibly monotherapy. Other serious infections reported include sepsis secondary to *Listeria monocytogenes* and histoplasmosis. Severe disseminated opportunistic infections have been reported also in the context of HIV.

3. Malignancy

The risk of developing a lymphoprolifertive disorder in treated patients in comparison to the normal population are nil, however, patients with PUVA therapy may represent a particular risk group.

4. Heart disease

Anti-TNF agents should be avoided in patients with severe congestive heart failure. Those with milder disease should be carefully assessed prior to initiation and treatment withdrawn at onset of new symptoms or worsening of pre-existing heart failure.

5. Neurological disease

TNF blockers may be associated with development of or worsening of demyelinating disease and hence should not be give in patients of multiple sclerosis or optic neuritis.

6. Hepatitis

The safety of TNF blockers in patients with chronic hepatitis B and C is not known. Rare cases of severe hepatitic reactions following infliximab have been reported with symptoms occurring from 2 weeks to more than a year after treatment initiation. Infliximab should be stopped in the event of

jaundice or marked elevation of liver enzymes (>5 times normal limit).

7. Antinuclear antibodies and lupus like syndromes

Antinuclear antibodies and less commonly anti-double-stranded DNA antibodies may develop during therapy but do not seem to be associated with symptoms or signs of lupus in the vast majority.

8. Thrombocytopenia

This may occur following therapy with efalizumab and warrants regular monitoring of platelet counts.

Conclusion

It is quite evident that the pathogenesis of psoriasis is modulated by immune-mediated mechanisms that involve activated T cells and inflammatory cytokines such as TNF-α. Current immunosuppressives may be effective in controlling psoriasis to a certain degree, but have significant drawbacks such as toxicity and relapse of the disease on discontinuation. Biological immunomodulators have demonstrated efficacy in the treatment of several dermatologic disorders due to their selectivity in targeting specific pathways in the inflammatory cascade of psoriasis with virtually no clear indication to date of organ toxicity. Though their cost is a limitation, their unique mechanism of action has definitely give a new ray of hope in the management of psoriasis.

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