Comparison of Various Biological Agents in the Treatment of Psoriasis

Dr. KH Lau  MBBS(HK), FRCP, FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service.

Introduction

In recent years, there has been considerable breakthrough in understanding the pathogenesis of psoriasis as a T cell mediated autoimmune disease. In genetically predisposed individuals, a triggering antigen, the nature of which is still not clear, is captured by Langerhans’ cells in the epidermis. The Langerhans’ cell migrates into the regional lymph node and presents the antigen to the T lymphocyte. When the antigen-Langerhans’ cell complex interacts with the T cell in the lymph node, the T lymphocyte is activated by two co-stimulatory signals 1 and 2. In predisposed individuals, these activated T cells undergo TH1 differentiation into effector memory T cells and selectively traffics back to the skin and releases inflammatory cytokines such as tumour necrosis factor (TNF) alpha. These cytokines act on the epidermal keratinocytes, dermal blood vessels and other inflammatory cells, producing inflammatory responses that result in clinical lesion of psoriasis.

Biologic agents are synthetic proteins designed to block one or more of these specific steps in the pathogenic pathway. Four targets are aimed:

- **Target 1**: Inhibiting T cell activation by blocking the co-stimulatory signal 2 (e.g. by efalizumab, alefacept);
- **Target 2**: Inducing immune deviation from TH1 differentiation to TH2 differentiation in the activated T cell;
- **Target 3**: Eliminating activated T cells selectively (e.g. by alefacept);
- **Target 4**: Inhibiting the action of cytokines, especially tumour necrosis factor (TNF) alpha (e.g. by infliximab, etanercept).

Four of these new biologic agents, namely alefacept, efalizumab, infliximab and etanercept are discussed below. Comparison of their modes of actions, clinical uses, efficacy, side effects and precautions are summarized in Table 1.

Alefacept

In psoriasis, the lymphocyte function-associated antigen (LFA)-3 presents on the Langerhans’ cell binds to the CD2 expressed on activated T cell, producing co-stimulating interaction (signal 2) and leads to T cell activation and a cascade of inflammatory response resulting in psoriasis. Alefacept is a recombinant human LFA-3/ IgG1 dimeric fusion protein that binds to CD2 receptor expressed on these activated T cells, thus inhibiting T cell activation (Target 1) and proliferation. In addition, it also causes apoptosis and selective elimination of these pathogenic T cells (Target 3) while preserving the naive T cells. In January 2003, Alefacept was approved by FDA of USA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. It is administered weekly either by intramuscular injection of 15mg or by intravenous bolus injection of 7.5mg. A course of 12 weeks is usually recommended.

In most clinical trials on efficacy of treatment for psoriasis, the widely adopted parameter is the PASI 75 which measures the percentage of patients achieving at least 75% reduction of their Psoriasis Area and Severity Index (PASI) score from the pretreatment baseline. In alefacept, PASI 75 was achieved in 33% of patients after weekly intramuscular injection for 12-week. Similarly, 28% of patients achieved PASI 75 after a 12 week course of once weekly intravenous alefacept injection while a second course further enhanced clinical efficacy up to 40%. Significant clinical response occurred at around eight weeks after starting treatment. The best clinical efficacy occurred approximately six weeks after the last dose. Comparing with other biologics, remission in the responders was long-lasting and at week 24, 24% of patients still remained clear or almost clear without additional therapy and 71% maintained at least PASI 50 (i.e. 50% reduction of PASI as compared with baseline).

For those who needed retreatment, a median interval of 10 months (range: 6 to 18) between the last dose to subsequent retreatment was noted. The most common side effects were pharyngitis, headache, rhinitis and dizziness. Mild injection site reaction occurred more often in the intramuscular administration while transient chill during the first day of treatment occurred more often in the intravenous route. One of the important side effects is the reduction of circulating T cell counts. Weekly CD4 T lymphocyte
Efalizumab

Efalizumab is a recombinant humanized monoclonal antibody against the alpha subunit of LFA-1 (i.e. the CD11a) expressed on T lymphocytes. It inhibits the interaction between CD11a and the intercellular adhesion molecule (ICAM)-1 expressed on antigen presenting cells hence stopping the co-stimulatory signal 2 (Target 1) that activates the T cells which lead to a sequence of inflammatory events. Efalizumab was approved by FDA in October 2003 to treat moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. It is usually given by subcutaneous injection of single first conditioning dose at 0.7 mg/kg followed by weekly dose at 1 mg/kg for a course of 12 weeks.

Twenty-two to 29.2% versus 28 to 41% of patients achieved PASI 75 after 12 week treatment with dose of 1 mg/kg versus 2 mg/kg respectively.5,6 Seventy-seven percent of these good responders maintained their improvement when additional 12 week treatment were given.6 The improvement occurred as early as four weeks.7 Study showed that additional clinical improvement could be achieved by prolonged treatment beyond 12 weeks.8 Treatment up to 24 and 60 weeks, which were well tolerated, increased the percentage of patients achieving PASI 75 to 51% and 64% respectively.9 However, when stopping treatment, signal 2 (Target 1) pathophysiological role of the major disadvantages and 0.7% of patients experienced rebound after discontinuation, suggesting long term maintenance therapy with efalizumab is necessary.7

Common minor side effects such as flu-like symptoms occurred in 37% of patients during the first few injections.8 It can be minimized by the use of reduced conditioning dose in the first injection. More serious side effect of thrombocytopenia was rarely reported.7 Monitoring of platelet count is recommended every month initially and then three-monthly during the treatment period and treatment should be stopped if significant thrombocytopenia occurs.

Infliximab

Infliximab is a chimeric monoclonal antibody which binds to transmembrane and soluble TNF alpha. It binds to TNF specifically and blocks its interaction with cell surface receptors (Target 4). Thus, TNF alpha, which is an important mediator secreted by the activated pathogenic T cells, cannot bind with its natural receptors in various sites and the inflammatory response leading to psoriasis ceases. Infliximab is approved for the treatment of Crohn’s disease and rheumatoid arthritis by FDA and is currently under review by the authority for other indications including psoriasis. The drug is usually given 3 mg/kg to 5 mg/kg by intravenous infusion over two hours at week 0, 2, 6 then every 8 week if maintenance is necessary.

Infliximab is highly efficacious and 72% versus 88% of patients achieved PASI 75 at week 10 after infusion at 3 mg/kg versus 5 mg/kg respectively.9 Almost half of the responders achieved PASI 75 at 4 weeks.5 Other studies showed that 40% and 73% of patients receiving 5 mg/kg and 10 mg/kg infliximab respectively were able to maintain at PASI 50 at week 26.10 Hence, infliximab could produce a rapid, effective and sustainable effect in the treatment of psoriasis.

Common side effects are mild including headache, pruritus, fatigue and myalgia. Five percent of patients may develop infusion reactions ranging from mild hypotension and allergic reactions to severe anaphylaxis and seizures which usually occur during or within two hours of infusion.11 Serious opportunistic infections such as disseminated or extrapulmonary tuberculosis were reported.11,12 Reactivation of latent tuberculosis may develop within the first three to six months after starting treatment. Pretreatment tuberculin test, chest x ray and anti-tuberculosis prophylaxis are recommended before the commencement of infliximab.11,12 Infliximab is also contraindicated in patients with moderate to severe heart failure.

Etanercept

Etanercept is a dimeric fusion protein consisting of two TNF receptor components linked to the Fc portion of human IgG. Similar to infliximab, etanercept binds to TNF specifically and blocks its interaction with cell surface receptors (Target 4). In April, 2004, FDA has approved the use of etanercept for the treatment of moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. It is also approved for treating psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis. It is given subcutaneously 50 mg twice per week usually for a course of 12 weeks, then 50 mg once per week for maintenance if necessary.

PASI 75 was achieved in 49% of patients at week 12 and increased to 59% when twice weekly treatment was extended to 24 weeks.13 Clinical improvement was evident as early as 2 weeks. The main side effects were upper respiratory infection (57%), injection site reactions (20%), and headache (13%). Eleven percent and 15% reported induction of antinuclear antibodies and anti-double-stranded DNA but full cases of lupus erythematosus are rare.14

Conclusion

These new biologic agents are exciting additions of armamentarium for the treatment of psoriasis. As compared with the conventional immunosuppressive therapy (e.g. cyclosporin), they seem to have an improved risk-efficacy ratio. Among them, infliximab seems to be highly efficacious while alefacept apparently offers longer remission to responders. Furthermore, some of them (e.g. efalizumab and etanercept) can conveniently be administered by the patients themselves at home. The downside of these new treatments are the need of laboratory monitoring in some agents (e.g. platelet count in efalizumab and CD4 count in etanercept) as well as the potential serious side effects.
effects such as infusion reaction and opportunistic infections (e.g. tuberculosis in infliximab). The cost of all these new therapeutic agents are very high. Further studies are needed to compare the cost-effectiveness of these new agents with the current systemic anti-psoriatic therapies.

References


Table 1 summary of four biological agents for the treatment of psoriasis

<table>
<thead>
<tr>
<th>Biological agent</th>
<th>Ailefacept(Amevive®)</th>
<th>Efaluzumab(Raptiva®)</th>
<th>Infliximab(Remicade®)</th>
<th>Etanercept (Enbrel®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Fusion protein of human LFA-3 and Fc portion of IgG1</td>
<td>Humanized form of murine antibody against CD11a</td>
<td>Chimeric antibody against TNF alpha and blocks its activities</td>
<td>Fusion protein of the Fc of human IgG1 and the extracellular TNF receptor</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Block LFA-3/CD2 interaction and selective elimination of activated T cells</td>
<td>Block LFA-1/ICAM-1 interaction and inhibit T cell activation and inflammatory events</td>
<td>Binds soluble and bound TNF alpha and blocks its activities</td>
<td>Binds soluble and bound TNF alpha and blocks its activities</td>
</tr>
<tr>
<td>Target of action</td>
<td>Target 1 &amp; 3</td>
<td>Target 1</td>
<td>Target 4</td>
<td>Target 4</td>
</tr>
<tr>
<td>FDA indication</td>
<td>Mod to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (approved Jan 2003)</td>
<td>Mod to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy (approved Oct 2003)</td>
<td>Crohn’s disease and RA</td>
<td>Mod to severe plaque psoriasis in adults (approved Apr 2004); psoriatic, rheumatoid and juvenile rheumatoid arthritis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intramuscular or intravenous bolus</td>
<td>Subcutaneous (by patients at home after training)</td>
<td>Slow intravenous infusion over 2 hours</td>
<td>Subcutaneous (by patients at home after training)</td>
</tr>
<tr>
<td>Dosing for one course</td>
<td>15mg imi or 7.5mg ivi weekly for 12 weeks</td>
<td>Begin with single dose of 0.7mg/kg sc, then 1mg/kg sc weekly for 12 weeks</td>
<td>3 to 5 mg/kg iv infusion at week 0,2,6.</td>
<td>50mg sc twice a week for 12 weeks (50mg sc weekly if maintenance)</td>
</tr>
<tr>
<td>Time of onset of improvement</td>
<td>~8 weeks</td>
<td>~4 weeks</td>
<td>~4 weeks</td>
<td>~2 weeks</td>
</tr>
<tr>
<td>Relative efficacy: % of patients achieving PASI 75 after a course of 12 week Pxs</td>
<td>~28-40%</td>
<td>~22-41% (Increase to 64% if prolonged treatment)</td>
<td>~72-88%</td>
<td>~49% (Increase to 59% if prolonged treatment)</td>
</tr>
<tr>
<td>FDA baseline &amp; monitoring</td>
<td>CD4 count (baseline and weekly)</td>
<td>Platelet count monthly, then every 3 months</td>
<td>Screening for latent TB(tuberculin test, CXR) at baseline</td>
<td>None</td>
</tr>
<tr>
<td>Side effect</td>
<td>Flu-like symptoms, injection site reaction, transient chill</td>
<td>Flu-like symptoms</td>
<td>Headache, myalgia, infusion reactions, opportunistic infections</td>
<td>Upper respiratory infection, injection site reaction, headache</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Hypersensitivity to ailefacept; sepsis if CD4&lt;250 cells/ul for 4 weeks</td>
<td>Hypersensitivity to efaluzumab or any murine or murine monoclonal antibody</td>
<td>Hypersensitivity to infliximab or murine products; congestive heart failure</td>
<td>Hypersensitivity to etanercept; tuberculosis or sepsis; congestive heart failure; poorly controlled diabetes</td>
</tr>
<tr>
<td>Advantage</td>
<td>Long lasting remission</td>
<td>Self administered by patients possible</td>
<td>Highly efficacious</td>
<td>Also effective against psoriatic arthritis; self administered by patient possible</td>
</tr>
<tr>
<td>Disadvantage</td>
<td>Need for CD4 count monitoring, withhold if CD4&lt;250 cells/ul, discontinue if persists for 4 weeks</td>
<td>Significant relapse after treatment; long term maintenance necessary</td>
<td>Manpower for iv infusion; risk of anaphylactic infusion reaction; risk of serious opportunistic infection</td>
<td>Serious opportunistic infection reported, prior tuberculosis test and CXR advisable in TB endemic area</td>
</tr>
<tr>
<td>Estimated drug cost (US$)</td>
<td>~$10,000 per course depending on dosing</td>
<td>~$15,000 per year for maintenance treatment</td>
<td>~$12,000 per year depending on dosage</td>
<td>~$12,000 per year</td>
</tr>
</tbody>
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MCHK CME Programme Self-assessment Questions

Please read the article entitled “Comparison of Various Biological Agents in the Treatment of Psoriasis” by Dr.KH Lau and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 September 2006. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. The following statements concerning treatment of psoriasis by etanercept are correct except:
   a. Comparing with other biological agents, the onset of clinical improvement is slow.
   b. Etanercept has a similar mode of action as infliximab.
   c. It is approved by FDA for the treatment of moderate to severe chronic plaque psoriasis patients who are candidates for systemic therapy or phototherapy.
   d. The main side effects are upper respiratory tract infection and injection site reactions.
   e. Induction of antinuclear antibodies and anti-double stranded DNA were reported after treatment with etanercept.

2. The following are relevant side effects of alefacept except:
   a. Pharyngitis
   b. Headache
   c. Rhinitis
   d. Lymphocytosis
   e. Injection site reaction and transient chill during the first day of treatment

3. FDA recommends monitoring of the following parameter(s) during treatment with efalizumab:
   a. Chest X ray
   b. White cell count
   c. Tuberculin test
   d. Platelet count
   e. All of the above

4. The following are correct modes of action of the biological agents designed to block the specific steps in the pathogenetic pathway of psoriasis except:
   a. Alefacept inhibits T cell activation by blocking the co-stimulatory signal 2.
   b. Etanercept binds soluble and bound tumour necrosis factor (TNF) alpha and blocks its action.
   c. Alefacept eliminates activated T cells selectively.
   d. Efalizumab induces immune deviation from TH1 to TH2 differentiation in the activated T cell.
   e. Infliximab inhibits the action of cytokines, especially tumour necrosis factor (TNF) alpha.

5. The following is/are disadvantage of treatment with infliximab in psoriasis:
   a. High treatment cost.
   b. Reactivation of latent tuberculosis.
   c. Potential serious anaphylaxis during drug administration.
   d. a and c.
   e. All of the above

6. The following statements concerning the use of alefacept in the treatment of psoriasis are correct except:
   a. Comparing with other biologics, the remission induced by alefacept is transient and significant clinical relapse is one of the major disadvantages.
   b. It was already approved by FDA of USA for the treatment of moderate to severe plaque psoriasis in adult patients.
   c. Alefacept is a recombinant human LFA-3/IgG1 dimeric fusion protein.
   d. Alefacept is administered weekly either by intramuscular or by intravenous bolus injection.
   e. The best clinical efficacy usually occurs few weeks after completing the course of treatment.

7. The following biological agent(s) can be administered at home by trained patients themselves:
   a. Efalizumab
   b. Infliximab
   c. Etanercept
   d. a and c
   e. all of the above

8. The following statements concerning the use of efalizumab in the treatment of psoriasis are correct except:
   a. The usual dosage is 1mg/kg weekly for a course of 12 week.
   b. Long term treatment of efalizumab up to 60 weeks was proven to be safe and well tolerated.
   c. Comparing with other biologics, remission in the responders was long lasting and a significant number of patients still remained clear even after stopping treatment.
   d. It is usually given by subcutaneous injection.
   e. Additional clinical improvement could be achieved by prolonged treatment beyond 12 weeks with enhanced clinical efficacy.

9. In treating patients with psoriatic arthropathy complicating extensive stable plaque psoriasis, the following biological agent is an FDA approved treatment option:
   a. Alefacept
   b. Efalizumab
   c. Infliximab
   d. Etanercept
   e. None of the above

10. Which of the following statement(s) concerning the use of infliximab in the treatment of psoriasis is/are correct:
    a. It is administered subcutaneously.
    b. It is given in 50mg twice a week for a course of 12 week.
    c. It is approved by FDA for the treatment of Crohn’s disease and rheumatoid arthritis.
    d. No laboratory monitoring is required by FDA.
    e. All of the above.
Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2006 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Dr. KH Lau  MBBS(HK), FRCP, FHKCP, FHKAM(Med)
Yaumatei Dermatology Clinic, Social Hygiene Service.

Answers to August 2006 issue

Aesthetic Dentistry and Orthodontics