Update on the New Biologic Therapies for Psoriasis

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Topic Areas

Overview of Psoriasis: Rationale for the Use of Biologic Therapy

Overview of Biologic Therapies in the Treatment of Psoriasis

Integrating the New Biologic Therapies Into Clinical Practice

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CME Test and Post-Test Evaluation

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Target Audience

This activity has been developed for dermatologists who treat patients with moderate to severe psoriasis.

Educational Needs

For more than 20 years there have been few significant developments in the treatment of psoriasis. Today, an entirely new approach to therapy has been made possible as a result of our increased understanding of the pathophysiology of psoriasis. Four new biologic therapy agents are currently approved or in development to treat psoriasis. Two agents inhibit the cytokine tumor necrosis factor alpha (TNF-α), and the other two agents target T cells. This CME activity provides the dermatologist with an overview of the immunopathology of psoriasis as well as new information about these biologic therapies.

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Dr. Gordon and Dr. Gottlieb discuss the investigational uses of efalizumab, etanercept, and infliximab for the treatment of psoriasis.
Overview of Psoriasis: Rationale for the Use of Biologic Therapy

Psoriasis can have significant adverse effects on a patient’s physical, psychological, and social functioning and touches virtually every aspect of a patient’s life. Because the condition often causes absence from work and can affect the ability to perform normal work activities, psoriasis can negatively affect a person’s job and income. In many cases, an individual’s family life, social life, and leisure activities are compromised by psoriasis. Patients with psoriasis reported reduction in physical and mental functioning similar to that of other major medical diseases. Among the findings of a large survey conducted by the National Psoriasis Foundation in July 1998 was that, among respondents 18 to 34 years of age, 10% reported having contemplated suicide.

Psoriasis even impacts one’s sexual relations, as many people with the condition shy away from intimate relationships for fear of embarrassment and rejection. Overall, psoriasis has a negative effect on patients’ functional status and well-being, physical symptoms (including itch), and social relationships.

Although people with psoriasis experience severe impairment in functional health, well-being, and the ability to perform activities of daily living, many give up on treatment because conventional therapies have disappointing efficacy and are often inconvenient to administer. There is an unmet need for a psoriasis treatment that can improve these aspects of patients’ lives.

According to the results of the National Psoriasis Foundation survey, much of the frustration patients feel is due to the perceived inadequacy of common psoriasis treatments. Among patients with severe psoriasis, 78% reported feeling frustrated that their treatment did not work well enough. Nearly half (49%) of the patients with severe psoriasis reported that they were “only somewhat” or “not at all” satisfied with the treatment they were receiving. In addition, nearly one third (32%) of patients thought their treatment was not aggressive enough.

In recent years, our increased understanding of the role of immunology in the pathophysiology of psoriasis has led to the development of biologic therapies designed to interfere with the underlying molecular mechanisms at play in the disease. Initially, T cells become activated in the lymph nodes (Figure 1). The lymph nodes concentrate antigen drained from the skin and other tissues and contain high numbers of antigen-presenting cells (APCs). T-cell activation is a complex process that requires interaction between a specific antigen presented by the APC and a receptor of the interacting T cell. At present, the identity of any specific psoriasis antigens is unknown. Activation depends on multiple interactions between the T cell and the APC-antigen complex. The initial binding is mediated by lymphocyte function–associated antigen-1 (LFA-1) on the T cell and intracellular adhesion molecule-1 (ICAM-1) on the APC. This is followed by delivery of an antigen-specific signal and a costimulatory signal, resulting in T-cell activation. The resulting expression of surface molecules on activated T cells leads to increased binding of the T cells to endothelial cells. T-cell adherence to the vascular endothelium is mediated by specific interactions between their surface molecules and molecules that are expressed on the surface of the endothelial cells. These interactions include the interaction between LFA-1 on the surface of the T cells and ICAM-1 on the surface of the endothelial cells. Trafficking of T cells from the circulation into the dermal tissue, and subsequently into the epidermis, occurs. T cells then undergo a secondary activation (reactivation) in the skin when they encounter APCs displaying the appropriate specific antigen.
Overview of Biologic Therapies in the Treatment of Psoriasis

Numerous biologic therapies that arrest psoriasis at different steps are being evaluated (Table 1). These include agents that interfere with the interaction between the reactivated T cells and the keratinocytes in the dermis by binding postsecretory cytokine tumor necrosis factor-\(\alpha\) (infliximab and etanercept); those that decrease the number of activated T cells (alefacept); and those that block T-cell activation, binding, and trafficking to the dermis and epidermis (efalizumab). Of these agents, alefacept was approved by the United States Food and Drug Administration (FDA) in January 2003 for the treatment of psoriasis. Etanercept is approved for use in juvenile rheumatoid arthritis, psoriatic arthritis, and rheumatoid arthritis; and infliximab is approved for use in rheumatoid arthritis and Crohn's disease. Both etanercept and infliximab are in phase III trials for the treatment of psoriasis. Efalizumab is currently under FDA review (Biologics License Application submitted) for the treatment of psoriasis.

Assessing the Efficacy of Biologic Therapies

The FDA has set PASI 75, a decrease of 75% from baseline in the Psoriasis Area and Severity Index (PASI) score following treatment, as the primary end point for biologic agents in clinical trials for psoriasis. The National Psoriasis Foundation (NPF) Medical Advisory Board has suggested that PASI 50 (a 50% decrease from baseline in the Psoriasis Area and Severity Index score after treatment) may be a clinically more relevant end point. The PASI scale was developed to quantify the components of erythema, induration, scaling, and body surface area (BSA) affected.

Table 1: Biologic Therapy Agents for the Treatment of Psoriasis

<table>
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<tr>
<th>AGENT</th>
<th>DESCRIPTION</th>
<th>MECHANISMS OF ACTION</th>
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| Efalizumab | Humanized monoclonal antibody to the CD11a chain of LFA-1 | • Blocks T-cell activation and reactivation  
• Blocks T-cell binding and trafficking into dermis and epidermis |
| Alefacept | Fusion protein composed of the external domain of LFA-3 and a human IgG1 Fc region | • Eliminates pathogenic T cells by binding to natural killer (NK) cells  
• Blocks T-cell activation |
| Etanercept | Fusion protein composed of human TNF type II receptor (TNF-RII) and human IgG1 Fc region | • Specifically binds TNF-\(\alpha\)  
– Blocks interaction with cell-surface TNF receptors  
– Inhibits TNF-\(\alpha\)-mediated inflammation, cell infiltration, keratinocyte proliferation, osteoclast activation, and metalloproteinase synthesis |
| Infliximab | Chimeric monoclonal antibody to TNF-\(\alpha\) composed of murine-variable regions and human IgG1 Fc region | • Specifically binds TNF-\(\alpha\)  
– Blocks newly bound surface and soluble TNF-\(\alpha\) forms  
– Inhibits TNF-\(\alpha\)-mediated inflammation, cell infiltration, and keratinocyte proliferation, osteoclast activation, and metalloproteinase synthesis  
• Induces apoptosis in monocytes |

The PASI scale was developed to quantify the components of erythema, induration, scaling, and body surface area (BSA) affected.

In one study, 63% and 26% of patients receiving 15 mg/wk to 30 mg/wk of methotrexate achieved PASI 50 and 75, respectively, at week 24.6 In addition to PASI scores, other end points used in psoriasis clinical trials include Overall Lesion Severity (OLS), Physician's Global Assessment (PGA), Dermatology Life Quality Index (DLQI), Psoriasis Symptom Assessment (PSA), and Itching scores. OLS is a static, global, physician-performed assessment of overall lesion severity based on plaque elevation, scaling, and erythema. The six categories are Clear, Minimal, Mild, Moderate, Severe, and Very Severe.

The PGA is a dynamic global assessment that captures and categorizes the response to therapy of all clinical signs and symptoms of disease relative to
baseline. The physician is instructed to use all available information for this assessment, including subjective information gathered from the patient and photographs taken at baseline. The categories are Worse, Unchanged, Slight, Fair, Good, Excellent, and Cleared.

The DLQI is a 10-item measure of dermatology-related limitations. The DLQI measures the impact of skin disease on patient-reported outcomes. Cumulative responses place patients on a 0-to-30 scale, with lower scores indicating greater health and higher scores indicating more severe disease. The DLQI incorporates patients’ assessments of itch; pain; feelings of embarrassment and self-consciousness; interference of their psoriasis with daily activities, relationships, and sexual activity; and problems with their psoriasis treatment.

The PSA, derived from the Skindex-29, evaluates eight components that address both the frequency and severity of psoriasis-related symptoms. Scores range from 0 to 32, with lower scores indicating fewer symptoms.

On the Itch Visual Analog Scale (VAS), scores range from 0 to 10, with higher scores indicating more severe itch. The NPF Scorecard Itch is scored from 0 to 5, with higher scores indicating more severe itch.

**Update on Biologic Therapy Data**

**Efalizumab—Pooled Results of Three Phase III Studies**

The pooled results of the three phase III trials conducted to evaluate the safety and efficacy of subcutaneously administered efalizumab in moderate-to-severe plaque psoriasis in a large number of patients were recently presented in San Francisco. The study design was the same in all three trials. Of the 1,650 patients in these three studies, 479 received placebo and 1,172 received efalizumab. At the end of the first 12 weeks of therapy, a significantly greater proportion of patients in the efalizumab-treated groups demonstrated clinical improvement as measured by PASI, compared with the placebo group. Of patients receiving 1 mg/kg/wk of efalizumab, 28% achieved PASI 75 and 57% achieved PASI 50. Of patients receiving 2 mg/kg/wk of efalizumab, 28% achieved PASI 75 and 55% achieved PASI 50. In the placebo group, 4% achieved PASI 75 and 15% achieved PASI 50.

Efalizumab treatment resulted in a statistically significant enhancement in mean percentage improvement in PASI score, compared with placebo as early as day 14 (Figure 2). The positive response to efalizumab was confirmed by the significant improvement achieved in OLS scale and PGA scores. Thirty percent of the efalizumab patients had PGA scores of “Excellent” or “Cleared,” as compared to 5% of those in the placebo group. In addition, 24% of the efalizumab patients showed “Minimal” to “Clear” on the OLS scale, compared to 3% of those in the placebo group.

Is the statistically significant response that is seen as early as 2 to 4 weeks following treatment clinically relevant? As can be seen from the most recent of the three 12-week studies, a statistically greater improvement was seen in the DLQI as early as 4 weeks following initial treatment (the first time point measured), compared to the placebo group (P<0.001) (Figure 3). A review of the Itching Scale scores over time reveals that patients receiving efalizumab experienced improvement in itch as early as
4 weeks following initial treatment (the first time point measured), compared to the placebo group. By week 4, there was also a statistically significant improvement in the PSA Frequency and Severity Scores in efalizumab-treated patients, compared to the placebo group. The improvement in PSA Frequency and Severity Scores at 12 weeks mirrored that of itch relief. Both efalizumab groups had a reduction of 45% in frequency of psoriasis and a similar reduction of 46% in psoriasis severity, as compared to a 14% reduction on both tests in the placebo group. Figure 4 shows a representative response to efalizumab therapy at 12 weeks.

Safety and Tolerability. The pooled 12-week safety analysis from the three placebo-controlled phase III studies revealed that the adverse events reported most frequently (i.e., occurring in ≥5% of all patients) included headache, infection (the most common were colds, upper respiratory infections, and skin infections), chills, nausea, pain (generalized pain, not pain on injection), fever, myalgia, asthenia, pharyngitis, diarrhea, accidental injury, and rhinitis. Of these, headache, chills, nausea, pain, fever, myalgia, asthenia, and pharyngitis occurred more often in those who received placebo. The acute adverse events (i.e., those that occurred within 48 hours of treatment) with efalizumab were mild to moderate. After the first two doses, the percentage of efalizumab-treated patients experiencing adverse events due to study drug was similar to that of patients in the placebo group (Figure 5). The rate of rebound (defined by the National Psoriasis Foundation Medical Advisory Board as a PASI of 125% of baseline or new pustular or erythrodermic psoriasis occurring within 3 months of stopping therapy) for efalizumab observed in all clinical trials was 3% (14.7% efalizumab vs 11.4% placebo). In the efalizumab phase III studies, <1% of patients were hospitalized due to rebound.

Continuous Therapy Study. Results from an ongoing, open-label study conducted to characterize the safety, tolerability, and efficacy of long-term efalizumab treatment were also presented in San Francisco in March 2003. Preliminary results from an as-treated analysis of all patients completing up to 15 months of continuous efalizumab therapy show that approximately 65% maintained PASI 75 (Figure 6).

As with previous studies, the adverse events reported most frequently were headache (36%), nonspecific infection (e.g., common colds, 16%), chills (12%), pain (11%), and nausea, asthenia, and fever (10% each). Acute adverse events of headache, fever, chills, nausea, vomiting, and myalgia occurred primarily in association with the first two efalizumab doses. No new adverse events emerged during long-term efalizumab therapy. With time, the percentage of patients who experienced at least one adverse event decreased from 57% during weeks 12 to 24 to 47% during weeks 48 to 60.

Alefacept

Alefacept, a human LFA-3/IGG1 fusion protein, was approved by the FDA in January 2003 for the treatment of moderate to severe chronic plaque psoriasis. Alefacept has been clinically evaluated in two phase III studies—one utilizing IV bolus administration and...
one utilizing IM administration. Both studies followed the same study design and consisted of two treatment courses: Course 1 was 12 weeks of weekly administration of alefacept followed by 12 weeks of follow-up, and course 2 was an additional 12 weeks of weekly therapy followed by another 12-week follow-up period.

In the IV bolus study, patients were given 7.5 mg of alefacept once weekly in courses 1 and 2. In the IM study, patients were given 15 mg of alefacept once weekly in courses 1 and 2. In both studies, the Psoriasis Area and Severity Index (PASI) was evaluated every 2 weeks during the dosing period and every 2 to 4 weeks during the observation period. Reductions in PASI of ≥75% (i.e., PASI 75) from baseline were evaluated 2 weeks after the last dose. In the IV bolus study, 14% of patients receiving one course of alefacept and 23% of patients receiving two courses of alefacept achieved the primary end point of PASI 75.10 In the IM study, 21% of patients receiving one course of alefacept and 20% of patients receiving two courses of alefacept achieved PASI 75.10

In those patients who achieved PASI 75 with alefacept treatment, response was durable. After two IM courses of therapy, patients who were followed for 1 year from the initiation of therapy (i.e., 108 days after the completion of the second course of therapy) maintained their response (Figure 7).10

Data recently presented in San Francisco, show alefacept to be effective in patients with chronic plaque psoriasis, irrespective of disease severity at baseline. Patients treated with alefacept in combination with narrow-band ultraviolet B phototherapy experienced a faster reduction in PASI than those treated with alefacept alone.11

The alefacept studies employed a means of measuring efficacy called the “overall response rate.” This measurement does not specify a time period after the first dose at which PASI 75 and PASI 50 are achieved. Trials of all the other biologic agents for psoriasis measured PASI 75 and PASI 50 at defined time points. Therefore, the data obtained from the alefacept studies cannot be compared with the results of the other agents.

Safety and Tolerability. Commonly observed adverse events seen in the first course of placebo-controlled clinical trials with at least a 2% higher incidence in the alefacept-treated patients, compared to patients who received placebo, were pharyngitis, dizziness, increased cough, nausea, pruritus, myalgia, chills, injection-site pain, injection-site inflammation, and accidental injury. The only adverse event that occurred at a 5% or higher incidence among alefacept-treated patients, compared to those who received placebo, was chills (1% placebo vs. 6% alefacept), which occurred predominantly with intravenous administration.

Alefacept was well tolerated both alone and in combination with narrow-band ultraviolet B phototherapy. The most common adverse events were rash (6/21 patients) in the combination therapy group and pruritus (4/9 patients) in the alefacept monotherapy group.

Infliximab
Results from a small study (N=33) published in Lancet in 2001 first indicated that infliximab is effective in treating psoriasis.12 Results from the first 10
Weeks of a multicenter, randomized, double-blind, placebo-controlled phase II trial (N=249) of 3 infusions of infliximab, a monoclonal antibody, administered over a 6-week period showed that 72% of patients receiving 3 mg/kg and 88% of patients receiving 5 mg/kg achieved PASI 75 (versus 6% with placebo), with improvement noticeable by week 4 (Figure 8). This trial is ongoing (the evaluation will go to week 46), and 30-week data will be presented in the summer of 2003. It remains to be seen whether this level of efficacy will be maintained over time, since experience with infliximab in rheumatoid arthritis has revealed development of antibodies in 10% of patients and a need to increase the dose over time to maintain efficacy. Safety and Tolerability. Initial (first 10 weeks) results from this study indicate that infliximab therapy is generally well tolerated; adverse events included headache, pruritus, fatigue, and myalgia. The combined incidence of infusion reactions for both dose groups was 16% (vs. 2% for the placebo group).

Open-Label Study. Results of an open-label study (N=9) of low-dose (200 mg) infliximab showed that patients who received a fixed dose achieved a 62% reduction in PASI.

Case Reports. In addition, case reports were presented on four patients with moderate to severe psoriasis who were treated with 3.8 to 5.0 mg/kg infusions of infliximab at weeks 0, 2, and 6, followed by infusions every 6 to 8 weeks. The cases showed positive long-term improvement in the signs and symptoms of psoriasis, characterized frequently by complete clearing of psoriatic lesions. In these cases, infliximab treatment improved the pain of arthritis associated with psoriasis. One patient developed fever of unknown origin, possibly attributed to serum sickness.

Etanercept

A placebo-controlled phase III study (N=652) tested etanercept at 50 mg twice weekly for one group, 25 mg twice weekly (the FDA-approved dose for psoriatic arthritis) for a second group, and 25 mg once weekly for the third group. Results for the 25 mg twice-weekly group showed 34% of patients achieving PASI 75 at 12 weeks (vs. 4% for placebo) and 44% achieving PASI 75 at 24 weeks (vs. 33% for placebo crossover). With the 50 mg twice-weekly dose, 49% of patients achieved PASI 75 at 12 weeks and 59% achieved PASI 75 at 24 weeks.

As can be seen in Figure 9, patients receiving the 50 mg twice-weekly dose showed the largest percentage improvement from baseline in DLQI score.

Safety and Tolerability. Adverse events observed in etanercept-treated patients were similar to those in the placebo crossover group; the most commonly observed adverse events were injection-site reactions (13% at week 24). Other commonly reported adverse events (i.e., occurring in ≥5% of all patients) included headache, upper respiratory infection, asthenia, myalgia, accidental injury, sinusitis, nausea, injection-site bruising, and rash.
Integrating the New Biologic Therapies Into Clinical Practice

The advent of new biologic therapies is spurring change in how clinicians treat psoriasis, and these agents are poised to offer a new opportunity to help psoriasis patients. As with all therapeutic breakthroughs, there are many important issues to be addressed as patients begin receiving these new therapies. These issues include education of staff and patients, development of standard operating procedures, assuring congruence with state and federal statutes and national guidelines, documentation, and reimbursement policies.

One of the first decisions for patients and doctors to make will be whether to choose an agent that can be administered at home or one that requires office-based administration. This decision may be patient-driven. Etanercept and efalizumab are administered at home subcutaneously, efalizumab once weekly and etanercept twice weekly (Table 2). If the decision is made to have the patient self-administer the therapy at home, the dermatologist’s staff must be prepared to train patients to reconstitute and administer the agent.

Infliximab is administered by a 120-minute IV infusion in the doctor’s office (Table 2). Alefacept is administered once weekly by an IV push or IM (Table 2). Office-based IV infusion will require a comfortable room with a chair and IV pole and IV-trained personnel. For both the IV infusion and the IV push administration, the staff will need to know the state regulations on IV administration of biologics. IM administration will require a trained staff as well.

Documentation is also important. A log should be kept to document dose, date, time, method of administration, how the patient reacts to the drug, lab monitoring, and disease response at each time point.

### Table 2: Administration of Biologic Therapies

<table>
<thead>
<tr>
<th>AGENT</th>
<th>ADMINISTRATION</th>
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<tbody>
<tr>
<td>Efalizumab</td>
<td>At-home subcutaneous injection once weekly</td>
</tr>
<tr>
<td>Alefacept</td>
<td>In-office intravenous push or intramuscular injection once weekly</td>
</tr>
<tr>
<td>Etanercept</td>
<td>At-home subcutaneous injection twice weekly</td>
</tr>
<tr>
<td>Infliximab</td>
<td>In-office 120-minute intravenous infusion at 2 and 6 weeks after the initial treatment</td>
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Conclusions

Conventional psoriasis therapies (topical treatments, phototherapy, and systemic agents such as methotrexate, cyclosporine, and acitretin) leave many needs unmet. For systemic agents, the greatest need is for improved long-term safety, while for topical agents, the greatest need is for improved long-term efficacy and convenience.

Current topical treatments are often ineffective and inconvenient; their administration may require extensive patient time, and the medications may be messy, stain clothing and sheets, and interfere with daily activities. Access to some treatments, such as phototherapy, may be limited. Thick plaques are particularly problematic to treat. With systemic therapies, long-term safety concerns include the risk of birth defects, the potential for end-organ toxicity, and carcinogenicity.

Long-term efficacy concerns regarding current therapies include the lack of efficacy in moderate to severe disease, the slow onset of effect of some therapies, and the complexity of certain regimens. Because psoriasis is a chronic disease, options for cyclical therapy become limited when the duration period for safe treatment with conventional therapies is reached. Since treatment discontinuation results in eventual relapse, the need for long-term efficacy and safety is evident.

While their long-term efficacy is still to be determined, based on clinical studies to date, all of the new biologic therapies appear to be efficacious; they are generally safe and well tolerated, with little likelihood for major organ toxicity, bone marrow toxicity, teratogenicity, or drug interaction. The new biologic agents may well transform the way that moderate to severe psoriasis is treated.
References


11. Vaishnaw AK, Ticho B. Alefacept is efficacious in a broad spectrum of patients with psoriasis, including those with severe disease. Presented at the 61st Annual Meeting of the American Academy of Dermatology; March 21-26, 2003; San Francisco. Poster P14.


1. Which of the following has the United States Food and Drug Administration set as the primary end point for biologic agents in clinical trials for psoriasis?
   a. PASI 90  
   b. PASI 75  
   c. PASI 50  
   d. None of the above

2. The new biologic agents for the treatment of psoriasis will be available as:
   a. IM injection  
   b. IV infusion/IV bolus  
   c. SC injection  
   d. Oral therapy  
   e. All but d

3. In the phase III studies of efalizumab, the percentage of patients achieving PASI 75 at the end of the first 12 weeks of therapy was approximately:
   a. 21%  
   b. 25%  
   c. 28%  
   d. 52%  
   e. None of the above

4. Efalizumab continuous therapy studies are ongoing. An interim analysis indicated that approximately ___% of patients maintained a PASI 75 response over 15 months of treatment:
   a. 28%  
   b. 56%  
   c. 75%  
   d. 65%  
   e. 99%

5. Psoriasis-related itching:
   a. Is experienced by the majority of patients  
   b. Affects a patient's ability to function and perform daily activities  
   c. Is unresponsive to anti-itch remedies  
   d. Is an important factor in quality of life  
   e. All of the above

6. Which of the following immunobiologic therapies under investigation for the treatment of psoriasis appears to be efficacious, based on clinical studies to date?
   a. Alefacept  
   b. Infliximab  
   c. Efalizumab  
   d. Etanercept  
   e. All of the above

7. Which of the following immunobiologic therapies under investigation for the treatment of psoriasis is likely to produce organ toxicity?
   a. TNF-α inhibitors  
   b. Alefacept  
   c. Efalizumab  
   d. None of the above

8. Biologic therapeutic agents under investigation for the treatment of psoriasis include ones designed to do which of the following:
   a. Block T-cell activation, binding, and trafficking to the dermis and epidermis  
   b. Increase the number of activated T cells  
   c. Increase the interaction between the reactivated T cells and the keratinocytes in the dermis by binding TNF-α  
   d. Increase T-cell activation and transmigration to the dermis

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