

Improved outcomes with new biologic agents are prompting physicians to integrate them into therapy for psoriasis patients.

Treating Psoriasis Patients With Biologic Agents

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The advent of biologic response modifiers for the treatment of psoriasis is bringing a dramatic shift in the way that dermatologists provide care for patients with this major chronic disease, which currently affects more than 4.5 million American adults (National Psoriasis Foundation [NPF] 2003).

Limited experience with these specialty drugs and their unique delivery methods have given rise to reluctance among some dermatologists to utilize these agents in the care of psoriasis patients. Yet the extremely positive results that we as dermatologists see increasingly in our patients who are receiving these novel drugs make it incumbent on us to establish their place in our practice.

Plaque psoriasis is a painful and disfiguring condition that has severe adverse effects. These negative effects extend to patient quality of life, as

well as work, family, finances, social life, leisure activities, sexual relations, and physical and emotional well-being.

Measuring the effects of psoriasis

In a study using the Short Form-36, a standardized validated quality-of-life measurement that operates across many disease entities, psoriasis was compared to other major chronic diseases in terms of its negative impact on quality of life (Rapp 1999). The physical component of this measure indicates that psoriasis reduces quality of life to a greater extent than hypertension, diabetes, depression, arthritis, myocardial infarction, and cancer — with the extent of its negative impact superseded only by congestive heart failure.

Similarly, the mental health component score reveals that psoriasis ranks highly, second only to depression, when compared with these same major chronic diseases in terms of negative impact on quality of life (Rapp 1999).

In July 1998, a questionnaire from the NPF was mailed to 40,000 of its members — generally patients with psoriasis — and was followed up with a telephone survey. The NPF received more than 17,000 responses, providing a wealth of information on patients' impressions and experiences relative to psoriasis and its treatment (Krueger 2001).

Based on the survey results, the primary symptoms that these psoriasis patients experience were ranked in descending order of frequency, as follows: scaling, itching, skin redness, skin tightness, bleeding, skin burning,

and fatigue. These results contrast with the traditional view of psoriasis that dermatologists have held, which is that it is not a particularly itchy condition.

The survey also revealed that a host of physical activities are negatively affected by psoriasis, thus limiting the extent to which psoriasis patients can participate in such activities, with potential ramifications relative to socialization. In addition, the mental impact of this disease is great; from 9 to 12 percent of patients with psoriasis have, in fact, contemplated suicide at some point. Also, more than half the patients have reported that their psoriasis had been assumed wrongly to be a contagious condition, such as poison ivy or HIV infection. Among patients with severe psoriasis, 40 percent had had trouble receiving treatment in service establishments such as salons and barber-shops, public pools, and health clubs (Krueger 2001).

With respect to patients' satisfaction with treatment, the survey showed that 78 percent are frustrated with their treatment, and only about half of these patients felt at all satisfied. Interestingly enough, a third of these patients felt that the treatment they were getting was not sufficiently aggressive (Krueger 2001).

Immunopathology

The new understanding that psoriasis is an immune system dysfunction has promoted interest in developing better immunosuppressants — specifically, biologic agents. The immune system is first activated in psoriasis when antigen-presenting cells (APCs) in the dermis recognize an

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Purpose and overview

The article "Treating Psoriasis Patients With Biologic Agents," by David M. Pariser, MD, was derived from the author's presentation at a continuing education accredited online forum, which took place on Sept. 18, 2003. Dr. Pariser's article examines the effects of the influx of biological agents with respect to the treatment of psoriasis and offers comparisons relative to traditional methods of treatment for patients affected by this disease. This article and the accompanying commentary by Jeffrey L. Lenow, MD, JD, are being offered here for continuing education credit.

Educational objectives

- Analyze the disease state of plaque psoriasis, including patient demographics, treatment trends, emerging biologic therapies, and quality of life concerns.
- Compare characteristics of biologic agents that are used to treat plaque psoriasis with traditional agents.
- Discuss the American Academy of Dermatology Consensus Statement on Plaque Psoriasis relative to the treatment of plaque psoriasis.
- Assist managed care professionals in preparing for the influx of biologic agents that represent new treatment options for plaque psoriasis.

Target audiences

Medical directors, pharmacy directors, clinical pharmacists, and other targeted personnel in the managed care and pharmacy benefit management sectors.

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Faculty disclosures

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antigen. In the epidermis, APCs internalize and enzymatically process the as-yet unknown antigen. Subsequently, major histocompatibility complex molecules present fragments of degraded antigen on the APC surface to a T-cell receptor. APCs travel to lymph nodes, where they activate T-cells and produce clonal expansion of these memory-effector T-cells, which re-enter the circulation (Krueger 2002).

Costimulatory molecules mediate initial binding of T-cells with APCs in the lymph nodes. One such costimulatory interaction is between leukocyte function associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1), located on the T-cell and APC, respectively. Figure 1 shows the APC, which is the Langerhans cell in the skin, and depicts T-cell activation in the lymph nodes. T-cell activation is followed by T-cell proliferation and cytokine production (Krueger 2002). Another clinically important costimulatory interaction is between LFA-3 and CD2.

These activated T-cells undergo LFA-1/ICAM-1 interactions in the endothelial walls, which facilitate the migration of skin-homing T-cells into areas of inflammation in the dermis and then into the epidermis. Finally, T-cells undergo reactivation in the skin, on exposure to the offending antigen. Reactivation is followed by cytokine secretion (interferon gamma [IFN- γ] and tumor necrosis factor alpha [TNF- α]), keratinocyte hyperproliferation, and an inflammatory response. Again, LFA-1 and ICAM-1, on the memory T-cell and activated APC, respectively, facilitate reactivation.

Figure 1 demonstrates the ICAM-1 reaction with LFA-1 (top). This stabilization reaction puts the APC and the T-cell into proximity of each

other. The portion in the image that is immediately below the ICAM-1 reaction highlights the specific antigen reaction from the major histocompatibility complex, which presents the antigen — one that science has yet to identify — to the T-cell receptor.

Though this antigen is as yet unidentified, psoriasis appears to be an immunologic condition. The evidence points to epidermal proliferation as the end of the line, not the beginning of pathophysiology. The beginning of the pathophysiology is the presentation of this unknown antigen.

Various costimulatory factors help stabilize the interaction of APCs and T-lymphocytes (Figure 1, bottom). Note that the LFA-1/ICAM-1 interactions play a key role in this step.

Systemic therapy and the new biologic agents

The biologic agents that are available for psoriasis act at different sites. Alefacept, the first biologic drug approved for psoriasis, exerts an effect on the LFA-3/CD2 costimulatory pathway.

Efalizumab inhibits lymphocyte movement into the dermis and epidermis. This agent works through its effect on the LFA-1/ICAM-1 reaction.

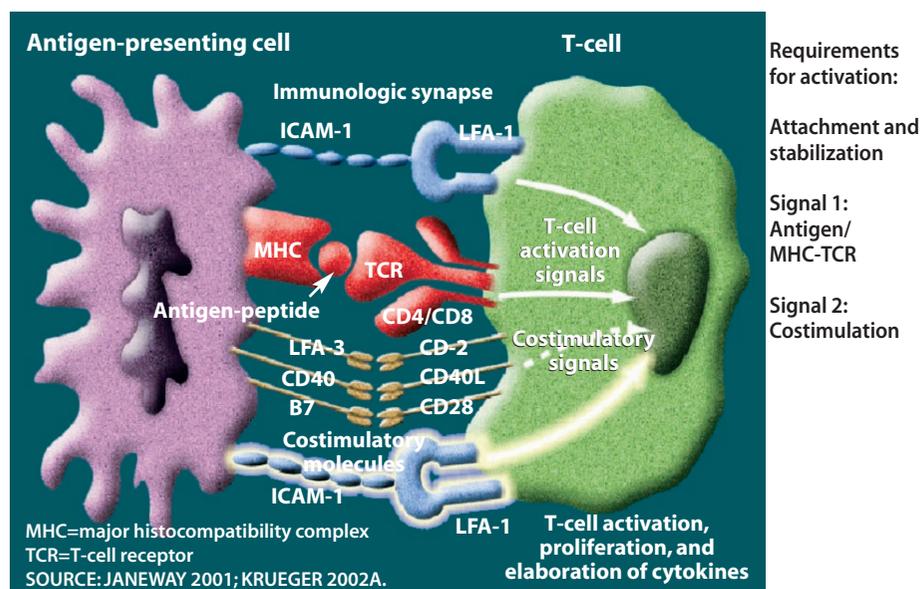
The two drugs that now are on the market for other indications, etanercept and infliximab, inhibit cytokines — predominantly TNF- α . Etanercept is a fusion protein that acts by blocking TNF receptors, and infliximab is a monoclonal antibody against TNF.

Figure 2 shows the second step in the immunopathology of psoriasis. Here, activated T-cells move into the small venules and capillaries of the skin, attracted by the same LFA-1/ICAM-1 interaction receptors in the cell wall of the blood vessels. This action causes those T-cells to flatten and then to transport into the dermis and the epidermis where LFA-1/ICAM-1 reactions occur.

Measuring systemic drug effects

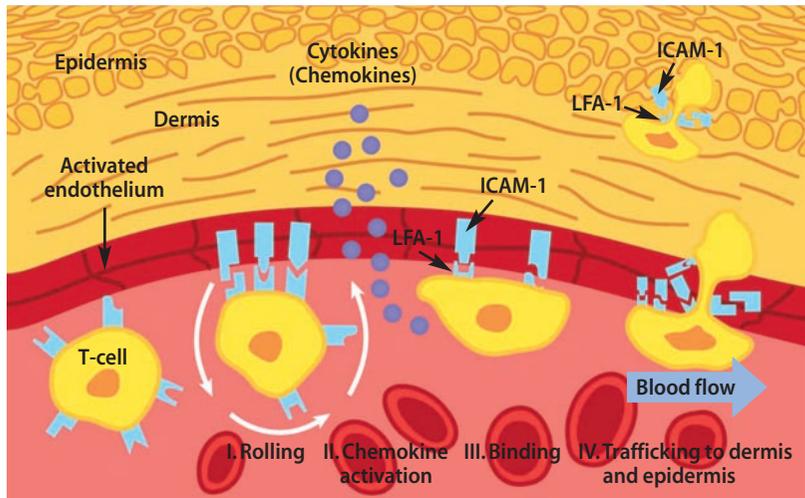
Systemic drugs, such as methotrexate, cyclosporine, and acitretin, an oral retinoid, were developed and approved for psoriasis long before there was a standard on how to measure

FIGURE 1 T-cell activation in the lymph nodes



The image represents the immunologic synapse between the antigen-presenting cell (APC) and the T-cell, illustrating attachment and stabilization, antigen presentation, and costimulation.

FIGURE 2 T-cell binding and trafficking into the dermis and epidermis



Trafficking of skin-homing T-cells into areas of inflammation is an important component of the immune response, and one in which LFA-1/ICAM-1 interactions play a key role. As skin-homing T-cells “roll” along the vascular endothelium, their progress through the bloodstream is slowed by the interaction between LFA-1 on their surface and ICAM-1 on the endothelial cell surface. This leads to an increased exposure of the T-cells to chemokines that are produced by the endothelial cells in response to inflammatory stimuli. As a result of increased exposure to these chemokines, the affinity of LFA-1 for ICAM-1 is increased, likely through a conformational change in the LFA-1 molecule. Bound T-cells flatten and pass through the epithelium into the surrounding tissue. Once they have exited the venule, T-cells respond to chemokines, drawing them toward the site of inflammation in the dermis, and from there, into the epidermis.

their efficacy. Further, no placebo-controlled comparisons between the older drugs and the biologic agents have been performed, either retrospectively or prospectively.

Recently, however, the Food and Drug Administration established a primary outcome measure for drug evaluation and approval as psoriasis therapy: PASI-75, which is a 75 percent reduction in the Psoriasis Area and Severity Index, the PASI score. Due to its relative complexity, this investigational form of assessment is not used in clinical practice but has become the standard for drug studies.

To determine an individual’s PASI score, the patient is evaluated in separate anatomical areas — the head and neck, the torso, the upper extremities, and the lower extremities.

The extent of psoriasis is noted in each area: the erythema, on a scale of 0 to 4; the induration of the plaque, on a scale of 0 to 4; and the scaling of the plaque, on a scale of 0 to 4. Also, in each of those anatomical areas, the percentage of surface area that is involved is estimated. Then, using a mathematical formula, a numerical score is calculated, ranging from 0 to 72, which is the PASI score. A PASI score above 10 is usually considered to be indicative of severe disease.

Conventional modes of therapy that are used for moderate to severe psoriasis include phototherapy — including long-wave ultraviolet (UV) light, UVB, narrow-band UVB, and psoralen UVA (PUVA) — cyclosporine, methotrexate, retinoids, and other therapies that are rarely used

anymore such as sulfasalazine, thioguanine, hydroxyurea, and some other immunosuppressive agents.

Phototherapy is useful in psoriasis patients for treating generalized disease. It works extremely well and has a long duration of response, particularly PUVA, which often promotes long-term remission. Moreover, we have more than 25 years’ experience with this treatment alone and in combination with drugs, which means that good records regarding safety exist.

Nevertheless, there are significant drawbacks to phototherapy for psoriasis, one of which is the development of squamous cell carcinoma, which occurs in many patients after a certain amount of phototherapy (particularly with PUVA). Phototherapy also has a slow onset of action. Burning, particularly from narrow band UVB, is another concern.

Phototherapy is also inconvenient in that it necessitates frequent patient visits — 3 times a week initially, for PUVA, UVB, and narrow-band UVB. Moreover, to provide phototherapy to patients, expensive equipment and dedicated office space are necessary. These requirements limit patient access, because phototherapy is not universally available.

A study in the *New England Journal of Medicine*, published last August, is the only prospective randomized study comparing methotrexate and cyclosporine using the PASI score, as commonly is done now for evaluating biologic agents. The numbers for the PASI-75 showed that 60 percent of patients can reach PASI-75 with methotrexate and 71 percent with cyclosporine (Heydendael 2003).

In this study, which was not placebo-controlled, twelve patients in the methotrexate group had to discontinue treatment because of reversible elevations in liver-enzyme levels, and one patient in the cyclosporine group discontinued treatment because of an elevation in the

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bilirubin level, but all 13 were included in the analysis.

These are both drugs that have been used for a long time. They have been found to work extremely well for generalized disease, and both are easy to administer. With respect to drug-acquisition costs, methotrexate is the least expensive. In fact, the liquid form of methotrexate, milligram for milligram, has the most inexpensive drug acquisition cost of any of the drugs for psoriasis.

Among the disadvantages of these systemic agents is organ toxicity, which limits treatment duration. Significant monitoring is required with these two drugs; with methotrexate, a liver biopsy is necessary after administration of 1.5 g.

These drugs clearly are inappropriate for patients with liver disease, renal disease, or hypertension. Carcinogenicity is an issue with cyclosporine, as are the potential development of bone marrow toxicity with methotrexate and teratogenicity with acetritin and methotrexate (Lebwohl 2001). Given that the average age of onset for plaque psoriasis is 28 years (NPF 2003), most patients will require 3 to 4 decades of treatment. These drugs cannot be used continuously due to the seriousness of these side effects, however.

Topical therapies — which include lotions, creams, ointments, and sprays — represent another option, but they are messy, as well as impractical and inappropriate, for patients with widespread disease.

Biologic therapies for psoriasis

A relatively new understanding of psoriasis as an immune system dysfunction rather than a primary skin disorder has given rise to the development of new biologic agents for the treatment of this disease. These biological response modifiers, which target the immune system, are rapidly gaining importance in this new era of psoriasis therapy. All can be characterized as either monoclonal anti-

bodies or fusion proteins.

The chimeric (mouse/human) monoclonal antibodies include infliximab; humanized monoclonal antibodies such as efalizumab; fully human monoclonal antibodies such as adalimumab; and receptor-antibody fusion proteins such as etanercept and alefacept.

Etanercept has been on the market for several years for rheumatoid arthritis (RA) and for psoriatic arthritis; juvenile RA and ankylosing spondylitis are the labeled indications. Phase 3 trials for etanercept have been completed, and a biologics license application has been filed; etanercept is expected to get approval for treating psoriasis in 2004. Infliximab is indicated for Crohn's disease and RA; early phase 3 work is underway. Alefacept and efalizumab are the only biologic agents that currently are approved for the treatment of patients with psoriasis.

There are three strategies for treating psoriasis with biologic response modifiers.

Strategy 1: Destroy T-cells

The first strategy is to eliminate the pathologic T-cells using alefacept, a recombinant fusion of glycoprotein that binds to leukocyte functional antigen number three (LFA-3) and has an IgG graft to promote stability. Specifically, alefacept blocks the costimulatory molecule by binding to CD2 molecules on the surface of activated T-cells and by selectively targeting memory-effector (CD45RO+) T-cells, which comprise more than 75 percent of T-cells in psoriatic plaques.

The alefacept phase 3 study results show the percentage change in the PASI score in patients who received the standard dosage — 15 mg intramuscularly (IM) once a week for 12 weeks. The study focuses on the 12-week dosing period, with the primary efficacy parameter being the results in the 2 weeks that followed the last dose. With the 15 mg alefacept dos-

age, at primary end point, 21 percent of patients met PASI-75 (Biogen 2003).

The phase 3 data also reveal that a third of the study patients who were taking alefacept achieved a 75 percent improvement in the PASI score, when looking at the period extending from study initiation through 12 weeks beyond its completion. In those patients, the median relapse time was 216 days, so these effects are long lasting (Lebwohl 2003).

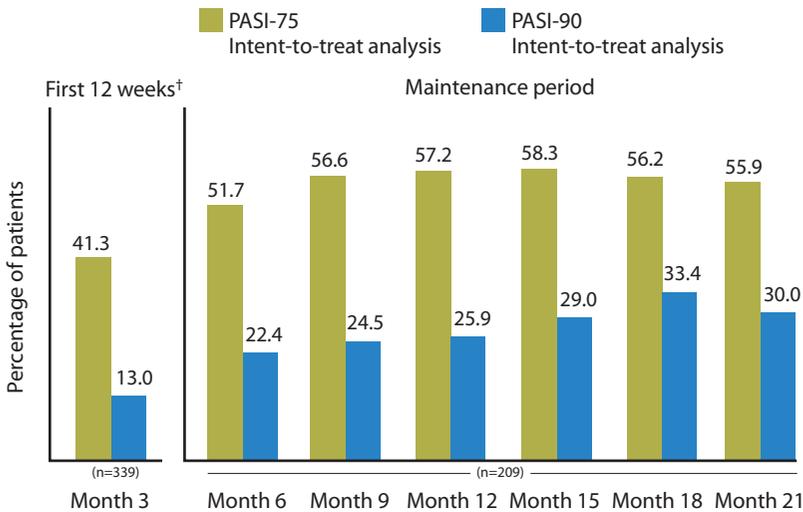
Alefacept is safe, despite some early injection reactions, which tend to occur with any protein injection. It is administered either IM once weekly, or by intravenous (IV) push once weekly. The IV form of alefacept is being discontinued, however, due to a lack of its use.

Alefacept's advantages include the long duration of positive effects in patients who respond and its lack of organ toxicity. A disadvantage is that most patients do not respond to treatment with alefacept, and for those patients who do, this agent is slow-acting. Because alefacept depletes T-cells, weekly monitoring of T-cells prior to each dose has to be carried out. If the T-cells are found to be at <250 cells/ μ L, the drug should be withheld.

Strategy 2: Modulate T-cells

The second strategy is to use efalizumab, which targets modulation rather than destruction of the T-cells. Efalizumab binds to the CD11a chain of the LFA-1. It also blocks trafficking of the T-cells into the dermis, inhibiting, to an extent, secondary activation of T-cells. It decreases epidermal hyperplasia, kertain-16 expression, and ICAM expression — all characteristics of active psoriasis.

With continuous dosing of efalizumab, an improvement in PASI scores was evident at weeks 12 and 24, with 26.6 and 43.8 percent of patients reaching PASI-75, respectively (Menter 2003). Many clinicians view PASI-50 as a more meaningful mea-

FIGURE 3 PASI-75 and PASI-90 response during 21 months of continuous efalizumab treatment*

*1.0 mg/kg/wk efalizumab dosage given continuously; the study is ongoing.

†With or without topical corticosteroid therapy.

SOURCE: GOTTLIEB 2003A

The PASI-75 response was maintained or improved during 21 months of continuous efalizumab therapy. This chart shows PASI-75 data from the intent-to-treat analysis and compares PASI-75 and PASI-90. Approximately 50 percent of patients achieving a PASI-75 response achieved a PASI-90 response.

sure of improvement than PASI-75, however, in that it is perceived to suffice for most patients.

At 12 weeks, 57 percent of psoriasis patients who are treated with efalizumab achieve PASI-50; at 24 weeks, two thirds of patients achieve PASI-50 (Menter 2003). In these cases, efalizumab is self-administered SC once a week, making it a pharmacy benefit rather than a once-weekly medical benefit, as is alefacept.

As efalizumab is continued for up to 21 months, patients who attained PASI-50 are maintained at that level. Approximately two thirds of patients maintain PASI-75 at 21 months (Gottlieb 2003a).

The PASI-90, a seldom-discussed measure, is an impressive level that can be reached by about 30 percent of these patients (Figure 3).

There have been 2,300 patients in efalizumab trials, who are in the safety database, many more than any other biologic agents have in their

phase 3 trials. The safety profile for this drug is extremely favorable.

In summarizing the clinical studies, as treatment with efalizumab continues over time, patients maintain good PASI results. The most common adverse events were those that could be expected — injection reactions consisting of mild headache, chills, and fever — and these occurred only after the first two injections; by the third injection, the side effect incidence did not differ from placebo.

The advantages of efalizumab are that it offers continuous control, a rapid response, and a statistical improvement that differed from placebo at as early as 2 weeks. Meaningful clinical improvement takes somewhat longer. Patients self-administer it once weekly, SC, and no organ toxicity has been observed. In the package insert, monitoring of platelets is recommended.

A disadvantage of efalizumab is

that the disease returns on therapy cessation, and early injection reactions may occur, as mentioned previously.

Strategy 3: Modify immune system

The third strategy is binding post-secretory cytokines and TNF- α , and this is done with infliximab and etanercept.

Infliximab, one of two TNF- α drugs, is a chimeric IgG₁ monoclonal antibody with both mouse and human sequences that bind TNF- α .

Infliximab shows the greatest improvement in PASI scores of any of these biologic agents. More than 80 percent of these patients achieve PASI-75, almost 100 percent attain PASI-50, and more than half of these patients reach PASI-90.

Infliximab has been used in several hundred thousand patients through the years for its approved indication. Most dermatologists do not administer infliximab infusions in their offices, as infusion reactions occur in about 5 percent of infusions and it requires at least a 2-hour infusion.

The advantages of infliximab are a quick response time and, for some patients, a long duration of response to therapy. The general dosage schedule for infliximab includes infusions at 0, 2, and 4 weeks, and then every 8 weeks afterward.

Another advantage of this agent is that it has no associated organ toxicity. Given that methotrexate is almost always used in conjunction with infliximab in treating RA, combination data are readily available. In fact, using infliximab without methotrexate commonly leads to development of anti-infliximab antibodies.

Infliximab is associated with impaired cell-mediated immunity, leaving patients vulnerable to opportunistic infections. As of Aug. 23, 2001, 101 cases were reported from among the more than 170,000 patients who have been treated with infliximab worldwide. Fifteen deaths — with most occurring outside of

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the United States — have been reported as a result of infliximab treatment; of these, 11 were attributable to tuberculosis (TB).

Etanercept, the second of the two TNF- α drugs, is a fully human receptor fusion protein. The TNF receptor is bound to the human IDG-1 FB domain. At 12 and 24 weeks, the PASI-75 response that patients attain with etanercept is similar to efalizumab. At 12 weeks, with the standard dosage of etanercept, 25 mg twice weekly, a third of the patients reach a score of PASI-75. Doubling the dosage to 50 mg twice weekly brings almost half the patients to PASI-75. The increased dosage does not appear to be associated with additional clinical toxicity, but the related expense is prohibitive (Gottlieb 2003b).

When etanercept therapy is continued for 24 weeks, results surpass those achieved at 12 weeks, similar to the phenomenon seen with efalizumab; 44 percent of patients treated with etanercept reached PASI-75 with the standard dosage of 25 mg twice weekly, and 59 percent reached PASI-75 with the 50 mg dosage (Gottlieb 2003b).

Etanercept has been used in more than 170,000 patients through the years for its approved indication. The patient self-administers etanercept twice weekly SC. Localized injection-site reactions are common but are usually mild and transient. Infection may be an issue with any TNF agent.

The advantages of etanercept include its convenience. The package insert indicates that no laboratory monitoring is required, although many clinicians do screen for TB with any of the biologic agents. Etanercept is associated with rapid improvement when used for psoriatic arthritis; it has a somewhat slower onset of action in the skin. Etanercept is an excellent treatment for a patient with both psoriasis and psoriatic arthritis. Also, as is the case with infliximab, combination data with methotrexate

are readily available.

Disadvantages of etanercept include rare reports of lymphoma, demyelination diseases such as multiple sclerosis and optic neuritis, and congestive heart failure. Because these occur in a small number of patients, it is not possible to assess causality, however.

Traditionally, dermatologists approached psoriasis therapy in a stepwise progression, with the first step being over-the-counter products (e.g., emollients), the second step being topical agents (e.g., steroids, calcipotriol, and topical retinoids), the third step being phototherapy (e.g., UVB, PUVA, or forms of targeted phototherapy with lasers), and the fourth step being systemic therapy, for severe cases.

The recently released American Academy of Dermatology (AAD) Consensus Statement on Psoriasis Therapies (Callen 2003) states that biologic agents should be considered among the first-line treatment options in patients who are candidates for systemic therapy and that systemic therapy may be considered for patients with psoriasis on the palms and soles, head and neck, or genitalia, or when more than 5 percent of the skin surface is involved.

In the AAD view, the various systemic therapies in treatment of psoriasis all come into play as tools in the toolbox or colors on the palette for consideration when a patient requires systemic therapy. Rather than step therapy, when a patient needs more than topical therapy, the AAO statement draws on treatment tools that include biologic and other systemic agents, as well as phototherapy.

Changing treatment paradigm

In the cyclical approach to treatment that dermatologists have used historically, patients are treated aggressively — using systemic agents like cyclosporine and methotrexate — when they are experiencing a severe flare. When the psoriasis symp-

toms subside, the treatment is slowed. Due to the physicians' avoidance of maintaining a patient on toxic therapies, the patient seems destined for a roller coaster ride of better and worse and better and worse.

The change in the treatment paradigm for psoriasis, which is attributable to the emergence of the biologic agents, is that these drugs can be given safely over long periods; we do not have to keep patients on a roller coaster any more. Patients now can be kept under control, without interruption, over long periods.

The AAD Psoriasis Education Initiative is a multiyear program that has been designed to educate dermatologists about the basic science of psoriasis as well as regarding the new therapies that are available, and to make dermatologists aware of the consensus statement. Increasingly, these educational efforts directed toward dermatologists focus on the expanding array of treatment options for psoriatic arthritis, and the NPF also is helping to manage patient expectations relative to treatment.

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Commentary on 'Treating Psoriasis Patients With Biologic Agents'

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The advent of the cutting edge technology of biologic response modifiers (hence "biologics") offers new hope to millions of patients suffering from a variety of debilitating chronic illnesses. The focus of this section is the troublesome condition of plaque psoriasis, which Pariser (Pariser 2003) summarizes in a well-balanced view of treatment options for this population of patients. Pariser describes the intriguing and complex pathology of psoriasis and offers the noteworthy observation that psoriasis appears to behave as an immunologic disease entity.

Exciting news of late has shown that the defining root-cause explanation for the etiology of the disease is closer than ever before. Researchers have identified a gene pattern that may be responsible for this devastating disease and that would further enable precision biologics development to vastly reduce patient suffering (NPF 2003a).

Anne Bowcock, a professor of genetics, medicine, and pediatrics at

Washington University School of Medicine in St. Louis, identified, with her colleagues, three genes on chromosome 17 in which the "on and off" switches are impaired in statistically significant numbers of psoriasis patients. Several other psoriasis susceptibility genes are likely to be identified in the months and years ahead, including one on chromosome 6. In all, more than a dozen genes appear to be involved in psoriasis. Bowcock notes: "Over the next few years, researchers are going to identify a large number of psoriasis susceptibility genes. These will be important building blocks toward finding a cure in the future" (NPF 2003a).

The advent of new treatment technologies does conjure the dichotomy of improved quality and extension of life with the concomitant cost of care increases that may accompany this phenomenon.

Quality of life

Quality of life considerations of course can run counter to the cost-

cutting strategies employed by third party payers looking to reduce seemingly out of control health care inflation (a discussion of which follows in the next section). Clearly, a case can be made for a new and even more aggressive treatment program in psoriasis from a quality of life perspective. The Short Form-36 analysis of both the physical and emotional impact of the disease indicates that they exceed the impact of other common disorders such as hypertension, diabetes, depression, arthritis, myocardial infarction, and cancer (Rapp 1999). As Pariser observes, the National Psoriasis Foundation survey (a remarkable 17,000 responses out of 40,000 requests for feedback) is striking in the identification of 9 to 12 percent of respondents suggesting suicidal ideation and 78 percent exhibiting frustration with existing forms of psoriasis therapy (Krueger 2001).

Cost of health care

Reasons for the rapid rise in health care costs are many. The primary

TREATING PSORIASIS PATIENTS WITH BIOLOGIC AGENTS

cause of Americans' spiraling health costs is private health insurance and the facility charges that are associated with it (MSNBC 2003). A recent Milliman USA survey demonstrated that HMOs will increase renewal rates by about 15 percent in 2004, with responding HMOs reporting that 2003 premium rates were 11 to 16 percent higher than 2002 premium rates — down from the 16 to 22 percent increases that were reported in last year's survey (Health and Medicine Week 2003). Rising health care expenses continue to drive up the premiums HMOs need to charge to break even. An increase in hospital admissions as well as in the prescription drug premium component are major factors in the rise in premiums that was measured by the survey.

The United States outspends other developed nations on pharmaceuticals, at \$605 per person per year. The cost of biologics can be considerable and often is contained within the penumbra of the pharmacy benefit in many insurance benefit designs. Morrow cites the recent "Pharmaceutical Evaluation Survey, 2002" by Health Strategies Group, which reports that 57 percent of medical directors see biotech drugs as a concern both now and in the future, with the segment growing at a compound annual rate of almost 28 percent — nearly double the rate of other drugs (Morrow 2003).

Morrow notes that there are no generic biologic products in the United States, with the FDA having no mechanism for reviewing generic biotech products, and that the earliest generics may become available in 2010. It is obvious that for managed care decision makers to enable benefits distribution for this advanced level of psoriasis care, considerable education and collaboration with providers will be necessary.

Policy directions and disease management

Perhaps one of the most compelling messages deriving from

Pariser's article is the suggestion that, in spite of the high costs of biologics therapy, thought leaders in the field of dermatology, through societal representation, are moving toward more aggressive first-line treatment approaches. Pariser states that, traditionally, dermatologists approached psoriasis therapy in a stepwise progression, beginning with over-the-counter products (e.g. emollients). He describes the next steps to include (in the following progression): topical agents (e.g., steroids, calcipotriol, and topical retinoids); phototherapy (e.g., UVB, PUVA, or forms of targeted phototherapy with lasers); and systemic therapy for severe cases (Pariser 2003).

Pariser refers to the recently released American Academy of Dermatology Consensus Statement on Psoriasis Therapies, which states that biologic agents should be considered among the first-line treatment options in patients who are candidates for systemic therapy, and that systemic therapy may be considered for patients with psoriasis on the palms and soles, head and neck, or genitalia, or when more than 5 percent of the skin surface is involved (Callen 2003).

Similarly, the American College of Rheumatology has issued a formal policy statement, which pays focused attention to cost issues as they relate to third party reimbursement, excerpted as follows (ACR 2003):

POLICY:

We believe that all patients with serious rheumatic disease must have these new biologic medications available when clinically appropriate.

Access

Attempts to restrict their use by guidelines or criteria that are outside the patient-physician relationship should be discouraged, and cost-based substitutions within this group are inappropriate...

Cost considerations

Because these newer agents are

costly, the rheumatologist has added responsibility in selecting appropriate treatment for rheumatic patients. Financial considerations are not limited to the direct cost of medication, however; they range from the loss of present and future earning capacities, if treatment is omitted, to the potential consequences of adverse effects of treatment. The optimal management for a given patient may be complex, but these decisions are to be made within the patient-physician relationship. It is not justifiable for third party payers to attempt to influence these medication selections by preauthorization requirements, "preferred drug status" (such as cost discounts negotiated by third party payers), or tiered levels of copayments.

Approaching disease management with third party payers incorporates the ability to advocate for the patient using the best available scientific evidence and effectively communicating with pharmacy benefits management companies who are working with their third party payer clients (or within the insurance company itself). Toward this end, the National Psoriasis Foundation includes template letters for both patients and providers in an attempt to derive more receptive benefits applications from the payer (NPF 2003b).

Any discussion of disease management must address concerns about the safety and efficacy of the treatment as well as the impact on quality of life. Given the high cost of biologic therapy in psoriasis, managed care payers will demand accountability for outcomes and any current supporting literature that justifies their use.

Pariser describes the study concept of the PASI-75 (the Food and Drug Administration's primary outcome measure for drug evaluation and approval as psoriasis therapy, which is a 75 percent reduction in the Psoriasis Area and Severity Index, the PASI score.)

Of particular interest is Pariser's observation regarding the strategic approaches for using the biologics treatment options that are to be made available by years' end. Alefacept involves a destruction of the T-cell, whereas the alternative strategy with efalizumab targets modulation rather than destruction of the T-cells.

With continuous dosing of efalizumab, an improvement in PASI scores was evident at weeks 12 and 24, with 26.6 and 43.8 percent of patients reaching PASI-75, respectively (Menter 2003). Pariser notes that many clinicians tend to view the PASI-50 as a more meaningful measure of improvement than the PASI-75, however, in that it is perceived to suffice for most patients. At 12 weeks, 58 percent of psoriasis patients who are treated with efalizumab achieve PASI-50; at 24 weeks, two thirds of patients achieve PASI-50.

In these cases, efalizumab is self-administered SC once a week, making it a pharmacy benefit. This is significant, as the payer needs to appreciate the big-picture cost reduction in light of the fact that facility and provider costs are significantly reduced relative to the costs that otherwise would be incurred with infusion centers or office visits.

Safety issues

Pariser makes it clear that the direction of care in psoriasis represents a significant paradigm shift that is attributable to the emergence of biologic agents. He notes that patients now can be kept under control without interruption and over long periods, without the "roller coaster" effect of treatment changes. The American

Academy of Dermatology Psoriasis Education Initiative is a multiyear program that has been designed to educate dermatologists about the basic science of psoriasis and the new therapies that are available, as well as to make dermatologists aware of the consensus statement. We are now in an "era of accountability," where treatment decisions involve quality of life determinations as well as issues of cost balance, if we prefer it or not.

Major program initiatives, such as those brought forth by the Institute of Medicine, have put the focus on medical and medication error reduction (Kohn 2001, Institute of Medicine 2001). The advent of the new biologics, which offer such promise for the population of psoriasis patients, must be accompanied by strident adherence to best practices in cost efficiency and appropriate use.

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CONTINUING EDUCATION POST-TEST**Emerging Treatment and Management Options With Biologic Agents**

Directions: Please tear out the combined answer sheet/assessment form on page 61 (physicians) or page 62 (pharmacists). On the answer sheet, place an X in the box for the letter that represents the best answer to each question. There is only ONE answer per question.

- 1. In the 1998 survey conducted by the National Psoriasis Foundation (NPF), the percentage of patients with severe psoriasis who reported frustration with current treatment was:**
 - a. 32.
 - b. 49.
 - c. 78.
 - d. 88.
- 2. Conventional forms of therapy for treating moderate to severe psoriasis include:**
 - a. Retinoids.
 - b. Phototherapy.
 - c. Cyclosporine.
 - d. Sulfasalazine.
 - e. All the above.
- 3. Measured by PASI-75 in a 2003 study by Heydendael, methotrexate showed greater efficacy than cyclosporine as therapy for moderate to severe psoriasis.**
 - a. True
 - b. False
- 4. The immune system is first activated in psoriasis when antigen-presenting cells in the dermis recognize _____.**
 - a. Memory effector T-cells.
 - b. An antigen.
 - c. A T-cell receptor.
 - d. Cytokines.
- 5. Study results (Rapp 1999) from the physical component measure of Short-Form 36 indicate that the negative impact of psoriasis on quality of life is superseded only by that of congestive heart failure.**
 - a. True
 - b. False
- 6. A strategy for treating psoriasis with biologic response modifiers is to:**
 - a. Eliminate the pathologic T-cells.
 - b. Modulate T-cells by blocking their activation and trafficking into the dermis.
 - c. Modify the immune system by binding postsecretory cytokines and TNFs.
 - d. All the above.

CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST

Emerging Treatment and Management Options With Biologic Agents

CME CREDIT FOR PHYSICIANS

See page 62 for answer sheet for pharmacists

Sponsored by The Chatham Institute

This activity is designated for a maximum of 1.5 category 1 AMA PRA credits.

I certify that I have completed this educational activity and post-test and claim _____ (number) credits.

Signature _____

Date _____

First name, M.I. _____

Last name, degree _____

Title _____

Specialty _____

Affiliation _____

Address _____

City _____ State _____ ZIP _____

Daytime telephone (_____) _____

Fax (_____) _____

E-mail _____

Complete answer sheet/evaluation form and mail or fax to:

**Office of Continuing Education
The Chatham Institute
26 Main Street, 3rd Floor
Chatham, NJ 07928**

Fax: (973) 701-2515

Credit will be awarded on successful completion of the post-test and activity evaluation form. If a score of 70 percent or better is not achieved, no credit will be awarded. Please allow up to 6 weeks for processing.

This activity is provided at no charge to the participant through an educational grant provided by Genentech.

CMC305A

EXAMINATION: Place an X in the box of the letter that represents the best answer to each question on page 60. There is only ONE answer per question. Place all answers on this answer form:

| | A | B | C | D | E |
|----|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 2. | <input type="checkbox"/> |
| 3. | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| 4. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 5. | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| 6. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

PROGRAM EVALUATION

So that we may assess the continuing education value of this activity, please complete the evaluation form.

Have the activity's objectives been met?

| | Yes | No |
|--|--------------------------|--------------------------|
| 1. Analyze the disease state of plaque psoriasis, including patient demographics, treatment trends, emerging biologic therapies, and quality of life concerns. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Compare characteristics of biologic agents that are used to treat plaque psoriasis with traditional agents. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Discuss the American Academy of Dermatology Consensus Statement on Plaque Psoriasis relative to the treatment of plaque psoriasis. | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Assist managed care professionals in preparing for the influx of biologic agents that represent new treatment options for plaque psoriasis. | <input type="checkbox"/> | <input type="checkbox"/> |

Was this publication fair, balanced, and free of commercial bias? Yes _____ No _____

If no, please explain: _____

This educational activity has contributed to my personal effectiveness and should improve my ability to:

| | Strongly agree | | | Strongly disagree | | |
|----------------------------|----------------|---|---|-------------------|---|-----|
| Treat/manage patients | 5 | 4 | 3 | 2 | 1 | n/a |
| Communicate with patients | 5 | 4 | 3 | 2 | 1 | n/a |
| Manage my medical practice | 5 | 4 | 3 | 2 | 1 | n/a |
| Other _____ | 5 | 4 | 3 | 2 | 1 | n/a |

Effectiveness of this method of presentation:

| Excellent | Very good | Good | Fair | Poor |
|-----------|-----------|------|------|------|
| 5 | 4 | 3 | 2 | 1 |

Time spent reading this publication: H _____ M _____

What other topics would you like to see addressed?

Comments: _____

CONTINUING EDUCATION ANSWER SHEET/REQUEST FOR STATEMENT OF CREDIT

Emerging Treatment and Management Options With Biologic Agents

CPE CREDIT FOR PHARMACISTS

See page 61 for answer sheet for physicians

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I certify that I have completed this educational activity and post-test and claim _____ contact hour credits.

Signature _____

Date _____

First name, M.I. _____

Last name, degree _____

Title _____

Specialty _____

Affiliation _____

Address _____

City _____ State _____ ZIP _____

Daytime telephone (_____) _____

Fax (_____) _____

E-mail _____

Pharmacist — This activity is approved for 1.5 contact hours (0.15 CEU).



ACPE Universal Program Number (UPN):
812-000-03-033-H01
Release date: Dec. 20, 2003
Expiration date: Dec. 20, 2004

Complete post-test answer sheet/evaluation form and mail or fax to:

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Credit will be awarded on successful completion of the post-test (a score of 70 percent or better) and activity evaluation form. If a score of 70 percent or better is not achieved, no credit will be awarded. Please allow up to 6 weeks for processing.

This activity is provided at no charge to the participant through an educational grant provided by Genentech.

CMC305A

EXAMINATION: Place an X in the box of the letter that represents the best answer to each question on page 60. There is only ONE answer per question. Place all answers on this answer form:

| | | | | | |
|----|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | A | B | C | D | E |
| 1. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 2. | <input type="checkbox"/> |
| 3. | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| 4. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 5. | <input type="checkbox"/> | <input type="checkbox"/> | | | |
| 6. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

PROGRAM EVALUATION

To receive continuing education credit, please provide all information requested below. This assures prompt and accurate issuance of your continuing education certificate.

Objectives

- Analyze the disease state of plaque psoriasis, including patient demographics, treatment trends, emerging biologic therapies, and quality of life concerns.
- Compare characteristics of biologic agents that are used to treat plaque psoriasis with traditional agents.
- Discuss the American Academy of Dermatology Consensus Statement on Plaque Psoriasis relative to the treatment of plaque psoriasis.
- Assist managed care professionals in preparing for the influx of biologic agents that represent new treatment options for various disease states.

Please rate this program as follows:

| | Very | | | | |
|---|-----------|------|------|------|------|
| | Excellent | good | Good | Fair | Poor |
| Overall quality of program | 5 | 4 | 3 | 2 | 1 |
| Content | 5 | 4 | 3 | 2 | 1 |
| Relevance to objectives | 5 | 4 | 3 | 2 | 1 |
| Effectiveness of this format for learning | 5 | 4 | 3 | 2 | 1 |
| Value to me in my daily responsibilities | 5 | 4 | 3 | 2 | 1 |

How long did it take you to complete this continuing education activity?

Hours _____ Minutes _____

Requested topics/skills to address in future programs:

Comments: _____

Did you detect any bias in this presentation?

Yes _____ No _____

If yes, please explain:
