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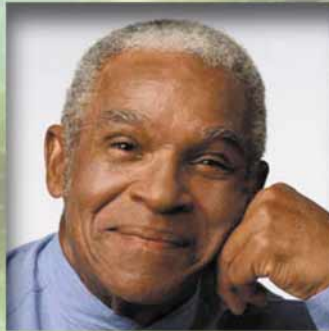
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Anti-TNF- α Therapies in the Treatment of Dermatologic Diseases

TNF- α -Inhibiting Biologics and the Treatment of Psoriasis, Psoriatic Arthritis, and Other Dermatologic Diseases

Efficacy and Safety of Anti-TNF- α Agents in Psoriasis

Making the Transition From Cyclosporine and Methotrexate to Biologic Treatment



Produced in affiliation with the 29th Annual Hawaii Dermatology Seminar

Bruce E. Strober, MD, PhD, Chair

New York University School of Medicine
New York, N.Y.

Alice Bendix Gottlieb, MD, PhD

University of Medicine & Dentistry of
New Jersey-Robert Wood Johnson
Medical School
New Brunswick, N.J.

Paul S. Yamauchi, MD, PhD

David Geffen School of Medicine at
University of California, Los Angeles
St. John's Hospital
Santa Monica, Calif.

President, Elsevier/IMNG
Alan J. Imhoff

Vice President,
Medical Education
& Business Development
Sylvia H. Reitman, MBA

Program Manager,
Medical Education
Sara M. Hagan

Clinical Editor
Joanne M. Still

National Account Manager
Cheryl J. Gromann

Graphic Design
Lehner & Whyte, Inc.

Production Manager
Judi Sheffer

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FACULTY

Bruce E. Strober, MD, PhD, Chair

Associate Director, Dermatopharmacology Unit
Assistant Professor
Ronald O. Perelman Department of Dermatology
New York University School of Medicine
New York, N.Y.

Alice Bendix Gottlieb, MD, PhD

Professor of Medicine, Department of Medicine
Professor, Department of Molecular Genetics,
Microbiology & Immunology
W.H. Conzen Chair in Clinical Pharmacology
Director, Clinical Research Center
University of Medicine & Dentistry of New Jersey-
Robert Wood Johnson Medical School
New Brunswick, N.J.

Paul S. Yamauchi, MD, PhD

Medical Director
Dermatology Institute of Southern California
David Geffen School of Medicine at University
of California, Los Angeles
St. John's Hospital
Santa Monica, Calif.

Treatment of Dermatologic Diseases

CME RECOGNITION

This SKIN & ALLERGY NEWS supplement is recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 CME credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

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TARGET AUDIENCE

This activity has been developed for dermatologists and other healthcare professionals who manage patients with psoriasis and other immune-mediated inflammatory diseases of the skin.

EDUCATIONAL NEEDS

Psoriasis is a relatively common skin disease, affecting more than 2% of individuals in the United States. Although the exact pathogenesis has not been established, the evidence to date demonstrates that T lymphocytes and cytokines play a crucial role. The evidence is strong that tumor necrosis factor- α (TNF- α) is a critical component of the disease process and that inhibition of this cytokine is an effective strategy for managing psoriasis. For mild to moderate psoriasis, topical and light therapies may be effective. However, for moderate to severe psoriasis, systemic therapies such as cyclosporine and methotrexate have been more effective in bringing the disease under control. Unfortunately, cyclosporine and methotrexate are too toxic for sustained long-term use. The biologic agents that block TNF- α have been proven safe and effective over the long term for the treatment of many patients with moderate to severe psoriasis. It is important for all clinicians who manage patients with psoriasis to understand the mechanisms of action of these new agents and to recognize their appropriate role in the treatment of selected patients.

LEARNING OBJECTIVES

After reading and studying this supplement, participants should be able to:

- Briefly explain what is known about the pathophysiology of psoriasis and describe the role of TNF- α in psoriasis and other dermatologic disorders.
- Explain the mechanism of action of the three anti-TNF- α agents currently available and list the current indications for each.
- Evaluate the efficacy and safety data of the agents that block TNF- α in patients with psoriasis.
- Discuss the optimum method for making the transition from cyclosporine or methotrexate to a biologic agent and for switching from one biologic agent to another.

FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr Gottlieb has received funding for clinical grants from Abbott Laboratories, Amgen Inc., Beiersdorf AG, Biogen Idec, Inc., Bristol-Myers Squibb Company, Celgene Corporation, Centocor, Inc., WH Conzen Chair in Clinical Pharmacology, Fujisawa Healthcare, Inc., Genentech, Inc., Ligand Pharmaceuticals, Inc., and Synta Pharmaceuticals Corp. She is a consultant to Abbott, Advanced ImmuniT Inc., Allergan Inc., Amgen, Beiersdorf, Biogen Idec, Bristol-Myers Squibb, Celgene, CellGate, Inc., Centocor, Eisai, Inc., Genentech, Kemia, Medarex, Inc., Novartis AG, Roche, Sankyo Pharma, Schering-Plough Corporation, Warner Chilcott PLC, and Wyeth. Dr Gottlieb is on the Speaker's Bureau at Amgen, Biogen Idec, and Wyeth. Dr Gottlieb discusses the investigational use of infliximab and adalimumab for the treatment of psoriasis and psoriatic arthritis. **Dr Strober** has received grant/research support from Abbott, Amgen-Wyeth, Biogen Idec, and Genentech. He is a consultant to Amgen-Wyeth, Biogen Idec, and Genentech and is on the Speaker's Bureau at Amgen, Biogen Idec, and Genentech. Dr Strober discusses the investigational use of infliximab and adalimumab in the treatment of psoriasis and psoriatic arthritis. He also discusses the experimental use of infliximab, adalimumab, and etanercept in the treatment of other dermatologic diseases including Behçet's disease, aphthous stomatitis, sarcoidosis, pyoderma gangrenosum, hidradenitis suppurativa, and some bullous disorders. **Dr Yamauchi** has received grant/research support from, is a consultant to, and is on the Speaker's Bureau at Amgen. He discusses the investigational use of etanercept combined with methotrexate or cyclosporine, and the use of other biologic agents in making a therapeutic transition to etanercept.

TNF- α -Inhibiting Biologics and the Treatment of Psoriasis, Psoriatic Arthritis, and Other Dermatologic Diseases

Bruce E. Strober, MD, PhD

Biologic therapy is the newest approach to the treatment of psoriasis and psoriatic arthritis (PsA). These drugs have been adopted by many practitioners as valuable options for therapy in appropriately selected patients. Currently, the biologic agents have a firm place in the treatment of patients with psoriasis, PsA, and, increasingly, other dermatologic diseases as well.

Tumor Necrosis Factor- α (TNF- α) in Psoriasis

The pathophysiology of psoriasis is not fully understood. The initial precipitating factors are unknown,^{1,2} but it is likely that an immune system dysfunction is the driving force of inflammation in psoriasis.^{1,3} This inflammation is responsible for many of the pathologic changes seen in psoriasis, including epidermal thickening, dermal inflammation, and the changes in the vasculature that allow the trafficking of inflammatory cells into the skin.^{1,4} These changes lead to psoriatic plaque formation.^{1,4}

The initial event in the “psoriatic cascade” likely involves an antigen-presenting cell (APC) within the skin (such as a Langerhan’s cell) encountering an unknown antigen—perhaps a protein derived from an invading bacterium or virus. The APC subsequently matures and migrates to a local lymph node. In the lymph node, the APC presents the antigen to naïve T cells (also called resting T cells) that have specific markers on their cell surfaces. In turn, those naïve T cells change those markers, clonally expand, and thereafter are referred to as activated, or memory-effector, T cells. Memory-effector T cells then

circulate freely in the vasculature of the body. A minority of memory-effector T cells may exit the vasculature, reenter the skin, and reencounter the original “trigger” antigen.

This process results in a vigorous release of a number of cytokines, one of which is TNF- α . These cytokines perpetuate both the inflammation and the histologic changes of the epidermis and dermis that are characteristic of psoriasis. From this perspective, cytokines such as TNF- α are essential for the development of psoriatic plaques.

The evidence for the pathogenic role of TNF- α in psoriasis is robust (Table). First, TNF- α production is increased in psoriasis, as demonstrated by elevations in TNF- α concentrations both in serum⁵ and in psoriatic plaque tissue.^{6,7} In addition, TNF- α levels correlate strongly with disease severity, as measured by the Psoriasis Area Severity Index (PASI).^{5,6} Finally, TNF- α levels have been shown to decrease with effective treatment for psoriasis, and the extent of TNF- α reduction correlates with the degree of clinical

improvement associated with the treatment.^{5,7}

The evidence for the central role of TNF- α in immune-mediated inflammatory diseases (IMIDs) is not limited to psoriasis. The literature includes evidence supporting the use of anti-TNF- α agents for the treatment of other dermatologic conditions, including Behçet’s disease, aphthous stomatitis, sarcoidosis, pyoderma gangrenosum, hidradenitis suppurativa, and some bullous disorders.⁸⁻¹⁰ Research is ongoing regarding the potential use of these biologic agents for these and other IMIDs.

Interestingly, it is becoming clear that some—but not all—TNF- α inhibiting biologics are effective for these “off-label” uses. For example, infliximab—an anti-TNF- α monoclonal antibody—effectively treats sarcoidosis, whereas etanercept likely is ineffective or is far less effective.

Mechanism of Action of Anti-TNF- α Agents

Etanercept, infliximab, and adalimumab are the three anti-TNF- α agents approved to date by the US

Table. Evidence for the Role of Tumor Necrosis Factor in Psoriasis

- **TNF- α production is increased in psoriasis**
 - TNF- α levels are elevated in serum⁵
 - TNF- α levels are elevated in psoriatic plaques^{6,7}
- **TNF- α levels correlate strongly with disease severity (PASI score)^{5,6}**
- **TNF- α levels decrease with effective treatment^{5,7}**

PASI=Psoriasis Area Severity Index; TNF- α =tumor necrosis factor- α

Food and Drug Administration. Etanercept is a soluble receptor that competitively binds to soluble and cell-bound TNF- α and prevents activation of cell-surface receptors. It appears that etanercept acts solely by blocking the ability of TNF- α to promote proinflammatory signals within cells without having a direct effect on the immune system's effector cells. Etanercept currently is indicated for the treatment of rheumatoid arthritis (RA), juvenile RA, ankylosing spondylitis, psoriasis, and PsA.

Infliximab is a chimeric immunoglobulin G1 κ monoclonal antibody with both murine and human sequences. Infliximab binds to both soluble and transmembrane TNF- α .

Infliximab is approved for the treatment of RA, ankylosing spondylitis, and Crohn's disease. Since the time the data were presented and the supplement was printed, infliximab received an FDA indication for PsA. Clinical studies have also demonstrated the use of infliximab for the treatment of psoriasis, although it is not yet approved for this indication.

The newest anti-TNF- α agent is adalimumab, a recombinant, fully human, immunoglobulin G1 monoclonal antibody specific for TNF- α . Similar to infliximab, adalimumab binds to soluble and transmembrane TNF- α . At present, adalimumab is indicated only for RA, but it is likely that it will be approved in the future for use in psoriasis, PsA, and Crohn's disease.

“The pathophysiology of psoriasis is not fully understood. The initial precipitating factors are unknown, but it is likely that an immune system dysfunction is the driving force of inflammation in psoriasis.”

The ability of both infliximab and adalimumab to treat Crohn's disease implies that these two drugs have a mechanism of action in certain tissues that distinguishes them from etanercept, which has not been shown to be effective in the treatment of Crohn's disease.

Conclusion

TNF- α inhibition constitutes effective therapy for both psoriasis and PsA. This class of drugs likely will become a mainstay of the systemic therapies for psoriatic disease for many years to come. Furthermore, TNF- α inhibition will likely be used for the treatment of specific, rarer dermatologic conditions not amenable to conventional therapies. Therefore, increasingly, dermatologists will need to be comfortable with the safe and appropriate use of these medications.

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Efficacy and Safety of Anti-TNF- α Agents in Psoriasis

Alice Bendix Gottlieb, MD, PhD

Three agents that inhibit the activity of tumor necrosis factor- α (TNF- α) have been developed. Etanercept is indicated for rheumatoid arthritis (RA), juvenile RA, psoriatic arthritis (PsA), ankylosing spondylitis, and psoriasis. Infliximab's current indications are RA, ankylosing spondylitis, Crohn's disease, and PsA, and phase III clinical trials now are underway for the treatment of psoriasis. The newest anti-TNF- α agent, adalimumab, currently has an indication for RA. Clinical trials now are underway for the use of adalimumab in the treatment of psoriasis, and an application has been filed with the US Food and Drug Administration (FDA) for the PsA indication. This article focuses on the data accumulated to date regarding the efficacy and safety of these agents in the treatment of psoriasis.

Etanercept Phase III Studies

In the global phase III study,¹ etanercept was given in a step-down fashion. After an initial 4-week washout period, patients at centers in the United States and Europe were randomized to receive etanercept 50 mg twice weekly (n=203), 50 mg weekly (n=204), or placebo (n=204). At the end of week 12, all patients began etanercept treatment at a dosage of 50 mg weekly (given as 25 mg twice weekly) for an additional 12 weeks. Improvements of 75% or greater in the Psoriasis Area Severity Index (PASI 75) at week 12 was the primary end point.

One major focus of this study was the issue of maintenance of clearance when the dosage of etanercept was reduced. Patients who had been taking 50 mg of etanercept

twice weekly began a regimen of 25 mg twice weekly, which they continued for an additional 12 weeks. At the end of that time, nearly 80% of those patients who had achieved a PASI 75 score at week 12 (on a dosage of 50 mg twice weekly) maintained a PASI 75 improvement after stepping down to 25 mg twice weekly. Ninety-seven percent maintained at least a 50% improvement in PASI (PASI 50) from baseline.

Another model for the use of etanercept is intermittent administration, the method approved in Europe. Leonardi and colleagues² enrolled 672 patients who were randomly assigned to receive one of three dosage regimens of etanercept—50 mg twice weekly, 25 mg twice weekly, or 25 mg once weekly—or placebo. The etanercept groups continued their assigned regimens for 24 weeks. At week 12, the patients in the placebo group were switched to a regimen of etanercept, 25 mg weekly, until week 24.

The primary end point was a PASI 75 response at 12 weeks, but at the end of week 24 (6 months), all patients who had achieved at least a PASI 50 response were withdrawn from the drug abruptly.

Those who relapsed were given the same dosage of etanercept that they had received in the initial part of the study. There were two purposes for this strategy. The first was to determine whether retreatment would bring patients to the same clinical status they had achieved during the first round of therapy. The second purpose was to determine how long clearance lasts after treatment with etanercept if therapy is discontinued.

The investigators found that retreatment resulted in excellent reestablishment of disease control (Table). The mean baseline PASI score in this group was 19.1, which dropped to 5.8 after the initial 12 weeks of therapy. After a period of no therapy, when patients relapsed—with relapse defined as a loss of 50% of PASI improvement—retreatment resulted in a mean PASI score of 6.4.

Although it is unlikely that most patients who achieve PASI 75 would be willing to stop treatment if given the choice, some circumstances may occur that make the successful intermittent therapy a welcome option. For example, the loss of health insurance or employment may necessitate

Table. Results of Retreatment With Etanercept: Primary Retreatment Analysis of Intermittent Use³

	Mean PASI Score (n=297)
Baseline	19.1
Double-blind week 12	5.8
Retreatment week 12	6.4
Difference (95% confidence interval)	-0.5 (-1.1 to 0.0)

PASI=Psoriasis Area Severity Index.

temporary interruption of therapy. Pregnancy is a situation in which abrupt cessation of therapy may be a clinical choice. Clinicians and patients can be confident that abrupt withdrawal of etanercept will not result in rebound or a rapid flare of psoriasis.

The treatment of PsA also is in the purview of dermatologists. Treatment with etanercept has been shown to slow the progression of structural damage in the joints in patients with PsA.

A phase IV, open-label study involving 1,122 patients treated at 125 dermatology sites demonstrated that community-based dermatologists can effectively manage patients with PsA. The primary objective of the study was to observe the effect of etanercept in treating the skin and joint manifestations of PsA in patients in community dermatology settings.

The study, called Experience Diagnosing, Understanding, Care, and Treatment With Etanercept in Psoriatic Arthritis (EDUCATE),^{3,4} is ongoing and has thus far supported previous findings that most patients have skin involvement before joint involvement. A crucial finding in this study is that, at the time of enrollment, more than 25% of patients with PsA had not had their joint disease diagnosed previously. This suggests that patients with PsA are undertreated or not treated until later in their disease, and indicates that clinicians must be more vigilant during history taking in patients with psoriasis and need to ask about symptoms that may suggest the onset of PsA.

Another important finding in the EDUCATE study is that the skin responses observed resulting from etanercept treatment were similar to those seen in the phase III psoriasis trials. Finally, factors affecting quality of life (including healthcare resource utilization, caregiver burden, and better ability to perform on the job) improved over 24 weeks of etanercept therapy.

“[The EDUCATE study] suggests that patients with PsA are undertreated or not treated until later in their disease, and indicates that clinicians must be more vigilant during history taking in patients with psoriasis....”

Experience With Infliximab in Psoriasis

The results of phase III studies using infliximab in psoriasis are expected in the near future. The phase II Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT)⁵ a multicenter, randomized, double-blind, placebo-controlled trial involving 249 patients, was conducted to investigate the safety and efficacy of infliximab for the treatment of severe plaque-type psoriasis. The primary end point of the SPIRIT trial was the percentage of patients achieving an improvement of at least 75% in the PASI score (PASI 75) between baseline and week 10. Patients were treated with an IV infusion of infliximab 3 mg/kg, infliximab 5 mg/kg, or placebo at weeks 0, 2, and 6.

At week 10, PASI 75 was achieved by 88% of those in the group treated with 5 mg/kg of infliximab, by 72% of those treated with 3 mg/kg of the drug, and by 6% of patients in the placebo group.

The investigators reported that adverse reactions generally were consistent with those observed in patients treated with infliximab for indications other than psoriasis.

Adalimumab Phase II Psoriasis Study

The step-down study design described for etanercept also was used in a study of adalimumab in patients with psoriasis.⁶ The adalimumab study began with a 12-week, open-label period during which all patients received an 80-mg loading dose at weeks 0 and 1, and then 40 mg of the drug weekly starting at week 2 (40 mg weekly is twice the marketed dosage used for the treatment of RA, the current FDA-approved indication). At the end of 12 weeks, a double-blind, placebo-controlled period began during which patients were randomized to receive either 40 mg of adalimumab (n=68) every other week (the marketed dosage) or placebo (n=68). This phase of the study lasted 12 weeks.

At week 24, a statistical analysis was performed, showing that 67.6% of patients who initially had received 40 mg of adalimumab weekly and then were stepped down to 40 mg of the drug every other week achieved a PASI 75 response. In these patients who were stepped down from 40 mg weekly to 40 mg every other week, 78% maintained a PASI 50 response at week 24. When the patients who received adalimumab 40 mg weekly for 12 weeks and then received placebo for 12 weeks were evaluated, the PASI 75 response was 48.5% at week 24. The physician's global assessment of “clear” or “almost clear” followed the same pattern.

Safety of Biologic Therapy

In the US phase III pivotal study of etanercept in patients with psoriasis, Leonardi and colleagues² showed that an injection-site reaction was the only adverse event that was more common with any experimental dose given than with placebo. In addition, this study demonstrated that etanercept given at twice the recommended dosage is not associated with increased toxicity. Thus, no special testing is

required prior to initiating treatment with etanercept.

More recently, a study of the safety of etanercept was conducted in patients with RA and comorbid disease.⁷ The purpose of the study was to identify any medically important infections in patients who were using etanercept 25 mg twice weekly versus placebo for 16 weeks. The comorbid conditions included both insulin-dependent and non-insulin-dependent diabetes, chronic obstructive pulmonary disease, and recent infections with sinusitis, bronchitis, or pneumonia. The study was terminated early when it became clear that patients were not at increased risk regardless of their study arm.

The data from the infliximab phase II psoriasis study showed that infusion reaction was the most common side effect.

The data from the phase II study for adalimumab demonstrated that injection-site pain was the major side effect with the use of that agent.

The accumulated data from clinical trials on the incidence of tuberculosis (TB) in patients using any of the three anti-TNF- α agents demonstrate that etanercept was not associated with TB, whereas both monoclonal anti-TNF- α drugs did show TB liability in their clinical trials. Many clinicians choose to administer a purified protein derivative (PPD) of tuberculin test before beginning treatment with any anti-TNF- α drug. PPD testing is not required with etanercept, but must be performed prior to starting therapy with infliximab or adalimumab. The worldwide postmarketing data on etanercept and infliximab (adalimumab data were not available at press time) show that the incidence of TB is higher with

infliximab, and the disease can occur early in the course of treatment.

Regarding lymphoma, it is important to remember that patients with RA and psoriasis are at a three-fold background risk for lymphoma associated with their disease, regardless of treatment. Thus, it is not possible at this time to establish the possible statistically increased risk for lymphoma associated with anti-TNF- α therapy.

All three anti-TNF- α agents have been associated with exacerbation of demyelinating disease. Thus, a patient with existing demyelinating disease should not receive any TNF- α blocker. The same is true for patients with congestive heart failure.

Recently, reports have emerged raising the question of a possible risk for liver failure related to infliximab in patients who had severely elevated liver enzyme levels. The patients who were the subjects of these reports were on multiple cytotoxic drugs, so it is not possible to determine the source of the toxicity. However, it is prudent to monitor liver function in patients who are using more than one systemic drug, such as methotrexate plus infliximab.

Conclusion

The biologic agents have been shown to be safe and effective treatments for dermatologic diseases. Etanercept is the only one of the three currently approved by the FDA for the treatment of patients with psoriasis and PsA. However, studies are ongoing with infliximab and adalimumab, and approval of these drugs for these other indications is likely. The availability of additional effective and safe biologic agents increases therapeutic options.

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Making the Transition From Cyclosporine and Methotrexate to Biologic Treatment

Paul S. Yamauchi, MD, PhD

The availability of biologic agents has made it possible to bring moderate to severe psoriasis under initial control with cyclosporine or methotrexate and then to switch patients to one of these safer drugs for effective long-term therapy. The optimum strategy for making such a transition seems to be overlapping treatment—that is, tapering cyclosporine or methotrexate during initiation of treatment with a biologic agent (Figure). Cyclosporine or methotrexate should not be stopped abruptly during the switch to a biologic agent because a rebound effect and flare of psoriasis may occur.

At our center, we conducted two small studies^{1,2} to examine the effects of combination treatment during the transition from the older systemic agents to biologic therapy with etanercept.

Transition From Cyclosporine

Eight patients (five women and three men) with severe plaque psoriasis participated in this study.¹ One patient also had psoriatic arthritis (PsA), and two had been treated previously by another physician and experienced a rebound of their disease.

All of the patients were given cyclosporine 200 mg twice daily (400 mg/day) in an effort to obtain rapid improvement of symptoms. Once each patient attained an improvement of 50% or greater in the Psoriasis Area Severity Index (PASI 50), etanercept therapy was started at a dosage of 25 mg twice weekly. Cyclosporine was continued at the previous dosage for 2 to 4 weeks.

The tapering strategy began with a reduction in cyclosporine of 100 mg/day, bringing the dosage from 400 mg/day to 300 mg/day for

“The optimum strategy for making such a transition seems to be overlapping treatment—that is, tapering cyclosporine or methotrexate during initiation of treatment with a biologic agent.”

2 to 4 weeks. Reductions in dosage of 100 mg/day continued every 2 to 4 weeks until the patient was using 100 mg/day. Then the cyclosporine dosage was reduced to 100 mg every other day for 2 to 4 weeks. After this time, cyclosporine was discontinued, and each patient was maintained on etanercept monotherapy. Clinical improvements were maintained throughout the cyclosporine tapering period and for at least 12 weeks after cyclosporine was discontinued.

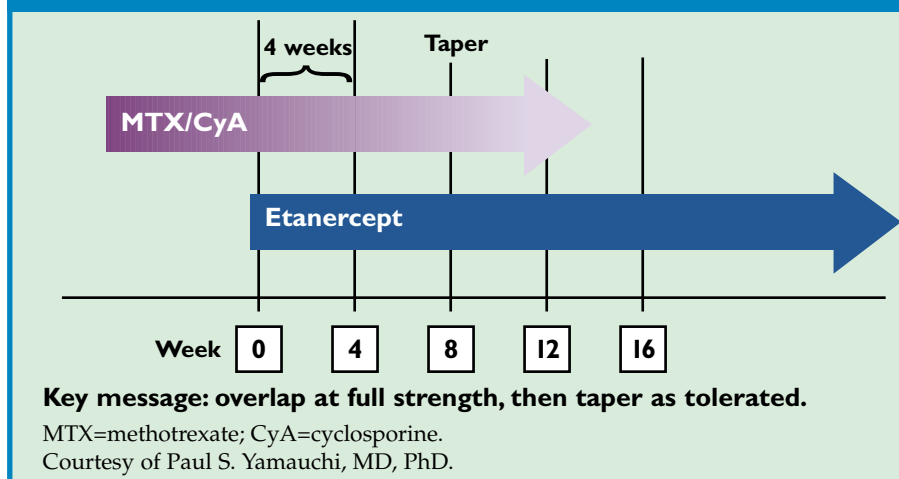
Throughout this process, blood pressure was monitored and laboratory testing was conducted every 2 to 4 weeks, including a complete metabolic panel with renal function tests, complete blood count (CBC), and lipid panel.

All patients were successfully tapered off cyclosporine. The one patient who had PsA experienced considerable improvement of joint pain during the transition from cyclosporine to etanercept, and that improvement was maintained after cyclosporine was discontinued.

The side effects with cyclosporine observed in this study were those that are anticipated with the use of high doses of this drug, including arthralgias, fatigue, myalgias, and hirsutism. (Although patients typically consider hirsutism a relatively small trade-off for clearance of severe psoriasis, it is still important to caution patients—particularly women—about the possibility of this side effect.)

No other toxicity was noted. Further, hypertension was not seen, and no infections or renal function abnormalities were observed. Thus,

Figure. Recommended Strategy for Transitioning From Conventional Agent to Etanercept



in our study, etanercept and cyclosporine did not significantly interact during combination therapy.

Transition From Methotrexate

The use of etanercept also allows tapering of methotrexate while preserving a clinical response. Using a protocol similar to the one described for the cyclosporine study, our group assessed the effects of making a transition from methotrexate to etanercept.²

Six patients (three men and three women) with moderate to severe plaque psoriasis participated in this study. Two patients also had PsA. Patients were given methotrexate at a starting dosage of 10 mg/week, which was increased as necessary to achieve clinical improvement. As each patient achieved a PASI 50 response on methotrexate monotherapy (in all patients, about 3 months after starting methotrexate), concomitant therapy was started with etanercept 25 mg twice weekly. The full dosage of methotrexate and 25 mg twice weekly of etanercept were continued in combination for 2 to 4 weeks.

After this time, the dosage of methotrexate was reduced by 2.5 mg/week every 2 to 4 weeks until improvement was maintained with etanercept monotherapy or until symptoms recurred and worsened to below PASI 50. Four patients maintained a PASI 50 improvement, and two patients experienced a worsening of symptoms when methotrexate was discontinued. In these two patients, treatment with methotrexate was resumed, at a dosage of 5 mg/week, and the dosage of etanercept was increased to 50 mg twice weekly. When these two patients achieved a PASI 50 score for the second time, the dosage of etanercept was lowered to 25 mg twice weekly and

methotrexate was continued. The combination therapy resulted in maintenance of improvement of at least PASI 50.

The patients with PsA both experienced improvement in joint symptoms when etanercept was added to the methotrexate regimen. Clinical improvement was maintained in all patients for at least 12 weeks.

Throughout the study, subjects underwent the standard laboratory tests for patients using methotrexate, including a complete metabolic panel with liver function tests and CBC. The side effects typically associated with methotrexate were seen in this study; nausea and vomiting were observed in two of the six patients. However, no increased incidence was seen in liver toxicity, infections, or myelosuppression in patients receiving combination therapy with methotrexate and etanercept. No serious adverse events were observed at any point during the study.

Transitioning Between Biologics: A Case Study

When a transition from one biologic agent to another is indicated—either because of side effects or lack of sufficient efficacy—it is important that the strategy followed does not result in a rebound or flare-up of the disease. The following case illustrates a method for making such a transition that was both effective and safe.

A 45-year-old woman with a 5-year history of psoriasis was started on infliximab 5 mg/kg. She had a good response for the first 6 weeks, but her disease recurred over the next 6 weeks and her condition returned to baseline. The decision was made to try another biologic rather than initiate a second course of therapy with infliximab.

The patient continued on the regular schedule of infliximab infusions; at week 12, cyclosporine 3 mg/kg/day was added to the regimen as a “bridge” therapy. At week 16, infliximab was stopped and treatment with etanercept was started at a dosage of 25 mg twice weekly. At this point, tapering of cyclosporine was begun, with the dosage reduced by 1 mg/kg every 3 to 4 weeks.

The patient experienced no rebound or flare-ups and continues to do well.

Conclusion

Patients on systemic therapy with standard agents can be safely and effectively switched to the safer biologic agents for long-term, effective therapy. The transition should be done slowly, as “overlapping” therapy, with cyclosporine or methotrexate continued when the biologic is introduced and then gradually tapered until the biologic is given as monotherapy.

When one biologic is used as monotherapy and must be discontinued because of side effects or inadequate efficacy, switching to another biologic is an option. A gradual transition is recommended, using one of the standard systemic agents such as cyclosporine as a “bridge” therapy to prevent rebound or flare-up.

References

1. Yamauchi PS, Lowe NJ, Koo S. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. Poster presented at: 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, La. Poster P3.
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Instructions: For each question or incomplete statement, one answer or completion is correct. Circle the most appropriate response. Five correct responses are required for credit.

- Which one of the following drugs is not classified as an inhibitor of tumor necrosis factor- α ?
 - Adalimumab
 - Efalizumab
 - Etanercept
 - Infliximab
- All three anti-TNF- α biologic agents currently have approval from the US Food and Drug Administration for the treatment of:
 - Ankylosing spondylitis
 - Crohn's disease
 - Psoriasis
 - Rheumatoid arthritis
- In the US phase III study of etanercept in patients with psoriasis, abrupt cessation of the drug resulted in:
 - Sudden flare-ups in most patients
 - No rapid relapses
 - Pustular psoriasis in many patients
 - Sudden rebound psoriasis in many patients
- The initial event in the "psoriatic cascade" probably involves:
 - An antigen-presenting cell encountering an unknown antigen
 - Migration of a mature antigen-presenting cell to a local lymph node
 - Presentation of antigen to naïve T cells (resting T cells)
 - Clonal expansion of activated T cells
- Tumor necrosis factor- α is a/an:
 - Antigen
 - Cytokine
 - Marker on a naïve T cell
 - Memory-effector T-cell marker
- In the US pivotal phase III study of etanercept in patients with psoriasis, Leonardi and colleagues showed that the most common adverse event was:
 - Headache
 - Injection-site reaction
 - Rash
 - Tuberculosis
- In patients starting monotherapy with etanercept:
 - Liver function must be tested and carefully monitored during treatment
 - A purified protein derivative (PPD) test is required
 - A PPD test is not required
 - No special testing is required

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