Tumor Necrosis Factor Inhibitors in Psoriasis: An Update

Francisco A. Kerdel, BSc, MBBS,* and Bruce E. Strober, MD, PhD†

Abstract

Three inhibitors of tumor necrosis factor (TNF) currently are approved for the treatment of psoriasis: etanercept, infliximab, and adalimumab. The other two TNF inhibitors, golimumab and certolizumab pegol, have shown efficacy against plaque psoriasis in clinical trials of psoriatic arthritis (PsA). This article reviews the most recent evidence on the efficacy and safety of the TNF inhibitors in psoriasis, with special attention to preventing and managing immunogenicity.
Semin Cutan Med Surg 33(supp2):S31-S36

Keywords

Immunogenicity; psoriasis treatment; TNF; tumor necrosis factor inhibitors

With the advent of biologic agents, the clinical management of moderate to severe psoriasis changed dramatically. The clinical photographs shown on pages S33 and S34 (**Figures 1-4**) illustrate the degree of improvement that patients can experience with tumor necrosis factor (TNF) inhibitors. This article reviews the clinical experience with with tumor necrosis factor (TNF) inhibitors and provides updated information based on literature published since the introduction of these medications.

Etanercept

Etanercept, approved for use in psoriasis in 2004, is a fusion protein that is composed of the p75 receptor bound to the Fc region of human immunoglobulin G_1 (IgG_1). The results of the pivotal trial showed that about 50% of patients can be expected to achieve a 75% improvement in the Psoriasis Area Severity Index (PASI 75) after 12 weeks of administration of 50 mg twice weekly; at this dosage, PASI 75 can be expected in about 60% of patients after 24 weeks of continued use. Reduction in dosing after 12 weeks to 50 mg once weekly, as per the labeled indication, would result in approximately 50% to 55% of patients demonstrating a PASI 75 response after 24 weeks of therapy.[1]

Continuous vs Interrupted Therapy

During the withdrawal phase of the phase III clinical studies, the investigators determined that, on average, patients lost approximately 50% of their PASI improvement over a period of 3 months. However, restarting treatment resulted in a gradual return to prewithdrawal improvement levels. Thus, etanercept was shown to be a flexible therapy: With discontinuation, symptoms can be expected to recur gradually, and re-treatment results in a therapeutic response comparable to what was seen before discontinuation.[1]

In 2007, Moore and colleagues[2] published the results of an open-label study in more than 2,500 patients, comparing continuous dosing with interrupted administration of etanercept, 50 mg twice weekly. All patients received etanercept for 12 weeks; at that point, 1,272 continued using the drug for the next 12 weeks, and 1,274 interrupted therapy for this time. The groups were comparable in proportion of initial response to therapy—71.3% in the continuous-therapy group and 72.0% in the interrupted-treatment group. The primary end point was the proportion of responders at week 24. At week 24, 71.0% of patients were responders in the continuous-therapy group, compared to 59.5% of patients in the interrupted-treatment group, a significant difference ($P<0.0001$). As in the pivotal trial, most of the patients who interrupted treatment regained their initial response once therapy was resumed.

Pediatric Psoriasis

No biologic agent currently is approved by the US Food and Drug Administration (FDA) for use in pediatric patients with psoriasis (ie, patients <18 years of age). In a landmark randomized, double-blind, placebo-controlled trial, Paller and colleagues[3] investigated the efficacy and safety of etanercept in children and adolescents (range, 4-17 years of age) with moderate to severe plaque psoriasis. The investigators randomly assigned the 211 patients to receive 12 weekly injections of etanercept (0.8 mg/kg, to a maximum of 50 mg) or injections of placebo, followed by 24 weeks of once-weekly injections of etanercept (open label). At week 36, patients were again randomized to receive either etanercept or placebo in order to determine the loss of response on withdrawal and the subsequent response on restarting therapy. The primary end point was PASI 75 or greater at week 12. Secondary end points were achievement of a 50% or 90% improvement in PASI (PASI 50 or PASI 90, respectively), a Physician's Global Assessment of clear or almost clear of psoriatic lesions, and safety assessments.

At week 12, PASI 75 was achieved by 57% of patients in the etanercept group compared with 11% in the placebo group ($P<0.001$). Also at week 12, differences between treatment and

*Director of Inpatient Dermatology, University of Miami Hospital Professor of Dermatology and Vice Chairman, Florida International University, Miami, FL.
† Associate Professor and Vice Chair, University of Connecticut Health Center, Farmington, CT.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Novartis Pharmaceuticals Corporation, Amgen Inc., and Celgene Corporation.

Dr Kerdel and Dr Strober have received an honorarium from Global Academy for Medical Education for their participation in this activity. They acknowledge the editorial assistance of Joanne Still, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Joanne Still has no relevant financial relationships with any commercial interests.

Francisco A. Kerdel, BSc, MBBS, has been a speaker for AbbVie, Amgen, Galderma Laboratories, L.P., Janssen Biotech, Inc., LEO Pharma, and Medicis Pharmaceutical Corporation.

Bruce E. Strober, MD, PhD, has been a consultant and/or speaker and/or advisor for AbbVie, Aldova, Amgen, Celgene, Forward, Johnson & Johnson Company, Maruho Co., Ltd., Medac, Inc., Merck & Co., Inc., Novartis, and Pfizer Inc.

Address reprint requests to: Francisco A. Kerdel, BSc, MBBS, Florida Academic Dermatology Centers, 1400 NW 12 Avenue, Suite 4, Miami, FL 33136; dr.kerdel@fadcenter.com

1085-5629/13/$-see front matter © 2014 Frontline Medical Communications
DOI: 10.12788/j.sder.0070

placebo groups were significant (P<0.001) in the proportion of patients who achieved PASI 50 (75% vs 23%, respectively) and PASI 90 (27% vs 7%, respectively), as well as in achievement of the assessment of clear or almost clear (53% vs 13%, respectively).[3]

After 24 weeks of the open-label etanercept treatment phase (ie, at week 36), PASI 75 was achieved by 68% of patients in the original treatment group and 65% of those in the original placebo group who began receiving etanercept after week 12. Between weeks 36 and 48 of the study (withdrawal period), 42% of patients (29/69) who were withdrawn lost response. On safety assessments, four serious adverse events occurred in three patients (including three infections) during the open-label etanercept treatment phase. All adverse effects resolved completely.[3]

This study is ongoing, with a total duration of 264 weeks (5 years). Interim data published in 2010[4] covered 2 years. At that point, 140 of the original 182 enrolled patients had completed week 96; 61% of patients had retained at least a PASI 75 response, and 47% had maintained a Physician's Global Assessment of clear or almost clear.

Etanercept vs Ustekinumab in Psoriasis

In the only head-to-head study published comparing etanercept to ustekinumab in patients with moderate to severe psoriasis, Griffiths and coworkers[5] sought to determine the risk-benefit profiles of the two therapies. In this study, 903 patients were randomly assigned to receive 45 mg or 90 mg of ustekinumab at weeks 0 and 4 or high-dose etanercept (50 mg twice weekly, for a total of 12 weeks). The primary end point was the proportion of patients who achieved at least PASI 75, assessed at week 12.

At week 12, 57% of patients in the etanercept group (n=347) had achieved PASI 75. In the lower-dose ustekinumab group (45 mg), 68% (n=209) had at least a PASI 75 response (P=0.012 compared to that seen with etanercept). In the 90-mg ustekinumab group, 74% of patients (n=347) achieved PASI 75 (P<0.001 compared to that seen with etanercept).

In addition to superior efficacy, an advantage of ustekinumab is the less frequent dosing: Over 12 weeks, only two injections of ustekinumab achieved greater efficacy than 24 injections of etanercept. The advantage of etanercept is its longer history of use with an extensive record of safety as studied over almost 20 years in a variety of inflammatory diseases and greater than 10 years of experience in patients with psoriasis, specifically.

Infliximab

Infliximab, a chimeric (murine/human) monoclonal antibody that binds to TNF-α with high specificity, affinity, and avidity, was, in 1998, the first TNF inhibitor introduced in the United States. It was initially indicated for the treatment of Crohn's disease. Since then, it has received approval for a number of other indications, and, in 2006, infliximab was approved by the FDA for use in severe plaque psoriasis. Approval was based on the results of the phase III *E*uropean Infli*x*imab for *P*soriasis (*R*EMICADE) *E*fficacy and *S*afety *S*tudy (EXPRESS) I[6] and EXPRESS II[7] trials.

EXPRESS I[6] was a randomized, controlled trial of infliximab vs placebo, involving 378 patients with plaque psoriasis at 32 centers in Europe and Canada. Patients were randomized in a 4:1 ratio to receive infliximab, 5 mg/kg, or placebo, administered at weeks 0, 2, and 6, and then every 8 weeks until week 46. After week 24, the patients in the placebo group were crossed over to receive 5 mg/kg of infliximab for the duration of the trial. Achievement of PASI 75 or greater at week 10 was the primary end point. Secondary end points included achievement of PASI 50 and PASI 90 at various times.

In the active-treatment group, 80% of patients achieved PASI 75 and 57% achieved PASI 90 after week 10, compared to 3% and 1%, respectively, in the placebo group (P<0.0001). At week 24, 82% of patients in the infliximab group maintained a PASI 75 response and 58% maintained PASI 90.

The subsequent EXPRESS II[7] trial compared two infliximab regimens in a placebo-controlled design to test whether some patients would do better with regular, as opposed to "as needed," infusions of the medication. Patients were randomly assigned in a 2:3 ratio to receive placebo or induction doses of infliximab, either 3 mg/kg or 5 mg/kg, at weeks 0, 2, and 6. At week 14, the patients in the infliximab groups were rerandomized to receive 8 weeks of infliximab administered continuously or on an as-needed basis at the same doses that were administered in the induction phase (ie, either 3 mg/kg or 5 mg/kg). At the study visits every 4 weeks thereafter to week 46, the patients in the as-needed group were given a dose of infliximab if their PASI was less than 75% of the improvement they had achieved compared with the baseline PASI score. Patients in the continuous group were given an infliximab infusion every 8 weeks. Patients in the placebo group were crossed over at week 16 to receive infliximab at the 5-mg/kg dose level at weeks 16, 18, and 22 and then every 8 weeks to week 46.

At week 10, 75.5% of patients who received 5 mg/kg of infliximab and 70.3% of those who received 3 mg/kg of the drug achieved PASI 75 vs 1.9% of patients on placebo (P<0.001). PASI 90 was achieved in 45.2% of patients in the 5-mg/kg infliximab group compared with 37.1% of those who received 3 mg/kg of the medication; 0.5% of controls achieved PASI 90, a significant difference (P<0.001).[7]

At the end of the continuous vs as-needed therapy phase of the trial, patients in the continuous-therapy group maintained their PASI responses better than did those in the intermittent-therapy group, at both infliximab dose levels.[7]

Although infliximab has an administration disadvantage—it requires intravenous infusion rather than subcutaneous injection, as with etanercept or adalimumab—it has an efficacy advantage with respect to its very rapid response time. In addition, the EXPRESS II trial demonstrated that 5 mg/kg, given every 8 weeks steadily, is the optimum dose and schedule.

Infusion Reactions, Antibody Formation, and Long-Term Therapy

Infusion reactions may occur with infliximab use, although they are not commonly seen. The combined data from all of the clinical trials completed to date (36,485 infliximab infusions) show that infusion reactions occurred in 1,469 cases (4.0% of infusions). In contrast, 249 infusion reactions were seen with 15,379 placebo infusions (a rate of 1.6%). In about 1% of patients who have infusion reactions, symptoms are so severe that discontinuation of therapy is warranted.[8] Immunogenicity is strongly associated with the development of infusion reactions; for further discussion, see the section "Understanding Immunogenicity" on page 35S.

Adalimumab

Adalimumab is a fully human monoclonal antibody with a high affinity to and selectivity for TNF; it has a long half-life, between 12 and 14 days. The drug is administered subcutaneously.

Among its other indications, adalimumab is approved for adult patients with chronic, severe plaque psoriasis who are candidates for systemic therapy or phototherapy and in cases in which patients do not tolerate other systemic therapies.

In the phase III multiphase pivotal trial of adalimumab in moderate to severe psoriasis (the *R*andomized Controlled *Ev*aluation of Adalimumab *E*very Other Week Dosing in Moderate to Severe Psoriasis Tri*al*, or REVEAL), Menter and colleagues[9] evaluated the efficacy and safety of adalimumab, 40 mg, administered as a loading dose of 80 mg during the first week, 40 mg the second week, and then 40 mg every other week. The study was divided into three phases. Period A was a 16-week, double-blind, placebo-controlled phase. Patients were given either adalimumab or placebo for 16 weeks. After week 16, 71% (578/814) of patients had achieved at least PASI 75, the primary end point; in contrast, 7% (26/398) of patients in the placebo group achieved this level of improvement.

The second large trial involving adalimumab in psoriasis was the *C*omparative Study of *H*umi*ra* vs *M*ethotrexate vs *P*lacebo *i*n Ps*o*riasis Patie*n*ts (CHAMPION) trial,[10] in which the efficacy and safety of this agent was compared with both methotrexate and placebo in a total of 271 patients. Patients in the adalimumab group (n=108) were given a loading dose of 80 mg the first week and then 40 mg every 4 weeks (as in the REVEAL trial); those in the methotrexate group (n=110) were given 7.5 mg of the drug weekly, with dosing increased (based on tolerability and normal laboratory tests) over the next 12 weeks to a maximum of 25 mg/week; 53 patients comprised the placebo group. Patients in the methotrexate group who had a response of PASI 50 or greater at week 8 and/or 12 continued at the same dose.

At week 16, 79.6% of patients (n=86) in the adalimumab group had achieved at least PASI 75; this level of response was seen in 35.5% (n=39) of patients in the methotrexate group; PASI 75 was achieved in 18.9% (n=10) of the patients who received placebo. A risk-benefit analysis determined the rate of achieving clinical response, with and without adverse events. In that analysis, adalimumab therapy was associated with significantly more days free of adverse events than were methotrexate and placebo ($P<0.001$).[10]

Golimumab and Certolizumab Pegol in Psoriatic Arthritis (PsA) and Psoriasis

PsA is of increasing concern to dermatologists; the National Psoriasis Foundation estimates that in about 85% of patients who develop PsA, skin disease precedes the onset of joint involvement, sometimes by a decade or more. Because PsA can lead to deforming, erosive arthropathy—including disability—it is important for dermatologists to monitor patients for signs and symptoms of joint disease in patients with psoriasis.

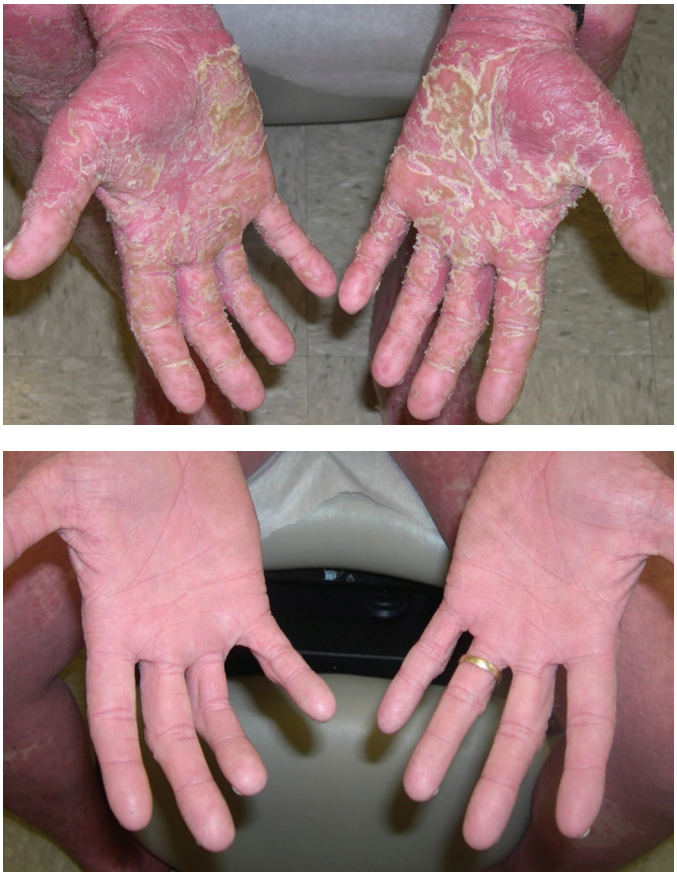

FIGURE 1 Psoriasis of the hands before (above) and after (below) a course of anti-TNF therapy.
Photos courtesy of Francisco A. Kerdel, BSc, MBBS.

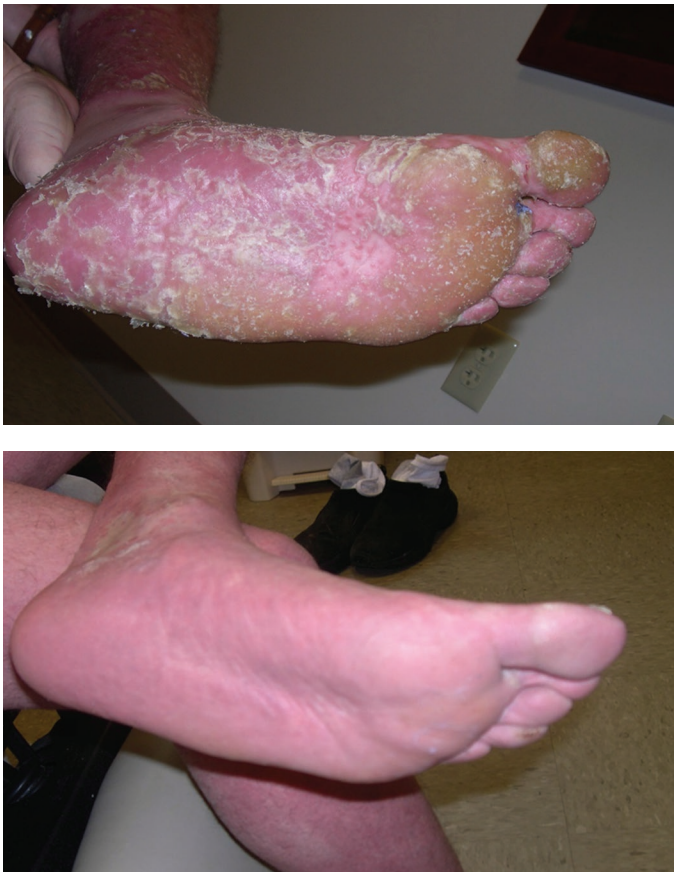

FIGURE 2 Psoriasis of the feet before (above) and after (below) a course of anti-TNF therapy.
Photos courtesy of Francisco A. Kerdel, BSc, MBBS.

It has been demonstrated that PsA can be effectively treated with the three anti-TNF agents that also are approved for psoriasis (etanercept, infliximab, and adalimumab In addition, two TNF inhibitors (golimumab and certolizumab pegol), introduced later than the others, currently are not approved for psoriasis but are now indicated for PsA. There is also evidence suggesting that ustekinumab also can be effective in PsA and recently received FDA approval for the treatment of this condition. (Ustekinumab is discussed in the article by by Leonardi and Gordon on page S37 of this supplement.[11])

Golimumab is a monoclonal antibody directed against TNF that is approved by the FDA for ulcerative colitis, rheumatoid arthritis (RA), PsA, and ankylosing spondylitis (AS). It is given monthly by subcutaneous injection at a fixed dose of 50 mg and may be administered concomitantly with methotrexate; an intravenous formulation also is available. In the phase III clinical study *Go*limumab—A *R*andomized *E*valuation of Safety and *E*fficacy in Subjects with Psoriatic *A*rthritis Using a Fully Human Anti-TNF Monoc*l*onal Antibody (GO-REVEAL) that led to the FDA approval of golimumab in PsA, Kavanaugh and coworkers[12] found that patients in the treatment groups had greater improvement in cutaneous disease than did patients in the placebo group: At week 52, among the patients with at least 3% body surface area skin involvement at baseline, 62% of those who received golimumab 50 mg and 60% of those who received golimumab 100 mg achieved PASI 75, compared to 48% of patients in the placebo group. Currently, no application is pending for an indication for psoriasis.

The fifth TNF inhibitor developed to date—and the most recently introduced—is a monoclonal antibody, certolizumab pegol, approved for Crohn's disease, RA, AS, and, recently, PsA. In the phase III clinical trial in psoriatic arthritis (the *R*heumatoid *A*rthritis *P*revent*i*on of Structural *D*amage in Psoriatic Arthritis [RAPID-PsA] study), Mease and coworkers[13] found that, in addition to superiority over placebo in treating joint disease, certolizumab pegol therapy also provided improvements in psoriatic plaques. The investigators noted that in patients with cutaneous disease involving 3% or greater body surface area at baseline, improvements were seen more frequently in patients treated with certolizumab pegol than in those in the placebo group. For example, at week 24, 62.2% of patients treated with 200 mg every 2 weeks achieved a PASI 75 response, and 60.5% of those treated with 400 mg every 4 weeks achieved PASI 75. In contrast, PASI 75 was seen in 15.1% of patients in the placebo group, a significant difference ($P<0.001$).

Loss of TNF Inhibitor Efficacy

Clinicians who have used TNF inhibitors understand and expect that loss of efficacy may be seen in some patients, an occurrence that can be disheartening and frustrating to both health care providers and patients. Loss of therapeutic response is seen with all of the biologic agents, and the accumulated evidence suggests that this occurs for two main reasons: (1) a decrease in drug level primarily as a consequence of immunogenicity and (2) altered pathophysiology of the disease in the presence of the therapy used.

Decreases in drug levels occur with suboptimal dosing, poor patient adherence, and immunogenicity. An effective drug given at a dosage that is too low is an ineffective therapy. One example of suboptimal dosing is the step-down dosing of etanercept. Although this agent is effective at 50 mg twice weekly for many patients, based on labeling in the United States, the dosage must be stepped down to 50 mg once weekly. At the lower dosage, many patients lose previous gains in disease control. In addition, infliximab infusions every 8 weeks is the approved schedule, but experience shows that some patients have a better response with administration every 6 weeks, an off-label dosing schedule. Of course, the failure of patients

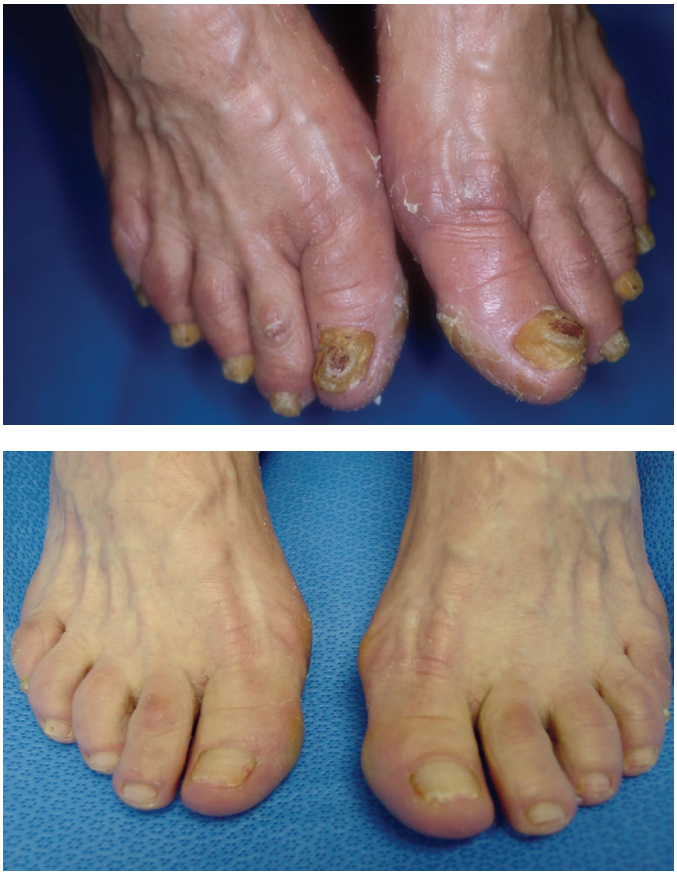

FIGURE 3 Psoriasis with nail involvement before (above) and after (below) a course of anti-TNF therapy.
Photos courtesy of Francisco A. Kerdel, BSc, MBBS.

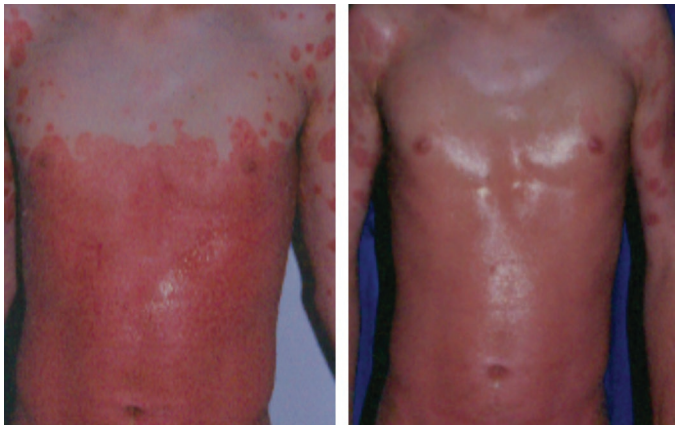

FIGURE 4 Psoriasis of the trunk before (above) and after (below) a course of anti-TNF therapy.
Photos courtesy of Francisco A. Kerdel, BSc, MBBS.

to adhere to the prescribed dosing schedule—either not self-administering the subcutaneous medications as directed or keeping scheduled appointments for infusions—adversely affects drug concentrations and, therefore, efficacy. However, immunogenicity probably is the most common cause of reduced drug concentrations and loss of efficacy in the face of good patient adherence.

Understanding Immunogenicity

All of the biologic agents in use today have structures that combine natural domains and fabricated structures; these foreign proteins are, by definition, immunogenic. However, different biologics demonstrate different degrees of immunogenicity, so it is clear that other factors are involved in loss of efficacy.[14]

Immunogenicity and Infliximab

Among the TNF inhibitors, immunogenicity was first discussed with respect to infliximab.

Data on infliximab maintenance therapy from patients with Crohn's disease demonstrate that infusion reactions are highly correlated with antibody formation. In the *A C*rohn's Disease *C*linical Trial *E*valuating Infliximab in a *N*ew Long-term *T*reatment Regimen (ACCENT) I trial at week 54, an episodic treatment regimen resulted in more antibodies and more frequent infusion reactions (28% of patients) than those in patients receiving every-8-week infusions of 5 mg/kg of infliximab (reactions seen in 9%) or 10 mg/kg of the drug (6%).[15]

An analysis of the subgroups of patients in ACCENT I who received infliximab, with and without concomitant immunosuppressants (in this study, 6-mercaptopurine or azathioprine), showed that immunosuppressant use seemed to inhibit immunogenicity. At week 54, among patients on 5 mg/kg every 8 weeks of infliximab who had not received immunosuppressants, antibody formation was seen in 11%; at this same infliximab dosage, 7% of patients who also received an immunosuppressant developed antibodies (not a statistically significant difference, at P=0.42). In the patients on 10 mg/kg of infliximab every 8 weeks, antibody formation was seen in 8% of patients not on concomitant immunosuppressants vs 4% of those who did receive immunosuppressants (not a statistically significant difference, at P=0.42). Even in the patients on episodic therapy, concomitant immunosuppressant therapy reduced the creation of antibodies in patients on infliximab: 38% of patients on infliximab alone developed antibodies compared to 16% of those on concomitant immunosuppressant therapy (P=0.003).[15]

Wee and colleagues[16] subsequently published a report on 9 years of experience with 59 patients with psoriasis who received a total of 858 infusions between January 2001 and June 2010 at a center in the United Kingdom. The incidence of infusion reactions was 1.5%, seen in 16.9% of patients. However, infusion reactions were much more common in patients who received infliximab alone than in those who also received concomitant methotrexate, a prevalence of 27% vs 4%, respectively.

The experience in these studies clearly demonstrates that the concomitant use of immunosuppressants can influence the development of antibodies to infliximab and can make the drug safer during the infusion process. In the context of psoriasis therapy, as the EXPRESS I study demonstrated, the proportion of patients on infliximab who had achieved PASI 75 at week 24 (82% of patients) dropped to 61% by week 50; the proportion of patients who had achieved PASI 90 at week 24 (58% of patients on infliximab) dropped to 45% by week 50. The investigators noted that the loss of clinical response was related to low serum concentrations of infliximab, which, in turn, was attributed—at least in part—to the development of antibodies to infliximab.[16]

Subsequently, Vena et al[17] conducted a retrospective analysis of 22 patients who were infliximab responders and who lost PASI 50 over time. Reinduction of infliximab (weeks 0, 2, and 6) resulted in a reversal of the loss to achievement of a PASI 50 response in 20 patients; 9 patients achieved PASI 75.

Etanercept and Loss of Long-Term Efficacy

The data on loss of etanercept efficacy over time largely parallels those seen with infliximab and adalimumab, but with some key differences. Antibodies to the TNF receptor portion or other protein components of etanercept were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS, or psoriasis.

Unlike what is seen with infliximab and adalimumab, antibodies detected with etanercept tend to be nonneutralizing, a finding that is not surprising because the foreign domain of etanercept is different than that seen in the other biologics. For example, adalimumab is a true immunoglobulin; its foreign domain rests within the antigen-binding domain in the Fab fragment. In contrast, etanercept is a receptor fusion protein, and the TNF receptor (TNF-binding) component of this biologic is fully human. When the etanercept receptor component links to an Fc domain of human IgG_1, a fusion segment is created between the TNF receptor in the Fc domain. Antibodies that bind this domain of etanercept do not neutralize its ability to bind TNF and therefore cannot be denoted as "neutralizing antibodies." To date, with regard to etanercept, no correlation with antibody development and clinical response or adverse events has been documented.

However, with etanercept other unknown mechanisms may reduce efficacy over the course of therapy. For example, in a prospective, single-center, observational cohort study from Amsterdam, Jamnitski and colleagues[18] assessed the clinical response to etanercept of 292 consecutive patients with active RA and a new etanercept prescription. Clinical response and etanercept levels were assessed at baseline and after 1, 4, and 6 months of treatment. Trough serum etanercept levels were measured by enzyme-linked immunosorbent assay. The investigators found that in patients who did not respond adequately to etanercept, the trough levels of the drug were significantly lower (P<0.05) than those in the responding patients. Interestingly, no antibodies against etanercept were detected in this study, and the absolute differences in etanercept serum levels in responders and nonresponders were small. Thus, an explanation other than immunogenicity may have been operational in the lack of etanercept response in some patients with RA in this study.

Loss of Response With Adalimumab

As part of the adalimumab pivotal study (REVEAL) discussed above, an analysis of long-term efficacy was conducted, in Periods B and C of the study.[19] Recall that Period A was a

16-week phase, during which PASI 75 or greater responders were identified. Period B was a 17-week, open-label, sustained-response evaluation phase during which only the patients who had PASI 75 responses were monitored. Those who sustained PASI 75 at week 33 were eligible for Period C. In Period C, the PASI 75 sustained responders were rerandomized to either continue adalimumab or receive placebo, beginning at week 33 and for an additional 19 weeks (to week 52).

Week 33 in Period C also became week 0 of the open-label extension study, on which data have been analyzed for more than 3 years. To date, among the patients on continuous treatment (n=233), 25% had dropped below PASI 75 at open-label extension phase week 108, and 75% of patients maintained PASI 75. The loss of PASI response was gradual over 108 weeks. Therefore, long-term continuous dosing of adalimumab as a monotherapy is associated with an attrition of responders.[19]

In an open-label study of adalimumab in patients with RA,[20] results were similar to those seen in the etanercept RA study by Jamnitski and colleagues.[18] The adalimumab study was a prospective, observational cohort design, involving 121 consecutive patients with RA treated with adalimumab alone or adalimumab plus methotrexate. Over the 28 weeks of follow-up, antibodies to adalimumab were detected in 17% (n=21) of patients, and the serum concentrations of adalimumab in patients with the anti-adalimumab antibodies were found to be significantly lower (range, 0.0-5.6 mg/L; median, 1.2 mg/L) than those in the patients without antibodies (range, 2.0-33.0 mg/L; median, 11.0 mg/L) (P<0.001). Anti-adalimumab antibodies were seen in nonresponders significantly more often than in responders (P=0.001).

When the investigators compared the data on the patients who received methotrexate with adalimumab, the correlation between methotrexate use and a lower rate of antibody formation was clear: 84% of the patients without anti-adalimumab antibodies had used concomitant methotrexate; 52% of those with anti-adalimumab antibodies had used concomitant methotrexate (P=0.003).[20]

In a similar, open-label, prospective, observational cohort study in patients with psoriasis, 29 patients were given adalimumab, 40 mg every other week after an initial dose of 80 mg.[21] Adalimumab trough concentrations were measured 12 and 24 weeks after initiation of therapy. Antibodies to adalimumab were found in 45% of patients (13/29) during the treatment period. At week 24, patients with low or no antibodies had the highest trough concentrations of adalimumab (P<0.001 compared to the group with high antibody levels) and also had significantly better clinical response (P<0.002). In contrast, patients with antibodies had loss of or no response to adalimumab. In this study, three patients out of the total population used concomitant methotrexate; none of these three patients developed antibodies against adalimumab, suggesting a benefit from concomitant methotrexate.

Conclusion

Several clinical implications are suggested from these updated data on TNF inhibitors. First, the evidence demonstrates that drug levels are most effectively maintained when biologics are given without interruption and at intervals that take their half-life into consideration. Second, loss of efficacy may be seen even when biologics are given according to recommendations and following even a robust therapeutic response, with immunogenicity being the most likely cause. However, because of the differences in the molecular structures of these biologics, immunogenicity to one biologic does not necessarily predict immunogenicity to another. Third, concomitant use of an immunosuppressant (usually methotrexate, but possibly also azathioprine) seems to lower the rate of antibody formation to a biologic agent and, therefore, prolong therapeutic efficacy. A sensible practice, therefore, would be to start methotrexate therapy and add a biologic if monotherapy does not produce an adequate response. The addition of an immunosuppressant such as methotrexate to a "failing" biologic might prolong efficacy, but once immunogenicity is established, it may be difficult to reverse.

References

1. Leonardi CL, Powers JL, Matheson RT, et al, for the Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014-2022.
2. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis *J Am Acad Dermatol.* 2007;56:598-603.
3. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med*. 2008;358:241-251.
4. Paller AS, Siegfried EC, Eichenfield LF, et al. Long-term etanercept in pediatric patients with plaque psoriasis. *J Am Acad Dermatol*. 2010;63:762-768.
5. Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362:118-128.
6. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance for moderate-to-severe psoriasis: A phase III, multi-centre, double-blind trial. *Lancet*. 2005;366:1367-1374.
7. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56:31.e1-e15.
8. Data on file. Janssen Biotech, Inc., 2011.
9. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
10. Reich K, Signorovitch J, Ramakrishnan K, et al. Benefit-risk analysis of adalimumab versus methotrexate and placebo in the treatment of moderate to severe psoriasis: Comparison of adverse event-free response days in the CHAMPION trial. *J Am Acad Dermatol*. 2010;63:1011-1018.
11. Leonardi CL, Gordon KB. New and emerging therapies in psoriasis. *Semin Med Cutan Surg.* 2014;33(suppl 2):S37-S41.
12. Kavanaugh A, McInnes I, Mease P, et al. Golimumab. *Arthritis Rheum*. 2009;60:976-986.
13. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomized placebo-controlled study (RAPID-PsA). *Ann Rheum Dis*. 2014;73:48-55.
14. Scott DW, De Groot AS. Can we prevent immunogenicity of human protein drugs? *Ann Rheum Dis*. 2010;69(suppl I):i72-i76.
15. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet*. 2002;359:1541-1549.
16. Wee JS, Petrof G, Jackson K, Barker JN, Smith CH. Infliximab for the treatment of psoriasis in the U.K.: 9 years' experience of infusion reactions at a single centre. *Br J Dermatol*. 2012;167:411-416.
17. Vena G, Loconsole F, Mastrandrea V, Buquicchio R, Cassano N. Therapeutic hotline: Re-induction may be useful to manage psoriasis relapse during long-term maintenance treatment with infliximab: A retrospective analysis. *Dermatol Ther*. 2010;23:199-202.
18. Jamnitski A, Krieckaert CL, Nurmohamed MT, et al. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis*. 2012;71:89-91.
19. Papp K, Menter A, Poulin Y, Gu Y, Sasso EH. Long-term outcomes of interruption and retreatment vs. continuous therapy with adalimumab for psoriasis: Subanalysis of REVEAL and the open-label extension study. *J Eur Acad Dermatol Venereol*. 2013;27:634-642.
20. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: Relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:921-926.
21. Lecluse LL, Driessen RJ, Spuls PI, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol*. 2010;146:127-132.