The Role of TNF Inhibitors in Psoriatic Disease

Brian F. Mandell, MD, PhD,* and Jeffrey M. Sobell, MD†

Abstract
In contrast to many other diseases, modern psoriasis therapy has a fairly brief history. Until about 15 years ago, clinicians and their patients had few options, with limited ability to rein in the disease process. The success of antifolate methotrexate in the treatment of rheumatoid arthritis (RA) led to clinical evaluation and adoption of the agent, a principal form of treatment for psoriasis, which, like RA, has its origin based in inflammation. The introduction of tumor necrosis factor-α inhibitors marked the beginning of the biologic era of psoriasis therapy. Also borrowed from the field of rheumatology, biologic therapy has evolved from improved understanding of the molecular basis of the disease process. An increased recognition of comorbid conditions that often accompany psoriasis, particularly psoriatic arthritis, can complicate clinical management. Dermatologists and other clinicians who treat psoriasis continue to benefit from insights gained in the field of rheumatology.

Semin Cutan Med Surg 33(suppl4):S64-S68 © 2014 published by Frontline Medical Communications

Keywords
Cardiovascular disease; methotrexate; obesity; psoriasis; psoriatic arthritis; psoriatic diseases; rheumatologic diseases; tumor necrosis factor inhibitors

Experience in clinical investigation often does not carry over to clinical practice. Clinical trials have shown that a majority of subjects with psoriasis obtain significant benefit from treatment with a tumor necrosis factor (TNF) inhibitor. Yet, only about 40% of real-world–treated patients remain on a given self-injectable TNF inhibitor after 1 year.1 Between 60% and 70% have gaps in therapy lasting 60 days or longer, and 15% to 20% of patients to whom a TNF inhibitor is prescribed switch to a different agent in the same class within a year.1 Several factors may contribute to the low persistence and prolonged therapy gaps among patients with psoriasis treated with TNF inhibitors. For some patients, therapy may fail to meet expectations. The rate of psoriasis improvement may not be as rapid as patients had expected, and this may lead to premature discontinuation of therapy. In many instances, closer examination shows that patients did not receive the recommended loading dose, as approved by the US Food and Drug Administration (FDA) for both etanercept and adalimumab for moderate to severe psoriasis. A study by Papp and colleagues2 suggests that the loading dose facilitates a more rapid onset of action and, thus, potentially may contribute to improved patient persistence with the medication.

Drug holidays are another possible explanation for low persistence rates. Patients feel better and may omit or delay injections; some may interpret their improved condition as a “cure.” Clinicians must remind patients that psoriasis is a chronic condition that requires ongoing therapy to attain or maintain disease control. Gaps in therapy may, in fact, lead to the formation of antibodies against the biologic agent that may render the therapy ineffective.

Not uncommonly, patients require interruptions in therapy, but the key is to avoid prolonged gaps leading to recurrence of disease. Clinical trials of etanercept and adalimumab showed that about 30% of patients who relapsed after discontinuation of therapy did not return to 75% improvement in Psoriasis Area Severity Index (PASI75) when they resumed treatment.3 Fear of side effects or concerns about the long-term safety of TNF inhibitors also may contribute to low rates of persistence. Patients and clinicians should be aware that multiple studies have demonstrated that long-term treatment with anti-TNF agents does not result in cumulative toxicity. Finally, anti-TNF therapy is expensive, and patients might not persist with therapy because of high health insurance deductibles and copayments. Several organizations exist that help with the cost of therapy, and many manufacturers have patient assistance programs that should be explored.

Loss or Diminution of Response
Some patients with psoriasis experience a loss of response to a TNF inhibitor after months of disease control. When this occurs, possible solutions include using an adjunctive concomitant medication (such as methotrexate or acitretin), increasing the dosing frequency of the TNF inhibitor, or switching to a different TNF inhibitor or a different medication.

Numerous studies have shown that loss of efficacy with one anti-TNF agent does not preclude use of a different agent in the same class. One recent study evaluated infliximab in patients who had an inadequate response to etanercept.4 Within 10 weeks after starting infliximab, almost two-thirds of patients had achieved Physician Global Assessment (PGA) scores of clear or minimal body surface area (BSA) involvement.

DOI: 10.12788/j.sder.0097

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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, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

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

Brian F. Mandell, MD, PhD, has no relevant financial relationships with any commercial interests.
Jeffrey M. Sobell, MD, has been a consultant and/or speaker and/or investigator for AbbVie, Amgen Inc., Celgene Corporation, Eli Lilly, Janssen Biotech, Inc., and Merck & Co., Inc.

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In another trial, adalimumab was given to patients who had not responded to etanercept (primary nonresponse) or had responded initially but lost the response over time (secondary nonresponse). Overall, 40 of 82 patients (48.8%) had a PGA score of clear or minimal BSA involvement after 16 weeks of treatment with adalimumab. The overall response included 15 of 26 (57.7%) patients with primary nonresponse to etanercept and 26 of 56 (46.4%) patients with secondary nonresponse. Successful use of etanercept in adalimumab failures has also been reported.

Some patients who lose response to a TNF inhibitor may subsequently respond to the same agent after a period of discontinuation. One case series involved 20 patients who were treated successfully with etanercept for 6 months or longer and then discontinued because of secondary loss of efficacy. Subsequently, most of the subjects received and failed two or more different biologic agent therapies before initiating re-treatment with etanercept. After 12 weeks of re-treatment with etanercept, 8 of 18 (44.4%) had a PGA rating of 0/1 (clear/almost clear response).

In some cases, augmenting a TNF inhibitor with a drug from a different therapeutic class may be more effective than single-agent anti-TNF treatment. In one randomized trial, 478 patients with moderate to severe plaque psoriasis were randomized to receive etanercept, either alone or in combination with methotrexate, or placebo. The primary end point was the proportion of patients who achieved at least 75% improvement in PASI175 at 24 weeks. The results showed that significantly more patients treated with etanercept plus methotrexate had achieved PASI175 (P<0.0001) and PASI90 (P<0.05) than those in either the etanercept monotherapy or the placebo groups. Importantly, the addition of methotrexate did not increase the incidence of adverse events, including serious adverse events, compared to etanercept monotherapy.

Extensive clinical experience with TNF inhibitor/methotrexate combinations also has shown that the combination may result in therapeutic synergy, increase the odds of durable responses, enhance protection of joint destruction in inflammatory arthritis, and decrease systemic inflammation more effectively than either agent alone.

**Impact of Comorbid Conditions**

Psoriasis seldom occurs in clinical isolation. Many patients have one or more comorbid conditions that can increase the complexity of treatment decision making and influence the approach to treatment for psoriasis (Table 1).

### Psoriatic Arthritis

As many as 39% of patients with psoriasis develop psoriatic arthritis. Large surveys have suggested a greater prevalence of concomitant psoriatic arthritis among European patients with psoriasis than among Americans with the disease. This disparity may relate to psoriasis severity. In general, European clinical trials involved patients with more severe psoriasis than seen in patients enrolled in North American clinical trials. Indeed, accumulated data suggest such a correlation between the severity of psoriasis and the presence—but not the severity—of psoriatic arthritis.

Among patients with both psoriasis and psoriatic arthritis, the skin disease occurs first in about 70% of cases. Co-occurrence of the two conditions accounts for about 15% of cases, and joint disease precedes skin disease in the remaining 15%.

As is the case with rheumatoid arthritis (RA), early recognition of psoriatic arthritis is essential to prevent joint damage. More than 50% of patients with psoriatic arthritis develop erosive arthropathy, 15% to 20% develop five or more joint deformities, and 10% to 20% of patients have functionally debilitating disease. Like patients with RA, those with psoriatic arthritis have increased mortality compared with the general population.

Common signs of psoriatic arthritis include an oligoarticular asymmetric arthritis, spondylitis, enthesitis, and dactylitis. During medical history taking, clinicians should ask patients about tender or swollen joints, prolonged morning joint stiffness, and family history of psoriatic arthritis.

Five TNF inhibitors have FDA approval for treatment of psoriatic arthritis: etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. All five agents are indicated for reducing signs and symptoms of active arthritis, inhibiting progression of structural damage, and improving physical function. Another biologic agent, the p40 antagonist ustekinumab, is approved for reducing signs and symptoms of psoriatic arthritis.

TNF inhibitors have a long track record for efficacy in psoriatic arthritis. One of the early studies evaluated etanercept versus placebo. The primary end point was the proportion of patients who attained 20% improvement in disease status by American College of Rheumatology (ACR20) criteria. After 12 weeks, 59% of etanercept-treated patients had ACR20 responses, compared to 15% of the placebo group (P<0.0001). After 24 weeks, the ACR20 response rates were 50% for etanercept and 13% for placebo (P<0.0001).

Similar results have been demonstrated with all members of the TNF inhibitor class of agents. A placebo-controlled trial of adalimumab in psoriatic arthritis had a radiographic end point of improvement in modified Total Sharp Score (mTSS) after 48 weeks. At both 24 and 48 weeks, patients treated with adalimumab had significantly greater improvement in mTSS (P<0.001), suggesting protection from ongoing joint damage. Similar results have been seen in clinical trials of all five TNF inhibitors.

### TABLE 1 Extracutaneous Manifestations and Comorbidities of Psoriasis

<table>
<thead>
<tr>
<th>Musculoskeletal</th>
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<tbody>
<tr>
<td>• Psoriatic arthritis</td>
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<tr>
<td>• Tendonitis/enthesitis</td>
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<td>• Gout</td>
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<th>Ocular</th>
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<td>• Uveitis</td>
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<table>
<thead>
<tr>
<th>Cardiovascular</th>
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<tbody>
<tr>
<td>• Metabolic risk factors increased</td>
</tr>
<tr>
<td>• Link to systemic inflammation</td>
</tr>
<tr>
<td>• Independent risk for CAD?</td>
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Cardiovascular Risk Factors and Disease

Patients with psoriasis have an increased risk for cardiovascular disease and factors that contribute to cardiovascular disease.\(^{18,19}\) The prevalence of metabolic syndrome in patients with psoriasis is almost double that of the general population. The characteristics of metabolic syndrome seen most frequently in patients with psoriasis are abdominal obesity (63%), hypertriglyceridemia (44%), and decreased levels of high-density lipoprotein cholesterol (34%).\(^{18,19}\)

Emerging evidence has suggested that psoriasis is an independent risk factor for myocardial infarction (MI) and stroke. The magnitude of the risk increases with the severity of psoriasis and appears to be magnified in younger patients who have severe psoriasis.\(^{18}\)

A 130,000-person cohort study of patients with psoriasis showed a 7% increase in the adjusted relative risk for stroke in association with mild psoriasis, increasing to 44% in patients with severe psoriasis.\(^{20}\) The risk remained elevated after adjustment for age, sex, and other risk factors for stroke.

The association between psoriasis and cardiovascular risk may involve TNF, which is a key proinflammatory cytokine associated with development of atherosclerosis.\(^{21}\) TNF modulates production or activation of other proinflammatory proteins, such as interleukin-6 and C-reactive protein. The chronic inflammation of metabolic syndrome appears to revolve around TNF, which promotes insulin resistance and adversely affects lipid metabolism.

Treatment with TNF inhibitors has been associated with favorable effects on multiple parameters associated with metabolic syndrome and cardiovascular disease (Table 2). A modest amount of data has suggested that treatment with TNF inhibitors might help reduce the risk for atherosclerosis and cardiovascular events.

In one study, patients treated with TNF inhibitors underwent carotid ultrasound to assess carotid intima-media thickness (cIMT), a surrogate for atherosclerosis.\(^{22}\) Patients treated with TNF inhibitors had significant reductions in cIMT (\(P<0.0001\)). Observational data have suggested a reduced risk for MI in patients with psoriatic disease treated with anti-TNF agents.\(^{23}\) The association does not prove that anti-TNF therapy reduces MI risk but, rather, is consistent with the hypothesis that anti-TNF agents favorably affect MI risk.

Obesity

Studies have demonstrated that patients who are overweight or obese have a less robust response to TNF inhibitors. For example, investigators in a randomized, placebo-controlled trial of etanercept evaluated PASI75 response by weight. Heavier patients had substantially lower response rates to both etanercept doses (50 mg weekly and 50 mg twice weekly) evaluated in the study.\(^{24}\)

Similar results have been observed with other TNF inhibitors, with the exception of infliximab because this drug is dosed by weight. Data from a placebo-controlled trial were stratified by body mass index (BMI). The results showed no significant difference in response rate by BMI (<25, 25-<30, ≥30) in the placebo or infliximab treatment groups.\(^{25}\)

Rheumatologic Perspective on Psoriatic Disease

Psoriasis often exhibits extracutaneous manifestations that cross different medical specialties, including several types of musculoskeletal disorders that extend into the purview of the rheumatologist. Musculoskeletal manifestations of psoriatic disease have some association with severity of the skin disease, but the association is not an extremely strong one. The musculoskeletal disorders may precede or follow appearance of the skin disease.

The musculoskeletal manifestations comprise several distinct patterns, including spondylitis, enthesitis, and dactylitis. Spondylitis often goes unrecognized because the presentation is subtle, something as simple as a backache, which is prevalent in patients with psoriatic disease and in the general population. Nonetheless, the condition can severely restrict a person’s function.

Psoriatic spondylitis is not the same as ankylosing spondylitis. About 60% of patients with psoriatic spondylitis test positive for HLA B27, whereas more than 90% of patients with ankylosing spondylitis are HLA B27 positive. For reasons that remain unclear, spondylitis appears to be especially sensitive to anti-TNF therapy and insensitive to other therapies.

### TABLE 2 Effects of TNF-Inhibitor Therapies on Various Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Study Outcome</th>
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<tr>
<td>Obesity with type 2 diabetes</td>
<td>4-week course of etanercept 25 mg BIW significantly reduced systemic inflammatory markers such as CRP and IL-6 but had no effect on vascular or metabolic insulin sensitivity ((N=20))(^1)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>4-week course of etanercept 50 mg QW lowered CRP and fibrinogen and elevated adiponectin levels, with no effects noted on insulin sensitivity and on either BMI or waist-to-hip ratio ((N=56))(^2)</td>
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| Vascular function                  | - Short-term adalimumab therapy improved endothelial function in 8 patients with RA refractory to infliximab\(^3\)  
|                                   | - 12 weeks of infliximab therapy was shown to improve endothelial function in 11 RA patients\(^4\) |
| Insulin resistance                 | Dramatic reduction in the serum insulin levels and insulin/glucose index observed in 27 patients with RA following infliximab infusion; significant improvement of insulin resistance and insulin sensitivity\(^6\) |

BIW=biweekly; BMI=body mass index; CRP=C-reactive protein; IL-6=interleukin-6; QW=every week; RA=rheumatoid arthritis; TNF=tumor necrosis factor.

Enthesitis arises in the Achilles tendon at the junction of the tendon and bone, making it difficult to manage. Most rheumatologists are reluctant to biopsy the area or to use injection therapy because of concern about weakening the connection between the tendon and bone. When injectable therapy is administered, the frequency of injections is carefully monitored to avoid damage to the delicate connection.

Dactylitis is specific to psoriatic disease and a few other forms of arthritis and is virtually nonexistent in RA. Characterized by diffuse swelling involving a finger or toe, dactylitis involves inflammation that has spread from the joint to surrounding tissues. The condition might be more correctly characterized as a form of tenosynovitis.

**Methotrexate and Psoriatic Arthritis**

Methotrexate has long been a mainstay of treatment for RA and psoriatic arthritis, although the latter condition is not an approved indication for this drug. Early experience with methotrexate in psoriatic arthritis led to some concern about hepatotoxicity. The concern likely resulted from the way the drug was used in early clinical experience. Patients received several doses a week or even daily doses, and folic acid supplements were not prescribed for concomitant use. In addition, patients were not routinely screened for underlying liver disease, including nonalcoholic fatty liver disease.

Treatment practices of 30 years ago cannot be compared to current use of methotrexate. The drug has a safety record in RA that led the ACR to eliminate its recommendation of liver biopsies for patients taking methotrexate, even in cases of prolonged use of 10 years or more. Transaminase measurement on a regular basis is still recommended.

The results of a recent randomized, placebo-controlled trial of methotrexate have given clinicians reason to reassess the use of the drug as monotherapy in psoriatic arthritis.26 The trial involved 221 patients with psoriatic arthritis treated for 6 months with methotrexate or placebo. The results showed improvement in skin lesions and patient-reported outcomes, but no significant improvement in objective measures of joint disease. However, this trial has been criticized for several reasons. First, the study population was not large. Second, the target dose of methotrexate used was 15 mg a week, whereas rheumatologists routinely prescribe 20 to 25 mg weekly. Third, only 78% of patients were receiving 15 mg of methotrexate when the study ended, and they had received that dose for just 3 months. Fourth, more than 10% of patients were taking less than 15 mg of the medication. Fifth, patients in the trial did not have severe or active psoriatic arthritis, and 81% were taking nonsteroidal anti-inflammatory drugs in addition to randomized therapy, which would increase the difficulty of demonstrating a significant difference between treatment groups. Finally, a large number of patients—20%—were lost to follow-up.

Given methotrexate’s long history of effectiveness in rheumatologic diseases and the methodologic problems described, the results of this single trial should not dissuade clinicians from prescribing methotrexate for patients with psoriatic arthritis. The drug is not effective for axial (spinal) disease, but more evidence is needed before determining methotrexate’s efficacy over placebo in psoriatic arthritis. In addition, methotrexate may be of value in limiting the generation of anti-drug (neutralizing) antibodies when used in conjunction with anti-TNF agents. The use of methotrexate requires monitoring of transaminase levels, and clinical guidelines have been developed to provide direction for testing.

**Anti-TNF Therapy in Psoriatic Arthritis**

The TNF inhibitors have become a cornerstone of therapy for psoriatic disease, including psoriatic arthritis. These agents have proven especially effective for treating skin lesions, which might require higher doses in severe cases, as compared with effective doses for joint disease.

Activity in psoriasis-related spondylitis and spinal disease has distinguished the TNF inhibitors from other options for the systemic treatment of psoriatic arthritis. None of the other therapies can match the level of activity in spondylitis and spinal disease.

Several practical issues should be considered when using TNF inhibitors in patients with psoriatic arthritis.27,28 Dosage adjustment might be required with etanercept in overweight and obese patients. A few reports in the literature have documented induction or worsening of skin disease with use of TNF inhibitors to treat arthritis. However, the phenomenon appears to be uncommon. Rarely, use of TNF inhibitors has been associated with induction of lupus and multiple sclerosis.

In addition to periodic liver enzyme (transaminase) tests, screening for hepatitis B and C virus (HBV and HCV) is recommended prior to initiating anti-TNF therapy, as drug-associated reactivation of HBV can lead to hepatic necrosis. Additionally, patients should be evaluated for exposure to tuberculosis before starting treatment with any of the anti-TNF agents. An interferon release assay should be repeated whenever a patient encounters a potential for exposures (such as travel abroad). Patients who have visited areas in which tuberculosis is endemic should have a chest x-ray.

A patient’s vaccination history should be reviewed prior to starting treatment with a TNF inhibitor. In particular, patients treated with anti-TNF agents have been advised to avoid live-virus immunization. An accumulation of retrospective data suggests that patients on TNF inhibitors may have an increased risk for perioperative infections.

**Summary**

Treatment of psoriatic disease has evolved dramatically over the past several years, and new and more effective therapies have become available. In particular, TNF inhibitors have proven effective in both psoriasis and psoriatic arthritis. Comorbid conditions often complicate clinical management of psoriatic disease, as patients have an increased prevalence of metabolic syndrome and cardiovascular disease. Clinical management of psoriatic disease often encompasses several medical specialties, and patients can benefit from a multidisciplinary approach.

**References**


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