Psoriasis: Evidence for the Efficacy and Safety of Anti–TNF-α Treatment
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Benefits of Anti–TNF-α Agents in Psoriatic Arthritis: Evidence From Clinical Trials
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Quality of Life in Patients With Psoriasis and Psoriatic Arthritis
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Cover illustration: Emily Brannan
Psoriasis: Evidence for the Efficacy and Safety of Anti–TNF-α Treatment

Craig L. Leonardi, MD

Over the past decade, our understanding of the pathogenesis of psoriasis has evolved from a keratinocyte-mediated disorder to that of an immune system dysfunction. A number of strategies for modulating the inflammatory response seen in psoriasis have been proposed, and many of the new biologic agents for treating the disease employ one or more of these approaches to effect a therapeutic response. These strategies have been condensed into five categories and are listed in Table 1.1

The concept of immune deviation is appealing because psoriasis is thought to be driven by a classic T helper type 1 (TH1) cell response. An upregulation of TH1 responses at the opposite end of the T-cell response spectrum—would theoretically downregulate TH1 responses and have some benefit in psoriasis. This strategy has been tested in clinical trials, but to date has not shown impressive efficacy.

Of the currently available biologic agents, efalizumab and alefacept both block T-cell activation during the primary and secondary activation steps. In addition, efalizumab also interferes with the migration of pathogenic T cells into the target tissues, whereas alefacept also eliminates pathologic T cells as a primary mechanism of its action.

The fifth strategy involves inhibition of proinflammatory cytokines as they are released by activated lymphocytes. This supplement focuses on the inhibition of tumor necrosis factor-alpha (TNF-α), one of the key cytokines that have been implicated in the inflammatory process in psoriasis, in a variety of arthritides, and in Crohn’s disease. To date, biologic agents that inhibit TNF-α—etanercept, infliximab, and adalimumab—have demonstrated impressive efficacy and safety in psoriasis treatment.

**Table 1: Strategies for Biologic Therapy**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Treatments Available Using This Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune deviation</td>
<td>None</td>
</tr>
<tr>
<td>Block T cell activation</td>
<td>efalizumab, alefacept</td>
</tr>
<tr>
<td>Block migration of pathogenic T cells</td>
<td>efalizumab</td>
</tr>
<tr>
<td>Eliminate pathogenic T cells</td>
<td>alefacept</td>
</tr>
<tr>
<td>Inhibit activity of key cytokines (TNF-α, IFN-γ, IL-12, IL-4, IL-10, IL-11)</td>
<td>etanercept, infliximab, adalimumab</td>
</tr>
</tbody>
</table>

1. IFN = interferon, IL = interleukin, TNF = tumor necrosis factor.

Source: Singri P, et al. 1

**Anti–TNF-α Therapy in Psoriasis: Major Clinical Trials**

The three currently available TNF-α inhibitors are being studied in psoriasis. Infliximab is now in phase III studies and etanercept recently was approved for use in psoriasis. Adalimumab is earlier in development and the first study of this drug in patients with psoriasis recently has been completed.

**Etanercept Phase III Study**

A phase III study² of etanercept in 672 patients with psoriasis was a double-blind, placebo-controlled trial, with a crossover to active treatment in the placebo group. Patients were randomized into one of four groups, receiving subcutaneous injections of either a low dosage of etanercept (25 mg once weekly), the standard dosage of etanercept (25 mg twice weekly), a high dosage of etanercept (50 mg twice weekly), or placebo. The primary end point was achievement of 75% improvement in the Psoriasis Area and Severity Index (PASI 75) at week 12, the midpoint of the study. At the midpoint, the patients in the placebo group began treatment with the standard dosage (25 mg twice weekly) of etanercept.

A marked response to therapy was seen in this study at 12 weeks. At the low dosage, 14% of patients achieved PASI 75. At the standard dosage, 34% of patients achieved PASI 75, and at the high dosage, 49% of patients achieved PASI 75. Only 4% of patients in the placebo group achieved PASI 75 by week 12 (P<0.001).

PASI 90 responses were observed with 22% of the patients in the high-dosage group, 12% of those in the standard-dosage group, and 3% in the low-dosage group, compared with 1% of patients who received placebo.

No increase was seen in serious adverse events between the placebo group and any of the treatment groups. The most common side effect seen with
etanercept in this study is a minor injection-site reaction.

Infliximab Phase II Study
The Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT) trial, a multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of infliximab induction therapy in 249 patients with plaque psoriasis. The patients were randomized to receive either placebo (n=59), or infusions of either 3 mg/kg (n=99) or 5 mg/kg (n=99) of infliximab at weeks 0, 2, and 6.

The primary endpoint analysis was conducted at week 10, and other evaluations were conducted at weeks 14, 18, 22, and 26. Patients whose psoriasis worsened by week 26 were candidates for an additional infusion. The final evaluation was performed at week 30, and a final blood test for antibodies to infliximab was conducted at week 46.

To qualify for enrollment, patients had to be at least 18 years of age, have at least a 6-month history of plaque psoriasis, and have involvement of 10% or greater body surface area and a PASI score of at least 12. In addition, patients were required to have undergone previous treatment with psoralen and ultraviolet light or any systemic medication. Patients were excluded if they were using any of the standard concomitant treatments for psoriasis that could not be stopped. Those with active tuberculosis (TB) or a history of latent TB, or a history of chronic infectious disease, opportunistic infection, or any serious infectious disease within the past 2 months also were excluded from the study. Patients with a history of lymphoproliferative disorders, malignancy in the last 5 years (except for common basal cell carcinomas), and previous anti–TNF-α therapy also were not eligible for enrollment.

At the primary endpoint, week 10, the investigators noted that substantially more patients in the infliximab groups achieved a 75% or greater improvement in PASI than those in the placebo group. This was true across all subgroups; the results for various subgroups are shown in Table 2.

More complete data from the SPIRIT trial will be published elsewhere over the next several months.

CONCLUSION
Laboratory and clinical studies have demonstrated that TNF-α plays an important role in the pathogenesis of psoriasis and psoriatic arthritis. Clinical studies have demonstrated the efficacy and safety of inhibiting TNF-α in patients with these conditions.

REFERENCES

Table 2: Results from the SPIRIT Trial: Percent of Patients Who Achieved ≥ 75% PASI Improvement at Week 10

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Infliximab-Treated (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>79.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Women</td>
<td>80.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>87.1</td>
<td>14.3</td>
</tr>
<tr>
<td>40 - &lt;60 years</td>
<td>78.5</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>69.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (BMI &lt;25)</td>
<td>77.5</td>
<td>16.7</td>
</tr>
<tr>
<td>Overweight (BMI 25 - &lt;30)</td>
<td>83.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td>78.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Baseline PASI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>78.0</td>
<td>6.7</td>
</tr>
<tr>
<td>&gt;20</td>
<td>82.0</td>
<td>4.8</td>
</tr>
<tr>
<td>BSA involved at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;27%</td>
<td>76.3</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;27%</td>
<td>83.2</td>
<td>8.0</td>
</tr>
<tr>
<td>History of systemic antipsoriasis therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80.8</td>
<td>3.6</td>
</tr>
<tr>
<td>No</td>
<td>77.9</td>
<td>8.7</td>
</tr>
</tbody>
</table>

SPIRIT = Study of Psoriasis With Infliximab (Remicade) Induction Therapy. BMI = body mass index; BSA = body surface area; PASI = Psoriasis Area and Severity Index. Source: Gottlieb AB, et al.³
Benefits of Anti–TNF-α Agents in Psoriatic Arthritis: Evidence From Clinical Trials

Zuhre Tutuncu, MD

Psoriatic arthritis affects men and women equally in the third and fourth decades of life. Classic symptoms and signs include morning stiffness, erythema, and swelling of the joints. Changes in the nails frequently occur when psoriatic arthritis accompanies psoriasis. In approximately 75% of patients, psoriasis presents prior to arthritis symptoms. No widely accepted criteria exist yet for diagnosing psoriasis and psoriatic arthritis, but international efforts are under way to develop such guidelines.

Currently, the assessment of disease activity in psoriatic arthritis lies in the count of joints that are swollen and tender, an evaluation of clinical damage such as flexion contractures and deformities, the presence of spondylitis, dactyliitis, and enthesopathy, and the value of acute-phase reactants.

In psoriatic arthritis trials, endpoints to evaluate arthritis typically include American College of Rheumatology (ACR) response criteria, the Disease Activity Score-28, and Psoriatic Arthritis Response Criteria. Quality-of-life measures include the Health Assessment Questionnaire (HAQ) and the 36-item Short Form Health Survey commonly referred to as SF-36. Radiographic changes are evaluated according to Sharp and Steinbrocker criteria.

Anti–TNF-α Agents Evaluated for Psoriatic Arthritis

To date, clinical trials have been performed using two agents that inhibit tumor necrosis factor-α (TNF-α): etanercept and infliximab.

A double-blind, placebo-controlled, multicenter, phase III clinical trial was completed on etanercept in 205 patients randomized to receive either active treatment (n = 101) or placebo (n = 104). To be eligible to participate in the study, patients were required to have active disease (swelling and tenderness) in at least three joints. Those who were taking methotrexate were required to be on a stable dose of that drug. The primary endpoint in this study was achievement of a minimum of 20% improvement according to ACR criteria (ACR 20).

After 6 months of treatment, 50% of patients in the active treatment group had achieved ACR 20 compared with 13% of patients in the placebo group. Thirty-seven percent of patients in the etanercept group had achieved ACR 50, compared with 4% of the placebo group, and 9% of patients on etanercept achieved ACR 70, compared with 1% of patients on placebo.

Skin disease in that study was evaluated according to the Psoriasis Area and Severity Index (PASI). Forty-seven percent of patients on etanercept achieved a 50% improvement in PASI (PASI 50), compared with 18% of patients in the placebo group. PASI 75 was achieved by 23% of patients in the active-treatment group compared with 5% of those in the placebo group. ACR and PASI results were similar, whether or not patients were also using methotrexate.

The double-blind, randomized, placebo-controlled, multicenter Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) involved 102 patients at nine sites in the United States, Canada, and Europe. The study compared infliximab with placebo over a period of 16 weeks; this was followed by an open-label phase through week 50. The primary endpoint was achievement of ACR 20. To be considered for enrollment, patients were required to have active disease in at least five joints in addition to an erythrocyte sedimentation rate >28 mm/h, or C-reactive protein (CRP) >15 mg/L, or morning stiffness for longer than 45 minutes. In addition, patients must have failed treatment on at least one disease-modifying antirheumatic drug (DMARD). Patients currently on DMARDs were required to be on stable dosages for at least 4 weeks.

The patients were randomized to one of two groups, which were well matched for all demographics and disease and treatment parameters, including concomitant DMARD and methotrexate use. In addition, mean baseline disease activity was similar in both groups: tender joint counts, swollen joint counts, physician global, patient global, and patient pain assessment, HAQ scores, and CRP levels.

Group 1 received placebo infusions at weeks 0, 2, 6, and 14, followed by infusions of 5 mg/kg of infliximab at weeks 16, 18, 22, 30, 38, and 46. The schedule for Group 2 was as follows: infusions of infliximab, 5 mg/kg, at weeks 0, 2, 6, and 14, followed by placebo infusions at weeks 16 and 18, and infliximab, 5 mg/kg, infusions at weeks 22, 30, 38, and 46.

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Quality of Life in Patients With Psoriasis and Psoriatic Arthritis

Alexa Boer Kimball, MD, MPH

Data that demonstrate the efficacy of treatments for psoriasis and psoriatic arthritis represent a crucial—but not the only—factor in judging clinical improvement for patients. For clinicians and their patients, the efficacy that is measured according to American College of Rheumatology (ACR) criteria and the Psoriasis Area and Severity Index (PASI) in clinical trials must be considered in the context of quality of life (QoL).

GOALS FOR TREATMENT

The short-term goals for skin psoriasis include achieving rapid control of the disease, decreasing body-surface area involvement, and decreasing erythema, scaling, and induration. For psoriatic arthritis, the goals previously have been to control pain and disability. With the advent of the new therapies that inhibit tumor necrosis factor (TNF), another short-term treatment goal for psoriatic arthritis has been added: preventing progression of joint disease to reduce the risk for morbidity and mortality. The data available suggest that it is possible to achieve these goals with TNF-inhibiting agents, particularly if psoriatic arthritis is detected early. Ideally, one treatment would address both skin and joint disease simultaneously.

The long-term treatment goals for psoriasis and psoriatic arthritis are maintenance of long-term control of disease with medications that have an acceptable safety profile and that are well tolerated by patients. For patients with psoriatic arthritis, this includes reduction in further joint destruction. A final and important treatment goal is the improvement of patient QoL.

THE ROLE OF QOL MEASURES IN DRUG STUDIES

Measures of QoL should be included in treatment trials for several reasons. First, psoriasis must continue to be considered an important disease. Patients with psoriasis experience their disease in ways that parallel that of patients with other diseases, including diabetes, congestive heart failure, and chronic obstructive pulmonary disease.

Second, the clinical meaning of improvements in lesions must be shown. The US Food and Drug Administration has established a 75% improvement in PASI as an endpoint, but this benchmark does not demonstrate what such an improvement means in terms of a patient’s life experience. Such an evaluation is helpful in determining the cost-effectiveness of a treatment. What impact do increased efficacy, decreased toxicity, and improvements in QoL have on the cost of newer agents, which seem more expensive than standard therapies when viewed strictly in terms of purchase price?

Third, the concept of complete clearance or nearly complete clearance must be addressed as a realistic goal. “Clearance” may be different from “improvement” for patients, and some provision should be made for this experience in clinical trials.

Fourth, and finally, those who conduct and evaluate clinical trials must take into consideration the experience of living with a chronic disease and the toll that this takes on the lives of patients and their families. Psoriasis affects an individual’s choice of work and, therefore, may affect a patient’s ability to earn a wage commensurate with his or her skills. Patients with more severe psoriasis have lower socioeconomic status. It also affects patients’ ability and willingness to be seen in public, limiting social opportunities. Other areas affected include sexual relations and general physical and emotional well-being.

GENERAL AND DERMATOLOGY-SPECIFIC MEASURES

The use of general measures to evaluate QoL permit comparisons across diseases—such as psoriasis versus congestive heart failure. One example is the Health Assessment Questionnaire (HAQ), developed by Fries and colleagues as a comprehensive measure of outcome in patients with a wide variety of rheumatic diseases. The HAQ was one of the first self-report disability measures and has become the dominant instrument in many disease areas. The HAQ is used widely throughout the world and often is used as an outcome measure for clinical trials in rheumatoid arthritis and other diseases, such as HIV/AIDS, as well as in studies of normal aging. This is a generic rather than a disease-specific instrument, focusing on self-reported, patient-oriented outcome measures rather than process measures.

Another important general measure is the Medical Outcomes Study Short Form-36 (SF-36), an instrument that has been validated across a wide range of diseases. The SF-36 is a self-reported assessment of function and well-being to determine baseline values, changes in function and well-being over time, and the effects of interventions.

Relevance to Psoriasis

Although these general measures are invaluable in assessing how a broad range of diseases and interventions affect patients’ lives, they are relatively insensitive to the specific impact of a skin disease. For example, the ability to lift or carry groceries may be relevant to patients with congestive heart failure or arthritis but is not necessarily a factor in a patient with skin disease such as psoriasis.

Dermatology-specific measures are more sensitive to the impact of skin disease and are useful in clinical trials to evaluate skin-disease-related QoL measurements. These instruments include the Dermatology Life Quality Index (DLQI), Psoriasis Disability Index, Skindex, and Dermatology-Specific Quality of Life Measure.

The DLQI was developed to conduct clinical evaluations rather than as a research tool. Nonetheless, it has been used in a number of studies to evaluate QoL. The DLQI covers 10 questions in...
Relevance to Psoriatic Arthritis

At present, relatively little is known about QoL in psoriatic arthritis. According to a National Psoriasis Foundation survey, 84% of patients with psoriatic arthritis reported that the disease has a moderate to significant impact on their day-to-day activities, 75% said they lose sleep or sleep poorly, and 69% reported that psoriatic arthritis interferes with education, vocational, and social activities.

Several measures commonly are used in clinical practice and drug trials, including general measures such as the HAQ and the SF-36. The HAQ and the SF-36 have been validated in studies of patients with psoriatic arthritis. Husted and colleagues conducted a study involving both the SF-36 and the HAQ to determine how well these instruments measured QoL in patients with psoriatic arthritis versus those with rheumatoid arthritis. These investigators found that, although QoL was adversely affected in both groups of patients, there were some meaningful differences in how each disease affects QoL. They note that there may be unique disabilities associated with the skin disease dimension of psoriatic arthritis. For example, the patients with psoriatic arthritis had levels of vitality, but they had more bodily pain and more psychosocial and vocational role limitations resulting from disease-related emotional problems.

CONCLUSION

Psoriasis clearly has a significant impact on the lives of our patients. Many of the biologic agents, particularly the TNF inhibitors, are highly effective, both clinically and in terms of improving QoL.

REFERENCES


Benefits

Continued from page 5

Eighty-eight of the original 102 patients completed the study according to the protocol. Ninety-three patients were available for an evaluation at week 50. Assessments at week 16 showed that 69% of patients on infliximab had achieved ACR 20, and 72% had achieved ACR 20 at week 50. Forty-nine percent of infliximab-treated patients achieved ACR 50 at week 16 and 54% achieved this benchmark at week 50. At week 16, 29% of patients achieved ACR 70 and 54% achieved ACR 70 at week 50.

In the placebo group, 8% of patients achieved ACR 20 at week 16. The percentage of patients achieving ACR 20 increased to 77% in this group at week 50 (following the crossover to infliximab treatment at the 16-week point).

Patients with baseline PASI scores ≥2.5 who were in the infliximab group had a mean improvement in PASI from 8.4 to 1.6 at week 16. By week 50, this improvement had been maintained, at 2.3. Fourteen patients in the active-treatment group achieved PASI 75 or greater at week 16; 12 of these patients maintained that improvement through week 50. Among those in the placebo group, 8 of 16 achieved PASI 75 or greater by week 50.

Overall, the safety profile in this clinical trial was very similar to what was seen in previous clinical studies. Only one serious infusion reaction occurred during the study.

CONCLUSION

The anti-TNF-α agents etanercept and infliximab have been shown in clinical trials to be effective and safe in treating signs and symptoms of psoriatic arthritis.

REFERENCES

Experience With Anti–TNF-α Therapy in Dermatologic Immune-Mediated Inflammatory Disorders

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INSTRUCTIONS: For each question or incomplete statement, one answer is correct. Circle the most appropriate response. Four of five correct responses are required for credit.

1. The primary endpoint in major clinical studies of efficacy of tumor necrosis factor inhibitors in patients with psoriatic arthritis is ___ improvement in the American College of Rheumatology criteria.
   a. 20% (ACR 20)
   b. 35% (ACR 35)
   c. 50% (ACR 50)
   d. 75% (ACR 75)

2. In the phase III study of etanercept in patients with psoriasis, the primary endpoint (75% improvement in the Psoriasis Area and Severity Index) was achieved after 12 weeks by ____ of the patients who received the standard dose of the drug (25 mg twice weekly).
   a. 14%
   b. 24%
   c. 34%
   d. 44%

3. Of the following, the most appropriate measure of quality of life in a patient with psoriasis is:
   a. Dermatology Life Quality Index
   b. Health Assessment Questionnaire
   c. Psoriasis Area and Severity Index
   d. Short Form-36

4. All of the following are key actions of tumor necrosis factor except:
   a. Downregulation of interleukin-1
   b. Increased expression of metalloproteinases
   c. Induction of increased expression of adhesion molecules
   d. Upregulation of vascular endothelial growth factor

5. To qualify for enrollment in the Study of Psoriasis With Infliximab (Remicade) Induction Therapy (SPIRIT) trial, patients were required to have a 6-month history of plaque psoriasis, involvement of 10% or greater body surface area, and a minimum baseline Psoriasis Area and Severity Index score of:
   a. 2
   b. 12
   c. 22
   d. 32

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