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PSORIASIS (J WU, SECTION EDITOR)

# TNF Inhibitors for Psoriasis and Psoriatic Arthritis

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**Abstract**
*Purpose of Review* A growing body of research highlights the use of TNF inhibitors in the treatment of psoriasis and psoriatic arthritis. We aim to review the literature, compile psoriasis efficacy data for TNF inhibitors, and offer advice regarding the approach to treating this condition.
*Recent Findings* The results of randomized placebo-controlled studies indicate that TNF inhibitors are efficacious and well tolerated in the treatment of psoriasis. There is a greater prevalence of anxiety, depression, cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, fatty liver disease, metabolic syndrome, and inflammatory bowel disease in psoriasis patients than in the general population. Severe psoriasis portends an increased risk of mortality.
*Summary* Although patients with mild-to-moderate psoriasis do not have an increased mortality rate, the inherent inflammatory nature of psoriasis and its association with serious comorbid conditions may warrant the use of systemic medications, such as TNF inhibitors.

**Keywords** Psoriasis · Psoriatic arthritis · Biologics · Tumor necrosis factor · Treatment · Comorbidities · Inflammation

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## Introduction

Psoriasis is a chronic, inflammatory disease with both dermatologic and systemic manifestations. Biologics targeting TNF-alpha, interleukin (IL)-17, IL-12, and IL-23 have revolutionized our approach to treating psoriasis [1]. Though these immunomodulators pose some risk and require periodic monitoring, risk-benefit analysis often favors their use. A growing body of research highlights the use of TNF inhibitors including etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol in the treatment of psoriasis and psoriatic arthritis. Etanercept, adalimumab, and infliximab are approved by the Food and Drug Administration (FDA) for use in psoriasis and psoriatic arthritis. Certolizumab pegol and golimumab are approved for use in psoriatic arthritis. We aim to review the literature to compile psoriasis efficacy data for these TNF inhibitors and offer advice regarding the approach to treating this condition.

## Structure and Mechanism of Action

Etanercept is a dimeric fusion protein that consists of two domains of the human p75 TNF receptor combined with the Fc portion of IgG1. It inhibits TNF binding to cell surface receptors [2, 3]. Infliximab is a chimeric monoclonal antibody that binds to both soluble and transmembrane TNF-alpha with high affinity and specificity. It is composed of the constant regions of human IgG1 that is coupled to the variable regions of a mouse anti-TNF-alpha monoclonal antibody. It prevents binding of TNF-alpha to the TNF receptor [3, 4]. Adalimumab is a human anti-TNF-alpha monoclonal antibody which binds with high affinity to soluble and transmembrane TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors [3]. Golimumab is a human anti-TNF-alpha

monoclonal antibody that targets and neutralizes soluble and membrane-bound TNF-alpha [3]. Certolizumab pegol is a TNF inhibitor composed of a humanized Fab fragment fused to a polyethylene glycol (PEG) moiety. The PEG component increases the products circulating half-life. The product recognizes and neutralizes the soluble and membrane-bound forms of human TNF [3, 5•]. Each of these TNF inhibitors prevents the TNF-alpha-induced pro-inflammatory activity, which is present in psoriasis and other immune-mediated inflammatory conditions (Fig. 1, Table 1).

**Table 1** Molecular structure of TNF-α inhibitors

| TNF-α inhibitors | Structural components |
|---|---|
| Etanercept | Human TNFR2, human IgG1 Fc |
| Infliximab | Murine Fv, human IgG1 Fc |
| Adalimumab | Human Fv, human IgG1 Fc |
| Golimumab | Human Fv, human IgG1 Fc |
| Certolizumab pegol | Humanized Fv Fab, PEG moiety |

Structural components of etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol

*Fab* fragment antigen binding, *Fc* fragment crystallizable, *Fv* fragment variable, *PEG* polyethylene glycol, *TNF-α* tumor necrosis factor alpha

## Efficacy and Tolerability

### Etanercept

Etanercept is effective in reducing the clinical manifestations of psoriatic arthritis and psoriasis. A 12-week, randomized, double-blinded, placebo-controlled study assessing the efficacy and safety of a twice-weekly subcutaneous injection of etanercept 25 mg noted improvement in psoriatic arthritis and psoriasis. Study endpoints included meeting Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks, American College of Rheumatology 20% improvement criteria (ACR20) at 12 weeks, and 75% improvement from baseline in the Psoriasis Area and Severity Index score (PASI75) at 12 weeks. The PsARC endpoint was achieved in 87% of the subjects in the etanercept-treated group and 23% of the subjects in the placebo-treated group. The ACR20 endpoint was achieved in 73% of the subjects in the etanercept-treated group and 13% of the subjects in the placebo-treated group. The PASI75 endpoint was reached in 26% of the subjects in the etanercept-treated group, compared to none of the subjects in the placebo-treated group ($p = 0.015$). The median PASI improvement was 46% in the etanercept-treated group compared to 9% in the placebo-treated group. Etanercept was well tolerated in this cohort [6].

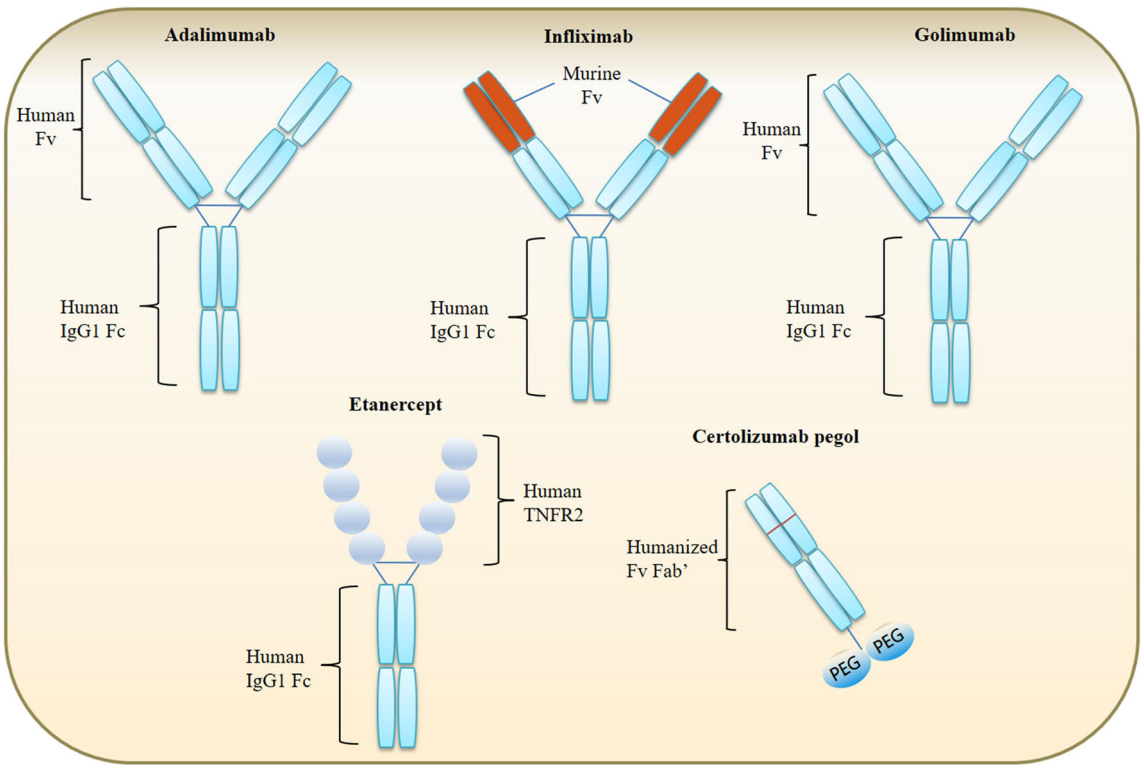


**Fig. 1** The molecular structure of five TNF-α inhibitors. Adalimumab and golimumab both contain similar human IgG1 Fc and Fv portions. Infliximab contains the variable regions of a mouse anti-TNF-alpha monoclonal antibody alongside its constant human IgG1 Fc. Etanercept contains a constant human IgG1 Fc region as well as a TNFR2 region. Certolizumab pegol contains a PEGylated humanized Fab' region. *Fab* fragment antigen binding, *Fc* fragment crystallizable, *Fv* fragment variable, *PEG* polyethylene glycol, *TNF-α* tumor necrosis factor alpha

A randomized, double-blinded, placebo-controlled study assessing the safety and efficacy of etanercept in the treatment of plaque psoriasis noted reduction in disease severity over a 24-week time period. Subjects were randomized to receive placebo, low dose of etanercept (25 mg/week), medium dose of etanercept (25 mg twice weekly), or high dose of etanercept (50 mg twice weekly) during the first 12 weeks of the study. Subjects in the placebo group crossed over to receiving a medium dose of etanercept during the last 12 weeks of the study. The primary outcome measure was PASI75. Of the patients that received a low dose, medium dose, or high dose of etanercept, 14, 34, and 49% reached PASI75 at 12 weeks, respectively. In the placebo-treated group, just 4% of subjects reached PASI75 at 12 weeks ($p < 0.001$). Etanercept was generally well tolerated in this cohort [7].

A 24-week, randomized, double-blinded, placebo-controlled study assessing the efficacy, safety, and effect on radiographic progression of etanercept in patients with psoriatic arthritis noted reduction in the signs and symptoms of psoriatic arthritis and psoriasis. A total of 205 subjects were enrolled; 101 subjects received etanercept 25 mg twice weekly, and 104 subjects received placebo. Primary study endpoints assessing etanercept efficacy in psoriatic arthritis and psoriasis were ACR20 and PASI75. In the group that received etanercept, 59% achieved ACR20 at 12 weeks compared to 15% in the placebo group ($p < 0.0001$). Of the subjects who were eligible for psoriasis evaluation, 23% of the subjects in the etanercept group achieved PASI75, compared to 3% in the placebo-treated group ($p = 0.001$). Etanercept was well tolerated in this study cohort [8]. In a phase III, multicenter, randomized controlled trial assessing the safety and efficacy of etanercept, subjects were randomized to receive etanercept 25 mg twice weekly (BIW), etanercept 50 mg BIW, or placebo. PASI75 was achieved at week 12 in 49, 34, and 3% of subjects in the etanercept 50 mg, etanercept 25 mg, and placebo group, respectively [9]. In a pediatric study assessing the efficacy and safety of etanercept, subjects aged 4 to 17 with moderate-to-severe plaque psoriasis were randomized to receive etanercept 0.8 mg/kg weekly (QW) or placebo. PASI75 was achieved at 12 weeks in 57 and 11% of subjects in the etanercept group and placebo group, respectively [10] (Table 2).

## Infliximab

Infliximab is an effective treatment for psoriasis and psoriatic arthritis. In a randomized, double-blind, placebo-controlled study of 33 subjects with moderate to severe plaque psoriasis, participants were randomized to receive intravenous placebo, intravenous infliximab 5 mg/kg, or intravenous infliximab 10 mg/kg at weeks 0, 2, and 6 and were clinically assessed at week 10. The primary endpoint was Physician's Global Assessment (PGA) of "good," "excellent," or "clear." Eighty-two percent of subjects treated with the 5 mg/kg infliximab dose, 91% of subjects treated with the 10 mg/kg infliximab dose, and 18% of subjects in the placebo group achieved a good, excellent, or clear rating on PGA over a 10-week period. There were no serious adverse events; infliximab was well tolerated in this cohort [11].

In an open-label, randomized, active-controlled trial comparing the efficacy of infliximab versus methotrexate in the treatment of moderate-to-severe plaque psoriasis, infliximab was superior in efficacy and was efficacious in subjects who initially failed methotrexate. Subjects were randomized to receive infliximab 5 mg/kg at weeks 0, 2, 6, 14, and 22 or methotrexate 15 mg weekly. Subjects in the methotrexate group were allowed to increase dose to 20 mg weekly after 6 weeks if PASI was less than 25% and switch to the infliximab group at week 16 if PASI was less than 50%. The primary efficacy endpoint was PASI75 response at week 16. This endpoint was achieved in 78% of infliximab-treated subjects and 42% of methotrexate-treated subjects ($p < 0.001$). The overall incidence of adverse events was similar between the methotrexate and infliximab groups; however, serious adverse event incidence was slightly higher in the infliximab group [12].

In a 46-week, phase III, randomized, double-blinded, placebo-controlled, multicenter trial, the efficacy of infliximab induction and maintenance regimens were assessed in subjects with moderate-to-severe plaque psoriasis. Subjects were randomized to receive either infliximab 5 mg/kg or placebo at weeks 0, 2, and 6 and every 8 weeks until 46 weeks. Subjects in the placebo group crossed over to infliximab treatment at week 24. The primary endpoint was 75% improvement from baseline PASI. Eighty percent of subjects treated with infliximab and 3% of subjects in the placebo group achieved PASI75 at week 10 ($p < 0.0001$). Eighty-two percent of subjects treated with infliximab and 4% of subjects in the placebo group achieved PASI75 at week 24 ($p < 0.0001$). Infliximab was well tolerated in the majority of patients [13] (Table 2).

## Adalimumab

Adalimumab has utility in the treatment of both psoriasis and psoriatic arthritis. In a randomized, double-blinded, placebo-controlled trial assessing the efficacy and safety of adalimumab in the treatment of active psoriatic arthritis, subjects were randomized to receive subcutaneous injections of adalimumab 40 mg or placebo every other week for 24 weeks. Relevant endpoints were ACR20 and PASI75. Fifty-eight percent of subjects in the adalimumab group and 14% of subjects in the placebo group achieved ACR20 at week 12 ($p < 0.001$). Fifty-nine percent of subjects in the adalimumab group, who were eligible for evaluation with PASI, achieved PASI75 at week 24, compared to just 1% in the placebo group ($p < 0.001$). Adalimumab was generally well tolerated in study subjects [14]. In a randomized, placebo-controlled

**Table 2** Efficacy of TNF inhibitors in psoriasis and psoriatic arthritis

| Drug | Reference; year | Patient characteristics | Number of subjects | Study duration | Study regimen | Study design | Endpoints | Results |
|---|---|---|---|---|---|---|---|---|
| Etanercept | Mease; 2000 | Psoriatic arthritis; psoriasis | 60 | 12 weeks | Etanercept 25 mg SC BIW | R, DB, PC | PsARC at week 12<br>ACR20 at week 12<br>PASI75 at week 12 | PsARC—87% of etanercept group; 23% of placebo group at 12 weeks<br>ACR20—73% of etanercept group; 13% of placebo group<br>PASI75—26% of etanercept group; 0% of placebo group ($p = 0.015$) |
| | Leonardi; 2003 | Psoriasis | 652 | 24 weeks | Etanercept 25 mg SC QIW (low dose)<br>Etanercept 25 mg SC BIW (medium dose)<br>Etanercept 50 mg SC BIW (high dose) | R, DB, PC | PASI75 at week 12 | PASI75—14% of low dose group; 34% of medium-dose group; 49% of high-dose group ($p < 0.001$) |
| | Mease; 2004 | Psoriatic arthritis; psoriasis | 205 | 24 weeks | Etanercept 25 mg SC BIW | R, DB, PC | ACR20 at week 12<br>PASI75 at week 12 | ACR20—59% of etanercept group; 15% of placebo group ($p < 0.0001$)<br>PASI75—23% of etanercept group; 3% of placebo group ($p = 0.001$) |
| | Papp; 2005 | Stable plaque psoriasis | 583 | 24 weeks | Etanercept 25 mg BIW<br>Etanercept 50 mg BIW<br>Placebo | R, DB, PC | PASI75 at week 12 | PASI75—49% of etanercept 50-mg group; 34% of etanercept 25-mg group; 3% of placebo group |
| | Paller; 2008 | Moderate-to-severe psoriasis | 211 | 48 weeks | Etanercept 0.8 mg/kg QW<br>Placebo | R, DB, PC | PASI75 at week 12 | PASI75—57% of etanercept group; 11% of placebo group |
| Infliximab | Chaudhari; 2001 | Psoriatic arthritis; psoriasis | 33 | 10 weeks | Infliximab 5 mg/kg IV at weeks 0, 2, and 6<br>Infliximab 10 mg/kg IV at weeks 0, 2, 6 | R, DB, PC | PGA of "good," "excellent," or "clear" at week 10 | PGA of "good," "excellent," or "clear"; 82% of 5 mg/kg infliximab group; 91% of 10 mg/kg infliximab group |
| | Reich; 2005 | Moderate-to-severe plaque psoriasis | 378 | 46 weeks | Infliximab 5 mg/kg IV at weeks 0, 2, and 6, then every 8 weeks | R, DB, PC | PASI75 at week 10 | PASI75—80% of infliximab group; 3% of placebo group ($p < 0.0001$) |
| | Barker; 2011 | Moderate-to-severe plaque psoriasis | 868 | 22 weeks | Infliximab 5 mg/kg IV at weeks 0, 2, 6, 14, and 22<br>Methotrexate 15 mg QIW | R, OL, AC | PASI75 at week 16 | PASI75—78% of infliximab group; 42% of methotrexate group ($p < 0.001$) |
| Adalimumab | Mease; 2005 | Psoriatic arthritis; psoriasis | 313 | 24 weeks | Adalimumab 40 mg SC QOW | R, DB, PC | ACR20 at week 12<br>PASI75 at week 24 | ACR20—58% of adalimumab group; 14% of placebo group ($p < 0.001$)<br>PASI75—59% of adalimumab group; 1% of placebo group ($p < 0.001$) |
| | Menter; 2008 | Moderate-to-severe plaque psoriasis | 1212 | 16 weeks | Adalimumab 40 mg SC QOW | R, PC | PASI75 at week 16 | PASI75—71% of adalimumab group; 7% of placebo group |
| | Strober; 2011 | Psoriasis patients; suboptimal response to etanercept, methotrexate, or NBUVB | 152 | 16 weeks | Adalimumab 80 mg at week 0, then 40 mg QIW | OL | PGA of "clear" or "minimal" at week 16 | PGA "clear" or "minimal" 52% of subjects |
| Golimumab | Kavanaugh; 2009 | Psoriatic arthritis; psoriasis | 405 | 20 weeks | Golimumab 50 mg SC Q4W | R, PC | ACR20 at week 14<br>PASI75 at week 14 | ACR20—48% of golimumab group; 9% of placebo group |

**Table 2** (continued)

| Drug | Reference; year | Patient characteristics | Number of subjects | Study duration | Study regimen | Study design | Endpoints | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | Golimumab 100 mg SC Q4W | | | PASI75—40% of golimumab 50-mg group; 58% of golimumab 100-mg group; 3% of placebo group |
| | Kavanaugh; 2013 | Psoriatic arthritis; psoriasis | 405 | 2 years | Golimumab 50 mg SC Q4W<br>Golimumab 100 mg SC Q4W | R, PC | ACR20 at week 104<br>PASI75 at week 104 | ACR20—63–70% of golimumab group<br>PASI75—56–72% of golimumab group |
| Certolizumab pegol (CZP) | Reich; 2012 | Moderate-to-severe plaque psoriasis | 176 | 12 weeks | CZP 400 mg SC at week 0, then CZP 200 mg QOW<br>CZP 400 mg SC at week 0, then CZP 400 mg QOW<br>CZP 400 mg SC at week 0, then placebo QOW | R, DB, PC | PASI75 at week 12 | PASI75—75% of CZP 400 mg/200-mg group; 83% of CZP 400 mg/400 mg; 7% of CZP 400 mg/placebo group |

Efficacy studies detailing the utility of TNF inhibitors in the treatment of psoriasis and psoriatic arthritis

*R* randomized, *DB* double-blinded, *OL* open label, *PC* placebo-controlled, *AC* active-controlled, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *QIW* once weekly, *QOW* every other week, *BIW* twice weekly, *SC* subcutaneous injection, *IV* intravenous injection, *PGA* Physician's Global Assessment, *PsARC* Psoriatic Arthritis Response Criteria, *ACR20* American College of Rheumatology 20% improvement criteria, *PASI75–75%* improvement from baseline in the Psoriasis Area and Severity Index score, *NBUVB* Narrowband ultraviolet B therapy

phase III trial assessing its efficacy and safety in patients with moderate-to-severe psoriasis, adalimumab was efficacious and well tolerated. Subjects were randomized to receive adalimumab 40 mg or placebo every other week for 15 weeks. Primary endpoint was PASI75. Seventy-one percent of the adalimumab group and 7% of the placebo group achieved PASI75 by week 16 [15]. In a 16-week, phase IIIb, open-label study evaluating the efficacy and safety of adalimumab in psoriasis patients with prior suboptimal response to etanercept, methotrexate, or narrowband (NB) ultraviolet (UV) B therapy, subjects who had a suboptimal response to these other treatment options had a 50% likelihood of achieving optimal response to adalimumab. Study participants had either discontinued suboptimal etanercept between 11 and 17 days or suboptimal methotrexate or UVB between 4 and 10 days prior to starting adalimumab 80 mg at week 0 and 40 mg per week thereafter for 16 weeks. The primary endpoint was achievement of a PGA rating of clear or "minimal." Fifty-two percent of study subjects achieved this endpoint by 16 weeks [16] (Table 2).

## Golimumab

The efficacy of golimumab in the treatment of psoriasis and psoriatic arthritis has been well documented in the literature. A randomized, placebo-controlled study assessing golimumab efficacy and safety in patients with active psoriatic arthritis established efficacy in the study cohort. Patients were randomized to receive subcutaneous injection of placebo, golimumab 50 mg, or golimumab 100 mg every 4 weeks for 20 weeks. Primary study endpoints included ACR20 and PASI. Forty-eight percent of subjects who received golimumab and 9% of subjects who received placebo reached ACR20 at week 14 ($p < 0.001$). Forty percent and 58% of subjects reached PASI75 by week 14 in the golimumab 50 mg and golimumab 100 mg groups, respectively. Only 3% of the placebo group reached this endpoint ($p < 0.001$) Golimumab was generally well tolerated in study subjects [17]. A 2-year long, randomized, placebo-controlled study assessed the clinical efficacy, radiographic findings, and safety findings of golimumab in patients with active psoriatic arthritis. Subjects were randomized to receive placebo, golimumab 50 mg, or golimumab 100 mg every 4 weeks for 20 weeks. After 24 weeks, all subjects would receive either golimumab 50 mg or golimumab 100 mg. Primary endpoints included ACR20 and PASI75. PASI75 was achieved at 104 weeks in 56–72% of golimumab recipients. ACR20 was achieved at 104 weeks in 63–70% of patients in the golimumab treatment group [18••] (Table 2).

## Certolizumab Pegol

Certolizumab pegol is efficacious in the treatment of psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-

controlled study evaluating efficacy and safety of certolizumab pegol in the treatment of moderate-to-severe plaque psoriasis noted improved psoriasis in the certolizumab pegol treatment groups. Primary endpoint was PASI75 at week 12. Subjects were randomized to receive placebo or certolizumab pegol 400 mg at week 0 followed by placebo or certolizumab (200 or 400 mg) every other week for 10 weeks. Seventy-five percent, 83%, and 7% of subjects achieved PASI75 in the certolizumab pegol 200 mg, certolizumab pegol 400 mg, and placebo group at week 12, respectively ($p < 0.001$) [19].

In a randomized, placebo-controlled study assessing the efficacy and safety of certolizumab pegol in patients with psoriatic arthritis, subjects were randomized to receive certolizumab pegol 200 mg every 2 weeks (Q2W), 400 mg every 4 weeks (Q4W), or placebo. Primary endpoints included ACR20 at week 12 and modified total sharp score change from baseline (mTSS) at week 24. ACR20 response was 58.0, 51.9, and 24.3% in Q2W group, Q4W group, and placebo group, respectively ($p < 0.001$) [20••] (Table 2).

TNF inhibitors are generally safe and tolerable in adults with moderate-to-severe psoriasis. Though some patients did report adverse events during clinical trials, these events could not be directly attributed to the TNF inhibitor and may have been the result of an underlying comorbidity. Rarely reported adverse effects included opportunistic infection, latent tuberculosis reactivation, demyelinating disorder onset or exacerbation, psoriasis onset or exacerbation, lymphoma, drug-induced lupus, congestive heart failure, liver toxicity, hematologic abnormalities, and anaphylaxis. Common adverse effects included headaches, upper respiratory tract infections, cellulitis, urticaria, injection site reactions, subclinical elevated liver enzymes, and pruritus. Due to the potential causative relationship between TNF inhibitors and the aforementioned adverse events, procurement of a comprehensive patient history and patient education are crucial prior to prescribing these medications [21].

## Conclusions

Psoriasis is a chronic inflammatory disorder with both cutaneous and systemic manifestations. Recent research has uncovered the association of psoriasis with several medical conditions. Metabolic syndrome, which includes features such as central obesity, insulin resistance, dyslipidemia, and hypertension, predisposes patients to developing cardiovascular disease [22•]. The greater the severity of psoriasis, the greater the association with metabolic syndrome [23]. There is a direct relationship between the risk of cardiovascular disease and the severity of psoriasis [24•]. There is a greater prevalence of anxiety, depression, cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, fatty liver disease, metabolic syndrome, and inflammatory bowel disease in psoriasis patients compared to the general public [25, 26•]. It is unclear whether this association is due to the systemic inflammatory mediators generated in psoriasis or shared risk factors. Modern pharmacotherapy research has dramatically improved the psoriasis armamentarium. Limited disease is typically managed with topical medications. In patients with more extensive involvement, topical medications may be used, but patients may opt for oral and injectable medications with systemic activity. We highlight the efficacy and tolerability of TNF inhibitors in the treatment of psoriasis. These medications allow practitioners to target the underlying inflammatory nature of psoriasis on a molecular level. Targeting TNF-alpha not only curbs cutaneous inflammation but also controls the systemic inflammation associated with psoriasis. Biologic medications have revolutionized how we approach the treatment of psoriasis. The morbidity associated with psoriasis is well documented and frequently discussed. Now, with research highlighting the potential cardiovascular and metabolic impact of psoriasis, a discussion on the mortality of psoriasis is appropriate. Severe psoriasis is associated with an increased risk of death; this finding persisted after adjustment for risk factors of mortality [27]. Although patients with mild-to-moderate psoriasis do not have an increased mortality rate, the inherent inflammatory nature of psoriasis and its association with serious comorbid conditions may warrant the use of systemic medications even in this patient group. Aggressive treatment of psoriasis is prudent; TNF inhibitors and other biologics present a highly efficacious treatment option with a relatively favorable side effect profile.

### Compliance with Ethical Standards

**Conflict of Interest** Steven Feldman declares research, speaking, and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Baxter, Boeringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Taro, Abbvie, Cosmederm, Anacor, Astellas, Janssen, Lilly, Merck, Merz, Novartis, Regeneron, Novan, Parion, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. Dr. Feldman also consults for others through Guidepoint Global, Gerson Lehrman, and other consulting organizations. Dr. Feldman is founder and majority owner of www.DrScore.com. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment.

Leah A. Cardwell, Brandy Sullivan, Emilia Baran, and Elias Oussedik declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance


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