

TNF inhibitors for psoriasis

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■ Abstract

Tumor necrosis factor (TNF)- α has been identified as a key cytokine mediating cutaneous inflammation in the pathogenesis of psoriasis. The TNF inhibitors (TNFi's) infliximab, adalimumab, and etanercept are efficacious, Food and Drug Administration-approved medications for the treatment of moderate-to-severe plaque psoriasis. Each drug has a unique pharmacological profile that can have therapeutic implications when choosing a particular TNFi for a patient. An understanding of these idiosyncrasies can help guide therapeutic decisions for patients with psoriasis that also have inflammatory bowel disease, hepatitis C, hepatitis B, latent tuberculosis, obesity, cardiovascular disease, and heart failure. It can also help when selecting the right treatment for pregnant patients, children and adolescents, or those with insurance constraints or compliance issues.

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In psoriasis, tumor necrosis factor (TNF)- α has been identified as a key cytokine mediating cutaneous inflammation in the pathogenesis. Derived from activated dendritic cells, keratinocytes, T helper 1 cells, and T helper 17 cells, TNF- α is increased in psoriatic skin versus healthy controls.¹ It has therefore become an important target for the treatment of psoriasis. Currently, there are 3 TNF- α inhibitors (TNFis) Food and Drug Administration (FDA) approved for the treatment of moderate-to-severe psoriasis: infliximab, adalimumab, and etanercept. Each drug has a different pharmacological profile that can have clinical implications when deciding which one to choose for a given patient.

We will discuss the pivotal trials behind these 3 medications and 2 additional TNFis not approved for treatment of psoriasis but that have shown efficacy in treating psoriasis. We will also discuss specific patient scenarios in which we feel certain TNFis are stronger therapeutic choices than others (Table).

Infliximab

Infliximab (Remicade; Janssen Biotech, Inc., Horsham, Pennsylvania) is a chimeric (75% human and 25% mouse) immu-

noglobulin G1 (IgG1) monoclonal antibody that both blocks membrane-bound TNF- α and neutralizes soluble TNF- α . It is given by infusion. Its efficacy for use in plaque psoriasis has been assessed in 3 randomized, double-blind, placebo-controlled clinical trials in adults with chronic, stable plaque psoriasis of $\geq 10\%$ body surface area (BSA). These subjects were candidates for systemic therapy or phototherapy and had a minimum Psoriasis Area and Severity Index (PASI) score of 12. The proportion of patients achieving a reduction in PASI score of at least 75% (PASI 75) at week 10 was the common primary endpoint of the studies.

The EXPRESS I study evaluated 378 subjects who were randomized to receive infliximab 5 mg/kg at weeks 0, 2, and 6 for induction, and then every 8 weeks after that for maintenance (n = 301), or placebo (n = 77). Patients who were randomized to placebo crossed over in a double-blind fashion at week 24 to receive both induction and maintenance therapy. Both groups continued to receive infliximab until week 46 and were followed until week 50. Significantly more patients in the infliximab group achieved PASI 75 (80%) versus placebo (3%) at week 10. More than half (57%) of patients in the active treatment arm achieved PASI 90 by week 10 compared to placebo (1%). Notably, there was a very rapid, significant difference in PASI 50 scores between the treatment groups as early as week 2 and in PASI 75 by week 6. Of the 80% of patients assigned to infliximab who achieved PASI 75 by week 10, 71% continued to have a PASI 75 until week 50.²

The EXPRESS II trial evaluated the efficacy of infliximab 3 mg/kg and 5 mg/kg versus placebo. It also evaluated different maintenance dosing in the 835 patients enrolled. At baseline, subjects were randomized to receive infliximab 5 mg/kg, 3 mg/kg, or placebo at weeks 0, 2, and 6 as induction therapy. Those who were randomized to receive either dose of active treatment were then randomized to receive either scheduled (every 8 weeks) or as needed (prn) maintenance therapy at week 14 through week 46. Subjects assigned to placebo at baseline crossed over to infliximab 5 mg/kg for induction and maintenance therapy. At week 10, 75% of the 5-mg/kg group, 70% of the 3-mg/kg group, and 2% of the placebo group achieved PASI 75. Those receiving infliximab who achieved PASI 75 by week 10 were most likely to maintain this PASI 75 response to week 50 if they received scheduled maintenance dosing versus prn dosing. The best response was in those receiving scheduled maintenance with 5 mg/kg.³

The SPIRIT trial evaluated 249 patients who were randomized to receive infliximab 3 mg/kg, 5 mg/kg, or placebo at weeks 0, 2, and 6. By week 10, 88% of the 5-mg/kg group and 72% of the 3-mg/kg group achieved PASI 75 compared to 6% of the placebo group. These subjects did not receive maintenance therapy, and the majority of the treatment groups maintained PASI 75 for 3 to 4 months.⁴

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TABLE. Selected TNFi prescriber information

Drug	Dose for Adult Psoriasis	Contraindications	Most Common Reactions	Selected Warnings	Drug Interactions
Etanercept	50 mg twice weekly for 3 months, followed by 50 mg once weekly	Sepsis	(>5%) Infections, injection site reactions	Serious infection, invasive fungal infection, demyelinating disease, lymphoma and other malignancies, congestive heart failure, cytopenia and aplastic anemia, hepatitis B reactivation, lupus-like syndrome	Abatacept, anakinra, live vaccines
Adalimumab	80-mg initial dose, followed by 40 mg every other week starting 1 week after initial dose	None	(>10%) Infections (eg, upper respiratory, sinusitis), injection site reactions, headache, rash		
Infliximab	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks	>5 mg/kg in moderate-to-severe heart failure, previous hypersensitivity to inactive components or to any murine proteins	(>10%) Infections (eg, upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, abdominal pain		

Note: This is not a complete list of adverse events and warnings.

ABBREVIATION: TNFi, tumor necrosis factor inhibitor.

Etanercept

Etanercept (Enbrel; Immunex Corporation, Thousand Oaks, California) is a fully humanized, dimeric fusion protein that also targets membrane-bound and soluble TNF- α . It is a subcutaneous injection. Two large double-blind, placebo-controlled studies have demonstrated its efficacy in chronic, stable, moderate-to-severe plaque psoriasis for patients with $\geq 10\%$ BSA and a PASI of at least 10. The common primary endpoint for both studies was proportion of subjects achieving PASI 75 after 3 months.

In the first study, 652 subjects received placebo, 25 mg once weekly, 25 mg twice weekly, or 50 mg twice weekly for 3 months. After 3 months, subjects assigned to active treatment continued for an additional 3 months. Those randomized to placebo crossed over to receive 25 mg twice weekly for the next 3 months. At 3 months, 47% of the 50-mg-twice-weekly group, 32% of the 25-mg-twice-weekly group, and 14% of the 25-mg-weekly groups achieved PASI 75 compared to placebo (4%). At 6 months, 59% of the 50-mg-twice-weekly group, 44% of the 25-mg-twice-weekly group, and 25% of the 25-mg-once-weekly group achieved PASI 75.⁵

The second study of 583 patients yielded similar results. Subjects were randomized to receive 25 mg twice weekly, 50 mg twice weekly, or placebo for 3 months. Then, all groups received open-label etanercept 25 mg twice weekly for 9 months. Forty-six percent of the 50-mg-twice-weekly and 32% of the 25-mg-twice-weekly groups achieved PASI 75 by 3 months compared to placebo (3%). Of those achieving PASI 75 in the high-dose group at week 12, 77% maintained PASI 75 by week 24 despite having their etanercept dose de-escalated to 25 mg twice weekly in the open-label phase.⁶

Although the primary endpoint for both studies was at week 12, the median time to achieving PASI 75 was approximately 2 months. Additionally, the median time to PASI 50 was approximately 1 month. This was seen for all doses studied.

Adalimumab

Adalimumab (Humira; AbbVie, Inc., North Chicago, Illinois) is a fully human recombinant monoclonal antibody to TNF- α and prevents TNF- α interaction with either p55 or p75 TNF receptor. Its efficacy in the treatment of plaque psoriasis has been assessed in 2 large randomized, double-blinded, placebo-controlled clinical trials for patients with chronic, moderate-to-severe psoriasis affecting more than 10% BSA and a PASI of at least 12. The proportion of patients achieving PASI 75 at week 16 was the common primary endpoint of both studies.

In the REVEAL trial, 1,212 patients were randomized to receive adalimumab or placebo in 3 treatment periods. During treatment period A, subjects received placebo or adalimumab 80 mg at week 0, then 40 mg every other week starting week 1 for 16 weeks. At week 16, those achieving PASI 75 entered into open-label period B to receive adalimumab 40 mg every other week for 17 weeks until week 33. At that time, those who maintained PASI 75 entered treatment period C and were randomized to continue receiving adalimumab 40 mg every other week or placebo for the next 19 weeks. Those who did not achieve PASI 75 at week 16 entered an open-label phase to receive 40 mg every other week for the remainder of the study. At week 16, significantly more subjects in the treatment group achieved PASI 75 (71%) compared to placebo (7%). For those who qualified to continue to

treatment period C and were randomized to placebo, the median time to relapse was 5 months.⁷

The second study randomized 99 patients to receive adalimumab 80 mg at week 0, followed by 40 mg every other week from weeks 1 to 16, and 48 patients to placebo. PASI 75 was achieved by 78% of the active treatment group compared to 19% in the placebo group.⁸

Other TNFis

Certolizumab (Cimzia; UCB Inc., Smyrna, Georgia) is a humanized PEGylated monoclonal antibody targeted against TNF- α currently approved for use in rheumatoid arthritis, Crohn disease (CD), ankylosing spondylitis, and psoriatic arthritis. Phase 2 studies have been promising in showing its efficacy^{9,10} in plaque psoriasis, and phase 3 studies are currently underway.¹¹⁻¹³

Golimumab (Simponi; Janssen Biotech, Inc.) is another TNFi that is not currently approved for plaque psoriasis. This human IgG1 monoclonal antibody binds both soluble and transmembrane forms of TNF- α and is currently approved for ankylosing spondylitis, rheumatoid arthritis in combination with methotrexate, and psoriatic arthritis with or without methotrexate. In a large phase 3, randomized, double-blind, placebo-controlled trial for psoriatic arthritis, patients received monthly injections of golimumab 50 mg, 100 mg, or placebo for 20 weeks. Randomization was stratified by baseline methotrexate use. Patients with psoriatic skin involvement of at least 3% BSA at baseline were assessed for PASI 75 at week 14 as a major secondary endpoint. Of the 74% of patients with at least 3% BSA skin involvement, 40% receiving golimumab 50 mg and 58% receiving 100 mg achieved PASI 75 by week 14 (3% in placebo group). This improvement was not significantly influenced by methotrexate use.¹⁴

Children and adolescents

For pediatric patients with psoriasis requiring systemic therapy, we almost always choose etanercept when using a TNFi. It is the only TNFi approved for children in the United States. A randomized, double-blind, placebo-controlled clinical trial has been conducted to demonstrate its efficacy in this population. In this study, 211 children with psoriasis (4 to 17 years old) were randomized to receive placebo or etanercept 0.8 mg/kg (up to a maximum of 50 mg) weekly for 12 weeks. Subjects then received open-label etanercept of the same dose weekly for 24 weeks. A second randomization was performed at week 36 to investigate withdrawal and retreatment. Significantly more patients receiving etanercept (57%) achieved PASI 75 by week 12 than placebo (11%), which was the study's primary endpoint.¹⁵

Similar efficacy has been reported for adalimumab, which was approved by the European Medicines Agency for use in severe pediatric psoriasis. In a phase 3 trial of 4- to 17-year-olds with severe psoriasis, patients were randomized to receive adalimumab 0.8 mg/kg (up to 40 mg), 0.4 mg/kg (up to 20 mg), or methotrexate 0.1 to 0.4 mg/kg (up to 25 mg). Adalimumab was dosed at week 0, week 1, and then every other week. Methotrexate was dosed weekly. One of the primary endpoints was PASI 75 at week 16. Significantly more patients achieved PASI 75 in the adali-

mumab 0.8-mg/kg group (58%) than in the methotrexate group (32%) at week 16. Forty-four percent of patients who received adalimumab 0.4 mg/kg achieved PASI 75; however, this was not significant compared to methotrexate.¹⁶ There has been one case of successful treatment for a 13-year-old female treated with infliximab 3.3 mg/kg at weeks 0, 2, 6, and then every 8 weeks,¹⁷ and there has been one for a 14-year-old male successfully treated with 5 mg/kg after failing etanercept.¹⁸

In summary, etanercept and adalimumab have similar efficacy for the treatment of pediatric psoriasis. Choosing one drug over the other may be influenced heavily by geography. In the United States, only etanercept is approved, whereas both etanercept and adalimumab are approved in Europe. Although there have been case reports for infliximab, it has not been as well studied.

Psoriatic arthritis

TNFis are a good treatment options for patients with concomitant psoriatic arthritis. Etanercept, adalimumab, infliximab, golimumab, and certolizumab are all approved for use in psoriatic arthritis. Although not approved for psoriatic skin disease, golimumab has also shown to be effective for plaque psoriasis and can be a good option for patients with both skin and joint involvement (see "Other TNFis"). It is worth noting that the approved dosing of etanercept and adalimumab for psoriatic arthritis differs from their dosing for plaque psoriasis. Etanercept for psoriatic arthritis is given 50 mg once weekly, whereas for plaque psoriasis it is given 50 mg twice weekly for 3 months and then 50 mg weekly thereafter. Adalimumab for psoriatic arthritis is given 40 mg every other week versus 80 mg at week 0 followed by 40 mg every other week starting week 1 for plaque psoriasis. The dosing for infliximab is the same for both conditions.

Inflammatory bowel disease

The link between inflammatory bowel disease (IBD) and psoriasis has been described in epidemiological, genetic, and immunological studies. It is now well known that both CD and ulcerative colitis (UC) are associated with psoriasis, although a stronger relationship with CD has been described.¹⁹⁻²¹ Therapeutically, both IBD and psoriasis can be treated with TNFis, which further affirms the existence of a link between the 2 pathologies. Although TNFis have paradoxically precipitated psoriasis in some patients treated with IBD and other rheumatologic conditions,^{22,23} the concomitance of these 2 diseases is still observed even when patients have not been treated with a TNFi.¹⁹

It is therefore not uncommon to encounter patients with both IBD and psoriasis. Infliximab and adalimumab are the only TNFis approved for both IBD and psoriasis, making them the obvious choices for treatment in this case. Although not yet approved for psoriasis, certolizumab is approved for use in IBD, is efficacious in treating plaque psoriasis,^{9,10} and is another good option for treating patients with both IBD and psoriasis. Etanercept is not approved for IBD and should be avoided. Ustekinumab is approved for use in CD (not UC) and is a great option if not using a TNFi.

Uveitis

As with IBD, TNFis are a good treatment option for patients who suffer from concomitant uveitis. Uveitis broadly refers to inflammation in the midportion of the eye and can have many etiologies. The inflammation can affect different parts of the mideye and may impair vision. Noninfectious uveitis can be isolated or can be associated with other diseases. It is associated with psoriatic arthritis,²⁴⁻²⁶ roughly affecting 7% of these patients.²⁷ The association between psoriatic skin disease and uveitis is less well understood;²⁴ however, uveitis can occur in patients with isolated skin disease (without arthritis) and may be related to disease severity.^{25,28,29}

Systemic corticosteroids have been a mainstay treatment for uveitis that cannot be controlled topically³⁰; however, TNFis warrant consideration for psoriatic patients with uveitis. In particular, we favor the use of adalimumab in these patients because it is FDA approved for the treatment of noninfectious intermediate, posterior, and panuveitis. Two randomized trials demonstrated that adalimumab lowered the risk of uveitic flare or visual impairment as patients were tapering off corticosteroids.^{31,32} Etanercept and infliximab have also been used to treat noninfectious uveitis. Although infliximab has been reported to be more effective than etanercept,³³ one prospective study revealed an unusual increase in drug-induced lupus and other adverse events with infliximab for uveitis.³⁴

Latent tuberculosis

TNF has been implicated in protecting the immune system from *Mycobacterium tuberculosis*.³⁵ Therefore, the use of TNFis puts patients at risk for reactivating latent tuberculosis infection (LTBI) to active tuberculosis. Consensus guidelines suggest that all patients should be screened for LTBI prior to starting a TNFi. If a patient is found to have LTBI, he/she should complete chemoprophylaxis (typically isoniazid for 9 months). Ideally, TNFis should be delayed until then but can be initiated 1 to 2 months after starting chemoprophylaxis if the patient's condition requires it.³⁶ Reactivation of LTBI has been reported with infliximab, etanercept, and adalimumab; however, the risk is significantly higher with monoclonal antibodies adalimumab and infliximab compared to etanercept, a soluble receptor.³⁷⁻³⁹ For this reason, we typically choose etanercept when treating patients with psoriasis and TNFis for patients with LTBI. With the introduction of other biologic therapies such as anti-IL17 antibodies, we now have good alternatives to TNFis for treating patients with LTBI.

Hepatitis C

Psoriasis patients eligible to receive TNFis should be screened for hepatitis C virus (HCV) by checking for HCV antibodies.⁴⁰ In the event HCV antibodies are detected, collaboration with a hepatologist is necessary to determine whether the subject is chronically infected or has spontaneously cleared the virus after an acute infection. It is most likely that the patient will be found to have a chronic infection because 75% to 85% of people do not spontaneously clear viremia after acute infection.⁴¹ Even in the setting of chronic HCV infection, TNFis can safely be given and

may even help patients clear the infection.⁴² We favor the use of etanercept for these patients. Etanercept has been successfully used in the overwhelming majority of reported cases of HCV-infected patients with psoriasis compared to adalimumab and infliximab.⁴² Moreover, elevations of transaminases are common with the latter 2 TNFis. Additionally, etanercept was shown to have a favorable effect on the treatment of HCV in a phase 2 randomized, double-blind, placebo-controlled study in which etanercept was given as adjuvant to interferon and ribavirin for the treatment of HCV.⁴³ The patients who were treated with adjuvant etanercept had a significantly larger decline in alanine aminotransferase and viral load compared to placebo.

Hepatitis B

Prior to starting therapy with a TNFi, screening for hepatitis B virus (HBV) is recommended.⁴⁴ In the case of detection of one or more markers of HBV infection, collaboration with a hepatologist is necessary in determining the phase of HBV infection and treatment. If a patient is found to have active-phase HBV infection, any TNFi should be avoided; however, this scenario is quite rare. More frequently, patients will have serological markers indicative of previous exposure with low or undetectable viral loads. In these cases, more testing will help determine whether the patients have inactive, occult, or resolved infection. The ultimate concern is reactivation of the virus leading to fulminant liver failure, which has been reported for infliximab, adalimumab, and etanercept.⁴⁵ Although reactivation is much more likely to happen in inactive carriers as opposed to those with occult infection, the overall occurrence is rare⁴⁵ but carries significant morbidity and/or mortality if it does occur. Whether or not a patient has inactive or occult HBV, TNFis can still be used. Inactive carriers will need to delay starting a TNFi until they have had antiviral prophylaxis for 2 to 4 weeks. It is still debated whether or not occult carriers should receive antiviral prophylaxis at all, and this decision should be made with the help of a hepatologist. Additionally, it is not clear whether different TNFis carry different risks of reactivation^{45,46}; however, one study did suggest there may be a higher rate with infliximab.⁴⁷ Regardless, we usually choose to use etanercept as TNFi treatment in patients with concomitant HBV infection because it is the TNFi most frequently used in the literature.⁴² Monitoring of viral titers and liver function tests is necessary in those patients.

Needing results quickly

For patients looking for quick improvement with a TNFi, we recommend using infliximab. In clinical trials, infliximab consistently showed rapid and significant improvement from baseline PASI scores as early as 2 weeks (Figures 1 and 2).²

Obesity

Because there is a higher prevalence of obesity in patients with psoriasis than without,⁴⁸⁻⁵⁰ and because obese patients tend to have more severe psoriasis than those with normal body mass indices (BMIs), many obese patients will require systemic treatments for their psoriasis. Obesity itself has been implicated in



■ **FIGURE 1.** Lower-limb psoriasis prior to treatment with infliximab. Reprinted from: Tan M, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of pyoderma gangrenosum and psoriasis associated with crohn disease with anti-tumor necrosis factor α monoclonal antibody. *Arch Dermatol.* 2001;137(7):930-933.



■ **FIGURE 2.** Resolved lower-limb psoriasis after 5 infliximab treatments. Reprinted from: Tan M, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of pyoderma gangrenosum and psoriasis associated with crohn disease with anti-tumor necrosis factor α monoclonal antibody. *Arch Dermatol.* 2001;137(7):930-933.

inferior and/or suboptimal response to fixed-dose biologics in subgroup analyses compared to weight-based ones, most likely as a result of pathophysiologic changes affecting drug distribution and elimination.⁵¹ As a result, thoughtful therapeutic considerations should be made to ensure efficacy and safety of treatment in this population.⁵² We almost always reach for infliximab first because of its weight-based dosing and consistent response among obese, overweight, and normal-BMI patients.⁵³ Conversely, the use of fixed-dose etanercept and adalimumab has been associated with suboptimal and/or inferior responses in obese and overweight patients compared to those with a normal BMI.⁵⁴⁻⁵⁶

Insurance requires in-office administration

Occasionally, we find that insurance will only approve a TNFi for in-office and/or in-hospital administration. In this case, we recommend infliximab.

Compliance issues

There are 2 scenarios in which trouble with compliance manifests. It is very important to understand the social aspects that might affect the treatment outcomes for our patients. For patients who have mobility issues or trouble getting to appointments outside the home, we recommend etanercept or adalimumab for at-home dosing. For patients who do not have trouble getting to appointments or for whom you suspect compliance is an issue at home, infliximab is a better choice.

Heart disease

There are 2 topics to distinguish between when discussing TNFi, psoriasis, and the heart. The first is cardiovascular considerations and the other is heart failure.

Cardiovascular disease

Like many other systemic inflammatory diseases, psoriasis is

associated with a greater risk of developing significant vascular events like cardiovascular disease (CVD) and cerebrovascular disease, including myocardial infarction (MI).⁵⁷⁻⁵⁹ For patients who have a history of CVD or develop CVD during the course of treatment, we favor use of any TNFi for treatment of their psoriasis. Meta-analyses of randomized clinical trials have reported that treatment with a TNFi is not associated with an increased risk of major adverse cardiovascular events (MACEs; MI, cerebrovascular accident, or cardiovascular death).^{60,61} This was a topic of particular interest after concern was raised over a possible increased risk of MACEs with use of anti-IL-12/23 agents. Furthermore, TNFis are not simply associated with a lack of increased risk of MACEs; evidence suggests that they may even be protective in CVD. Three cohort studies have shown that treatment of psoriasis with a TNFi is associated with a significantly decreased risk of MI.⁶²⁻⁶⁴ These studies did not assess each TNFi separately, and therefore we do not recommend any one TNFi over another in this scenario; however, we do tend to reach for TNFis first for these patients.

Heart failure

The second heart-related scenario to address is heart failure, for which we typically avoid TNFis in treating patients with concomitant psoriasis if possible. The use of etanercept, adalimumab, and infliximab ≤ 5 mg/kg is not absolutely contraindicated in patients with heart failure; however, caution should be taken. This warning stems from (1) evidence of increased hospitalizations and death due to heart failure from randomized clinical trials of TNFis for treatment of heart failure itself and (2) post-marketing data suggesting a risk of new-onset heart failure and worsening of heart failure with TNF- α inhibition. Of note, infliximab >5 mg/kg is an absolute contraindication in patients with heart failure; however, this is more than the recommended dosing for psoriasis.

TNF- α levels are elevated in patients with heart failure and are proportional to the severity of disease.⁶⁵ It was therefore proposed that targeting TNF- α could provide therapeutic benefit in heart failure, and small initial pilot studies showed promise. However, larger randomized controlled trials involving etanercept and infliximab for heart failure did not show efficacy for patients with New York Heart Association (NYHA) functional class III/IV disease. Additionally, the etanercept studies were stopped early because of a dose-dependent trend toward higher heart failure-related morbidity and mortality.⁶⁶ The doses in these studies were not equivalent to the doses in psoriasis but were roughly smaller or similar. Similarly, a dose-related increase in death and hospitalization due to heart failure was also observed with infliximab 10 mg/kg. However, there was not an increase in hospitalizations and death due to heart failure in those receiving infliximab 5 mg/kg, which is the dose used in psoriasis.⁶⁷ There may be an association between TNFis and the development of new-onset heart failure;⁶⁸ however, the data are conflicting.⁶⁹

In summary, we typically avoid TNFis in patients with known moderate-to-severe heart failure, particularly NYHA III/IV disease, and usually transition to a different biologic in the event

that new-onset heart failure develops if possible. In the event that a TNFi could not be avoided, we would feel most comfortable using all but high-dose (10 mg/kg) infliximab after discussion with the patient's cardiologist.

Demyelinating disorders

In addition to heart failure, we recommend avoiding TNFis in patients with a history of demyelinating diseases such as multiple sclerosis (MS), Guillain-Barré syndrome, optic neuritis, or transverse myelitis and stopping TNFi therapy if these conditions develop. Avoiding TNFis in patients who have a first-degree relative with MS is also recommended. The labels for etanercept, adalimumab, and infliximab all have warnings that new onset or worsening of these conditions can happen, although these occurrences are estimated to be rare. It was once thought that TNFis could be an effective treatment for MS itself. However, a phase 2 study of lenercept (a TNFi) for patients with MS revealed that the treatment was associated with a worsening of disease.⁷⁰ Additionally, safety data from clinical studies of other TNFis for the treatment of non-neurologic conditions revealed the association between TNF blockade and demyelinating disease.⁷¹⁻⁷⁵

Nonmelanoma skin cancer

The use of TNFis has been associated with higher rates of non-melanoma skin cancer (NMSC),⁷⁶⁻⁸³ particularly squamous cell carcinoma (SCC)^{76,82} in various conditions, including psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and IBD. This increase in NMSCs has been associated with etanercept, adalimumab, and infliximab.⁷⁷ Additionally, the risk of developing NMSC after exposure to a TNFi may be higher for those with psoriasis than those with rheumatoid arthritis.⁸³ Although it is not completely contraindicated to use TNFis in patients with concomitant NMSC, we typically avoid them when a patient has multiple cutaneous SCCs or basal cell carcinomas.

Pregnancy

During pregnancy, women most commonly experience an improvement of their psoriasis (55%-56%),^{84,85} which is thought to be due to a shift in maternal factors favoring T-helper-2 cell immunity.⁸⁶ Although a smaller percentage of women report worsening of psoriasis during pregnancy (23%-24%) and even fewer had no change (16%-21%),^{84,85} many women will require systemic therapy during pregnancy. The major concerns with TNFis or any systemic therapy during pregnancy are limited data and the risk of potential harm to the fetus. It is known that infliximab, etanercept, and adalimumab are all transported across the placenta. The degree to which this happens is minimal in the first trimester, but it increases over the gestational course.⁸⁷ Of the TNFis approved for psoriasis, etanercept has less transplacental transport than infliximab and adalimumab.⁸⁸ Of all of the TNFis available, PEGylated certolizumab is the best option when treating pregnant women with psoriasis. It cannot actively be transported across the placenta resulting in minimal transmission,⁸⁹ goes undetectable (or nearly undetectable) in cord blood,⁹⁰ and is effective in treating psoriasis.^{9,10}

Conclusion

TNFis are safe and effective for the treatment of moderate-to-severe psoriasis. Currently, the three TNFis FDA approved for this indication are etanercept, adalimumab, and infliximab. As a class, TNFis share certain properties that can make them better or worse choices when treating psoriasis in various scenarios such as psoriatic arthritis, CVD, heart failure, or demyelinating disease. Individually, each of these drugs has a unique pharmacological profile that can make choosing one particular TNFi more advantageous for a given patient, such as those with concomitant conditions, obesity, or who are pregnant. Intimate knowledge of the similarities and differences between TNFis is imperative for choosing the right treatment for psoriasis and has important therapeutic implications for patients.

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