CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will weigh the risks associated with anti-tumor necrosis factor therapies

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Managing risks of TNF inhibitors: An update for the internist

ABSTRACT

Tumor necrosis factor (TNF) inhibitors have many beneficial effects, but they also pose infrequent but significant risks, including serious infection and malignancy. These risks can be minimized by judicious patient selection, appropriate screening, careful monitoring during treatment, and close communication between primary care physicians and subspecialists.

KEY POINTS

Over the past 10 years, TNF inhibitors have substantially altered the management of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease.

Safety concerns include risks of infection, reactivation of latent infection (eg, fungal infection, granulomatous infection), malignancy, and autoimmune and neurologic effects.

Before treating, take a complete history, including exposure to latent infections and geographic considerations, and bring patients' immunizations up to date.

Regular clinical and laboratory monitoring during treatment helps optimize therapy and minimize the risk of adverse effects.

Physicians must be aware of atypical presentations of infection and understand how their treatment may differ in patients on biologic therapy.

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Biologic agents such as those that block tumor necrosis factor (TNF) alpha have revolutionized the treatment of autoimmune diseases like rheumatoid arthritis and inflammatory bowel disease, dramatically improving disease control and quality of life. In addition, they have made true disease remission possible in some cases.

However, as with any new therapy, a variety of side effects must be considered.

WHAT ARE BIOLOGIC AGENTS?

Biologic agents are genetically engineered drugs manufactured or synthesized in vitro from molecules such as proteins, genes, and antibodies present in living organisms. By targeting specific molecular components of the inflammatory cascade, including cytokines, these drugs alter certain aspects of the body's inflammatory response in autoimmune diseases. Because TNF inhibitors are the most widely used biologic agents in the United States, this review will focus on them.

TNF INHIBITORS

TNF inhibitors suppress the inflammatory cascade by inactivating TNF alpha, a cytokine that promotes inflammation in the intestine, synovial tissue, and other sites.[1,2]

Several TNF inhibitors are available. Etanercept and infliximab were the first two to receive US Food and Drug Administration (FDA) approval, and they are extensively used. Etanercept, a soluble TNF receptor given subcutaneously, was approved for treating rheumatoid arthritis in 1998. Infliximab, a chimeric monoclonal antibody (75% human

Drugs mentioned in this article

acetaminophen (Tylenol)
adalimumab (Humira)
certolizumab pegol (Cimzia)
diphenhydramine (Benadryl)
entecavir (Baraclude)
etanercept (Enbrel)
golimumab (Simponi)
infliximab (Remicade)
lamivudine (Epivir)
tenofovir (Viread)

and 25% mouse protein sequence) given intravenously, received FDA approval for treating Crohn disease in 1998 and for rheumatoid arthritis in 1999. Other anti-TNF agents with varying properties are also available.

TABLE 1 lists anti-TNF agents approved for treating rheumatoid arthritis and inflammatory bowel disease. These are chronic, relapsing diseases that significantly and dramatically reduce quality of life, especially when they are poorly controlled.[3,4] Untreated disease has been associated with malignancy, infection, pregnancy loss, and malnutrition.[5–8] TNF inhibitors are aimed at patients who have moderate to severe disease or for whom previous treatments have failed, to help them achieve and maintain steroid-free remission. However, use of these agents is tempered by the risk of potentially serious side effects.

TNF inhibitors are for patients with moderate to severe disease or for whom previous treatments have failed

Special thought should also be given to the direct costs of the drugs (up to $30,000 per year, not counting the cost of their administration) and to the indirect costs such as time away from work to receive treatment. These are major considerations in some cases, and patients should be selected carefully for treatment with these drugs.

BEFORE STARTING THERAPY

Before starting anti-TNF therapy, several steps can reduce the risk of serious adverse events.

Take a focused history

The clinical history should include inquiries about previous bacterial, fungal, and tuberculosis infections or exposure; diabetes; and other immunocompromised states that increase the risk of acquiring potentially life-threatening infections.

Details of particular geographic areas of residence, occupational exposures, and social history should be sought. These include history of incarceration (which may put patients at risk of tuberculosis) and residence in the Ohio River valley or in the southwestern or midwestern United States (which may increase the risk of histoplasmosis, coccidioidomycosis, and other fungal infections).

Bring vaccinations up to date

Age-appropriate vaccinations should be discussed and given, ideally before starting therapy. These include influenza vaccine every year and tetanus boosters every 10 years for all and, as appropriate, varicella, human papillomavirus, and pneumococcal vaccinations. The US Centers for Disease Control and Prevention recommend an additional dose of the pneumococcal vaccine if more than 5 years have elapsed since the first one, and many clinicians opt to give it every 5 years.

In general, live-attenuated vaccines, including the intranasal influenza vaccine, are contraindicated in patients taking biologic agents.[9] For patients at high risk of exposure or infection, it may be reasonable to hold the biologic agent for a period of time, vaccinate, and resume the biologic agent a month later.

Recent data suggest that the varicella zoster vaccine may be safely given to older patients with immune-mediated diseases such as rheumatoid arthritis and inflammatory bowel disease taking biologic agents.[10] New guidelines from the American College of Rheumatology recommend age-appropriate vaccines for rheumatoid arthritis patients age 60 and older before biologic treatments are started. Case-by-case discussion with the subspecialist and the patient is recommended.

Screen for chronic infections

Tuberculosis screening with a purified protein derivative test or an interferon-gamma-release (Quantiferon) assay followed by chest

TABLE 1

Anti-tumor necrosis factor agents

Agent	Mechanism of action	Dosage schedule	Approved indications*
Infliximab	Mouse chimeric monoclonal antibody to tumor necrosis factor (TNF) alpha	Intravenously every 6–8 weeks	AS, CD, JIA, PP, PA, RA, UC
Etanercept	Fully human soluble TNF receptor	Subcutaneously weekly	AS, JIA, PP, PA, RA
Adalimumab	Fully human monoclonal antibody against TNF alpha	Subcutaneously every other week	AS, CD, JIA, PP, PA, RA, UC
Certolizumab pegol	Humanized Fab fragment directed against TNF attached to two polyethylene glycol molecules	Subcutaneously every 4 weeks	AS, CD, PA, RA
Golimumab	Human monoclonal antibody against TNF alpha	Subcutaneously every month	AS, PA, RA, UC

*AS = ankylosing spondylitis, CD = Crohn disease, JIA = juvenile idiopathic arthritis, PA = psoriatic arthritis, PP = plaque psoriasis, RA = rheumatoid arthritis, UC = ulcerative colitis

radiography in patients with a positive test is mandatory before giving a TNF inhibitor.

Hepatitis B virus status should be determined before starting anti-TNF therapy.[11]

Hepatitis B vaccination has been recommended for patients with inflammatory bowel disease, but no clear recommendation exists for patients with rheumatic disease. Patients with inflammatory bowel disease tend to have low rates of response to hepatitis B vaccination[12,13]; possible reasons include their lack of an appropriate innate immune response to infectious agents, malnutrition, surgery, older age, and immunosuppressive drugs.[14] An accelerated vaccination protocol with recombinant hepatitis B vaccine (Energix-B) in a double dose at 0, 1, and 2 months has been shown to improve response rates.[15]

Whenever possible, it may be better to vaccinate patients before starting immunosuppressive therapy, and to check postvaccination titers to ensure adequate response.

Perform an examination

A full physical examination with special attention to skin rashes should be performed. This may serve as a baseline to assist early detection of new rashes associated with anti-TNF therapy.

A baseline complete blood cell count and complete metabolic panel should be routinely obtained before starting therapy (and thereafter at the discretion of the physician). In conjunction with follow-up tests, they can help detect an unexpected decrease in white blood cell count or abnormal results on the liver panel.[16] These baseline and follow-up tests are generally performed by the subspecialist, and the results are shared with the primary care physician.

TABLE 2 summarizes key information to be sought before starting a patient on a TNF inhibitor.

In general, live-attenuated vaccines are contraindicated in patients taking biologic agents

ADVERSE EFFECTS OF ANTI-TNF DRUGS

Infusion reactions, infections, cardiac arrhythmias, demyelinating disorders, skin infections, and malignancies have been reported with anti-TNF therapy. The relative frequencies of these adverse events are summarized in TABLE 3.[17–22]

NONINFECTIOUS COMPLICATIONS OF TNF INHIBITORS

Injection site reactions

When anti-TNF agents are given subcutaneously, injection site reactions are common (occurring in up to 40% of patients) and are considered minor.[11] Reactions, including sig-

TABLE 2

Key information to be obtained before starting anti-TNF therapy

Comorbidities
New York Heart Association class III or IV heart failure
Demyelinating disease
Malignancy (current or prior)
Infection history

Immunization status
Influenza
Hepatitis B
Pneumococcal
Shingles

Tuberculosis exposure and status
Purified protein derivative or Quantiferon test
Chest radiography

Geographic exposure
Endemic areas for opportunistic infection
Travel history

Physical examination
Documentation of a rash

TABLE 3

Adverse events and estimated frequencies associated with anti-TNF therapy

Event	Estimated frequency
Stopping therapy because of an adverse event	10%
Infusion or injection site reactions	3%–20%
Drug-related lupus-like reaction	1%
Serious infections	3%
Skin infections	1%–20%
Tuberculosis	0.05%
Non-Hodgkin lymphoma (combination therapy)	0.06%
Multiple sclerosis, heart failure, serious liver injury	Case reports only

COURTESY OF COREY A. SIEGEL, MD, MPH, DIRECTOR, INFLAMMATORY BOWEL DISEASE CENTER, DARTMOUTH- HITCHCOCK MEDICAL CENTER, LEBANON, NH; ASSISTANT PROFESSOR OF MEDICINE, GEISEL SCHOOL OF MEDICINE, DARTMOUTH COLLEGE. DATA FROM REFERENCES 17–22.

Screening for tuberculosis is mandatory before starting TNF inhibitors

nificant pain, typically occur within the first few months of therapy. They can last 2 to 5 days but rarely warrant stopping therapy. Treatment with ice and an antihistamine is almost always sufficient to control symptoms.

Infusion reactions with infliximab

Infliximab can cause both acute and delayed infusion reactions. Acute reactions can occur up to 24 hours after infusion but usually appear within 10 minutes of administration and are handled by the infusion suite staff. They range from the severe immunoglobulin E-mediated type I reaction, manifesting with hypotension, bronchospasm, and urticaria, to the milder anaphylactoid-type reaction, which constitutes the majority.[23–25]

While most primary care physicians will not encounter an acute reaction, family doctors and emergency room physicians may encounter delayed reactions, which can develop 1 to 14 days after infusion. These reactions usually resemble serum sickness and present with joint pain, fatigue, myalgia, and fever. But, unlike classic serum sickness, these reactions are generally not associated with a rash.

With nonspecific symptoms, the diagnosis may be easy to overlook. However, establishing this diagnosis is important because repeat therapy may result in a more severe reaction upon reexposure to the drug.

Once diagnosed, these reactions can be treated symptomatically with a combination of acetaminophen and diphenhydramine after discussion between the primary care physician and subspecialist.[23,24]

Autoimmune syndromes

Several studies have reported a small percentage of patients treated with anti-TNF agents who develop paradoxical autoimmune conditions. These range from asymptomatic immunologic alterations, including the formation of antinuclear antibodies and antibodies to double-stranded DNA, to life-threatening systemic autoimmune diseases.[26,27]

Autoimmune diseases associated with anti-TNF treatment include a lupus-like syndrome, vasculitides, and psoriatic skin lesions. These syndromes warrant stopping the inciting drug and, on occasion, giving corticosteroids. Most cases arise between 1 month and 1 year of starting treatment, and almost 75% resolve completely after the anti-TNF therapy is stopped.[26]

Interestingly, anti-TNF agents are approved for treating psoriasis and psoriatic arthritis, but psoriasis has paradoxically developed in patients being treated with these drugs for other autoimmune diseases. The FDA has reviewed 69 cases of new-onset psoriasis with anti-TNF therapy, including 17 pustular and 15 palmoplantar cases. The 12 most severe cases resulted in hospitalization, and symptoms resolved in most after treatment cessation.[28]

Fiorino et al[29] counted 18 reported cases of psoriasis induced by anti-TNF therapy in patients with inflammatory bowel disease and concluded that it is rare. Harrison et al[30] reported similar findings in patients with rheumatoid arthritis, with an increased incidence rate of 1.04 per 1,000 person-years. New-onset psoriasis was most common in patients treated with adalimumab. An example of the rash is seen in **FIGURE 1.**

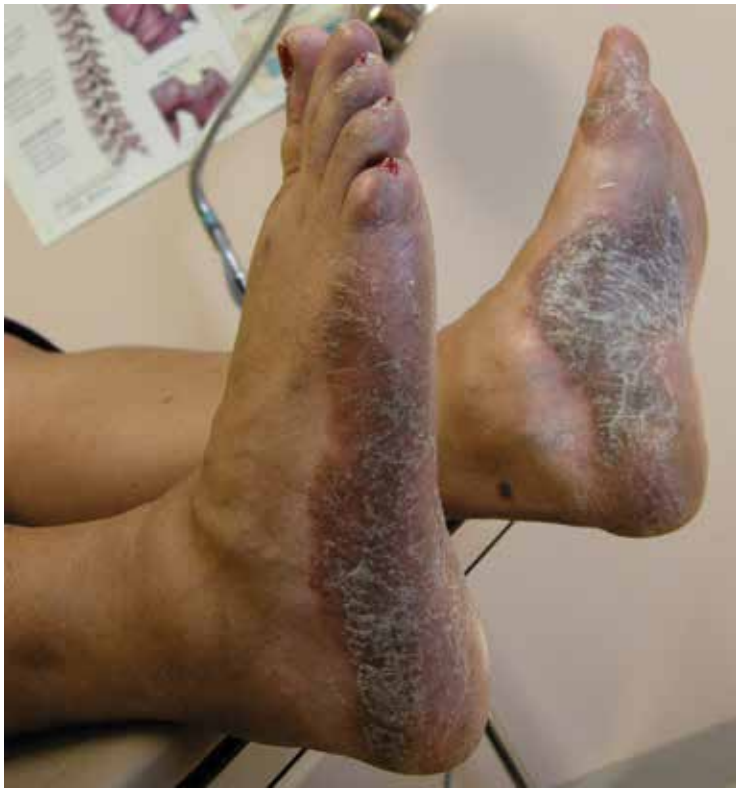

FIGURE 1. New-onset psoriasis in a patient receiving a tumor necrosis factor inhibitor.

CARDIOVASCULAR SIDE EFFECTS

Cardiovascular side effects of anti-TNF agents range from nonspecific and asymptomatic arrhythmias to worsening of heart failure.

Circulating levels of TNF are increased in patients with heart failure, and studies have evaluated the effects of TNF inhibition with infliximab on cardiac function and overall survival.[31,32] The combined risk of death from any cause or hospitalization from heart failure was significantly higher in the infliximab groups, and the effects persisted for up to 5 months after stopping therapy.

Other studies[22,33] have evaluated the effects of infliximab and etanercept on cardiac function and overall survival. Results showed possible exacerbation of heart failure with etanercept and increased risk of death with infliximab in patients with New York Heart Association (NYHA) class III or IV heart failure and left ventricular ejection fractions less than 35%.

Case reports have also described patients with worsening or new-onset heart failure on TNF inhibitors, including patients younger than 50 years and without identifiable cardiovascular risk factors.

Data analyses[31,34,35] from large clinical registries have reported no significant increase in heart failure attributable to TNF inhibitors. However, we have concerns about the methodology of these analyses.

Side effects range from infusion reactions to malignancies

Currently, anti-TNF therapy is contraindicated in patients with NYHA class III or IV heart failure. Data are inconclusive for patients with class I or II heart failure. Baseline echocardiography and cardiology consultation can be considered, with close monitoring and avoidance of high doses of TNF inhibitors. If heart failure develops in a patient on anti-TNF therapy, the drug should be discontinued and the patient should be evaluated further.[36]

DEMYELINATING DISEASE, INCLUDING MULTIPLE SCLEROSIS

Anti-TNF agents have been associated with the onset or exacerbation of clinical symptoms and radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis.[37–40] Mohan et al[38] identified 19 cases of demyelinating events occurring after administration of anti-TNF agents in early 2001. In most cases, symptoms improved or resolved after therapy was stopped.

Optic neuritis,[41,42] bilateral optic neuropathy,[43] and aseptic meningitis[44] have also been reported, but these have occurred only rarely.

How common are these effects? Postmarketing surveillance in patients with rheumatoid arthritis yields an estimated incidence of demyelinating disorders of 1 per 1,000 patient-years with adalimumab therapy.[45] Complicating the assessment is an observed slight increase in risk of demyelinating conditions associated with inflammatory bowel disease.

Symptoms that should heighten the physician's suspicion of this adverse effect include confusion, paresthesias, and ataxia. Patients on anti-TNF therapy who develop new visual symptoms should be checked for painless visual loss as a sign of early demyelinating disease.

Although data that conclusively link anti-TNF agents to multiple sclerosis are lacking, these drugs should not be initiated in patients who have a history of demyelinating disease, and treatment should be stopped promptly if the diagnosis is suspected.

MALIGNANCY

A delayed reaction can develop 1 to 14 days after infusion

Whether anti-TNF therapy is directly linked to development of malignancies is difficult to determine. There are many confounding factors, including the risk of malignancy in underlying inflammatory disease and the concomitant use of other medications such as thiopurines, which have a known association with lymphoma.[46]

The incidence of lymphoma is twice as high in rheumatoid arthritis patients as in the general population.[47] The risk is higher in those with more aggressive joint disease—the subset of rheumatoid arthritis patients who are more likely to be given anti-TNF agents.[5]

In patients with inflammatory bowel disease, the risk of cholangiocarcinoma is four times higher, and the risk of small-bowel adenocarcinoma is 16 to 18 times higher, but no increased risk of lymphoma has been identified in this population.[48,49]

Data from six clinical trials of infliximab, including a long-term study of its safety in Crohn disease, suggest it poses no increase in overall risk of malignancy.[50–52] Similar results have been reported in patients with other rheumatic diseases.[8] Information on this topic is constantly evolving, and studies range from case series to clinical trials to large patient registries.

The decision to use a TNF inhibitor should be based on the patient's clinical picture and risk factors. Discussion of the risks and benefits of therapy with the patient should be clearly documented.

Non-Hodgkin lymphoma

Evidence about the risk of lymphoma with anti-TNF use is mixed, as up to two-thirds of patients on anti-TNF therapy have received concomitant nonbiologic immunosuppressive medications, making it difficult to determine the true risk from the biologic agents alone.[53] Current evidence both supports[9,53–56] and refutes[7,55,57–60] the idea that anti-TNF agents increase lymphoma risk.

In patients with inflammatory bowel disease, several population-based studies have not shown a clear increase in lymphoma risk with anti-TNF use.[56,59,60] Pedersen et al,[61] in a meta-analysis of eight studies, confirmed these findings by showing no overall lymphoma risk in patients with inflammatory bowel disease.

However, a Canadian population-based study found a statistically significant increase in non-Hodgkin lymphoma in males with Crohn disease, with an incidence ratio of 3.63 (95% confidence interval [CI] 1.53–8.62).[61] Additionally, Siegel et al[62] found a significantly higher risk (6.1 cases per 10,000 patients) in patients treated with anti-TNF agents and thiopurines than in the general population (1.9 cases per 10,000 people). Although the difference was statistically significant, the overall risk is still very low.

Patients with rheumatoid arthritis seem to have a risk of lymphoma two to three times higher than in the general population. However, large population-based studies have not shown a statistically significant increase in the risk of lymphoma with anti-TNF therapy.[63]

Hepatosplenic T-cell lymphoma is a rare subtype of peripheral T-cell non-Hodgkin lymphoma; 25 cases have been reported in patients receiving anti-TNF therapy.[64] Although the risk is extremely low (< 0.05%), physicians must carefully consider the risks and benefits of combination therapy, especially in young male patients with inflammatory bowel

disease, since death is the usual outcome of this disease.[65–67]

Skin cancers

Wolfe and Michaud[8] evaluated malignancy risk in rheumatoid arthritis patients being treated with biologic agents, including TNF inhibitors, using a large longitudinal database. These data were compared with those of the US Surveillance, Epidemiology, and End-Results (SEER) national database. No increase in the overall cancer rate was seen in rheumatoid arthritis patients (standardized incidence ratio [SIR] 1.0, 95% CI 1.0–1.1).

However, melanoma was more common in rheumatoid arthritis patients compared with SEER rates (SIR 1.7, 95% CI 1.3–2.3).[8] In addition, biologic therapy was associated with a higher (but not statistically significant) risk of melanoma (odds ratio [OR] 2.3, 95% CI 0.9–5.4) and a higher risk of nonmelanoma skin cancer (OR 1.5, 95% CI 1.2–1.8), but not of other types of cancer.[8]

INFECTION

Patients on anti-TNF therapy are at a higher risk of infection, ranging from minor to life-threatening bacterial infections, and including the reactivation of granulomatous and fungal infections. More importantly, these agents are similar to steroids in blunting signs of infection, which may delay diagnosis and treatment.

The management of infection in patients on anti-TNF medications varies from case to case. In general, patients with a minor infection that does not require hospitalization or intravenous antibiotics can continue the biologic therapy while taking oral antibiotics. TNF inhibitors must be held in the event of a major infection.

Consultation with an infectious disease specialist is recommended, especially in complex cases.

Bacterial infections

An increased risk of minor bacterial infections such as urinary tract and respiratory infections has been well documented in several randomized control trials of anti-TNF agents, though other studies have shown no such increase in risk.[33,51–59]

The threshold for using antibiotics for a suspected bacterial infection is somewhat shifted in favor of treatment in patients on anti-TNF therapy. The reason is twofold: as previously noted, infections may be worse than they appear, because anti-TNF drugs can mask the signs and symptoms of a serious infection, and in patients on these drugs, an untreated bacterial infection may rapidly become life-threatening.

In general, broad-spectrum antibiotics are not warranted unless the source of infection is unclear or the patient is in danger of hemodynamic compromise.

Opportunistic infections

The association of anti-TNF agents with opportunistic infections could be viewed as an extension of their normal and intended therapeutic activity as potent immunosuppressive agents.[68] Rheumatoid arthritis and inflammatory bowel disease are usually associated with conditions and situations that predispose patients to opportunistic infections, such as decreased immune response, malnutrition or malabsorption, surgeries, and concomitant immunosuppressive medications.[7] Combination therapy with other immunosuppressive drugs and older age appear to markedly increase the risk of opportunistic infections, including mycobacterial and fungal infections, in patients with inflammatory bowel disease.[7]

Anti-TNF therapy is contraindicated in patients with NYHA class III or IV heart failure

Overall, opportunistic infections represent a measurable risk of anti-TNF therapy, and awareness and vigilance are important, especially in areas where opportunistic infections such as histoplasmosis and coccidiomycosis are endemic.[50] Furthermore, physicians must be aware of the higher risk of opportunistic infections when multiple immunosuppressive drugs are used concurrently.

Granulomatous infections such as tuberculosis

Anti-TNF agents increase the risk of de novo granulomatous infections and of reactivating such infections. Granuloma formation and intracellular destruction of mycobacteria depend on TNF. TNF is important in maintaining the anatomic integrity of granulomas where these organisms have been sequestered, and blocking TNF leads to breakdown of granulomas and release of virulent organisms.[69,70]

TNF inhibitors increase the risk of reactivation of latent tuberculosis infection. The risk is greater with infliximab and adalimumab than with etanercept,[71,72] and it has been described with certolizumab.[74] Study results are varied thus far but show a risk of tuberculosis reactivation five to 30 times higher than in the general population, with tremendous variability in risk depending on background rates of previous exposure.

The absence of typical tuberculosis symptoms further complicates care in these cases. Fever, weight loss, and night sweats tend to be TNF-mediated and are therefore masked by anti-TNF agents, leading to atypical presentations. In addition, active tuberculosis infection associated with TNF inhibitors is more likely to involve extrapulmonary sites such as the skin and musculoskeletal system and to be disseminated at presentation.

A paradoxical worsening of tuberculosis symptoms may also be seen in patients with latent tuberculosis reactivation, especially after discontinuing anti-TNF therapy. This is thought to result from an immune reconstitution inflammatory syndrome.

Evidence both supports and refutes increased risk of lymphoma with anti-TNF agents

The pretreatment evaluation should include a history of risk factors, a physical examination, and either a tuberculin skin test or an interferon-gamma-release assay. Interferon-gamma-release assays are particularly helpful in patients who have received bacille Calmette-Guérin vaccination. In patients who test positive or have been exposed, tuberculosis treatment should begin 4 weeks before starting anti-TNF therapy, though the optimal timing of antituberculosis agents is still controversial.[74–77]

If tuberculosis develops in a patient on anti-TNF therapy, he or she should receive antituberculosis drugs. Anti-TNF therapy should be stopped and should be resumed after 2 months only if no other treatment option is available.[75]

Invasive opportunistic fungal infections

Invasive opportunistic fungal infections have been reported with anti-TNF therapy, including histoplasmosis and coccidioidomycosis.[78–80] Most patients who had histoplasmosis were treated with other immunosuppressive therapies and resided in or were raised near the Ohio or Mississippi River valleys, where this disease is endemic. Similarly, most cases of coccidioidomycosis were in endemic areas of Arizona, California, and Nevada, and patients on concomitant immunosuppressive therapy.[78]

Currently, there is no evidence to recommend obtaining *Histoplasma capsulatum* or *Coccidioides immitis* serologies before initiating anti-TNF therapy in patients in endemic areas.[81] However, patients must be instructed to seek medical attention quickly for pulmonary or febrile illnesses.

Viral hepatitis infections

The data on hepatitis B and hepatitis C in patients on biologic therapies are mostly limited to case reports.

Hepatitis B. A small prospective study from Spain followed the liver biochemistry tests and hepatitis B status of 80 patients with Crohn disease treated with infliximab. Of three patients who were chronic hepatitis B carriers before starting infliximab, two experienced reactivation of hepatitis B after discontinuing infliximab, and one ultimately died. The third patient was treated with lamivudine concurrently with infliximab without clinical or biochemical changes during or after therapy.[82]

Similar findings were observed in two patients with rheumatoid arthritis on treatment with infliximab. One of the patients required liver transplantation, and both were treated with lamivudine, resulting in normalization of liver function test results.[83,84]

Recent reviews indicate that despite these findings, hepatitis B reactivation after anti-TNF withdrawal may not be common.[85] There are limited data on hepatitis B reactivation and associated liver dysfunction in patients with inflammatory bowel disease treated with immunosuppressants. In a retrospective multicenter trial by Loras et al[86] in patients with inflammatory bowel disease who had viral hepatitis, 36% of patients positive for hepatitis B surface antigen developed liver dysfunction, and six patients developed liver failure. In that study, treatment with more than two immunosuppressants was an independent predictor of hepatitis B reactivation.

Prolonged immunosuppression (longer than 3 months) has also been identified as

an independent predictor of liver dysfunction (OR 3.06; 95% 95% CI 1.02–9.16).[87]

The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend starting lamivudine before chemotherapy or immunomodulator or immunosuppressive therapy in hepatitis B virus carriers and continuing preventive treatment for at least 6 months after stopping immunomodulating drugs. Lamivudine at a dose of 100 mg/day may reduce the risk of reactivation of hepatitis B.[88–90] Tenofovir and entecavir may be useful alternatives in patients with hepatitis B who have never received nucleoside analogues. Hepatitis B reactivation did not occur in any of the 16 patients who received preventive entecavir treatment while receiving immunosuppressive treatments.[89,91]

In patients receiving immunosuppressive therapy, hepatitis B reactivation is associated with significant morbidity and mortality. Although risk factors for reactivation of hepatitis B virus infection have been identified, we recommend preventive treatment for all carriers positive for hepatitis B surface antigen. This should be done regardless of the number, type, and dosage of immunosuppressants and regardless of hepatitis B virus DNA levels.[90]

The frequency of hepatitis B and hepatitis C infection in patients with Crohn disease has been reported to be as high as 24%. The high incidence is thought to be secondary to multiple blood transfusions and surgeries.[92] The use of biologic agents, including anti-TNF agents, in chronic hepatitis B virus- or hepatitis C virus-infected patients can lead to enhanced viral replication and hepatitis exacerbation.

Although active viral replication can occur during treatment with biologic agents, reactivation or exacerbation can also occur after the anti-TNF agent is stopped.[82] This finding has prompted the recommendation that all candidates for biologic therapy be tested for hepatitis B immunization status, followed by immunization in nonimmune patients before starting anti-TNF therapy.[93,94]

Hepatitis C. There are no guidelines that adequately address the use of anti-TNF agents in patients with chronic hepatitis C infection.

Several small retrospective studies in rheumatoid arthritis patients with hepatitis C have shown that TNF inhibitors can be safely used without worsening liver function tests or changing the viral load.[95–98] This is reassuring and provides the subspecialist with another treatment option, as other therapies such as disease-modifying antirheumatic drugs and steroids are known to aggravate viral hepatitis and increase the risk of viremia.[96]

Although small retrospective studies and one large randomized double-blind placebo-controlled trial have shown TNF inhibitors to be relatively safe in rheumatoid arthritis patients with hepatitis C, their use in these patients should be considered only with caution if they have evidence of hepatic synthetic dysfunction (eg, hypoalbuminemia, thrombocytopenia, increased international normalized ratio). The American College of Rheumatology recommends avoiding TNF inhibitors in Child-Pugh classes B and C.[99]

PREGNANCY

Physicians caring for patients with rheumatoid arthritis and inflammatory bowel disease must be aware of how these diseases affect fecundity and fertility and how the medications can affect conception and pregnancy. Many patients have difficulty conceiving while their autoimmune disease is active, and better disease control may improve fecundity and result in unanticipated pregnancy. Patients should be advised of the need for contraception if pregnancy is ill-advised or undesired.

Infections may be worse than they appear, because these drugs can mask signs and symptoms

Many patients seek advice about teratogenicity before conceiving, or seek guidance about rheumatoid arthritis and inflammatory bowel disease treatment while pregnant.

Several studies have reported a higher risk of adverse pregnancy outcomes in patients with rheumatoid arthritis and inflammatory bowel disease than in the general population.[99–105] In inflammatory bowel disease, the odds of a premature delivery or having a low-birth-weight child are twice as high as in the normal population.[100,103] Higher rates of cesarean delivery and stillbirth have also been reported. The main predisposing factor appears to be the disease activity at the time of conception, as active disease seems to be linked to adverse pregnancy outcomes.

Treatment with anti-TNF agents may rapidly achieve and maintain remission, raising the question of the safety of continued anti-TNF use during pregnancy. The FDA classifies anti-TNF agents as category B drugs, as animal studies have not demonstrated fetal risk, and no well-controlled prospective study has yet been conducted with pregnant women.

In an observational study, Schnitzler et al[105] assessed the outcomes of 42 pregnancies in 35 patients with inflammatory bowel disease receiving either infliximab or adalimumab during pregnancy, compared with 56 pregnancies in 45 healthy patients without inflammatory bowel disease. There was no statistical difference in abortion rates between patients receiving anti-TNF agents and healthy women without inflammatory bowel disease (21% vs 14%, $P = .4234$). There was also no significant difference observed in birth weight, birth length, or cranial circumference of the children between the two groups. However, pregnancies with direct exposure to anti-TNF agents resulted in a higher frequency of premature delivery (25% vs 6%, $P = .023$).

Vigilance is important, especially where opportunistic infections are endemic

Similar results were noted from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool, or TREAT, registry, as well as from a large systematic review by Vinet et al[106] and case reports of rheumatoid arthritis and inflammatory bowel disease in women exposed to anti-TNF agents during pregnancy.

In addition, results from a recent systematic review of 38 studies of anti-TNF use and fetal risk, with a total of 437 women (189 on infliximab, 230 on adalimumab, 18 on certolizumab pegol), showed similar results.[107] In pregnancies exposed to anti-TNF agents, the rates of congenital abnormalities (3.4%), fetal deaths (8.5%), and preterm births (2.7%) were similar to those in the general population.

For patients in disease remission on TNF inhibitors, it is reasonable to continue these agents during pregnancy after careful discussion with the patient. Fetal safety and infant immunization response after delivery are the primary concerns in these cases.

Both infliximab and adalimumab cross the placenta and remain detectable in the baby's circulation 4 months (for adalimumab) to 6 months (for infliximab) after delivery. It is currently recommended that infliximab be stopped at 32 weeks of gestation for the remainder of the pregnancy and that adalimumab be stopped at 34 to 36 weeks, given a planned 40-week gestation.

Certolizumab does not cross the placenta in significant amounts and should be continued throughout pregnancy; drug levels in infants were shown to be less than 2 µg/mL, even when dosed the week of delivery.[108–112]

TAKE-HOME POINTS

- All health care providers of patients with rheumatoid arthritis and inflammatory bowel disease should be familiar with anti-TNF agents used in treating these diseases.
- The benefits of controlling the disease far outweigh the risks of therapy when used appropriately.
- Care of these patients should be multidisciplinary, with clear communication between primary care physician and specialist.
- Patient education and monitoring combined with prompt communication between primary care physician and specialist are key.

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