Biologic agents have revolutionized the treatment of moderate-to-severe plaque psoriasis among other inflammatory diseases, and their use has dramatically improved our patients’ lives. That said, these medications do come with some risks. Prudent and tailored monitoring is essential to maximize the benefits and minimize the risks associated with these drugs.

Currently, there are six biologic therapies FDA-approved for the treatment of moderate-to-severe plaque psoriasis. These drugs can be classified as 1) tumor necrosis factor-alpha (TNF-α) inhibitors, 2) interleukin (IL)-12/23 inhibitors, and 3) IL-17 pathway inhibitors. There is not a one-size-fits all monitoring protocol, as different medications confer different risks, and each patient’s health history is unique and must be considered. This article will summarize the risks associated with each therapy, highlight the current thinking on how to best monitor patients, and describe what to do in the event that these side effects occur.

SAFETY CONCERNS

The three TNF-α inhibitors approved for psoriasis are adalimumab, etanercept, and infliximab. Well-established risks associated with TNF-α inhibitors as a class include new or reactivation of latent opportunistic infections, lupus-like reactions, non-melanoma skin cancers (NMSC), and worsening or progression of demyelinating diseases and congestive heart failure. Other adverse events including malignancies such as lymphoma have been reported, but this may be due to combination therapy with other immunosuppressive medications or be associated with the underlying inflammatory disease being treated. In fact, studies of these drugs when used as monotherapy for psoriasis have revealed no increased risk of malignancy.

Ustekinumab is currently the only IL-12/23 inhibitor FDA-approved for the treatment of psoriasis. The most common adverse reactions (incidence ≥ 3%) include nasopharyngitis, upper respiratory tract infection, headache, and fatigue. Both secukinumab and ixekizumab are FDA-approved monoclonal antibodies that bind to and inhibit IL-17A, a cytokine produced by TH17 cells, blocking inflammation that is highly specific for psoriasis. The most common adverse events (incidence >1%) include candidiasis, nasopharyngitis, diarrhea, and upper respiratory tract infection.

MONITORING GUIDELINES

Tuberculosis. Baseline screening for latent tuberculosis (LTB) is recommended for all patients starting immunosuppressive therapy. All patients starting a TNF-α inhibitor should be screened for LTB via a thorough history testing prior to initiation of treatment. The risk of TB reactivation has been noted to be lower in studies of patients treated with ustekinumab compared with TNF-α inhibitors. This may be due to either IL-12 and/or IL-23 being less relevant to maintaining TB latency, or a heightened awareness and screening initiated prior to the drug’s development. Traditionally, screening for LTB was performed via tuberculin skin test (TST), however, this is being replaced with the more sensitive and specific Interferon Gamma Release Assay (IGRA), also known as the Interferon Gamma Release Assay (IGRA).

“A baseline history of malignancy does not exclude the use of biologic medications.”

Treatments are generally safe and well-tolerated, however, prescribers must monitor for risk factors.
QuantiFERON-TB Gold test.

**Next Steps.** If either method of testing is found to be positive, in an asymptomatic patient with a negative chest X-ray, guidelines recommend at least one month of LTB treatment before initiation of a biologic medication. The current recommendation is annual monitoring via TST or IGRA testing; though this frequency of testing might be relaxed in low-risk populations.

**Hepatitis.** Screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) should be performed prior to initiation of any biologic therapy. The recommended screening includes testing for hepatitis B surface (HBsAG) antigen and anti-hepatitis B core (anti-HBc) antibodies, with or without anti-hepatitis B surface (anti-HBs) antibodies. Testing for anti-hepatitis B surface antibodies (anti-HBs) is part of the traditional triple test and is usually positive in cases of vaccination and prior exposure. While it may be useful in verifying vaccination, the presence of anti-HBs antibodies does not eliminate the risk of reactivation of HBV in previously infected individuals.

The risk of HCV during treatment with biologic therapy is unclear, thus baseline screening is recommended. Positive results are not an absolute contraindication to biologic treatment, with some case studies indicating that HCV carriers might safely receive TNF-α inhibitors.

**Next Steps.** Patients with acute HBV infection should not receive immunosuppressive treatment. However, patients with chronic or resolved HBV may be considered for treatment with a TNF-α inhibitor or other biologic therapy after consultation with a hepatologist and consideration of concomitant anti-viral treatment. While not a mandate, vaccination prior to the initiation of therapy should be considered for uninfected and unvaccinated individuals.

If negative for HCV, repeated tests for infection during therapy need only be guided by the onset of suggestive signs and symptoms, or abnormal laboratory results (elevated liver function tests).

**Cancer.** Baseline screening should include a thorough history for previous cancers, baseline hematologic labs, and routine clinical monitoring for new symptoms or signs that suggest cancer, such as unexplained weight loss and fatigue. A baseline history of malignancy does not exclude the use of biologic medications.

The risk of non-melanoma skin cancers (NMSC) may be higher in patients on long-term therapy with TNF-α or IL-12/23 inhibitors but these data may be confounded by the fact that many psoriasis patients have an extensive history of both natural and in-office ultraviolet phototherapy. The data warrant higher-risk patients receiving full skin exams at regular (every six to 12 month) intervals. Other than NMSC, there are no conclusive data indicating an increased risk of malignancy in psoriasis patients treated with any of the approved biologics as a monotherapy. That said, some data, particularly from the rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) populations, suggest the use of a TNF-α inhibitor with additional disease modifying immunosuppressive agents (such as methotrexate, cyclosporine, 6-mercaptopurine and azathioprine) may lead to an increased risk of malignancy such as lymphoma.

**Next Steps.** Patients treated with biologic therapy often do so for a long, protracted time period, commonly when they are over the age of 40 when malignancy risk increases. For this reason, malignancies of all types may arise during therapy. In an individual patient the relationship of the medication to the malignancy will always be tenuous. Regardless, prudent medical practice necessitates the discontinuation of the biologic as the patient undergoes therapy for the malignancy.

**Other Infections.** Treatment TNF-α inhibitors leads to an increased risk of a panel of rare opportunistic infections including listeria monocytogenes, pneumocystis jirovecii (formerly, pneumocystis carinii), histoplasma capsulatum, candidiasis, and aspergillosis. Pre-treatment tests for the causative pathogens are not indicated. Patients in regions with known opportunistic fungi should be counseled on the increased risk and the symptoms of infection, and patients should be screened and monitored using a complete review of systems and appropriate laboratory testing.

Aside from a pre-treatment test for latent TB, there are no screening tests indicated before starting secukinumab or ixekizumab. However, patients should be counseled on the increased risk of oral yeast infections, which are usually mild and treatable. There is no evidence of increased risk of opportunistic infections in ustekinumab-treated patients, however all patients should be clinically monitored for evidence of such infections.

**Next Steps.** The nature of the infection will dictate how
to continue dosing with the biologic. Some biologics are so infrequently administered it is not possible to “stop” treatment for an infection. The best approach is case-by-case, erring on the side of caution. A good general rule is to hold the next scheduled dose of any biologic if the infection has not fully resolved with appropriate therapy.

**Hematologic effects.** Hematologic adverse effects of any biologic are very rare. Secukinumab trials saw a grade 3 neutropenia in 1.0 percent of patients and was not associated with serious infections,18 and hematologic abnormalities have rarely been reported in patients treated with TNF-α inhibitors. The same may hold for ixekizumab. While a direct correlation cannot be established with TNF-α inhibitors, it is still recommended that a baseline complete blood cell count be performed before starting any biologic therapy. In addition, it is recommended that all patients starting a biologic therapy have a baseline comprehensive metabolic panel performed.

**Next Steps.** For additional monitoring of blood dyscrasias, I usually perform follow-up laboratory measurement of the complete blood cell count every six to 12 months and sooner if symptoms or signs warrant. In the presence of blood count abnormalities, consideration should be given to discontinuation of the biologic therapy and an appropriate referral should be sought.

**Cardiovascular effects.** Some data suggest that treatment with TNF-α inhibitors may lead to congestive heart failure (CHF) exacerbation.11,19-20 Patients should be screened by history and review of systems prior to initiation of and during therapy. In patients with New York Heart Association class III or IV CHF, it is recommended that TNF-α inhibitors be avoided.19,21 While caution should be exercised in all TNF-α inhibitors, infliximab may demonstrate a higher risk than either adalimumab or etanercept. Ustekinumab does not appear to worsen CHF. There are currently no data in support of or against the use of either secukinumab or ixekizumab in patients with CHF, but clinical trials for these drugs revealed no consistent cardiovascular adverse event signal.

**Next Steps.** All follow-up visits for patients on immunosuppressive medications should query for the presence of new onset shortness of breath or dyspnea on exertion. Signs or symptoms of CHF mandate immediate referral and discontinuation of the biologic.

**Demyelinating Neurologic Diseases.** TNF-α is known to play a role in the pathogenesis of demyelinating neurologic disorders. Data have shown that there is a connection between TNF-α inhibitors and the development or progression of demyelinating disorders such as multiple sclerosis (MS), optic neuritis, Guillain-Barre syndrome, transverse myelitis, chronic inflammatory demyelinating polyradiculoneuropathy, and multifocal motor neuropathy.22-25 Patients should be screened for a personal and family history of such disorders. If a personal history is present, treatment with a TNF-α inhibitor is contraindicated. If personal history is questionable, a neurological referral is advisable. If a family history exists, though the risk is likely much lower, patients should be counseled about this risk and the symptoms and signs associated with demyelinating disease.

**Next Steps.** On follow-up exam, the patient should be queried for new onset numbness, pain, diplopia, or slurred speech. Unilateral signs are more suggestive of demyelination. If symptoms develop while on a TNF-α inhibitor, treatment should be stopped immediately and the patient should be referred to a neurologist. Unlike TNF-α inhibitors ustekinumab is safe to use in patients with MS. Though their causal relationship to ustekinumab therapy is unclear, there have been isolated cases of reversible posterior leukoencephalopathy syndrome.26-27

**Autoimmunity.** Patients who initially screen negative may develop positive antinuclear antibodies (ANA), including anti-double-stranded DNA (anti-dsDNA), anti-histone, anti-Sm, and anti-ribonucleoprotein antibodies, after treatment with TNF-α inhibitors. Rarely, some patients treated with TNF-α inhibitors may develop a lupus-like reaction, which usually resolves with treatment cessation.28-29 A positive baseline low titer positive test for ANA does not correlate with greater risk of a lupus-like reaction during therapy, nor is seroconversion while on therapy indicative of an ongoing or incipient lupus-like reaction. For these reasons, a baseline ANA is not necessary but may be performed at the discretion of the provider solely to be used as a comparison in patients who develop symptoms of a lupus-like reaction while on therapy.

**Next Steps.** Regardless of the baseline test result, follow-up monitoring is not recommended unless a patient develops signs and symptoms to suggest a lupus-like reaction.

**Treatment Failure.** Some patients demonstrate a blunted response to TNF-α inhibitors over time. The mechanism is not entirely clear, though, in part, it may relate to the development of anti-drug antibodies, or immunogenicity.30 Most commonly, anti-drug antibodies result in diminished serum levels of the biologic. Except for infliximab, tests for specific anti-drug antibodies are not a readily available yet, and rarely used in dermatology. However, the development of ANA appears to also coincide with secondary treatment failure and may potentially represent a surrogate marker for secondary failure. When loss of response is clinically obvious, the monitoring of ANA level for this purpose is not recommended. Anti-drug antibodies have also been observed with ustekinumab, secukinumab, and ixekizumab treatment, and similarly may have negative effects on drug levels and efficacy.15,18
Next Steps. Switching therapies may be advisable in the face of treatment failure. Patients who have been previously treated with an anti-TNF and have an initial response but subsequently lose their response can be treated with another anti-TNF agent. Secondary failure of one drug may portend a higher risk of a similar response for subsequent biologic therapies. Concomitant use of methotrexate has been shown to reduce the risk of secondary failure due to immunogenicity.21-33

A WORD ABOUT BIOSIMILARS

Biosimilars have arrived and will be a growing part of the treatment armamentarium. In all likelihood, biosimilars for etanercept, adalimumab, and infliximab will be monitored identically when compared with their reference drug (Enbrel, Humira, and Remicade, respectively). Biosimilars are being put through a rigorous approval process and are manufactured by very experienced pharmaceutical companies, most of which already manufacture branded biologic medications. There is currently little reason to believe biosimilars will be associated with novel safety issues. However, at this time, robust post-marketing safety and surveillance programs for biosimilars are either non-existent or very immature. In fact, there is no formalized system in place, and such a system would be very hard to develop if lax interchangeability rules allow undetectable and frequent switching between branded and biosimilar versions of the same drug. This might be the greatest unmet need with regard to biosimilars. Lacking is the infrastructure to detect and reliably ascribe rare yet real safety events.

CONCLUSIONS

Biologics provide a safe and effective treatment option for most psoriasis patients.

As a general rule, all patients starting a biologic therapy should have baseline testing including complete blood cell count, comprehensive metabolic panel, and screening for hepatitis B, C, and latent tuberculosis. Special considerations and more fastidious on-treatment monitoring should be given to patients with pre-existing risks associated with any specific biologic therapy.

As additional biologic therapies are approved for the treatment of psoriasis and as patients remain on these medications for longer periods of time, we will likely need to update and revise our monitoring protocols to either more or less stringent standards. ■

Bruce Strober, MD PhD, is the Professor and Chair of the Department of Dermatology at the University of Connecticut Health Center in Farmington, CT. He can be reached at strober@uchc.edu.