

Biologic Therapy and Risk of Infection

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ABSTRACT

Biologic compounds are being used more frequently to treat a multitude of systemic inflammatory conditions. These novel compounds are composed of antibodies or other peptides that act through one of three mechanisms: inhibiting inflammatory cytokine signaling (typically tumor necrosis factor or TNF), inhibiting T-cell activation, or depleting B-cells. The increase in use and ever expanding list of new immune modulating therapies make knowledge of the infectious complications associated with immune modulation even more important. Of particular concern is the risk for developing atypical and opportunistic infections including tuberculosis, herpes zoster, Legionella pneumophila, and Listeria monocytogenes.

Key words: adverse effects, anti-tumor necrosis factor-alpha, infections, monoclonal antibodies, psoriasis, risk factors, TNF- α inhibitors

Background

The availability of immune modulating drugs has revolutionized treatment for psoriasis and psoriatic arthritis, as well as a variety of other inflammatory diseases. After approximately one decade of post-marketing surveillance and experience with biologics, they are generally regarded as safe and efficacious therapy for an increasing number of diseases. However, the risk of infection is a concern with long-term immunosuppressive treatment. We review current literature regarding the risk of infection associated with the biologic therapies most commonly used by dermatologists today: tumor necrosis factor-alpha (TNF- α) inhibitors and ustekinumab.

Infliximab (a chimeric monoclonal anti-TNF antibody) (Remicade[®]), adalimumab (a fully human anti-TNF monoclonal antibody) (Humira[®]), and etanercept (a recombinant soluble decoy TNF-receptor) (Enbrel[®]) exert therapeutic effects via the suppression of TNF- α , a cytokine released by macrophages that is central to cell-mediated immunity.

Ustekinumab (Stelara[®]), an interleukin 12 and interleukin 23 antibody, targets the p40 subunit shared by the two cytokines to prevent receptor interaction, thereby inhibiting signaling and further cytokine production. Pooled data from phase 2 and 3 clinical trials suggest that there is no clear pattern of heightened infection risk compared with controls (placebo, etanercept) for up to 3 years.¹ However, ustekinumab has only been US FDA approved since 2009, so knowledge of long-term risk is limited. Some associations have been reported and are outlined below.

Herpes Zoster

Available evidence regarding the risk of herpes zoster (HZ) with TNF- α therapy is conflicting. One retrospective analysis of psoriasis patients treated with anti-TNF therapy, acitretin, cyclosporine, methotrexate, corticosteroids, UVB phototherapy, or PUVA showed an elevated incidence of HZ infection in patients receiving any treatment except alefacept, efalizumab, or adalimumab when compared with controls (patients without any treatment for 1 month or without treatment for 3 months if most recent treatment was infliximab). None of the biologic drugs studied were associated with a clinically significant increased risk of HZ, however, treatment with infliximab approached clinical significance (hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 0.92-3.43).²

Strangfeld et al. demonstrated a significantly higher risk of HZ in rheumatoid arthritis (RA) patients treated with etanercept, infliximab, or adalimumab compared with conventional disease-modifying antirheumatic drugs (DMARDs). The crude incidence rate per 1000 person-years of HZ was 11.1 (95% CI: 7.9-15.1) for infliximab or adalimumab, 8.9 (95% CI: 5.6-13.3) for etanercept, and 5.6 (95% CI: 3.6-8.3) for conventional RA treatments. Adjustments for age, rheumatoid arthritis severity, and glucocorticoid use demonstrated a significantly higher risk with treatment using monoclonal antibodies (HR: -1.82 [95% CI: -1.05-3.15]), but not for etanercept or the anti-TNF- α antagonists as a class.³

While ustekinumab was not included in the aforementioned studies, there is a report of two patients developing severe, multidermatomal herpes zoster 1 and 9 months after initiating therapy with ustekinumab. Vaccination against HZ is strongly encouraged before initiating therapy with ustekinumab.⁴ Currently, there are no clear recommendations regarding HZ vaccine (Zostavax®) administration during treatment with TNF- α inhibitors. Interestingly, results of a recent study suggest that treatment with TNF- α inhibitors may be associated with a lower incidence of postherpetic neuralgia,⁵ this finding is also supported by Strangfeld's data³ as noted by Whitley in his editorial discussing the prevalence of herpes zoster during immunosuppressive therapy.⁶

Tuberculosis

The risk of latent tuberculosis (TB) reactivation in patients treated with biologics is well-established. A Cochrane review evaluating the adverse reactions of all biologic therapies (all TNF- α inhibitors, anakinra, tocilizumab, abatacept, and rituximab) for any indication found an increased risk of TB reactivation (odds ratio [OR]: 4.68, 95% CI: 1.18-18.60) in comparison with the control treatment group, and a number needed to treat to harm (NNTH) of 681.⁷ Several of the drugs included in this review are not commonly used by dermatologists. A recent analysis of the risks associated with TNF- α inhibitors in psoriasis patients found that the lifetime risk of TB was 0-17.1% in comparison to 0.3% without the use of TNF- α inhibitors. The authors point out that while there is an increased risk, the risk of tuberculosis is still far lower than the lifetime risk of America's more common afflictions: cancer (40.4%), heart disease (36.2%), and stroke (18.4%).⁸

Variation in the risk of TB reactivation in patients treated with TNF- α inhibitors may be expected based on the endemic rates of TB. A recent Spanish study of psoriasis patients receiving any anti-TNF therapy found a 29% incidence of latent TB infection (LTBI), which was comparable to the incidence found in the general population.⁹ Conversely, a Swedish study found an increased risk of TB infection for RA patients compared with the general population. Treatment with either infliximab or etanercept was associated with a higher risk of TB in RA patients compared with RA patients not treated with TNF- α inhibitors.¹⁰

Among all TNF- α inhibitors, infliximab is the agent most heavily associated with greater risk of TB. A study of the FDA Adverse Event Reporting System (AERS) between 1998-2002 concluded an increased risk of developing TB for infliximab and etanercept users (144 per 100,000 infliximab-treated patients compared with 35 per 100,000 etanercept-treated patients, $p < 0.001$) with a rate ratio of 4.17.¹¹ In France, a case-control analysis of newly diagnosed TB associated with anti-TNF agents found that exposure to infliximab or adalimumab versus etanercept was an independent risk factor for TB, OR: 13.3 (95% CI: 2.6-69.0) and OR: 17.1 (95% CI: 3.6-80.6), respectively.¹²

Listeria monocytogenes

Infection with the intracellular bacterium *Listeria monocytogenes* (*L. monocytogenes*) in patients receiving biologic therapy is well-documented. An assessment of the incidence of *Listeria* infections in patients using TNF inhibitors was performed by

comparing data from the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) with the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR). RA patients treated with TNF- α antagonists had an increased rate of *Listeria* infection in comparison to RA patients treated with conventional therapy, as well as the general population.¹³

A recent review described the first case of *L. monocytogenes* endocarditis associated with infliximab, and identified 92 cases of *L. monocytogenes* infections related to infliximab treatment in the FDA AERS database. Meningitis was the most common type of infection reported (69 cases, 75%), followed by sepsis (20 cases, 21.7%) and listeriosis (3 cases, 3.3%). Further information was lacking on most of the cases in the AERS database, however, additional immunosuppressive therapy was being used in 22 out of 24 cases detailed in the review.¹⁴ Infectious complications with *Listeria* are seen more frequently in patient treated with infliximab versus etanercept,¹⁵ perhaps because of the more versatile binding of infliximab to both soluble and cell surface TNF- α instead of predominantly soluble TNF- α . However, there have been several cases of *L. monocytogenes* septic arthritis in patients treated with etanercept.¹⁵⁻¹⁷ Adalimumab is reported less frequently in association with *L. monocytogenes* infections, but a case of *L. monocytogenes* meningitis with this therapy has been documented.¹⁸

Legionella pneumophila

Legionella pneumophila (*L. pneumophila*) infections account for up to 15% of cases of community-acquired pneumonia requiring hospitalization.¹⁹ Antigenic components of *L. pneumophila* are potent stimuli of TNF- α production, which along with interferon-gamma, interleukin-6, and interleukin-1 drive induction of the innate immune response. Inhibiting this response with TNF- α antagonists should predispose to legionellosis.

In France, a registry of 486 multidisciplinary clinical departments was designed by Recherché Axée sur la Tolérance des Biothérapies (RATIO) to prospectively collect data on severe and opportunistic infections in people receiving TNF- α antagonists over a 1-year period. There were 10 cases of *L. pneumophila* infections; 6 of the patients were treated with adalimumab, 2 with etanercept, and 2 with infliximab. The median duration of therapy when infection occurred was 38.5 weeks. The relative risk of *L. pneumophila* infection in people receiving anti-TNF therapy was reported as 16.7-21.0 in comparison with the general population. However, this may be an overestimate as 9 out of 10 patients were receiving concomitant immunosuppressive therapy (prednisone, methotrexate, azothioprine, or sulfasalazine), except for one, who was receiving infliximab alone.²⁰ A recent case review of the incidence of legionellosis in patients receiving infliximab included 10 cases¹⁹ in addition to those reported by the French registry;²⁰ concomitant immunosuppressive therapy was being used in at least 8 out of 10 of those cases.¹⁹ A British study comparing rates of infection in rheumatoid arthritis patients receiving DMARDs therapy versus TNF inhibitors (etanercept, infliximab, adalimumab, and anakinra) found that the rate of serious infection was equal in both cohorts, but a higher rate of infection with intracellular microbes (*Legionella*, *Listeria*, and *Salmonella*) occurred in those using TNF inhibitors.²¹

While the exact relative risk of developing *L. pneumophila* during treatment with TNF inhibitors is difficult to predict, there seems to be a clear association in the literature. It is important for clinicians to be mindful of this association and to consider adding fluoroquinolone or macrolide antibiotics for coverage of *Legionella* (and other agents of atypical pneumonia) in patients on anti-TNF- α therapy who present with pulmonary symptoms.

Fungal Infections

In 2008, the FDA issued a 'black box warning' to alert clinicians of the risk of endemic mycoses in patients receiving anti-TNF- α therapy. The report included 240 cases of histoplasmosis in patients treated with infliximab, etanercept, or adalimumab. Most cases occurred in areas where the fungus is most prevalent. The most concerning point raised by this report was that in 21 patients, the signs of infection was unrecognized and antifungal therapy was delayed; 12 of those patients died.²² A recent review addressed challenges of diagnosing fungal infections in patients receiving TNF- α antagonists: atypical presentation and symptoms of infection mimicking the underlying disease. The higher incidence of *Histoplasmosis capsulatum* (*H. capsulatum*) compared to *Blastomyces dermatitidis* or *Coccidioides spp.* in patients taking TNF- α inhibitors is attributed to the wide geographic area of *H. capsulatum*, as well as the fact that infection with *H. capsulatum* is contained almost exclusively by cell-mediated immunity.²³ Multiple cases of aspergillosis have also been associated with TNF- α antagonists.²⁴

In patients who are starting treatment with TNF- α antagonists, there is no reliable method to predict the risk for acquiring fungal infections. However, patients should be counseled to avoid high-risk activities that may predispose them to exposure to the endemic mycosis in their geographic areas.²⁵ Patients who develop endemic fungal infection while receiving TNF- α inhibitors should immediately discontinue the biologic and initiate therapy with antifungal agents in concordance with the Infectious Diseases Society of America guidelines for treatment of these infections in immunocompromised hosts.²³

Conclusion

The risk of infection is always a concern with any immunosuppressive treatment, and such infections are documented with all biologic therapies. Of the TNF inhibitors, infliximab seems to carry the highest risk of infection. In comparison to infliximab, use of etanercept (HR: 0.64, 95% CI: 0.49-0.84), abatacept (HR: 0.68, 95% CI: 0.48-0.96), rituximab (HR: 0.81, 95% CI: 0.55-1.20), and adalimumab (HR: 0.52, 95% CI: 0.39-0.72) was associated with lower rates of hospitalized infections, although the authors attributed variability in patients' risk of infection to factors other than treatment with biologics.²⁶ Additionally, a 3-year national French registry (RATIO) study comparing incidence of non-tuberculosis opportunistic infections (45 cases in 43 patients) between TNF- α inhibitors found that risk factors were infliximab (OR: 17.6 [95% CI: 4.3-72.9]; $p < 0.0001$) or adalimumab (OR: 10.0 [95% CI: 2.3 to 44.4]; $p = 0.002$) versus etanercept.²⁷

Still, it is difficult to predict the true risk to patients commonly seen in the dermatologist's clinic when: 1) Most reviews of biologics-associated opportunistic infections are comprised of patients being treated for conditions other than psoriasis and

2) Most cases of opportunistic infections associated with biologic therapy occur when additional systemic immunosuppressive therapy is being utilized. Variation in dates of approval for these medications also translates to variation in experience.

The overwhelming majority of evidence supports the idea that biologics are safe for the treatment of psoriasis. Grijalva et al. recently published the results of a US multi-institutional collaboration examining whether or not TNF- α antagonists are associated with an increased risk of serious infections requiring hospitalization in comparison to non-biologic therapy.²⁸ The cohorts studied included 10,484 RA, 2,323 inflammatory bowel disease, and 3,215 psoriasis and spondyloarthropathies. In total, 1,172 serious infections were identified, the majority of which (53%) included pneumonia and skin and soft tissue infections. The conclusion was that TNF- α inhibitors are in fact, not associated with an increased risk for hospitalization for serious infection.²⁸ These findings contradict a general, replicated pattern seen in previous studies evaluating the safety of TNF- α antagonists, i.e., that there is a higher rate of serious infection in patients taking anti-TNF- α therapy compared to patients using non-biologic therapy that decreases with time. Dixon and Felson's editorial²⁹ addressed the question of why the time-dependent risk of serious infection was not seen in Grijalva's report. The authors attribute this finding to the unique design of Grijalva's study, i.e., comparing the risk of serious infections between new user cohorts, not between patients *initiating* treatment with anti-TNF- α therapy versus those *receiving* treatment with non-biologic agents. In other words, the time-dependent risk may disappear when both cohorts are examined at the same point in their course of treatment.²⁹ Of course, this finding has yet to be replicated, but it does warrant a re-evaluation of the safety of anti-TNF- α therapy. Most would agree that the benefits of biologics outweigh the risks and that clinical practice measures such as screening, prevention, and vigilance are effective in limiting the risk of potential opportunistic infections associated with immunotherapy.

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