Opportunistic Infections in Biological Therapy, Risk and Prevention

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KEYWORDS

• Opportunistic infection • Biologics • Tuberculosis • Zoster • Histoplasmosis
• Pneumocystosis

KEY POINTS

- The risk of opportunistic infections is increased with use of biological therapies.
- The risk of tuberculosis (TB) is increased with anti–tumor necrosis factor (TNF) therapy, and monoclonal antibodies (infliximab, adalimumab) have a higher risk of TB reactivation than etanercept.
- Anti-TNF therapy and tofacitinib are associated with an increased risk of zoster in patients with immune-mediated inflammatory diseases.

INTRODUCTION

Treatment of immune-mediated inflammatory diseases (IMIDs) with biological therapies has resulted in substantial improvement in patient symptoms and has slowed the natural progression of these often-debilitating conditions. Although these therapies have improved the quality of life for many patients, a consequence of biological therapies has been an increased risk of opportunistic infection (OI). In many patients, depending on the underlying disease, there already may be an increased baseline risk of infection independent of disease-modifying therapy.[1,2] A recent meta-analysis of 70 trials including more than 32,000 patients identified an overall increased risk of OIs at 1.7 excess infections per 1000 patients treated with biologics.[3] After the US Food and Drug Administration (FDA) approved infliximab for the treatment of Crohn disease (CD) in 1998, much of the early knowledge on the risk for OIs in the postmarketing period

Disclosures: P.A. Bryant: none; J.W. Baddley: consulting for Merck, Pfizer. Research grant from BMS.
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Rheum Dis Clin N Am 43 (2017) 27–41
http://dx.doi.org/10.1016/j.rdc.2016.09.005
rheumatic.theclinics.com

has come from spontaneous reporting and relied heavily on point-of-care diagnoses. Since that time, newer biological agents with variable mechanisms of action have been approved for a variety of conditions.

Previous reports have shown an increased risk of OIs, serious infections, and hospitalization among users of biologics.[4–7] The French RATIO (Research Axed on Tolerance of Biotherapies) study evaluated nontuberculosis OI risk in patients on anti–tumor necrosis factor (TNF) therapy for any indication and found that infliximab (odds ratio [OR] 17.6) and adalimumab (OR 10.0) carried an increased risk for OIs compared with etanercept.[8] The US Safety Assessment of Biologic Therapy (SABER) study found a higher rate of nonviral OIs among a large cohort of new users of TNF inhibitors (n = 33,324) versus those initiating therapy with nonbiological disease-modifying antirheumatic drugs (DMARDs).[9] In the study's rheumatoid arthritis (RA) cohort, new infliximab users experienced a higher rate of nonviral OIs compared with both nonbiological DMARD users (adjusted hazard ratio [aHR] 2.6) and etanercept users (aHR 2.9).

In contrast, a smaller (n = 570) prospective Japanese study evaluating OI incidence in patients with inflammatory bowel disease (IBD) found no increased risk of OIs among patients on infliximab over a 12-month period but did show a risk with other immunosuppressants and increasing age.[10] A Japanese anti-TNF agent switch study found increased incidence of OIs in the first year of treatment with TNF inhibitors,[11] similar to findings in a retrospective Spanish study showing an increased risk of OIs in the first year of therapy with infliximab.[12] Additional TNF antagonists, such as certolizumab pegol and golimumab, as well as targeted drugs with differing mechanisms of action, such as belimumab, rituximab, tocilizumab, ustekinumab, abatacept, anakinra, and tofacitinib, have also been studied; but data are limited to controlled trials.[13–16]

A major challenge in studying and defining OI risk lies in providing a workable OI case definition. OIs are often difficult to define, and reaching a consensus definition across studies within the area of biological therapy has proven challenging. Although OIs have been more consistently defined within certain diseases, such as human immunodeficiency virus (HIV) infection,[17] this is not the case for biologics. A recent review sought to define OIs in the setting of biologics and provide case definitions for specific candidate pathogens.[18] Although the investigators did reach consensus, they noted that prior attempts to define OIs with the use of biologics have been inconsistent, resulting in wide-ranging OI risk estimates. Herein, the authors review the risk of OIs in biological therapy, with a focus on several major OIs and the most rigorously studied biologics.

TUBERCULOSIS

Incidence and Drug-Specific Risk

Disease due to *Mycobacterium tuberculosis* remains a major cause of morbidity and mortality, with an estimated 9.6 million cases of incident tuberculosis (TB) worldwide in 2014 according to the most recent World Health Organization's Global Tuberculosis Report.[19] TB has been increasingly reported in patients receiving treatment with biological therapies for a variety of indications since the early 2000s, emphasizing its importance as an opportunistic pathogen. In 2001, Keane and colleagues[20] reported 70 cases of TB in patients on infliximab received through the FDA Adverse Event Reporting System as of May 2001. Cases developed a median of 12 weeks after initiation of therapy, underscoring the need to screen for latent TB infection (LTBI) and disease, especially in areas of high endemicity.

Early studies from North America and Europe found an increased incidence of TB associated with initiation of anti-TNF-α therapy (**Table 1**).[29–32] Surveillance studies