Preface

Infections Related to Biologics

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Editors

Biologics as a class of therapeutics are revolutionizing medicine by providing successful new treatment options for cancers, autoimmune diseases, neurodegenerative conditions, and many other devastating diseases. These drugs are large molecules that are manufactured using recombinant DNA technology in living systems, such as bacterial, fungal, animal, or plant cells. The field has expanded rapidly since 1982, when the first recombinant form of human insulin was approved by the Food and Drug Administration (FDA).\(^1\) Today the vast majority of the world’s top-selling medications are biologics. However, there were initial public fears of recombinant DNA technology, and there have been setbacks, such as when centoxin, a monoclonal antibody against the lipid A moiety of endotoxin thought to have great promise in gram-negative sepsis, was not approved by the FDA in 1992.\(^2\) Thankfully, many hurdles were successfully overcome, and numerous biologic agents are now available to patients for previously untreatable conditions. There are currently over 1000 biologics in development, and the global biologics market is forecast to exceed $285 billion by 2023.\(^3\)

Along with the promise of great benefit from the immunomodulatory effects of these biologics comes the risk of unintended consequences, including infection. Over the years it has become clear that each of these classes of agents has unique infectious risks that often correspond to their direct or indirect targets in the immune system.\(^4\) The challenge for care providers is how to screen prior to administering the agents, what prophylaxis and preventative measures may be required, and how to predict for which infections to maintain a high index of suspicion.

When deciding on prophylaxis or treatment with antibiotics, there are multiple considerations to keep in mind. Not only do clinicians need to avoid promoting antimicrobial resistance with overuse of antibiotics, but also there are data showing that the use of antibiotics can render the biologic agents less effective through their effects on the gut microbiome.\(^5\) Therefore, a thoughtful approach to understanding the
infection risks of individual agents and providing prevention strategies is essential. Given the explosion of new agents on the market, it is becoming increasingly difficult for clinicians to keep up with such data. In this issue of *Infectious Diseases Clinics of North America*, the authors seek to provide timely guidance for clinicians caring for patients who are on biologics, by discussing the different classes of biologics and their infection risks in the first eight articles, then providing a survey of important infections potentiated by biologics with strategies to mitigate their risks in the following six articles.

This issue first addresses biologic drugs targeting B cells, which are widely used in treating B-cell proliferative malignancies and diseases where autoantibody production is responsible for pathologic condition. Their specific infection risks can be difficult to tease out given the frequent coadministration of other immunosuppressive agents, but there are unique risks that are critical for care providers to understand, with hepatitis B reactivation being a prominent example. Interestingly, the risks are not limited to the direct effects of hypogammaglobulinemia alone, so a nuanced look at these agents is required.

The next two articles address agents targeting T-cell activation, the majority of which are used in rheumatoid arthritis and psoriasis, and agents that directly inhibit T-cells function or target T-cell migration and chemotaxis, some of which are used to treat multiple sclerosis. The rates of serious infection are low with many of these drugs, with the exception of those like alemtuzumab. This agent can cause profound CD4⁺ cell depletion and confers higher risks of infections, such as *Pneumocystis jirovecii* pneumonia.

Biologics that target the interleukin-1 (IL-1) and IL-6 pathways diminish inflammatory responses to pathogens and increase the risk of bacterial and opportunistic infections, while those that target the T-helper 2 cell pathway do not carry these same risks. Immune checkpoint inhibitors are being successfully used to treat a variety of solid tumors, improving outcomes in these conditions that were previously fatal. Unfortunate consequences of these agents include a 40% risk of immune-related adverse events, which often require the use of corticosteroids or other immunosuppressive agents. The infectious complications related to checkpoint inhibitors therefore include those related to the use of this enhanced immunosuppression as well.

Tyrosine kinase inhibitors (TKI) have demonstrated great success for patients with many hematologic diseases. Patients often are at risk of infections due to their underlying malignancy and prior chemotherapy, but understanding the additive risk of TKI is important. The TKIs used for solid tumors, including epidermal growth factor receptor inhibitors, are discussed separately, as are agents used to target the JAK-STAT signaling and complement pathways to abrogate inflammation.

The next six articles discuss important viral, fungal, and mycobacterial infections potentiated by biologics. There are existing guidelines on prophylaxis for herpesviruses, such as herpes simplex virus, varicella-zoster virus, and cytomegalovirus, in solid organ transplant and hematopoietic cell transplant recipients. However, strategies for prevention of reactivation of these viruses in patients on biologic agents are not available. Understanding which biologic agents potentiate the reactivation of herpesviruses is critical to targeting appropriate prevention strategies. Progressive multifocal leukoencephalopathy caused by JC polyomavirus can be a devastating opportunistic infection. Exploring the pathogenesis of JC polyomavirus and which biologics increase the risk of this condition is covered by the authors in this issue. Furthermore, a very important infectious risk for certain biologics is hepatitis B virus reactivation. This is preventable with the correct prophylactic approach; thus the authors’ guidance in this area is very helpful.
Fungal infections can cause high morbidity and mortality and are especially important to consider with immunosuppression. The risk of certain fungal infections can be geographically limited, so correlating the epidemiology of infection to the biologic agents that increase the risks is key to correct diagnosis and treatment. Tumor necrosis factor-alpha inhibitors can especially predispose patients to both fungal and mycobacterial infections. The diagnosis of mycobacterial infections requires a high index of suspicion. In the 13th article, the authors discuss when screening for *Mycobacterium tuberculosis* is indicated and in which situations to consider nontuberculous mycobacterial infections.

One of the most important weapons in our armamentarium against infection is vaccination. The final article in this issue discusses the optimal use of vaccines in patients on biologics. Timing of immunization is important as vaccines should generally be given prior to starting immunosuppressive agents to optimize their efficacy and to reduce adverse effects when live vaccines are concerned. Understanding whom to target with vaccinations to maximize benefit while minimizing risk is the focus.

We are thankful to Consulting Editor, Dr Helen Boucher and Developmental Editor Donald Mumford, for inviting us to compile this issue on infections in biologics. We are especially thankful to all the authors, who are truly experts in their field, for their outstanding contributions to this issue of *Infectious Disease Clinics of North America*. The topics they have covered in great depth are of immense importance to practicing clinicians. The number of biologics and the indications for their use are growing exponentially. They provide great hope and promise for many of our patients. We truly believe the information and strategies covered in this issue will help clinicians mitigate the risk of infection associated with the use of these new agents and improve patient outcomes.

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REFERENCES


