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Pharmacovigilance Considerations for Therapeutic Biologic Protein Products

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In medicine, the term "biologic" refers to a wide range of medicinal products. These can include blood, blood components, vaccines, allergenics, recombinant therapeutic proteins, somatic cells, gene therapy, and tissues. Biologic agents may consist of cells or tissues, or they may be composed of proteins, carbohydrates, nucleic acids, or combinations thereof. These products may be extracted from a biological source, or they may be produced by biotechnology techniques. In contrast, medicinal products traditionally termed "drugs" are non-protein, organic, small-molecule substances that are generally chemically synthesized.

This article will focus on the special pharmacovigilance considerations in the post-approval evaluation of therapeutic biologic proteins. While pharmacovigilance for all biologic products is important, the therapeutic biologic proteins are often prescribed in the same clinical settings as are small-molecule drugs, so that comparisons and contrasts between the approaches to pharmacovigilance between these two types of therapies can be made. In contrast, approaches to post-approval safety monitoring of vaccines, blood and blood components, and other biologic products present issues that are beyond the scope of this article.

In the past two decades, and especially in the past decade, increased attention has been paid to therapeutic biologic proteins, as more and more have been developed and become available for clinical use. Like traditional drug therapies, therapeutic biologic proteins undergo pre-approval testing. Efficacy for the treatment of the intended condition must be demonstrated, and the safety profile of the product is characterized. Like drug therapies, the complete safety profile of the therapeutic biologic protein is incompletely understood at the time of approval. As with traditional drug products, more widespread use of a product

leads to its use in more clinically diverse populations, relative to those tested in clinical trials. Similarly, more widespread use can involve use of doses different from those that were studied, for treatment of conditions that have not been studied, and with a wider variety of concomitant medications than those permitted in clinical trials. However, there are certain aspects of therapeutic biologic proteins that require special attention in the post-approval safety monitoring.

One important characteristic of therapeutic biologic protein products is their capacity to induce immunogenicity¹. Many factors can affect the development of an immune response to the product. Protein structure, glycosylation, formulation, and degradation products can each contribute to this effect, as can the dose, dosing regimen, route of administration, and concomitant use of other immunomodulators. In some cases, the development of an immune response to a therapeutic biologic protein can decrease the efficacy of the product, with only mild adverse events. However, in other cases, immune responses can lead to serious, and sometimes fatal, adverse events. For example, the development of neutralizing antierythropoietin antibodies in patients who have received certain erythropoietin products led, in some cases, to the development of pure red-cell aplasia². Immune complex diseases, such as glomerulonephritis, vasculitis, and arthritis, can also be complications of treatment with therapeutic biologic protein products. Thus, when clinicians and pharmacovigilance experts review serious adverse events in patients receiving therapeutic biologic protein products, they must consider immunogenicity and immune-mediated reactions as causes of the adverse events. In addition to antigen-antibody binding phenomena, anaphylactic (IgE-mediated) and anaphylactoid (non-IgE-mediated) infusion reactions can occur with therapeutic biologic protein products. Because the manifestations of these reactions can be broad, and at times non-specific, it is important that review of adverse events include searching for broad range of reactions that could be manifestations of an infusion reaction.

Many therapeutic biologic protein products are immunosuppressants or immunomodulators, though the specific mechanism of immunosuppression may vary from one agent to the next. When these biological properties are present, there are risk of opportunistic infection and malignancies that raise challenges for pharmacovigilance systems. While standard passive, spontaneous adverse event reporting systems are well suited to detecting adverse events that occur relatively shortly after treatment with a medicinal agent begins, they are generally not well suited to detecting adverse events that occur several months or years after a medication is begun. Thus, when reviewing reports of opportunistic infections or malignancies, it is important to review the time course of each potentially immunosuppressant medication the patient is receiving or has received. In addition, it is important to understand the cumulative dose of the agent that the patient has received. The time to clinical recognition of opportunistic infections and malignancies may vary considerably from agent to agent, and may also vary from patient to patient receiving the same agent. Because spontaneous reports do not allow for full population-based assessment of the range of opportunistic outcomes in patients receiving immunosuppressant agents, other methods, such as registries that capture the short- and long-term outcome of patients treated with immunosuppressant agents, can provide valuable information on the frequency and time course of these outcomes. Importantly, registries can help shed light on whether an opportunistic process can occur with monotherapy with the product, or if it occurs more frequently when the product is used with other immunosuppressant agents.

Are adverse events more common with biologic products than with small-molecule medications? The answer is not known for sure, but a recent publication looking at safety-related regulatory actions for biological in the United States and the European Union recently began to examine this issue³. The researchers found that the probability of a first safety-related regulatory action was 14% three years after approval, and 29% 10 years after approval. Administration site reactions, infections, neoplasms, and immune system disorders were the subject of most of the safety-related regulatory actions. After ten years, 17% of products in the United States had received a Boxed Warning. The authors noted that Lasser and colleagues⁴ had found a 10-year probability of receiving a Boxed Warning of 10%. While they noted differences between their study and that of Lasser and colleagues, they suggested that biologic products may be more likely to receive boxed warnings than other products.

In sum, therapeutic biologic protein products require careful post-approval safety monitoring, with particular attention to immune-mediated adverse events, infusion reactions, and, for immunomodulatory agents, careful surveillance for opportunistic infections and malignancies.

References

- 1 Chamberlain P and Mire-Sluis AR. An Overview of Scientific and Regulatory Issues for the Immunogenicity of Biological Products. In Brow F, Mire-Sluis AR (eds): Immunogenicity of Therapeutic Biological Products. Dev Biol. Basel, Karger, 2003; vol 112, pp3-11.
- 2 Bennett CL, Luminari S, Nissenon AR, et al. Pure Red-Cell Aplasia and Epoetin Therapy. N Engl J Med -2004;351:1403-8.
- 3 Giezen TJ, Mantel-Teeuwisse AK, Strauss SMJM, Schellekens H, Leufkens HGM, and Egberts ACG. Safety-Related Regulatory Actions for Biological Approved in the United States and the European Union. JAMA 2008;300:1887-1896.
- 4 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein SM, Bor DH. Timing of new black box warnings and withdrawals for prescription drugs. JAMA 2006;295:2275-2285.