IgNS Immunoglobulin National Society

# CLINICAL UPDATE

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# Beyond Infection: The Realities of Primary Immunodeficiency

**Lesson 1**
*Secondary Immune Deficiencies From Biological Agents*
**Mark Ballow, MD**

**Lesson 2**
*Autoinflammatory Disorders*
**Lori Broderick, MD, PhD**

**Lesson 3**
*Immune Dysregulation – A New Facet of Primary Immunodeficiency Disease (PIDD)*
**Jennifer Leiding, MD**

**Lesson 4**
*Pulmonary Complications of Primary Immunodeficiency*
**Paul J. Maglione, MD, PhD**

**Lesson 5**
*The Complex PI Patient: The Tangled Web of Immunodeficiency and Its Complications*
**Richard Wasserman, MD, PhD**

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# Secondary Immune Deficiencies from Biological Agents

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## OBJECTIVES

1. Review the nomenclature for monoclonal antibodies
2. Understand the mechanisms for prolonged hypogammaglobulinemia with Rituximab
3. Review the immune and infectious consequences of some of the most frequently used biologics on the immune system
4. Review the adverse effects of immune check point inhibitors

### Introduction

There are many risk factors for the adverse effects of drug therapy. These factors include the action of the drug itself, the dose that is used for the drug, and the duration of treatment with the medication. For example, a patient who receives a drug while undergoing stem cell transplant for malignancy may have more immune complications than a patient receiving the drug for chronic stable disease. Hospitalized patients and the elderly are more likely to develop immune complications from medication.

Drugs used for the treatment of rheumatic disease or anti-inflammatory medication can cause decreases in immunoglobulin levels. Anticonvulsants, particularly phenytoin anticonvulsants, may lower serum IgA. The mechanism for this drug-induced hypogammaglobulinemia is not known.

In this presentation, we will discuss the secondary immune deficiencies caused by biologic drugs.[1] A biologic drug is a medicinal product that is produced from living organisms. Biologic products may contain proteins that control the action of other proteins or cellular processes, such as gene transcription, hormone regulation, or regulation of the immune system. Biologic drugs are sometimes referred to as *biologic response modifiers* because they change the manner of operation of natural biologic intracellular and cellular actions.

Biologic response modifiers include substances that are nearly identical to the body's own key signaling proteins. Some are receptor constructs that mimic a receptor on the surface of a cell and are usually linked to the constant region of the immunoglobulin frame. Others are monoclonal antibodies similar to the antibodies of the human immune system used to fight off bacteria and viruses. These monoclonal antibodies are custom designed and may be produced to specifically counteract or block a given substance in the body or to target a specific cell type to achieve a specific therapeutic effect. The nomenclature for monoclonal antibodies is shown in Table 1. In addition to their therapeutic effects, biologics can have unintended effects on the immune system that can compromise host defenses and lead to serious infections.

### Monoclonal antibodies to B cells

Rituximab (Rituxan) is a *chimeric* human mouse monoclonal antibody used for the treatment of hematological malignancies and autoimmune diseases. It is directed at the CD20 receptor expressed on B lymphocytes (B cells). Treatment with this monoclonal antibody results in a rapid depletion of B cells. It may take 9 to 12 months for the B cells to return after treatment is completed. However, if therapy is coupled with chemotherapy, B cell recovery may take 18 to 24 months. Typically, when the B cells recover, the majority of patients do not have any residual immune dysfunction that may result in infections. In most patients, rituximab does not significantly reduce the levels of existing antibodies. However, a subset of patients develops hypogammaglobulinemia, which can be persistent and clinically significant, resulting in serious infections and necessitating antibiotic prophylaxis or immune globulin replacement therapy to prevent infections. In a small study by Kaplan et al., patients treated with rituximab who were receiving intravenous immunoglobulin (IVIG) because of infections and hypogammaglobulinemia were analyzed by retrospective chart review.[2] Eleven patients had received rituximab for autoimmune disorders or lymphoma. Nine patients had prolonged hypogammaglobinemia (13 to 54 months) after completion of the rituximab treatment. Five of these patients also had undetectable B cells. The authors hypothesized that patients who develop recurrent infections while on rituximab treatment may have some type of baseline subclinical immune dysfunction that is unmasked and/or augmented by rituximab. Barmettler et al. reported on a large retrospective cohort study of 4479 patients who had received rituximab at a large tertiary referral medical center.[3] Eighty-five percent of the patients did not have their immunoglobulin levels checked before therapy. Of those who had levels measured, 48% had low serum IgG levels before rituximab. Following treatment with rituximab, the serum IgG levels were reduced even lower. Many of these patients had severe infections. Increased mortality was associated with age, male sex, and prior complications of severe infection. A total of 4.5% received immunoglobulin therapy following rituximab therapy to reduce the risk of serious infection. These authors concluded that many patients are not screened for low serum IgG levels prior to or after rituximab therapy. Screening these patients before and after therapy may allow for earlier identification of patients at risk, and help identify patients who may benefit from immunoglobulin replacement therapy. Rituximab therapy may impair vaccine responses, especially to polysaccharide vaccines. Immunization prior to starting rituximab therapy is recommended. A common question is how long to use immunoglobulin replacement therapy for hypogammaglobulinemia after rituximab therapy. Barmettler and Price[4] have suggested that in patients who recover B cells but who have prolonged hypogammaglobulinemia it may be helpful to measure switched ($CD27^+IgD^-IgM^-$) or unswitched ($CD27^+ IgM^+$) memory B cells. In those patients with a decrease in these B-cell subpopulations, health care providers may wish to continue immunoglobulin replacement therapy.

**TNF Inhibitors**

Blocking tumor necrosis factor (TNF) can markedly disrupt granuloma architecture and, ultimately, enable dissemination of mycobacteria. Patients are also at risk for other intracellular pathogens such as *Aspergillus fumigatus*, *Coccidioides* species (the causative agent of coccidioidomycosis), *Histoplasma capsulatum, Listeria monocytogenes,* and nontuberculous mycobacteria. The most frequent issue with TNF inhibitors is reactivation of latent mycobacteria, usually from the lung. Patients should be skin tested and have a chest X-ray prior to therapy. The risk is higher with infliximab (Remicade, Inflectra, and other brand names) and adalimumab (Humira) than with etanercept (Enbrel). Other biologics may also be associated with reactivation of mycobacteria. Abatacept (Orencia) and tocilizumab (Actemra) have an intermediate risk of causing reactivation, and anakinra (Kineret) and rituximab have a low risk of reactivating tuberculosis (TB). Older age, diabetes, smoking, glucocorticoid dose, and previous infection history are important risk factors for serious infections. The most serious infections occur within the first 1–2 years of exposure to biologics, with the highest risk in the first few months of biologic use. Patients on these biologics should not receive live viral vaccines. Influenza vaccines administered by injection are without risk.

**Complement inhibitors**

Eculizumab (Soliris) is a humanized monoclonal antibody that blocks the cleavage and activity of complement factor 5 (C5). This monoclonal biologic is approved for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS)- associated thrombotic microangiopathy. Eculizumab increases the risk of infection by inhibition of complement effector mechanisms (C5–C9). The most common infection associated with Eculizumab is *Neisseria meningitidis.* Other infections include those associated with *Pseudomonas aeruginosa*, *Aspergillus* species, and herpes simplex viruses.

**Biologics directed at cytokines**

There are many biologic therapies that target cytokines directly. Some of these are shown in Table 2. For the most part, these biologics have few adverse effects and generally do not cause an increase in infectious disease susceptibility. The IL-1 blocking agents (e.g., anakinra, canakinumab [Ilaris], and rilonacept [Arcalyst]) have been an important therapeutic approach in the treatment of several autoimmune and autoinflammatory diseases. Although they have been associated with an increased risk of respiratory infections, they are usually well tolerated. With the IL-5 blocking agents (e.g., mepolizumab [Nucala], reslizumab [Cinqair] and benralizumab [Fasenra]), published studies have not shown any significant increase in infections, although in two studies herpes zoster infections were reported in two patients treated with mepolizumab. The manufacturers suggest vaccination with herpes zoster vaccine and treatment of patients with pre-existing helminth infections. Dupilumab (Dupixent), a fully human monoclonal antibody directed at the alpha subunit of the IL-4 receptor, blocks both IL-4 and IL-13 signaling. It is approved for the treatment of moderate-to-severe atopic dermatitis and as add-on therapy for moderate-to-severe eosinophilic or steroid-dependent asthma. There are also several IL-17A blocking biologics. Secukinumab (Cosentyx) is approved for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. The major issue with this group of IL-17A inhibiting biologics is mucosal or cutaneous candidiasis.

A more serious infectious process related to JC virus (JCV) is progressive multifocal leukoencephalopathy (PML).[5] PML is caused by reactivation of latent polyoma JC virus. Cognitive impairment and behavioral changes are the earliest clinical manifestations. The diagnosis can be confirmed by quantitative detection of JCV DNA in the cerebrospinal fluid (CSF). Prior chemotherapy or immunosuppressive drug use increases the risk of PML by 2- to 4-fold. PML was first recognized with the use of natalizumab (Tysabri), a humanized monoclonal antibody against the cellular adhesion molecule α4-integrin, for treatment of multiple sclerosis and Crohn's disease. This biologic was removed from the market but subsequently reintroduced for multiple sclerosis. PML can occur with a number of biologics (see Table 2).

In summary, biologic therapies can be associated with a variety of adverse effects due to the fact that they target immune responses and host protection mechanisms that protect against environmental pathogens. The risk of immune complications and the type of infection is dictated by the specific biologic response modifier and its target(s). There are also patient-specific factors that play an important role such as the underlying disease, the patient's immune status and comorbid conditions, and the use of concomitant combinations of other immunosuppressive agents. The use of biologic agents to treat diseases is a rapidly growing field of medicine. Physicians and patients have to be vigilant when new biologic agents are being used due to the fact that phase III clinical trials used by the FDA to approve drugs may not have uncovered all possible adverse consequences in every patient population.

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**Table 1 Nomenclature for monoclonal antibodies**

- Suffix - *mab* - used for mAb
- Animal source of the mAb
  - Mouse - *omab*
  - Chimera - *ximab*
  - Humanized - *zumab*
  - Human – *umab*
- Disease or target class
  - Immune - lim (dac li(m) zumab)
  - Tumor - tum- (Ri tu(m) xi mab)
- Unique prefix -
  - Nata li(m) zu mab (Tysabri)
  - Mepo li(m) zu mab (Nucala)
  - Oma li(m) zu mab (Xolair)
  - Ada lim umab (Humira)
  - Cana kin umab (Ilaris)

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The use of stems in the selection of International Nonproprietary names (INN) for pharmaceutical substances. *World Health Organization, Geneva INN Working Document* 17.406 20/01/2017

**Table 2 | Secondary immunodeficiency induced by biologics**

| Biologic | FDA Approved | Target | Immune Effects | Infections |
|---|---|---|---|---|
| Abatacept | RA, kidney transplant, PJIA | B7-1/B7-2 | Disrupt CD28 co-stimulation | Pneumonia, cellulitis, UTI |
| Alemtuzumab | Chronic B-cell leukemia, MS | CD52 | Profound depletion of T cells (and B cells) | TB reactivation, DNA viruses, opportunistic |
| Basiliximab | Renal transplantation | CD25(IL-2R-a chain) | Block IL-2 receptor on T cells | CMV reactivation |
| Belimumab | SLE | BlyS/BAFF | B cells | Influenza, pneumonia, PML |
| Cetuximab | Metastatic colorectal cancer | Epidermal growth factor | Bind and inhibits Epidermal growth factor receptor | Anaphylactic reactions - IgE Abs to galactose-α-1,3 galactose (sensitization to lone star tick) |
| Eculizumab | PNH, aHUS | C5 | Binds C5/inhibits terminal C activation | Neisseria infections |
| IL-1 antagonist (anakinra, canakinumab, rilonacept) | RA, Periodic fever syndromes, SJIA | IL-1α and IL-1β | Block IL-1R – anakinra<br>Neutralize IL-1β – canakinumab<br>Neutralizes IL-1β - rilonacept (fusion protein IL-1 R components) | Bacterial and viral infections |
| Natalizumab | MS, Crohn | α4 integrin antagonist | Block migration of leukocytes into CNS | PML, CNS VZV and HSV |
| PD-1 antagonist (pembrolizumab, nivolumab) | Melanoma, NSCLC, HNSCC | PD-1 | Hypothyroidism, hepatitis, colitis, pneumonitis | 85% bacterial infections -pneumonia; other infections herpes viruses |
| Rituximab | NHL, CLL, GPA, RA | CD20 | Profound depletion of B cells | DNA viruses, PML, HBV and HCV, Parvovirus |
| Secukinumab | Psoriasis, AS | IL-17A | Block the IL-17 pathway | Candidiasis (2%-5%) |
| TNF inhibitors | RA, UC, Crohn, Psoriasis, AS, PJIA, Uveitis | TNF-α | Innate immune system | Mycobacterial infections (reactivation), fungal infections |
| Tocilizumab | RA, SJIA, PJIA | IL-6R | B cells, Treg cells | Pneumonia, HZ |
| Ustekinumab | Psoriasis, Crohn | P40 subunit (IL-12/IL-23) | Blocks IL-12 and IL-23 | URI, pneumonia |
| Vedolizumab | Crohn, UC | α4b7 antagonist | Block migration of gut homing lymphocytes | PML, URI |

aHUS – atypical hemolytic uremia syndrome, AS – ankylosing arthritis, AS – ankylosing spondylitis, CLL – chronic lymphocytic leukemia, CMV – cytomegalovirus, GPA – granulomatosis with polyangiitis, HBV – hepatitis B virus, HCV – hepatitis C virus, HNSCC – Head-neck squamous cell carcinoma, HSV-herpes simplex virus, HZ – herpes zoster, MS – multiple sclerosis, NHL–non-Hodgkin lymphoma, NSCLC – non-small cell lung cancer, PJIA – polyarticular juvenile idiopathic arthritis, PML – progressive multifocal leukoencephalitis (infection with JC virus), PNH – paroxysmal nocturnal hemoglobinuria, RA – rheumatoid arthritis, SJIA – systemic juvenile idiopathic arthritis, TB – tuberculosis, TNF– tumor necrosis factor, UC – ulcerative colitis, URI – upper respiratory infection, UTI – urinary tract infection, VZV – varicella zoster virus

Adapted from Davis BP and Ballas ZK [6] and Ballow M and Fleisher T[1]