REVIEW

# Immunologic Responses to Therapeutic Biologic Agents

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**Abstract**

Recombinant protein technology and the subsequent development of biologic agents for pharmacotherapy have greatly improved the treatment of a wide variety of diseases in humans. These products are subject to reactions not previously seen in other drug classes. Additionally, subtle alteration in the manufacture or administration of a biologic agent may cause reactions in subjects who previously tolerated it. This review highlights the unique immunologic reactions that are associated with the more commonly used biologic agents.

Key words: Biologic agents. Neutralizing antibody. Recombinant protein. Monoclonal antibody.

**Resumen**

La tecnología de las proteínas recombinantes y el posterior desarrollo de los fármacos biológicos para la farmacoterapia han mejorado de modo notable el tratamiento de una gran diversidad de enfermedades en seres humanos. Estos productos están sujetos a reacciones no observadas previamente con otras clases de fármacos. Además, la alteración más sutil en la elaboración o administración de un fármaco biológico puede causar reacciones en sujetos que previamente los toleraban. Esta revisión destaca las reacciones inmunitarias únicas que se relacionan con los fármacos biológicos utilizados más frecuentemente.

Palabras clave: Fármacos biológicos. Anticuerpo neutralizante. Proteína recombinante. Anticuerpo monoclonal.

## Introduction

Biologic agents are protein-based products derived from a living source such as bacteria, yeast, or mammalian cells used to treat diseases in humans. They include recombinant proteins, monoclonal antibodies, and fusion proteins. Since their introduction in the early 1980s, the development of biologic agents has exploded, and today there are over 60 approved for use by the US Food and Drug Administration [1]. Half of all novel pharmaceutical products are projected to be biologic agents by 2010 [2].

The introduction of recombinant protein technology and hybrid antibody technology has greatly improved the treatment of a vast spectrum of disease. However, medicine has yet to produce a therapeutic agent with no risk of adverse effects. As novel agents come to market and existing agents find new indications, there is a need to understand the known adverse effects of current biologic agents and remain vigilant for as yet unidentified outcomes. This review addresses the immunologic and allergic reactions associated with the most commonly prescribed biologic agents.

## Immunology and Biologic Agents

Nonbiologic molecules, such as penicillin, are not immunogenic per se but bind to carrier proteins to form a complex that is capable of inducing an immune response. Biologic agents are large globular proteins and as such can induce a range of immune responses. Adverse reactions can be as minor as local irritation or as serious as cardiovascular collapse [3]. Although immunoglobulin (Ig) E-mediated hypersensitivity to biologic agents occurs, it is uncommon. More frequently, neutralizing antibodies are responsible for adverse immune responses. As their name suggests, neutralizing antibodies bind the agent and prevent it from performing its intended biologic function. Rarely, these antibodies neutralize not only the recombinant protein but also the endogenously

produced analogues, with life-threatening consequences, as is the case with erythropoietin-induced pure red cell aplasia (PRCA) [4]. The immunogenicity (the tendency to cause an antibody response) of biologic agents is influenced by the molecule itself, the route of delivery, the degree of exposure, and the simultaneous use of immunosuppressive agents during administration, as well as other factors (Table 1).

Table 1. Factors Affecting Immunogenicity of Biologic Agents

| Production | Host | Administration |
|---|---|---|
| Presence of non-human protein sequences | Congenital deficiency | Route |
| Product contaminants | Atopy | Frequency |
| Oxidation | Immunosuppression | Use of immunosuppressants |
| Aggregation | | |
| Stabilizing agents | | |
| Storage medium/ temperature | | |
| Glycosylation | | |

Older biologic agents, such as streptokinase, are bacterial proteins and are highly immunogenic. In many cases, subjects exposed to these agents develop neutralizing antibodies, often after only a single dose. Subsequent administration of the agent results in a significantly reduced clinical response as it is neutralized by preformed antibodies. Host-specific factors also play a role in the immune response. Subjects with a congenital protein deficiency are less likely to recognize a therapeutic protein as "self" and are therefore more likely to mount an immune response. For example, hemophilia A patients who produce no factor VIII have a significantly higher rate of antibody formation compared to those who produce factor VIII but at reduced levels [5].

The emergence of recombinant protein technology has made the production of human analogue proteins possible. In theory, artificially producing a protein with an amino acid sequence identical to its human counterpart should result in a molecule with no adverse effects. In fact, experience has shown that unanticipated immune responses can and do occur for a variety of reasons. Compared to older, more immunogenic bacterial proteins, antibody formation to recombinant proteins occurs less frequently and requires longer periods of exposure, sometimes several years. The mechanism underlying the immune response to recombinant proteins appears to be a loss of immunogenic tolerance rather than a classic immune response to a foreign protein [6]. If these agents are discontinued, the antibodies may even disappear [7]. Intentional or unintentional alteration of protein structure is often implicated in antibody formation. After a recombinant protein is produced, many factors can contribute to alteration in protein structure to elicit an antibody response. Glycosylation, contaminants, temperature changes, and storage media can all play a role in protein alteration [4,8]. For example, an interferon (IFN) α formulation was found to oxidize at room temperature, changing the tertiary structure of the protein such that it generated an antibody response. Changing the formulation and storage procedures resulted in reduced antibody formation. Similar post-manufacturing structural changes have been implicated in other immune-mediated responses to recombinant proteins [4].

Although antibody formation is reported for all recombinant proteins, the clinical consequence is highly variable (Table 2). Many antibodies have no clinical effect, while others have adverse effects ranging from loss of efficacy to life-threatening disease, as in the case of PRCA.

Recombinant protein technology utilizes bacteria, such as *Escherichia coli*, or mammalian-derived cells, such as Chinese hamster ovary (CHO) cell lines, to produce human protein analogues from DNA templates. The first recombinant protein was produced in 1972, and the first drug based on recombinant DNA technology, recombinant insulin, was approved by the US Food and Drug Administration in 1982. Today there are over 70 recombinant products on the market that replace or supplement endogenous human proteins [9].

Table 2. Clinically Important Antibodies Against Biologic Agents

| Product | Antibody formation (%) | Consequence | Reference |
|---|---|---|---|
| Erythropoeitin | <1 | PRCA | 4 |
| Factor VIII | 15-52 | Loss of efficacy | 5,24 |
| Factor IX | 1-2 | Loss of efficacy, anaphylaxis | 28,29 |
| Interferon α | 44 | Loss of efficacy | 22 |
| Interferon ß | <5 | Loss of efficacy | 20,21 |
| IL1 Ra | 2 | Loss of efficacy | 35 |
| Growth hormone | 1-2 | No significant effects | 37 |
| Infliximab | 17-60 | Loss of efficacy, infusion reactions, anaphylaxis | 44 |

Abbreviations: IL 1 Ra, interleukin-1 receptor antagonist; PRCA, pure red cell aplasia.

## Recombinant Insulin

Recombinant insulin is produced from human genes by *E coli* or other expression systems. The product is identical to naturally produced human insulin and its immunogenicity is lower than porcine or bovine insulin [10]. Hypersensitivity reactions to recombinant human insulin occur but are rare [11,12]. Antibodies to recombinant insulin are reported but appear to have no clinical significance [13]. Parenteral analogues of recombinant human insulin differ only in minor amino acid substitutions at the C terminal of the α or ß subunits [13]. These substitutions are in a relatively nonimmunogenic portion of the molecule,

and this may explain why there is no increased rate of adverse immune reactions to these analogues [14]. Insulin lispro, a rapidly absorbed parenteral insulin, is used for patients with antibodies to either porcine insulin or human recombinant insulin [11]. Its rapid absorption may explain the low rate of immunogenicity and usefulness in subjects with antibodies to other kinds of insulin [15]. An approved inhaled formulation of recombinant insulin results in higher rates of antibody formation compared to parenteral insulin, but without loss of efficacy or other clinically significant side effects [16]. Although it was reported to be safe and effective, low sales prompted the manufacturer to discontinue it in January 2008 [17].

## Erythropoietin

Recombinant erythropoietin was introduced in 1988 to treat anemia of chronic renal disease [18], and it is also approved for malignancy-associated anemia. It is produced by CHO cells utilizing recombinant DNA techniques and differs from the naturally produced hormone mainly in its pattern of glycosylation [18]. Antibody formation is a rare but serious consequence because it can present as life-threatening PRCA [18]. An increased incidence of antibody formation was observed in patients receiving recombinant erythropoietin in the late 1990s. No single cause was implicated, but several reports suggest that substituting polysorbate 80 and glycine for human albumin in the final preparation may have resulted in increased immunogenicity. Also, subcutaneous rather than intravenous administration is associated with higher rates of antibody formation [18].

Antibodies against erythropoietin begin to form at least 3 weeks after initial administration, and in subjects with anti-erythropoietin antibody formation, the average time to loss of efficacy is approximately 9 months. Anti-erythropoietin antibodies cross-react with all forms of recombinant erythropoietin so that the use of alternate formulations is contraindicated and has resulted in non-IgE-mediated anaphylaxis [19]. Discontinuation of the drug and supportive measures, such as blood transfusions, is the treatment of choice for PRCA. Immunomodulator therapy, intravenous immunoglobulin, and renal transplantation have also been reported with variable success.

## Interferon

IFN-ß is produced naturally by fibroblasts and is involved in a complex array of immune responses. Its overall effect is to downregulate the inflammatory cascade via alterations in gene transcription. There are 2 forms of recombinant IFN-ß; IFN-ß 1b is produced by bacterial vector expression, has a slightly different protein structure compared to human IFN-ß, and is not glycosolated. IFN-ß 1a is produced using CHO cells and is identical to human interferon in both protein structure and glycosylation. Antibodies resulting in a significant loss of clinical efficacy are reported for both formulations but are much higher for IFN-ß 1b compared to IFN-ß 1a [20,21]. When neutralizing antibodies form, there is a high degree of cross-reactivity between the 2 formulations that results in loss of efficacy and increased rates of exacerbation of disease [21].

IFN-$\alpha$ is used to treat hairy cell leukemia and chronic hepatitis, and neutralizing antibodies occur in up to 41% of subjects using this product [22]. Higher antibody titers correlate with loss of efficacy and, in contrast with other uses, anti-IFN antibodies recede with prolonged use in hairy cell leukemia [23].

## Coagulation Proteins

Recombinant factor VIII and factor IX were developed in the late 1980s to treat patients with hemophilia A and hemophilia B, respectively. Although highly successful in treating these diseases, formation of neutralizing antibodies is a significant problem. The incidence of antibody formation is 15%-35% for hemophilia A patients receiving recombinant factor VIII [24]. In severe hemophilia A, where little or no natural factor VIII is produced (< 5%), antibody formation is as high as 52% [24]. Antibody formation can occur at any time during therapy, but the majority of subjects who develop antibodies do so quickly, with a median of only 10 days of exposure before antibodies can be detected [25]. In addition to the severity of hemophilia, several other risk factors have been postulated for antibody formation. Protein aggregation occurs but does not appear to increase immunogenicity per se, even though it can be immunogenic in mice [26]. Whether the presence of von Willebrand factor affects the immunogenicity of factor VIII is highly disputed and requires further study [5,27]. Neutralizing antibodies result in significant loss of efficacy and subsequent bleeding risk. Protocols for induction of immune tolerance utilizing prolonged courses of high-dose recombinant factor VIII have been successful but are not standardized [28].

Formation of antibodies to recombinant factor IX is reported at a lower rate than with factor VIII (< 5%) [28]; however, antibody formation is associated with anaphylaxis, sometimes as the presenting sign of antibody formation [29]. As with hemophilia A, subjects with severe hemophilia B are at highest risk for antibody formation. Immune tolerance induction is not as successful as for factor VIII antibodies and is associated with nephrotic syndrome and anaphylaxis [30,31]. Infusion of factor VII or activated prothrombin complex concentrates are alternative therapies and may need to be utilized in actively bleeding patients with high antibody titers [25, 32].

## Anti-interleukin-1

Interleukin (IL)-1 is produced by many cells, exerts local proinflammatory effects in a manner similar to tumor necrosis factor (TNF), and is implicated in the joint destruction associated with rheumatoid arthritis [33]. Endogenous IL-1 receptor antagonist (IL-1Ra) is produced by mononuclear phagocytes and prevents activation of the receptor by competitive inhibition. Anakinra is recombinant IL-1Ra used for the treatment of rheumatoid arthritis and is identical to endogenous IL-1Ra except for an N-terminal methionine [34].

 

The most common adverse effects are mild local injection-site reactions that resolve after 2-3 weeks of continuous treatment [34]. IL-1Ra-induced neutropenia is rare and resolves after discontinuation of the drug. One study, evaluating the administration of anakinra for up to 3 years, reported antibody formation in 1.9% of subjects, about half of whom reported a loss of efficacy of the agent [35].

## Human Growth Hormone

Human growth hormone, introduced in 1979, is produced using recombinant DNA in *E coli*. The original product was identical to the human form with the exception of an additional methionine residue at the N terminal (met-rhGH). This form of growth hormone was highly immunogenic, with greater than 60% antibody formation reported [36]. A refined form of recombinant growth hormone without the extra methionine residue was produced in 1987 (rhGH). Antibody formation to this form occurs in only approximately 2% of subjects [37]. One long-term study demonstrated that antibodies that developed to met-rhGH disappeared when subjects switched to rhGH [38]. That same study reported no alteration of the growth-promoting effect of rhGH even in the presence of antibodies.

## Monoclonal Antibodies

Kohler et al [39] reported a method to produce large quantities of antibodies against a specific target in 1975 and for this discovery won the Nobel Prize in 1984. Monoclonal antibodies, introduced in the late 1990s, are now important therapeutic agents. To produce them, mice are first immunized with the molecule of interest. B cells that secrete the antibodies to this antigen are isolated and fused with immortalized myeloma cells, resulting in a hybridoma that produces large amounts of the antibody ex vivo. These mouse antibodies are highly immunogenic and generate human anti-mouse antibodies. Efforts to decrease the immune response to these molecules resulted in the development of chimeric molecules and eventually to humanized monoclonal antibodies.

DNA encoding the murine variable region is fused with DNA encoding a human IgG constant region to form a human-mouse chimeric molecule with a variable region that encodes approximately 25% murine protein. Recognition of the murine protein region as non-self results in human anti-chimeric antibodies that may result in a significant reduction in efficacy as well as hypersensitivity reactions. Humanized monoclonal antibodies still contain murine protein sequences, although at a much lower level (5%), restricted to the complementary determining region. The incidence of antibodies to humanized monoclonal antibodies is significantly lower than with murine or chimeric molecules.

## Omalizumab

Omalizumab is a humanized monoclonal antibody against IgE approved in 2003 for use in allergic asthma. Only minor reactions to omalizumab, such as injection-site reactions and increased incidence of viral infections, were reported initially. However, in 2007, recognition of delayed onset anaphylaxis in post-marketing surveys prompted the addition of a black box warning to the prescribing information. Two unusual features of omalizumab-related anaphylaxis are the delayed onset and the protracted course of the reactions [40]. One-third of the subjects experienced anaphylaxis more than 6 hours after administration and 2 subjects reported symptoms more than 24 hours after receiving the injection, although detailed information regarding these episodes is not available [40]. The authors of this review comment that the course of anaphylaxis in some of these subjects is not refractory or biphasic anaphylaxis but appears to be a gradual escalation of symptoms over several hours. These unusual features can make recognition of omalizumab-related anaphylaxis extremely difficult and challenge conventional wisdom regarding anaphylaxis. The cause of these reactions is not known but several possibilities are under investigation. Polysorbate, used to solubilize omalizumab, causes anaphylaxis [41]. Glycosylation has been implicated in both IgE and IgG immune reactions [18] and may be involved in these reactions. Studies investigating these possibilities are ongoing. Currently there are no readily identifiable risk factors for delayed or protracted anaphylaxis [40]. A recently published summary of omalizumab-induced anaphylaxis recommends monitoring subjects for 2 hours after their first 3 injections of the drug, and for 30 minutes thereafter [40]. Patients receiving omalizumab should receive instruction on the recognition of anaphylaxis and an epinephrine auto-injector.

## Tumor Necrosis Factor Inhibitors

TNF-α plays a central role in the inflammatory cascade and is critical in the defense against invading pathogens, particularly intracellular organisms. Produced mainly in neutrophils and activated macrophages, it initiates a wide spectrum of inflammatory events including upregulation of the proinflammatory cytokines IL-1 and IL-6. Its central role in inflammation makes it a useful therapeutic target in autoimmune inflammatory disorders. There are 3 biologic TNF-α inhibitors approved in the United States. Adalimumab and infliximab are both monoclonal antibodies, whereas etanercept is a fusion protein.

TNF-α inhibitors are associated with opportunistic infections, particularly reactivation of tuberculosis, but they are also a concern for an increased risk of malignancies. One meta-analysis concluded that there is an increased risk of solid tumors [42], but this association has not been observed in national registries. Whether or not the increased incidence of lymphoma seen in rheumatoid arthritis patients treated with TNF-α inhibitors is related to therapy or to the disease process itself continues to be debated. Antibody formation has been reported for all TNF-α inhibitors but, with the exception of infliximab, is rarely of clinical consequence.

### *Infliximab*

Infliximab is a chimeric monoclonal antibody introduced in 1998 and is licensed for use in moderate-to-severe or fistulizing

Crohn disease. It is also used in the treatment of rheumatoid arthritis and is reported to be effective in a variety of other autoimmune conditions, including ulcerative colitis, Wegener granulomatosis, and psoriasis. This chimeric antibody contains 25% mouse-derived proteins and antibody formation is reported to be as high as 60% [44]. The level of anti-infliximab antibody predicts the risk of infusion reactions and decreased therapeutic efficacy [44]. Although anaphylaxis is rare, IgE-mediated reactions characterized by flushing, urticaria, shortness of breath, and chest tightness occur with higher frequency in the presence of anti-infliximab antibodies [44]. Delayed-type hypersensitivity reactions, 2-10 days after infusions, are characterized by myalgias, arthralgias, angioedema, fever, generalized rashes, pruritus, and headache [43]. The concomitant use of immunomodulators, such as prednisone or methotrexate, reduces the incidence of antibody formation [44].

Greater than 50% of patients who receive infliximab develop antinuclear antibodies, and a small minority also develop anti-double stranded DNA antibodies [43]. Clinical symptoms consistent with systemic lupus erythematosus (SLE), such as skin rashes, serositis, or arthralgias, occur in only 2% of patients [43], and discontinuing the drug resolves these symptoms. Other rare complications include demyelination of peripheral nerves or of the optic nerves [45], manifested as weakness or numbness of the extremities or visual disturbances.

### *Adalimumab*

Adalimumab, a fully humanized monoclonal antibody that binds TNF-α, was approved in 2002 for use in rheumatoid arthritis. As of June 2005 there were approximately 78 000 patient years of exposure with a favorable clinical response in rheumatoid arthritis as well as with other inflammatory diseases such as psoriasis, Crohn disease, ulcerative colitis, and Wegener granulomatosis [46]. In one study, 12% of subjects receiving injections every other week developed anti-human antibodies within the 6-week study period but this did not result in an increased frequency of adverse reactions or a decreased clinical response at recommended doses [47]. Acute adverse reactions include headache, localized reactions, and rash at sites other than the injection site. More serious adverse effects occur rarely and include demyelinating disorders, reactivation of latent tuberculosis, opportunistic infections, and congestive heart failure. Rates of lymphoma are similar in rheumatoid arthritis patients naïve to adalimumab [47].

### *Etanercept*

Etanercept is a fusion protein composed of 2 ligand-binding regions of the human TNF-α receptor (p75) that competively inhibits TNF-α, and it is currently approved to treat rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, and ankylosing spondylitis. Common adverse reactions are minor, mostly involving localized reactions at injection sites, although urticaria and angioedema are occasionally reported in post-marketing reports. Antibody formation occurs in 6% of patients treated with etanercept, but it has no effect on clinical efficacy or side-effect profiles [47]. Eleven percent of patients using this drug in a 6-month clinical trial developed antinuclear antibodies, but none developed clinical symptoms of SLE [47]. Another study reported 4 cases of clinical SLE with positive antibodies that resolved after treatment was discontinued [48].

## Anti-leukocyte Antibodies

Cluster of differentiation (CD) molecules are cell-surface proteins expressed on leukocytes that play a critical role in cell signaling and are highly specific to cell lines. Anti-leukocyte monoclonal antibodies capitalize on the high specificity of these proteins to exert a clinical effect by either cell-mediated or cytotoxic killing, depending on the target cell. The majority of therapeutic anti-leukocyte antibodies are used in oncology and in anti-rejection protocols. Radionuclides are conjugated to some of these molecules to deliver highly potent anti-cancer agents to tumor cells with favorable results.

### *Rituximab*

Rituximab is a chimeric IgG1 anti-CD20 approved in 1997 as a therapeutic monoclonal antibody for the treatment of non-Hodgkin lymphoma. It is being used increasingly for a variety of autoimmune diseases [49,50]. CD20 is expressed on pre-B and mature B cells, but not on stem cells or plasma cells. Administration of rituximab results in a depletion for up to 6 months of $CD20^+$ B cells via complement-mediated cell lysis and antibody-dependent cellular cytotoxicity followed by a gradual return to normal levels within 9-12 months [51]. Reactions to administration of rituximab occur primarily during infusions and include fever, rigors, nausea, vomiting, and fatigue, most of which occur during the first dose and decline with subsequent administration [52]. No clinical evidence of sensitization to rituximab was observed after 24 months of maintenance therapy at 6-month intervals for up to 24 months [52].

### *Alemtuzumab*

Alemtuzumab is a humanized monoclonal antibody directed against CD52. The precise function of CD52 is unknown, but it is expressed on multiple leukocyte lineages including B and T lymphocytes, monocytes, and eosinophils, and not on hematopoietic $CD34^+$ cells [53]. It is also expressed in the male genitourinary tract. The first therapeutic monoclonal antibody to be humanized, it is used to treat chronic lymphocytic leukemia and to prevent organ rejection in transplant patients. Administration of alemtuzumab results in profound and prolonged depletion of lymphocytes, and although B lymphocytes return to normal levels within 3-12 months, $CD4^+$ and $CD8^+$ cells can remain depressed for up to 3 years following therapy. Severe neutropenia also occurs in approximately 50% of subjects and is common along with opportunistic infections from *Aspergillus*, *Candida*, and *Pneumocystis* species. Reactivation of hepatitis B and cytomegalovirus are also reported, and prophylaxis for *Pneumocystis* pneumonia and cytomegalovirus reduces the rate of these infections but does not eliminate them. So-called first-dose reactions, particularly with intravenous use, most commonly include fever, rigors, and nausea.

 

## Miscellaneous

### *Trastuzumab*

Approximately 30% of breast cancers are associated with overexpression of the tyrosine kinase HER-2/neu. HER-$2^+$ breast cancer is typically more aggressive and results in shortened survival for women with this tumor. Trastuzumab, approved in 1998 for HER-$2^+$ breast cancer, is a humanized monoclonal antibody that targets HER-2 and has multiple anti-tumor effects. Most reactions to trastuzumab are first infusion reactions characterized by chills, fevers, and nausea that resolve with subsequent treatments. Serious reactions or anaphylaxis are rare, occurring in less than 0.5% of infusions. A pulmonary syndrome characterized by infiltrates, effusion, and adult respiratory distress syndrome following more severe infusion reactions has been reported in post-marketing studies. Symptomatic intrinsic primary or metastatic lung disease is a predisposing factor for this syndrome [54]. Decreased left ventricular ejection fraction is documented but does not appear to be related to an immunologic mechanism. Only 1 instance of anti-trastuzumab antibody formation associated with disease progression has been reported [55].

### *Cetuximab*

Cetuximab is a chimeric monoclonal antibody directed against the epidermal growth factor receptor, which is overexpressed in the majority of carcinomas [56]. It is used in conjunction with other chemotherapeutic agents to treat metastatic colorectal cancer and squamous cell cancer of the head and neck. Acneiform rash is a common adverse reaction, occurring in as many as 70% of patients [57]. There is a strong correlation between the presence of this rash and the efficacy of the agent. Other common reactions include nausea, fevers, chills, and transient elevation of aminotransferase levels [57]. Anaphylaxis is reported to occur in 3% of patients receiving cetuximab [58]. An unusual geographic clustering of anaphylaxis to cetuximab was reported in 2007, with some regions of the United States reporting severe first dose hypersensitivity rates as high as 22% [59]. IgE specific to galactose-$\alpha$ 1,3-galactose, an oligosaccharide present on the $F_{ab}$ portion of the cetuximab heavy chain, is present in the majority of subjects who experience severe hypersensitivity reactions [58]. Galactose-$\alpha$ 1,3-galactose is expressed normally in non-primate mammals. IgG to this molecule is found in nearly all humans, but the reason for IgE sensitization is unclear [58].

### *Palivizumab*

Palivizumab is a humanized monoclonal antibody against the F protein of respiratory syncytial virus indicated for use in the prevention of respiratory syncytial virus infection in high-risk pediatric populations. It is well tolerated with only mild local injection-site reactions reported when administered intramuscularly and no reported serious reactions when administered intravenously [60]. Null et al [61] reported no increased antibody formation or loss of efficacy after 2 seasons of palivizumab administration in high-risk patients.

## Conclusion

Biologic agents have revolutionized the medical management of many diseases. Since their introduction over 20 years ago they continue to provide safe and effective treatment alternatives for a wide variety of diseases. Their use continues to expand as current agents find new indications and novel agents are introduced. Experience has demonstrated that these agents, although highly effective, are capable of a wide range of unusual and atypical reactions, some of which can be life-threatening. As older biologic agents go off patent, subtle production alterations have the potential to cause immune reactions or antibody formation in previously relatively nonimmunogenic agents. Physicians must remain vigilant for and report adverse events related to their use.

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