Monoclonal Antibody Therapeutics and Risk for Infection

Juan C. Gea-Banacloche, MD, * and Geoffrey A. Weinberg, MD†

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The discovery of a method to produce continuous mouse cell lines synthesizing antibodies of predetermined specificity so revolutionized diagnostics and therapeutics that the scientists responsible were awarded a Nobel Prize only 9 years after their publication.1,2 The therapeutic application of monoclonal antibodies (MAbs) as “magic bullets” began with the approval of a murine antibody, muromonab (Ortho-Biotech’s “Orthoclone OKT3”) directed against the lymphocyte surface marker CD3. Muromonab is still used as an agent for the treatment of rejection in solid organ transplantation. Some of the side effects observed with the use of murine MAbs are related to sensitization to murine proteins. Technical advances have permitted the development of chimeric, “humanized,” and fully human antibodies, in which the whole amino acid sequence is human. The main advantage of the “humanization” process is that it allows for long-term administration without the development of anti-bodies. With the development of so many MAbs, a systematic naming system was required to differentiate them (Table 1). Currently, more than twenty MAbs have been approved by the Food and Drug Administration (FDA), and >100 are in development (Table 2). Some therapeutic antibodies are administered intact, and some are conjugated to radioisotopes or toxins for use as antineoplastic agents.

Many MAbs act as immunomodulators (in transplantation and for autoimmune conditions), as antineoplastic agents, or as both. In this review, we summarized the infectious complications that have been reported with these agents, and with selected related, non-MAb immunomodulatory agents. It should be noted that the attribution of a particular complication to an individual drug is difficult for 2 reasons. First, the patient populations that receive MAbs generally are already immunosuppressed and are thus at greater risk of infection. Second, the available clinical trials data often include too few patients to have adequate power to detect rare infections or to distinguish differences in the rates of infections among comparison drugs.

TUMOR NECROSIS FACTOR-ALPHA INHIBITION AND INFECTION

Inhibition of tumor necrosis factor-alpha (TNF-α) has demonstrated therapeutic value in rheumatoid arthritis, seronegative spondyloarthritides, psoriasis, and inflammatory bowel disease. Some of the available drugs that inhibit TNF-α also have been used in difficult-to-control inflammatory conditions, such as steroid-refractory graft-versus-host disease. The anti-TNF-α agents include 2 MAbs (infliximab, a chimeric mouse-human IgG1 and adalimumab, a fully human IgG1, both directed against the TNF-α molecule) and etanercept, a fusion protein combining 2 molecules of the 75-kd TNF-α soluble receptor with the Fc portion of an IgG1.

Infections have been among the most commonly reported complications of TNF-α inhibition. Granulomatous infections such as tuberculosis have received the most attention, but many clinical trials suggest increased infections of many types (bacterial and viral respiratory tract and skin or soft tissue infections, intracellular bacterial, fungal, and parasitic infections). The quantification of the infectious risk has been difficult and data are conflicting. A metaanalysis of rheumatoid arthritis trials showed at least a 2-fold greater risk, but prospective registry data showed similar risks, of serious infections among patients receiving anti-TNF-α agents compared with those receiving other disease-modifying drugs.3,4 However, most reports document increases in infectious complications after anti-TNF-α therapy.3,5,6
LYMPHOCYTE INHIBITION OR DEPLETION AND INFECTION

Several MAbs are directed against proteins expressed on the surface of B- and T-cells and cause depletion of specific lymphocyte subsets. Muromonab-CD3, a murine IgG2a immunoglobulin, binds the CD3 molecule adjacent to the T-cell receptor. The initial result of binding CD3 is nonspecific T-cell activation with cytokine release syndrome. This is followed by transient, profound lymphocyte depletion followed by reappearance of CD3-negative T-cells. Both lymphocyte depletion and T-cell receptor modulation contribute to the immunosuppressive effect. Muromonab may result in more infections than antithymocyte globulin or daclizumab (neither of which modulates the T-cell receptor) when given as induction therapy to prevent solid organ transplant rejection. Bacterial infections are most common, but these patients are often receiving prophylaxis for opportunistic pathogens, perhaps skewing the distribution of infections.9

Rituximab is a chimeric monoclonal against CD20, a protein expressed by mature B-cells but not plasma cells. It results in B-cell depletion that may be long-lasting (frequently 6–9, but sometimes as long as 12–15 months). It was originally approved for the treatment of B-cell malignancies that expressed CD20. It has also been approved for rheumatoid arthritis refractory to TNF antagonists, and is increasingly being used in a variety of autoimmune conditions such as autoimmune thrombocytopenia and lupus. The initial clinical oncology trials did not show an increased risk of infections. However, a randomized controlled trial of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, with or without rituximab, in acquired immunodeficiency syndrome-associated lymphoma showed twice as many infectious deaths in the rituximab arm.10 The increased risk was seen almost exclusively in the subgroup of more immunocompromised patients. Similarly, the long-term follow-up of patients enrolled in the seminal trial that showed the benefits of rituximab in diffuse large B-cell lymphoma also showed an increased risk of infection in the patients who received rituximab.11 Additionally, reports of late infections related to hypogammaglobulinemia, and sporadic case reports of Pneumocystis pneumonia, suggest that the risk of infection associated with rituximab may be higher than initially thought.12

Tositumomab and ibritumomab tiuxetan are 2 murine MAbs that also target the CD20 B-cell antigen, but which are conjugated to radioisotopes (131I, or either 90Y or 111In, respectively) to directly kill B-cells in non-Hodgkin lymphoma. Toxin-conjugated MAbs are also available, similar to the radioimmunoconjugates. For example, gemtuzumab ozogamicin is directed against the CD33 antigen for therapy for acute myelocytic leukemia. Infections have not been reported after their use as have been for rituximab, perhaps because of lower dosing per person, fewer patients receiving the agents, or other as yet undefined factors.

Alemtuzumab is a humanized IgG1 directed against CD52, a membrane glycoprotein present in T- and B-lymphocytes, monocytes, and natural killer cells. The only FDA-labeled indication is the treatment of chronic lymphocytic leukemia refractory to fludarabine, but it is also used for other hematologic malignancies and in solid organ transplantation (either as part of the induction regimen or for the treatment of acute rejection), and for selected autoimmune conditions such as aplastic anemia. Alemtuzumab administration results in prolonged lymphopenia as well as profound immunosuppression. Opportunistic and nonopportunistic infections have been described, particularly in cancer patients.13 The opportunistic infections are typical of cellular immunodeficiency states, with viral reactivation (eg, cytomegalovirus and Epstein-Barr virus) and intracellular pathogens predominating. When alemtuzumab induction is used after solid organ transplantation, it is given at a significantly lower dose than for rejection, and often without corticosteroids. In this case, the incidence of infection is lower than that of patients not receiving alemtuzumab but receiving corticosteroids alone. A greater incidence of opportunistic infections is seen in patients who receive higher dose alemtuzumab for the treatment of acute rejection.14 The manufacturer recommends Pneumocystis and HSV prophylaxis until the CD4 T-lymphocyte count is consistently above 200/μL. More

Interestingly, the risk of infection (especially granulomatous infections such as tuberculosis) appears to be about 3-fold less with etanercept therapy than with MAb therapy.3 This difference in risk may be related to their different mechanisms of action; etanercept blocks only free TNF-α, whereas infliximab and adalimumab not only block free TNF-α but are also capable of inducing cell lysis and apoptosis in cells expressing TNF-α on their surface.7 There are also differences in pharmacokinetics and cell signaling between etanercept and the MAbs, which may contribute to differences in infectious complication rates.7 Because of the reported increased risk of tuberculosis reactivation and progression with anti-TNF-α MAb therapy, current guidelines direct clinicians to perform screening for latent tuberculosis infection (eg, purified protein derivative testing), and, if detected, to begin treatment for latent (or active) tuberculosis at least 1 to 2 months before commencing TNF-α blockade.5,8 Although such FDA “Black Box Warnings” are mandated only for infliximab and adalimumab, many experts would perform tuberculosis screening before etanercept therapy as well.6

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**TABLE 1. Understanding Monoclonal Antibody (MAb) Nomenclature**

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<th>A MAb name has 4 components:</th>
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<tr>
<td>● A random prefix defining the individual product</td>
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<tr>
<td>● A disease or target sub- stem (bacterial, -ba(c)-; cardiovascular, -ci(s)-; immunomodulatory, -li(m)-; tumor, -tu(m, a)-) [also specific tumor sub-stems exist, e.g., colon, -co(l)-; viral, -vi(r)-]</td>
</tr>
<tr>
<td>● A source sub- stem (chimeric, -xi(-); human, -hu(-); mouse, -mo(-); rat, -ra(-))</td>
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<tr>
<td>● The stem for monoclonal antibodies (-mab)</td>
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Examples:

- **Aleciximab**, a cardiovascular (anti-platelet), chimeric MAb
- **Alemtuzumab**, an anti-tumor, humanized MAb
- **Edobacimab**, an antibacterial, murine MAb (previously available as Centoxin J5 anti-lipopolysaccharide)
- **Infliximab**, an immunomodulatory, chimeric MAb
- **Palivizumab**, an antiviral, humanized MAb

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extensive recommendations for infectious disease prophylaxis in patients receiving alemtuzumab have been advanced. Abatacept and belatacept are fusion protein products that exert an immunosuppressive effect by “costimulation blockade.” Abatacept (CTLA4Ig) and its derivative belatacept (LEA29Y) are thought to act by preventing the interaction between the CD80 molecules on the antigen presenting cell and CD28 on the T-cell. Abatacept is FDA-approved for moderate to severe rheumatoid arthritis that has not responded well to other disease-modifying drugs. An increased risk of serious infections, mainly bacterial, was reported in a large randomized trial of abatacept compared with placebo; the risk appeared to be greater when abatacept was administered with biologic therapies, in particular etanercept. Abatacept and belatacept have been compared with cyclosporine as maintenance immunosuppression in kidney transplant with good results and no increased risk of infection. Of note, 3 cases of Epstein-Barr virus lymphoproliferative disorder occurred among the 145 patients randomized to belatacept.

### OTHER INHIBITORS AND INFECTION

Basiliximab and daclizumab are chimeric and humanized MAbs, respectively, directed against CD25, one of the subunits of the high-affinity interleukin-2 receptor. They are used extensively in transplantation to prevent rejection. No increased risks of infection have been reported in this setting with respect to other antirejection agents.

Natalizumab is a humanized IgG4 antibody against the \( \alpha_4 \) subunit of \( \alpha_4\beta_1 \) and \( \alpha_4\beta_7 \) integrins, present on the surface of all leukocytes. It results in the inhibition of lymphocyte migration, and it has been associated with progressive multifocal leukoencephalopathy (PML).
activity in multiple sclerosis (for which it is FDA-approved) and Crohn’s disease. Unfortunately, 3 cases of progressive multifocal leukoencephalopathy were reported among approximately 3000 patients receiving the drug (resulting in its temporary withdrawal from the market).20

Other MAbs that may be encountered by the infectious diseases clinician include omalizumab, an anti-IgE MAb used for severe asthma and allergy; trastuzumab, panitumumab, and cetuximab, 3 epidermal growth factor receptor antagonists used to treat various malignancies; and of course, palivizumab, used to provide prophylaxis against respiratory syncytial virus infection. No serious infections have been reported after the use of any of these agents, although theoretical concerns have been raised about whether an increased incidence of parasitic infection will occur during IgE blockade by omalizumab.

Finally, anakinra is a novel interleukin-1 receptor antagonist used to treat rheumatoid arthritis and sepsis. It has been associated with a small (3- to 4-fold) increase in serious infections, mostly pneumonia and cellulitis, during blinded and open-label trials.21 The risk differences in infection appear concentrated in patients receiving both anakinra and corticosteroids, analogous to the situation described above with alemtuzumab.

SUMMARY

In summary, patients receiving many of the currently available therapeutic MAbs are at increased risk for infection. The risk is compounded by previous and current therapies, as well as individual and disease-specific factors. The infectious diseases physician should be familiar with the most commonly reported associations, even if their full significance is often uncertain. In particular, the TNF-α antagonists require evaluation of patients before, during, and after therapy.6,8 Those treated with alemtuzumab15 and natalizumab22 may as well.

REFERENCES