# Complications of Monoclonal Antibody Therapy

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**Monoclonal antibodies (MCA) are an** increasingly important class of drugs for treating autoimmune and neoplastic disorders. They have been associated with a variety of adverse events which will be discussed in this paper.

## Infusion Reactions

An infusion reaction may range from mild to lethal. The severity is given a rating on a scale of one (mild) to five (lethal). Most often the signs and symptoms are mild (grade one or two). Common signs and symptoms include fever, flushing, rigors, chest discomfort, abdominal pain, nausea, vomiting, diarrhea, and rashes. Rarely, MCAs can cause anaphlaxis.[1] It may be initially difficult to distinguish a mild reaction from anaphylaxis. However, the presence of respiratory changes and urticaria are more specific to anaphylaxis and in contrast, myalgias are more likely to accompany a mild reaction. A generalized symptomatic response to infusion of MCAs typically occurs within the first two hours, but may be delayed up to 14 days after treatment. The highest risk of a reaction is during the first or second exposure to the MCA. The risk declines with repeated exposure, but 10-30% of reactions occur beyond the first two doses.[2] MCAs most associated with early infusion reactions are infliximab, rituximab, gemtuzumab, alemtuzumab, trastuzumab, cetuximab, ofatumumab.

Prevention of mild infusion reactions with premedication is routine; however, anaphylaxis may still occur. Commonly prescribed premedication regimens are diphenhydramine and acetaminophen. A patient with a mild reaction should temporarily stop the infusion, and receive symptom relief using an IV antihistamine with oral acetaminophen. They may be re-challenged at a reduced infusion rate (50%) after symptoms have resolved. If a patient develops repeated mild reactions then a referral to an allergy specialist for a desensitization protocol may be considered. A patient with a severe response consistent with anaphylaxis should not be re-challenged.

Initial management of suspected anaphylaxis is to stop the infusion. Then intramuscular injection of epinephrine should be given while support is called. If there is no pulmonary contraindication the patient is placed in a supine position, given supplemental oxygen, and a safe airway should be maintained. Volume resuscitation, intravenous antihistamines, and bronchodilators may be administered.[3]

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## Infectious Complications

Since monoclonal antibodies modulate the patient's own immune function, latent infections represent a serious threat. Latent infections like herpes zoster may manifest in the immunocompromised state induced by monoclonal antibodies. TNF-alpha inhibitors commonly used to treat inflammatory conditions like rheumatoid arthritis or seronegative spondyloarthropathies are associated with increased risk of latent **tuberculosis (TB)**. Therefore, when using TNF-alpha inhibitors such as infliximab, adalimumab, golimumab the patient should undergo a chest x-ray and placement of **purified protein derivative (PPD)** before initiating therapy.[4]

Agents targeting B-cells like rituximab are associated with reactivation of latent hepatitis B and JC virus infections (causes progressive multifocal leukoencephalopathy, PML).[5] Natalizumab, a MCA that inhibits leukocyte migration has been associated with over 100 cases of PML. Natalizumab was marketed for treatment of relapsing remitting **multiple sclerosis (MS)** and in post-marketing surveillance it was found to be associated with an increased incidence of PML. The risk of developing PML is one in a thousand for patients on therapy for 18 months.[6] It is rare to develop PML in the first 12 months of natalizumab therapy.[7] Initially it was believed that prior exposure or concurrent use of other immunosuppressive agents in MS patients led to the development of PML, but it is now clear that natalizumab alone increases the risk of PML. PML may cause encephalopathy, ataxia, visual field loss, diplopia, paresis, and seizure.[8] Brain CT studies typically reveal bilateral hypointense signal changes in the white matter in a patchy or confluent pattern. MRI findings include lesions that are T1 hypointense, T2 hyperintense and do not enhance or cause mass effect.[9] Early discontinuation of natalizumab and treatment with plasmapharesis may result in improved survival. Patients withdrawing from natalizumab may develop **Immune Reconstitution Inflammatory syndrome (IRIS)** and remain at significant risk of developing a severe relapse.

Infliximab, a MCA against TNF-alpha, was shown to have an adjusted relative risk of three (95% CI 1.8 to 5.1) for moderate to severe infection when compared to standard anti-rheumatic drugs.[10] Listeriosis represents a serious opportunistic bacterial infection from contaminated food that can lead to meningoencephalitis or septicemia at a higher rate in patients treated with infliximab.[11] The increased incidence of opportunistic fungal infections with histoplasmosis, coccidiodomycosis, blastomycosis in patients on MCAs targeting TNF-alpha led to a 2008 Food and Drug Administration warning. Concerning signs and symptoms are fever, lethargy, dyspnea, diaphoresis, cough, and chest x-ray with pulmonary infiltrates.[12] The risk of opportunistic infections is higher in patients on additional immunosuppressive agents, those who recently started treatment, older age, and patients with co-morbid pulmonary disease. In high risk patients, pneumo-

cystis carinii (jiroveccii) prophylaxis with **trimethoprim-sulfamethoxazole** (**TMP-SMX**) should be considered.[13] All patients treated with OKT3, a MCA targeting T cells, should be placed on TMP-SMX and ganciclovir to prevent PCP and CMV infection respectively.[14] In addition, live vaccines should not be given during treatment with MCAs.

## Pulmonary Complications

Specific MCAs are associated with an increased risk of direct **interstitial lung disease** (**ILD**). Symptoms of ILD are high fever, dyspnea, and cough. Patients who develop these symptoms require discontinuation because of the potentially lethal consequences.[15] Patients should be treated with glucocorticoids after infectious etiologies are excluded by obtaining cultures and perhaps bronchoalveolar lavage. Empiric antibiotics against atypical pathogens can also be used to reduce secondary infection. ILD is reported with the use of rituximab in about eight percent of patients, and rarely in those treated with trastuzumab for breast cancer.[16] Studies of cardio-pulmonary toxicity with these agents have found increased risk in those patients on adjunctive chemotherapy agents such as **CHOP** (**cyclophosphamide, doxorubicin, vincristine plus prednisone**), anastrozole, or anthracycline/cyclophosphamide compared to MCA monotherapy.[17] Patients treated with MCAs targeting epidermal growth factor receptors used in colorectal cancers (cetuximab and panitumumab) are also known to rarely cause pulmonary toxcitiy.[18]

## Hematologic-Oncologic Complications

The use of MCA may increase the risk of future malignancies. MCAs that target TNF-alpha were found in post marketing safety analysis to be associated with an OR 3.3 of malignancies (95% CI 1.3-3.1). This evidence led to an FDA warning for adults and children using TNF-alpha inhibitors. There is conflicting evidence whether all malignancy risk is truly elevated when compared to patients with **rheumatoid arthritis** (**RA**) instead of the general population. However, there is substantial evidence that the use of TNF-alpha inhibitors confers an increased risk of lymphoma.[19]

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Blood dyscrasias are common side effects of many MCAs. Since hematologic malignancies themselves can cause similar effects as the MCAs used to treat them evidence of a direct relationship is often uncertain. However, in the setting of an autoimmune hematologic abnormality the etiology is likely the MCA. Occasionally, these hematologic effects can be life threatening. During a trial of alemtuzumab for multiple sclerosis a patient died from idiopathic thrombocytopenic purpura. Patients taking this medication should be monitored with frequent platelet counts while on treatment and should discontinue alemtuzumab if they develop evidence of autoimmune hematologic toxicity.[20] Infliximab and rituximab are also hematologically toxic, causing leukopenia, neutropenia, thrombocytopenia, and pancytopenias. Patients typically become neutropenic within the first three to six months of starting therapy. The treatment begins with withdrawal of the offending medication. For the patient who is febrile, cultures should be obtained and broad-spectrum intravenous antibiotics started. If a patient requires a blood transfusion they should only receive irradiated blood products. The efficacy of granulocyte colony-stimulating factor administration to improve blood dyscrasias is uncertain, but remains a therapeutic option. .

## Neurologic Complications

Patients taking MCAs do not commonly complain about neurologic difficulties which are typically not serious and include headaches, myalgias, and dizziness. However, rare complaints include paresthesias and peripheral neuropathies. Cetuximab, a MCA targeting epidermal growth factor used in head/neck cancer and colorectal cancers, rarely can cause aseptic meningitis. In addition, cetuximab and panitumumab can cause hypomagnesemia that is manifested clinically as cramps and fatigue.[17]

More serious neurologic side effects of headache, seizure, encephalopathy and blindness may indicate that the patient has **posterior reversible encephalopathy syndrome** (**PRES**). PRES is associated rarely with bevacizumab, a MCA against vascular endothelial growth factor, used in glioblastoma, colon, lung and breast cancers.[21] The likely etiology of PRES is endothelial dysfunction leading to vasogenic edema. This can be seen on head CT as bilateral posterior hypodensities. PRES is often seen in patients with hypertension, but not necessarily malignant hypertension. Aggressive treatment of hypertension and removal of the offending agent is the recommended management strategy. In addition, even in the absence of PRES, bevacizumab is associated with an increased risk of thromboembotic stroke. (RR 1.31 [95% CI 1.08-1.6]) and intracranial hemorrhage.[22]

MCAs against TNF-alpha (infliximab and adalimumab) are rarely associated with demyelinating disease. Patients may present with encephalopathy, ataxia, paresthesias, optic neuritis, transverse myelitis, and ascending motor neuropathy. The relationship of demyelination and TNF-alpha inhibitors is unclear; however, a temporal relationship is noted between MCA and symptoms. Additional support for a causal relationship is that discontinuation of the drug usually results in resolution of symptoms. Therefore, it is reasonable to avoid these agents in patients with a known personal or family history of demyelinating diseases like multiple sclerosis.

## Conclusion

Monoclonal antibodies represent an important and growing category of targeted therapeutic agents. Despite the promise of improved side effect profiles of MCA targeted therapies compared to relatively indiscriminate anti-neoplastic or anti-inflammatory agents serious side effects may still occur. Clinicians will be

seeing increasing numbers of patients on MCAs and should be aware of the diverse spectrum of side effects

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### Disclosure of Financial Interest

Karl Meisel and/or spouses/significant other have no financial interests to disclose.

Syed A. Rizvi, MD, discloses the following Consultant/Speakers Bureau/ Grant Research Support: Teva, Biogen, Serono, Novartis, Acorda.


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