

Alemtuzumab and natalizumab: The monoclonal antibody story continues

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In the July/August 2006 issue of this journal, the infectious complications associated with the use of infliximab, etanercept and adalimumab were reviewed (1). These represent only three of the many monoclonal antibodies either licensed or in clinical trials for therapeutic use in cancer and autoimmune disease or to prevent rejection in both solid organ and hematopoietic stem cell transplantation. While most of these agents have not been associated with increased infection rates, alemtuzumab and natalizumab have gained particular attention related to either the frequency or type of infection seen in some individuals who have received them.

Rituximab, which targets the CD20 on B lymphocytes and was approved for use in Canada in non-Hodgkin's lymphoma in 1997, was the first monoclonal antibody licensed for treating cancer (2). The perceived benefits of monoclonal antibodies as cancer therapies are that they more selectively target the abnormal cells and may, therefore, have less associated toxicity (3). In terms of hematological malignancies, two other agents that have been licensed for use are gemtuzumab in the United Kingdom, and ibritumomab in Canada and the United States (US), both of which are conjugated to either a toxin or radionuclide to enhance cidal activity (2). Ibritumomab tiuxetan, similar to rituximab, targets CD20 on B lymphocytes, but differs in being linked to a radionuclide (2). Gemtuzumab ozogamicin, linked to calicheamicin, targets CD33 on leukemic blasts and is indicated for use in acute myelogenous leukemia (2).

More familiar to Canadian physicians might be the monoclonal antibody alemtuzumab. This is a humanized monoclonal antibody that targets the CD52 receptor on B, T and natural killer lymphocytes and monocytes (2). It is generally administered by intravenous infusion. The abundance of the CD52 antigen on lymphocytes is postulated to contribute to the profound and prolonged lymphopenia seen in patients who receive alemtuzumab (4). Lymphopenia may persist for longer than one year (5). Originally licensed in the treatment of B cell chronic lymphocytic leukemia, it has been shown to have efficacy in non-Hodgkin's lymphoma and T cell malignancies (6). Because of its T cell-depleting capabilities, alemtuzumab is being used as part of a reduced intensity conditioning regimen for hematopoietic stem cell transplantation (HSCT) (7-9). Reduced intensity conditioning regimens are desirable to reduce transplant-related mortality (7). On the other hand, some reduced intensity conditioning regimens may be associated with an increased risk of graft versus host disease (GVHD) or graft rejection (7). Alemtuzumab, which targets the CD52 antigen on lymphocytes, seems an ideal agent to prevent both graft rejection and GVHD, while avoiding the toxicity seen with the broader myeloablation that is

part of other chemotherapies. Clinical trials have shown that alemtuzumab is able to decrease the incidence of GVHD without impairing engraftment (10).

Alemtuzumab is also used as an antirejection agent in solid organ transplantation (SOT). Clinical studies in the United Kingdom, US and Asia have examined alemtuzumab induction therapy in cadaveric renal transplantation (11-13). In one uncontrolled study (11), alemtuzumab induction therapy was associated with similar graft survival and infection rates as the standard regimen, but allowed avoidance of steroid therapy. Two small randomized, comparative trials (12,13) have had similar results, but have also demonstrated marked and prolonged lymphopenia in the alemtuzumab arm. Two reviews of the role of alemtuzumab in SOT have recently been published (4,14). Morris and Russell (4), in their review, note that alemtuzumab has been used in forms of organ transplantation other than renal with similar results. However, it should be noted that apart from the two randomized controlled trials in renal transplantation (12,13), all other studies of alemtuzumab in SOT have been observational (4,14). In liver transplantation, alemtuzumab has been found to be associated with increased viral loads in hepatitis C-infected recipients (14).

The strength of a therapeutic agent frequently also represents its Achilles' heel. Note has already been made of the profound and prolonged lymphopenia seen with the use of alemtuzumab. Loss of circulating T cells is likely to result in impaired cell-mediated immunity. The additional role that this depletion plays in patients already immunosuppressed by either their hematological malignancy or immunosuppressive therapies may be difficult to determine. Confounding this observation is that most published studies of alemtuzumab in B cell chronic lymphocytic leukemia have included patients previously treated with other chemotherapeutic agents (5). Martin et al (3) have published their experience with the infectious complications associated with alemtuzumab for lymphoproliferative disorders and contrasted it with the literature. They followed 27 patients over 2.5 years. All patients received *Pneumocystis jirovecii* (PCP) and herpes simplex prophylaxis. Fifteen patients (56%) developed an opportunistic infection (OI) during the study period, with 44% having cytomegalovirus (CMV) viremia. Excluding herpes virus family infections, 11 additional OIs developed in nine patients. These infections consisted of three cases of invasive pulmonary aspergillosis, two of pyomyositis and bacteremia, and one each of adenoviral pneumonia, progressive multifocal leukoencephalopathy (PML), histoplasmosis, cryptococcosis, cerebral toxoplasmosis and disseminated acanthamoebiasis. The median time to developing an OI was 169 days. There were an additional 30 non-OIs among 22 (82%) patients. In a comparator group of HSCT

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recipients who did not receive alemtuzumab, OI and mortality rates were similar to that of individuals who received alemtuzumab. Mortality in the alemtuzumab recipients was 37%, and seven of the 10 deaths were attributed to infection. In their literature review, there were 262 episodes of infection in 410 patients. Herpes simplex reactivation was the most common OI (32.3% of OIs), followed by CMV reactivation (31.1%), PCP (6.6%) and invasive pulmonary aspergillosis (6%). Additionally, there were 95 non-OIs, of which sepsis was the most commonly diagnosed problem, accounting for 29.5% of non-OIs. The overall infection-related mortality in their literature review was 7.1%. The importance of CMV reactivation in relation to alemtuzumab therapy has also been demonstrated in HSCT recipients (7-9). In these patients, there is a high incidence of early CMV reactivation, with a median reactivation time of 24 days (7). However, the investigators have identified that in the majority of patients, there were no or only mild symptoms, and that viremia was usually easily controlled with anti-CMV therapy (7-9).

Based on their observations from the literature, Thursky et al (5) have offered recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. In keeping with the manufacturer's recommendations, they recommend PCP and herpes simplex virus prophylaxis for all patients treated with alemtuzumab, continuing the preventive therapy for at least two months from the last dose or until the CD4 counts are greater than $0.2 \times 10^9/L$. They also recommend weekly polymerase chain reaction monitoring for CMV with pre-emptive ganciclovir for a positive result in a symptomatic patient and consideration of starting it in the asymptomatic patient with a rising viral load. They recommend targeted screening for tuberculosis in patients from endemic areas or those with a history of exposure. Thursky et al offer two strategies to manage invasive fungal infections, either prophylaxis with itraconazole or maintaining a very high index of suspicion for invasive infection and performing pre-treatment screening for colonization. A caution is given to keep in mind the potential for reactivation of certain endemic infections, such as histoplasmosis and coccidioidomycosis.

The risk for infection in SOT recipients who receive alemtuzumab is less clear. Not unexpectedly, the small studies to date have not shown an increased risk of infection in the alemtuzumab arm (11-13,15). However, a large case-control study of SOT patients at the University of Wisconsin who received alemtuzumab or conventional induction found that CMV, BK virus, varicella zoster virus and disseminated invasive fungal infections were more common in alemtuzumab recipients (16). Viral disease, when it occurred, was more often disseminated (16). More studies are needed to definitively quantify the infection risk associated with alemtuzumab use in SOT recipients.

An intriguing story over the past three years has been that of natalizumab. This monoclonal antibody is an anti- $\alpha 4$ integrin-specific antibody. Research has demonstrated that endothelial cells play a role in the pathogenesis of inflammation, regulating the type and number of leukocytes migrating from the intravascular to the interstitial space (17). Several cell adhesion molecules, including integrins, mediate these leukocyte-endothelial interactions. Leukocytes can express 13 different integrins, but those of the $\alpha 4\beta 1$ and $\alpha 4\beta 7$ subfamilies are expressed only on lymphocytes and monocytes (17). Simplistically, the integrin recognizes its ligand, a vascular cell adhesion molecule, and thereby adheres to cytokine-activated

endothelial cells (17). In the gastrointestinal tract, this enables adherence to gut-associated lymphoid tissue. However, this interaction can occur wherever lymphocytes and vascular endothelium cells have contact. Natalizumab binds to $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins, blocking the interaction between them and their vascular cell adhesion molecules, thereby inhibiting lymphocyte adherence (17,18). Preventing the transmigration of activated lymphocytes into tissues should reduce the inflammatory response and have a beneficial clinical effect in patients with inflammatory disorders. Unlike alemtuzumab, natalizumab does not deplete lymphocytes (18). This suggests that infectious complications may not be seen as frequently with natalizumab as with alemtuzumab.

Proof of concept for the anti-inflammatory effects of natalizumab was reported in two back-to-back publications in *The New England Journal of Medicine* in January 2003. A randomized, controlled trial in 248 patients with moderate to severe Crohn's disease showed that treatment with natalizumab increased the rate of clinical remission and response, and improved quality of life (19). In a similar trial of patients with relapsing multiple sclerosis (MS), treatment with natalizumab led to fewer inflammatory brain lesions and fewer relapses over six months (20). Both trials reported that therapy was well tolerated and, in particular, that infection was not more common in the natalizumab recipients than in placebo controls (19,20). Based on the impressive outcomes noted in the MS trials, natalizumab was fast tracked for early approval and introduced into the US market in November 2004 (18).

Three months later, the occurrence of two cases of PML, a brain infection caused by JC virus, was reported by the US Food and Drug Administration (18). These two cases of PML in MS patients, as well as a third in a patient with Crohn's disease, were subsequently published in *The New England Journal of Medicine* in July 2005 (21-23). Both MS patients were also being treated with interferon β -1a, although PML had not previously been reported in MS patients, including those receiving interferon monotherapy (21,22). The Crohn's patient had also been treated with infliximab and corticosteroids, but JC virus appeared in the serum only after the reintroduction of natalizumab as monotherapy (23). All three patients had been on natalizumab for approximately two years, and two of the three patients died from PML four and five months after presentation, respectively, despite stopping the drug (21,23). The illness manifested by these patients was considered to be a form of immune reconstitution syndrome. Natalizumab was voluntarily withdrawn from the market by its manufacturer in February 2005.

Since these cases were reported, work has continued on elucidating the pathogenesis of PML in patients receiving anti-integrin antibodies. One hypothesis is that with natalizumab's effect on reducing lymphocyte migration into tissues, the JC virus can replicate unchecked (24). In one study (25), cerebrospinal fluid and peripheral blood cell numbers and phenotypes were examined in 23 patients who received natalizumab and 51 control patients with other neurological diseases, including 35 with MS not treated with natalizumab. The investigators found that natalizumab treatment resulted in a decrease in all major lymphocyte subsets in cerebrospinal fluid, an effect that persisted six months after stopping therapy (25). Peripheral blood cell counts were not affected. Another group of investigators demonstrated through in vivo studies that natalizumab diminishes the migratory capacity of immune

cells, cell subsets were differentially affected, the effects did not persist through the monthly dose interval, and that the infusion effect varied across patients (26). The evidence supports the hypothesis that natalizumab impairs immune surveillance of the central nervous system (25,26). It also provides insight into why there are differential risks and benefits associated with natalizumab therapy in different patients, as well as into the pathogenesis of MS. The challenge will be to identify those patients who will benefit the most from this promising therapy.

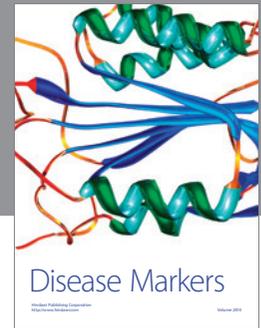
Over the past year, there have been further published studies of clinical trials with natalizumab. In two controlled trials to evaluate its use as induction and maintenance therapy in patients with Crohn's disease, natalizumab was found to have small, nonsignificant improvements in response and remission rates (27). Patients who did respond, on the other hand, had increased rates of sustained response and remission (27). It would seem that the role of natalizumab in Crohn's disease needs further elucidation. Two fairly large trials of patients with relapsing MS (28,29) showed that natalizumab significantly reduced the progression of disability and clinical relapse rate. Despite a number of study design limitations, it was estimated, through follow-up of 3116 patients who had received natalizumab in the context of a clinical trial, that the risk of

PML was approximately one in 1000 patients treated with natalizumab, for a mean of 17.9 months (30). An editorial accompanying this series of articles suggested that the data supports the value of natalizumab as a potent therapy for MS (31). In March 2006, a US Food and Drug Administration advisory committee recommended that natalizumab be returned to the market as monotherapy for patients with relapsing MS (32). In June 2006, the drug returned to the US market with restricted indications (33). Clearly, there needs to be vigilance for the development of PML in patients receiving natalizumab. Unfortunately, it is not known how best to screen for this.

The introduction of monoclonal antibodies as therapeutic agents has provided tremendous gains for certain patients with inflammatory diseases and cancers. On the other hand, some of these have been associated with initially unanticipated toxicities; however, as these agents have been examined in more detail in light of those complications, insights into their mechanism of action, and indeed an understanding of the immune system's response to infection, have emerged. The challenge ahead is to be able to better predict some of these complications, and to identify patients who may benefit the most from these treatments with the least amount of risk.

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