Potential Risk of Progressive Multifocal Leukoencephalopathy With Natalizumab Therapy

Possible Interventions

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Natalizumab (Tysabri) is an effective therapy for multiple sclerosis. Recently, 3 patients who were treated with natalizumab developed progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the brain with the polyomavirus JC. The pathogenesis of natalizumab-associated PML may be different from that of PML not associated with the drug. We reviewed biologically feasible interventions for patients diagnosed as having PML or other infections while receiving natalizumab therapy. Existing interventions include antiviral treatment, immunomodulatory therapies, hematopoietic growth factors, plasma exchange, intravenous immunoglobulins, and leukapheresis and autotransfusion of leukocytes. In addition, we examined the feasibility of experimental therapies, including small interfering RNA, the in vivo use of antiserum, and recombinant natalizumab-blocking molecules.

There is only circumstantial evidence that any of the proposed treatments will benefit patients with multiple sclerosis treated with natalizumab who may develop PML. In addition, the expected incidence of PML in this patient population will likely be too low to test any of the proposed interventions in a controlled manner. Because it is currently impossible to identify patients at risk, and thus to prevent PML as a consequence of natalizumab therapy, it is important that neurologists be aware of possible therapeutic interventions.

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Natalizumab (Tysabri) is a humanized monoclonal antibody that binds to the α4 chain of the α4β1 and α4β7 integrins. Natalizumab was designed to reduce the migration of leukocytes from the peripheral blood into tissues. In multiple sclerosis (MS), the rationale for natalizumab therapy is the reduction of leukocyte extravasation into the central nervous system (CNS) by specifically targeting α4β1, or very-late-activation antigen 4 (VLA-4).1 Based on the results of 2 phase III clinical trials,2,3 natalizumab was approved by the Food and Drug Administration for the treatment of relapsing forms of MS on November 24, 2004. After 2 patients with MS and 1 patient with Crohn disease who were treated with natalizumab in clinical trials developed progressive multifocal leukoencephalopathy (PML),4,6 the manufacturers of natalizumab voluntarily withdrew this agent, and the use of natalizumab and other VLA-4–blocking agents in clinical trials was halted. In the United States, natalizumab was reapproved on June 5, 2006, by the Food and Drug Administration as monotherapy for relapsing forms of MS. In addition, the drug was approved in the European Union by the European Agency for the Evaluation of Medicinal Products for the same patient population.

The risk of PML in patients treated with natalizumab was recently assessed in a study...
involving 3116 patients who had been treated with this agent. Specifically, the medical history, physical examination, findings on magnetic resonance imaging, and JC virus (JCV) polymerase chain reaction of patients were reviewed by an expert panel. On the basis of the results of that study, the risk of developing PML while receiving natalizumab therapy is estimated at 0.1%. The risk of PML associated with longer treatment remains unknown.

Progressive multifocal leukoencephalopathy is a demyelinating CNS disorder caused by infection of oligodendrocytes by JCV. The JCV is presumably acquired in childhood, and seroprevalence of antibodies to the virus is 80% to 90% in adults. Progressive multifocal leukoencephalopathy is thought to occur when the virus reactivates, and the incidence is highest in patients with underlying immunodeficiency, particularly those infected with human immunodeficiency virus (HIV). The site of viral latency is not known. The JCV DNA can be identified in urine from normal individuals, suggesting that the kidney may be a site of latent JCV infection. Also, JCV can be detected in peripheral blood lymphocytes, particularly B cells, from people with and without PML. Finally, JCV was identified in post-mortem brain tissue from individuals who did not have PML, suggesting that JCV may be latent in the CNS.

On the basis of all available data, the occurrence of PML in natalizumab-treated patients should prompt the immediate cessation of natalizumab therapy. Our own data suggest that natalizumab is very effective in preventing the extravasation of T cells and B cells into the CNS for at least 6 months. Thus, the biological half-life of natalizumab far exceeds its pharmacokinetic half-life, and even immediate withdrawal of this agent may not guarantee a positive clinical outcome in patients who develop PML.

We discuss interventions that may benefit natalizumab-treated patients who develop PML or other life-threatening infectious complications. Although some of the potential technical, economic, and safety limitations of the proposed methods are outlined, the purpose of this article is to discuss the biological feasibility of different treatment strategies. Specifically, we discuss antiviral therapies, immunomodulatory therapies, hematopoietic growth factors (HGFs), plasma exchange, intravenous immunoglobulins (IVIGs), and leukapheresis and autotransfusion. In addition, we outline possible experimental therapies, including small interfering RNA, the in vivo use of antiserum, and recombinant natalizumab-neutralizing molecules.

THERAPEUTIC INTERVENTIONS: GENERAL CONSIDERATIONS

According to our current knowledge of PML and natalizumab, therapeutic interventions should ideally meet the following criteria: (1) the elimination of JCV, (2) the generation of new immunocompetent leukocytes with unbound VLA-4, (3) the neutralization of free natalizumab, or (4) the elimination of free natalizumab (Figure). Although several therapies against JCV have been used in AIDS-associated PML, there is no conclusive evi-

**Figure.** Graphic depiction of the 3 potentially viable approaches to treatment of progressive multifocal leukoencephalopathy induced by natalizumab. IVIGs indicates intravenous immunoglobulins; VLA-4, very late-activation antigen 4.
idence that these agents have any impact on the course of this disease. There is even less evidence that those antiviral therapies will be effective in non–AIDS-associated PML.

There are several reasons why the restoration of immunocompetence with leukocytes not bound by VLA-4 should be attempted in natalizumab-associated PML. Highly active antiretroviral therapy in HIV-infected individuals reduces the retroviral load in most body fluids and increases the number of CD4 T cells. Numerous studies show improved survival of patients with PML treated with highly active antiretroviral therapy.22,23 In addition, JCV-specific CD8 T cells are associated with a more favorable clinical outcome.24,25 Most CD8 T-cell responses are directed against an HLA-A*0201–restricted JCV epitope, VP1p36. In addition, the initiation and perpetuation of antigen-specific CD8 T-cell responses against most foreign antigens require CD4 T-cell help,27 and at least some studies have associated a higher CD4 T-cell count with prolonged survival in HIV-infected patients.28,29 In another example of an opportunistic viral infection in an immunosuppressed host, cellular therapy to restore immunity to individuals with Epstein-Barr virus is a successful treatment for Epstein-Barr virus–associated posttransplant lymphoproliferative disorder.30,31 Thus, reconstitution of CD4 and CD8 lymphocytes may be required to ensure a positive outcome from PML in natalizumab-treated patients.

The neutralization and elimination of natalizumab largely depends on its interaction with VLA-4. Serum concentrations of natalizumab are detectable for 3 to 8 weeks after a 1- to 3-mg/kg dose intravenously.21 The interaction between natalizumab and VLA-4 is influenced by several factors, including electrostatic forces, hydrogen bonds, hydrophobic interactions, and van der Waals forces.32-34 As is true for all antibody-antigen binding, the interaction of natalizumab and VLA-4 is reversible, and it follows the basic thermodynamic principles of reversible bimolecular interactions. Reversible binding of an antibody to its target results in an off–on binding equilibrium, which can vary considerably for each antibody-antigen combination and depends on the properties of the antibody, the antigen, and the rate of diffusion. It has to be assumed that the in vivo binding equilibrium between natalizumab and VLA-4 is not constant. Specifically, we know that VLA-4 and other integrins are capable of altering adhesiveness to their ligands by conformational changes and the degree of cell surface expression.35,36 Thus, in the case of natalizumab and VLA-4, it is difficult to quantify 2 measures that are commonly used to describe the strength of association between an antibody and an antigen association: affinity, which describes the binding strength between the antibody and a single specific antigen epitope, and avidity, a term that provides information about the overall strength and stability of antibody-antigen interactions. Even in the absence of this information, the reversibility of the interaction between natalizumab and VLA-4 provides the potential for therapeutic interventions in patients who develop life-threatening complications under therapy.

EXISTING INTERVENTIONS

Antiviral Therapies

In recent decades, with advances in our understanding of the mechanisms of viral infections, new and specific antiviral treatments have emerged. A specific agent for JCV is not yet available.

Pros. As with other viral infections of the CNS, an effective and specific therapy for JCV infection would be the most promising approach to treat patients with PML.

Cons. To date, no antiviral therapy has demonstrated efficacy in the treatment of PML. Hou and Major37 showed that cytarabine decreased JCV replication in an immortalized human neuralig cell line, but zidovudine and cidofovir were not effective in this culture system. However, cytarabine given intravenously or intrathecally did not result in a survival benefit in a clinical trial in HIV-infected patients with PML.38 Although cidofovir was not effective against JCV in vitro, initial case reports and retrospective series described efficacy in HIV-infected and uninfected patients with PML. A subsequent open-label study of this agent in HIV-infected individuals showed no benefit in terms of neurologic abnormalities, although subjects who entered the study with suppressed plasma HIV viremia had a better outcome than those who did not.39

Potential adverse effects of antiviral therapies include renal failure and myelosuppression.

Immunomodulatory Therapies

Case reports and retrospective series address treatment of HIV-infected patients with PML with immunomodulatory agents, including interferon alfa, interferon beta, and interleukin 2. Formal clinical trials are required to determine whether these findings can be translated to the clinical setting.

Pros. Interferon alfa, interferon beta, and interleukin 2 have been used extensively in other clinical settings. The adverse effect profiles of these agents are well known. Case reports describe improvement in PML-related neurologic dysfunction or recovery from PML in 3 patients who underwent transplantation for lymphoma and in 1 patient with myelodysplastic syndrome who were treated with interleukin 2.40-43 Finally, there is theoretical evidence that serotonin 2a receptor blockers may prevent JCV infection of oligodendroglia or even spread of infection from infected oligodendroglia to uninfected cells. Specifically, Elphick and coworkers44 showed that the serotonin 2a receptor could act as the cellular receptor for JCV in a glial cell culture system. On the basis of their potency to block the serotonin 2a receptor and their adverse effect profile, olanzapine, ziprasidone hydrochloride, or risperidone may be particularly useful for treatment of PML.

Cons. Despite an initial retrospective analysis that suggested that interferon alfa may improve survival of HIV-
infected patients with PML, a subsequent retrospective analysis did not show benefit of this agent beyond that afforded by highly active antiretroviral therapy. A single report describes failure of interferon beta treatment of HIV-associated PML.47

Hematopoietic Growth Factors

Hematopoietic growth factors catalyze the mobilization and maturation of hematopoietic stem cells. The HGFs are routinely used to promote rapid hematopoietic engraftment after hematopoietic stem cell transplantation.

Pros. Theoretically, interleukin 7, recombinant human granulocyte colony-stimulating factor (G-CSF), or recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) could accelerate the generation of mature leukocytes with unbound, available VLA-4 (Figure). Administration of G-CSF and GM-CSF stimulate primarily the myeloid cell compartment. Increasing cell number in the myeloid compartment might act as a “sink” for natalizumab and cause a more rapid clearance of the antibody. In contrast, interleukin 7 mobilizes predominantly the lymphocyte cell compartment and may be more effective in this specific scenario.30-33

In combination with plasma exchange or IVIGs (see subsequent sections), the use of HGF may be an effective method to generate an immune response against JCV and other pathogens (Figure). Interestingly, 1 of the natalizumab-treated patients with MS who was diagnosed as having PML and who survived was treated with G-CSF for pancytopenia and subsequently developed an immune-reconstitution inflammatory syndrome that was characterized by inflammation and hemorrhages in the brain.4

Cons. In 1 study, 4 of 10 patients with MS who had received high-dose immunosuppression with peripheral blood stem cell rescue experienced a relapse while receiving recombinant human G-CSF.34 As it was thought that G-CSF might create an inflammatory environment in the CNS, hematopoietic progenitor cells are now typically being mobilized with a combination of cyclophosphamide, corticosteroids, and G-CSF in clinical trials evaluating the efficacy of hematopoietic stem cell transplantation in MS. As previous studies indicate that inflammatory CNS reactions in PML are generally associated with a favorable prognosis,35 the concomitant administration of corticosteroids with HGF should not routinely be recommended.

Other reported adverse effects of HGF include anaphylaxis, chest pain, diaphoresis, nausea, and syncope.48,49,56 A theoretical concern is the potential worsening of leukocytosis that has been reported under natalizumab therapy.57 Leukocytosis has been identified as an independent risk factor and prognostic indicator in cardiovascular disease58 and ischemic stroke.59

Plasma Exchange

The clinical benefit of plasma exchange is based on the principle that plasma is separated from the cellular elements of the blood.60 Specifically, the reduction of circulating autoantibodies, immune complexes, cytokines, and other inflammatory mediators in the peripheral blood is postulated to be the principal mechanism of action.60,61

Pros. While it is impossible to completely remove antigen-specific antibodies by plasma exchange in patients with a persistent antigenic challenge, the scenario is very different with an exogenously administered antibody like natalizumab. The unbound fraction of this antibody could be eliminated by repeated plasma exchange (Figure). As first-order kinetics apply, the exchange of a single volume of plasma will lower the level of a specific target molecule by 50% to 60%. Thus, multiple daily treatments with 1 to 1.5 plasma volume exchanges would remove more than 95% of unbound natalizumab from the plasma.

During the past 25 years, plasma exchange has been used in several neurologic disorders, including myasthenia gravis, Lambert-Eaton myasthenic syndrome, and acute inflammatory demyelinating polyradiculoneuropathy. Although plasmapheresis is associated with some adverse effects, which are listed below, the overall safety and tolerability of this procedure is excellent.60

Cons. Biophysical properties of natalizumab, including antibody-binding kinetics, will influence the efficacy of plasma exchange in immune reconstitution. It was reported that a natalizumab dose of 3 mg/kg resulted in 82% receptor saturation 1 week after treatment and 52% 4 weeks after treatment.65 Receptor saturation with natalizumab, 4 mg/kg, was 90% at 1 week and 68% at 4 weeks.65 Natalizumab is approved at a dose of 300 mg per month. Several factors will influence the pharmacokinetic properties of natalizumab in an individual patient, including the white blood cell count.

In patients with severe disease, including PML, daily plasma exchange may be challenging because of clinical adverse events caused by this procedure. These include complications resulting from central venous catheter anticoagulation with citrate, which may lead to disturbance of acid-base homeostasis and symptomatic hypocalcemia. Repeated plasma exchanges are associated with depletion of coagulation factors and immunoglobulin, increasing the risk of coagulopathies.

Finally, there is a theoretical concern that immunoregulatory properties of plasma exchange may lead to the worsening of infectious complications of natalizumab therapy.

Intravenous Immunoglobulins

Although the exact mechanisms of action of IVIGs are still being investigated, several effects on humoral and cellular immune responses have been proposed. These include reduction of antibody production, modulation of Fc receptor-mediated phagocytosis (opsonization), blockade of superantigen-induced polyclonal T-cell activation, inhibition of complement binding and activation, and neu-
turalization of proinflammatory cytokines. In addition, anti-idiotypic antibodies in IVIGs may play an immunoregulatory role.

**Pros.** The presence of anti-idiotypic antibodies may be the best rationale for the use of IVIG in natalizumab-treated patients who are diagnosed as having PML. Anti-idiotypic antibodies are immunoglobulins that bind to the antigen-binding fragment (Fab) of another antibody (Figure). Binding of anti-idiotypic antibodies against the Fab site of unbound natalizumab may prevent its attachment to VLA-4 (Figure). Furthermore, there is anecdotal evidence that IVIGs may have beneficial clinical effects in some immunosuppressed patients with viral infections.

**Cons.** It is conceivable that the administered antibodies have low affinity and avidity to natalizumab and may ultimately have little therapeutic impact. Like any pharmacologic intervention, IVIGs have potential adverse effects. Relatively common and less severe adverse effects include arthralgias, fever, headache, malaise, and myalgia. Acute renal failure, anaphylaxis, aseptic meningitis, and thrombotic complications are the more serious risks associated with IVIG therapy.

As is the case with plasma exchange, IVIG has the potential to aggravate immunosuppression caused by natalizumab. Specifically, the IVIGs may contain antibodies directed against several surface molecules on human T lymphocytes, including CD4, the major histocompatibility complex, and the T-cell receptor. Neutralizing antibodies against molecules that can activate T cells, including bacterial or viral superantigens, are also present in current IVIG formulations.

**Leukapheresis and Autotransfusion of Leukocytes**

Leukapheresis has been used for decades to isolated circulating leukocytes from peripheral blood. Theoretically, patients who are candidates for natalizumab therapy could undergo leukapheresis before initiation of therapy. Leukocytes could then be frozen and stored for later use.

**Pros.** The transfusion of cryopreserved autologous leukocytes may be an effective method of immune reconstitution. Pretreatment leukocytes would express unbound surface VLA-4 and could migrate into peripheral tissues for immune surveillance (Figure). This method may be especially effective in combination with other methods that are aimed at decreasing the amount of unbound natalizumab, including plasma exchange and IVIGs (Figure).

**Cons.** Leukapheresis is a costly, time-consuming, and labor-intensive method. The effectiveness of leukocyte transfusions for the treatment of infections is still being investigated. It is also unclear how many sessions of leukapheresis would be required to collect sufficient cells to ensure effective immune reconstitution in the setting of PML or other opportunistic infections. Another theoretical concern is the occurrence of an immune-reconstitution inflammatory syndrome, similar to that with the use of hematopoietic growth factors (discussed in a previous section).

Currently, most blood banks and transfusion centers require transfusion of leukocytes within 24 hours of cell harvest. However, technically it is possible to store leukocytes after leukapheresis in liquid nitrogen for years, but experience with long-term storage and clinical use of leukocytes is sparse. Also, an infrastructure would be needed for leukocyte storage, which would likely not be cost-effective given that only 1 in 1000 patients would require leukocyte infusion for treatment of PML.

Common adverse effects of leukapheresis include fatigue, headaches, and nausea.

**EXPERIMENTAL TREATMENT INTERVENTIONS**

**Antiviral Therapy With Small Interfering RNA**

RNA interference is an evolutionarily conserved mechanism that promotes the degradation of messenger RNA with sequence homologies to small double-stranded ribonucleic acid. One of the primary biological functions of RNA interference may be the protection of host cells from viruses. Production of double-stranded RNA in the host cell after viral activation signals a series of events that ultimately results in degradation of complementary messenger RNA. A cytoplasmic RNase III-like enzyme termed Dicer recognizes double-stranded RNA and cleaves it into 21 to 23 nucleotide fragments that contain 2 or 3 nucleotide overlaps. These small interfering double-stranded RNA pieces (siRNA) are then intracellularly linearized, and the strands are separated. Single-stranded RNA can now hybridize to complementary messenger RNA, and the messenger RNA is enzymatically degraded. Thus, translation of the transcript is no longer possible.

**Pros.** The generation of synthetic siRNA is easy and inexpensive, and virtually any gene product can be readily targeted with synthetic siRNA. In patients diagnosed as having PML, replication of JCV could theoretically be reduced with synthetic siRNA therapy.

**Cons.** Currently, no siRNA therapy has been shown to be safe and effective in any human disease. Pharmacokinetics, pharmacodynamics, and drug delivery are only some of the issues that will have to be addressed before these agents are administered.

**Antiserum**

For many years, antiserum from immunized animals or volunteer donors has been used to transfer immunity to patients who are vulnerable to infectious diseases. Antiserum may be helpful not only in neutralizing infectious agents but also in removing undesired effects of new biopharmaceuticals. Indeed, 6% of natalizumab-treated patients develop persistent neutralizing antibodies to natalizumab. Antiserum from these individuals may be useful to antagonize the effect of natalizumab in patients who develop PML.
Pros. Serum from natalizumab-treated patients who developed antibodies is already available, and antiserum from animals could be readily generated. Because antiserum contains high levels of antibodies that abolish the effect of natalizumab, it is likely that these antibodies would rapidly decrease serum levels of free natalizumab on transfer to patients (Figure).

Cons. While antiserum therapy may inactivate free antibody, it may not be effective in stripping natalizumab from immune cells. A single administration may not be sufficient for removal of natalizumab, and repeated administrations are associated with a higher rate of adverse effects. Antiserum may contain pathogens. Finally, antibody therapies may result in serum sickness.79

Recombinant Natalizumab-Neutralizing Molecules

Recombinant proteins could be useful tools in neutralizing the biological effects of natalizumab. One example is the generation and administration of recombinant VLA-4 mimics to patients who develop PML or other life-threatening infectious complications during natalizumab therapy. Very-late-activation antigen 4 is a natural ligand of natalizumab. Recombinant VLA-4 mimics should bind to natalizumab but not to the natural ligands of VLA-4, including vascular cell adhesion molecule 1. This could further impair the capability of leukocytes to extravasate into tissues, including the CNS.

Another example would be the generation of recombinant natalizumab-neutralizing antibodies. In the absence of DNA from a plasma cell that generates such antibodies, it would perhaps be easiest to purify a natalizumab-neutralizing antibody from a patient, determine the amino acid sequence, and generate a recombinant monoclonal natalizumab-neutralizing antibody in a mammalian cell line.

Pros. Technically, the generation of recombinant human proteins is well established. During recent years, numerous protein therapeutics have been approved for clinical use and have been found to be safe, including botulinum toxin, erythropoietin, factor VIII and IX, human growth hormone, interferon beta-1a, interferon beta-1b, interferon alfa, and insulin.80 Recombinant VLA-4 mimics or recombinant natalizumab-neutralizing antibodies that form a high-avidity bond to natalizumab could potentially be a very useful tool to capture the unbound fraction of natalizumab and prevent it from binding natural VLA-4 on leukocytes (Figure). Long-term repetitive use of such agents could accelerate the elimination of natalizumab.

Cons. All recombinant proteins are immunogenic. Posttranslational modification of proteins, purification, and the route of administration are factors that determine the likelihood of an immune response.81 One of the worst possible treatment outcomes would be an immune response against recombinant VLA-4 mimics and endogenously expressed VLA-4, which could significantly worsen the immunosuppressed state of natalizumab-treated patients. This type of cross-reactivity has been observed with the use of recombinant erythropoietin.82,83

Finally, the incidence of PML in this patient population may be too low to make the production of recombinant VLA-4 mimics or recombinant natalizumab-neutralizing antibodies economically feasible for pharmaceutical companies.

CONCLUSIONS

The discontinuation of natalizumab in patients who are diagnosed as having PML may not be sufficient to provide a favorable clinical outcome. There are compelling scientific reasons to use pharmacologic interventions that will propagate immune reconstitution in these patients. Some treatments that are currently available and used in other clinical settings may promote immune reconstitution and accelerate neurologic recovery in natalizumab-associated PML but are untested in such a setting. These include hematopoietic growth factors, plasma exchange, IVIGs, and leukopheresis with autotransfusion of leukocytes. These therapies could potentially be used alone or in combination. Experimental approaches that may also be beneficial in patients immunosuppressed by natalizumab are the siRNAs, antiserum, or recombinant natalizumab-neutralizing molecules.

There is currently no evidence that any of these therapies will alter the clinical course of PML in patients who receive natalizumab. In addition, many of these therapies have potentially serious adverse effects and could theoretically worsen the immunosuppression caused by natalizumab. Owing to the expected low incidence of PML in patients receiving natalizumab, it will be challenging to study the efficacy of these agents in a controlled manner. Because it is currently impossible to identify patients at risk of developing PML during natalizumab therapy, it is important that neurologists be aware of possible existing therapeutic interventions.

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