EDITORIALS

Selective Treatment of Multiple Sclerosis

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Natalizumab, a recombinant monoclonal antibody against α_4 integrins, is the first selective immunomodulating drug for the treatment of multiple sclerosis and, by several criteria, is an advance over current therapies. The antibody was developed to block the adhesion of activated T cells to endothelial cells and thereby reduce the inflammatory feature of the multiple sclerosis plaque. Parenthetically, this advance attests to the value of translational research in a disease for which there is only partial knowledge of the mechanism. Natalizumab has also evinced interest for the treatment of Crohn's disease and rheumatoid arthritis but with less certain results in limited trials. Informed readers are aware of the preliminary report showing short-term benefits of natalizumab for multiple sclerosis that appeared in the *Journal* in 2003.[1] They are also mindful of the three cases of progressive multifocal leukoencephalopathy (PML) that were attributed to the drug,[2-4] which led to its withdrawal from the market after four months, an unusually brief period of use.

Now a pivotal trio of articles in this issue of the *Journal* extend the efficacy of the drug to the two-year mark and provide reassurance that the risk of PML is small with relatively brief use.[5-7] Beyond these findings, clinicians and patients are left wondering if and when natalizumab will be made available and what precautions might be taken to prevent the emergence of the JC virus, the causative agent of PML.

Clinical practice in multiple sclerosis is attentive to two pressing problems — namely, the prevention of acute demyelinating lesions and the forestalling of a transformation of the disease from the relapsing form to the chronic progressive form that causes the most serious disability. The presumption in clinical trials has been that control of the short-term biologic manifestations of disease, as measured by the number of acute relapses and of brain lesions detected by magnetic resonance imaging (MRI), will reduce neurologic damage. Furthermore, none of the drugs under discussion, including natalizumab, are unambiguously effective once the progressive phase of multiple sclerosis begins.

With this in mind, several points in the three *Journal* articles merit attention. The two-year Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study[5] of nearly 1000 patients indeed affirms that natalizumab has marked salutary biologic and clinical effects in multiple sclerosis. The annualized rate of clinical relapse was reduced by 68 percent (from 0.75 to 0.24), and the number of new or enlarging brain lesions on MRI was reduced by 83 percent. By way of perspective, the currently used drugs, interferon and glatiramer, diminish acute relapses by roughly one third. A further compelling result was the abatement of clinical progression (17 percent of patients receiving natalizumab had progression vs. 29 percent of those receiving placebo) and a similar prolongation of the interval before neurologic deterioration. It is tempting to project these improvements over a patient's lifetime, but there are no data yet to support such a view.

The two-year Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) trial[6] of the combined administration of natalizumab and interferon reports a marked reduction in the rate of annual-

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ized relapse from 0.75 with interferon alone to 0.34 with dual treatment. The progression of disability showed a moderate reduction, from 29 percent with interferon alone to 23 percent with the addition of natalizumab. Although the two study populations were not identical, it is noteworthy that the rates of relapse and clinical progression with interferon in this trial and in the placebo group of the AFFIRM trial were nearly the same, emphasizing again the unimposing effects of the current generation of treatments.

It is reassuring that no further instances of PML were detected in either of these two large studies, but their duration of two years allows only limited inferences. The aforementioned cases of PML occurred after natalizumab had been given with interferon beta (or other immunosuppressive agents) for a period of 8 to 30 months. This dual immune suppression offered a plausible explanation for the emergence of latent JC virus, possibly vindicating natalizumab monotherapy. This point has not been settled.

In order to frame the risk of PML, Yousry and colleagues[7] undertook an immense post facto surveillance program. Their methodology for identifying potential cases of PML among 3116 patients with multiple sclerosis, Crohn's disease, or rheumatoid arthritis in 11 trials was sound and probably would have detected most valid cases. However, 1700 patients in other trials were excluded, and scrutiny was purposely casual for some 7000 patients who received natalizumab commercially. The omissions concerning the latter group are surely of little concern since four or fewer doses had been given. (It bears emphasis that the huge number of treatments administered during only four months of open availability presumably reflected a vast unmet need of patients with multiple sclerosis.) An essential limitation of the survey was the average treatment of only 18 monthly doses (with a range of 8 to 37 months), a constraint that brackets any conclusions.

The authors of the PML survey fairly state, "We do not know the duration of exposure to natalizumab required to put patients at risk for PML." It seems that less than two years of treatment with natalizumab alone is relatively safe, but the possibility remains that PML will develop in 1 in 1000 patients. At the moment, it is doubtful that neurologists will chance using natalizumab in conjunction with other immunosuppressive agents, with the possible exception of corticosteroids when they are required for acute relapses.

The available data support the value of natalizumab as a potent treatment for multiple sclerosis in a new class of highly specific immune drugs. The convenience of a monthly infusion of natalizumab may hold more appeal for patients than weekly or more frequent self-injection of interferon and glatiramer. What clinical guidance is provided from these three studies would be enhanced by some method to predict which patients are at risk for PML and to determine during treatment if the JC virus has emerged from its latent state in the kidney. As suggested by previous editorialists, serial measurements of JC viral load could be used to interdict or to interrupt a course of natalizumab,[8] but it is not yet clear if this is a practical solution. It seemed self-evident to everyone when these cases of PML were described that impeding lymphocyte traffic to the brain led to opportunistic viral entry. Ransohoff has speculated that natalizumab also acts on bone marrow cells to promote the mobilization of JC virus, thereby making the therapeutic effect of the drug inseparable from the risk of PML.[9] If this theory is valid, investigators are challenged to design drugs that prevent sensitized T cells from entering the nervous system by mechanisms even more novel than those employed by natalizumab. Several of these drugs are already on the way.

Dr. Ropper reports having been the principal investigator for a multicenter trial of interferon for the treatment of peripheral neuropathy that was supported by a $15,000 grant from Biogen in February 2004. No other potential conflict of interest relevant to this article was reported.

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Catheter Ablation of Chronic Atrial Fibrillation — The Gap between Promise and Practice

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Atrial fibrillation remains the most common heart-rhythm abnormality seen in general clinical practice, and its incidence is increasing. Atrial fibrillation is an enormous health concern because it increases the risk of death, congestive heart failure, and thromboembolism and decreases the quality of life. It places an increasing burden on the health care system because of the associated costs of hospitalization and outpatient care. The pharmacologic approach to the maintenance of sinus rhythm in patients with atrial fibrillation is compromised by its limited efficacy, side effects, and concern about safety. For these reasons, since the initial description of pulmonary-vein ablation in the *Journal*,[1] intense efforts have been directed toward the use of catheter ablation to "cure" paroxysmal atrial fibrillation.

The importance of the pulmonary veins and surrounding left atrium in the initiation of atrial fibrillation is now widely accepted by electrophysiologists. Electrical isolation of the pulmonary veins by radiofrequency catheter ablation has a success rate approaching 75 to 85 percent in patients without clinically significant structural heart disease.[2,3] According to the latest guidelines of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology, catheter ablation is considered standard therapy for patients who have symptomatic paroxysmal atrial fibrillation after having had no response to a single antiarrhythmic drug.[4]

In contrast to its established use for paroxysmal atrial fibrillation, the role of catheter ablation for chronic atrial fibrillation is less well studied. Evidence to date suggests that the mechanisms of chronic atrial fibrillation are more complex than those causing paroxysmal atrial fibrillation.[5] The use of more extensive ablation procedures that modify the electrical substrate as well as the initiators of atrial fibrillation is often necessary to prevent chronic atrial fibrillation. Few studies have systematically examined the results of catheter ablation in patients with chronic atrial fibrillation.

The study by Oral et al. in this issue of the *Journal* evaluates the potential of catheter ablation as a treatment for chronic atrial fibrillation.[6] In this report, 146 patients with medically refractory, chronic atrial fibrillation were randomly assigned to undergo circumferential pulmonary-vein ablation or to receive short-term medical therapy with amiodarone. Clinically significant structural heart disease was present in 8 percent of patients. All patients had received at least two ineffective antiarrhythmic drugs and had undergone at least one cardioversion before participating in the trial. At the 12-month follow-up visit, 74 percent of patients who had undergone ablation were in sinus rhythm without antiarrhythmic-drug therapy, as compared with only 4 percent of control patients who did not cross over to ablation therapy.

This study is noteworthy for several reasons. It convincingly demonstrates that catheter ablation alone can lead to sustained sinus rhythm in specific patients with chronic atrial fibrillation. The nonpharmacologic maintenance of sinus rhythm is an important clinical goal with far-reaching implications. Although recent trials have demonstrated no advantage to pharmacologic rhythm control, as compared with rate control, for most clinical outcomes, there is genuine concern that the benefits of sinus rhythm are negated by the deleterious effects of antiarrhythmic drugs.[7] For example, the maintenance of sinus rhythm has been associated with a survival advantage that may be offset by the use of antiarrhythmic drugs.[8] The ability to maintain sinus

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