Natalizumab: benefit outweighs risk in selected patients with multiple sclerosis

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Neurologists have not traditionally commanded the capability of highly effective treatments for their diseases of interest. Notable exceptions in recent decades would include migraine and epilepsy therapies. Notwithstanding impressive advances in our understanding of the pathophysiologic mechanisms of many neurological disorders, there has not been a commensurate degree of progress in the development of effective disease-modifying treatment strategies. A highly conspicuous exception has occurred in multiple sclerosis (MS), where an accelerated pace of drug development has revolutionized our ability to treat both the clinical and radiographic measures of disease activity. Indeed, MS is one example of chronic neurological disease that we believe is in the active process of being therapeutically dismantled.

No generally effective therapies for MS existed prior to the demonstrated efficacy of interferon beta-1b (Betaseron/Betaferon) in the early 1990s. Although with clear benefits over placebo treatment, some dismissed interferon beta-1b, subsequent interferons (beta-1a; Avonex, Rebif), and glatiramer acetate (Copaxone) as having insufficient benefits to warrant the inconvenience of injectables, side effects and cost. Despite these objections, use of these immunomodulators in MS has grown steadily over the last 15 years, and most would agree that their promise as ‘disease-modifying’ therapies has been generally fulfilled, albeit at a level of modest impact upon the progressive elements of the disease process [Goodin *et al.* 2002]. As such, there remains much work to be done in order to more fully unravel those pathogenetic mechanisms that

are most germane to facilitating the identifying strategic therapeutic targets [Frohman *et al.* 2005].

Natalizumab (Tysabri), a selective adhesion molecule inhibitor, is the newest entry into the field of approved MS therapeutics. Its mechanism of action is based on reversible binding to alpha-4 integrin and resultant blockade of alpha-4 integrin and VCAM-1/MAdCAM interaction, thereby dramatically reducing transendothelial trafficking of mononuclear cells into the CNS. New MS inflammatory events are profoundly reduced by treatment with natalizumab and, concurrently, CSF compartment mononuclear cells are greatly but reversibly reduced [Stuve *et al.* 2006a,b]. Clinically, natalizumab treatment of relapsing MS results in a 67% reduction in relapse rate, and a 42–54% reduction in sustained disability progression compared with placebo, in a recent class I, phase III study [Polman *et al.* 2006]. Subsequent analyses of phase III secondary and tertiary end points continue to support the unprecedented efficacy of natalizumab in relapsing MS (e.g. the effect on quality of life and the preservation of sensitive measures of vision; potentially signaling a neuroprotective effect) [Balcer *et al.* 2007; Rudick *et al.* 2007]. These results arguably place natalizumab as the most effective agent yet approved for the treatment of relapsing MS. Side effects are generally absent, but when they occur are typically mild and do not impair adherence. Infectious and lesser-concerning complications overall appear quite similar between natalizumab and placebo-treated groups. Immediate hypersensitivity reactions can occur, but are rare and usually easily treated

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without significant clinical sequelae [Phillips *et al.* 2006].

Post-marketing surveillance has reported a few isolated cases of hepatotoxicity and melanoma, although neither adverse event was associated with natalizumab in phase I–III studies, and any ultimate causative association with natalizumab remains uncertain. However, the most severe and concerning adverse event arising from natalizumab (also observed with a variety of other immune modulating agents such as rituximab and mycophenolate) treatment is the risk of progressive multifocal leukoencephalopathy (PML), a rapidly progressive CNS infection, usually fatal, caused by the John Cunningham (JC) virus. This severe complication has been estimated to occur in 1 per 1000 based on a mean 18-month natalizumab exposure [Yousry *et al.* 2006]. Three instances were previously identified in persons involved in natalizumab studies in MS and Crohn's disease out of approximately 3000 persons exposed to natalizumab for a mean of 17.9 months. Each of these three individuals had been treated with natalizumab and concurrent immunomodulation or recent immunosuppression. Currently, natalizumab is used only as monotherapy in MS in the hope that PML risk will be consequently mitigated.

In July 2008, PML was confirmed in two additional persons with MS treated with natalizumab monotherapy for 14 and 17 months, respectively. At the time of these reports, out of approximately 39,000 persons treated with natalizumab worldwide, 6600 persons had been continuously treated with natalizumab for 18 months or longer, and approximately 14,000 persons had been treated for 12 months or longer. Therefore, based on these exposures, and including the two new PML reports, the PML risk could possibly be lower with natalizumab monotherapy than earlier estimates. Particularly in view of the two newest PML occurrences, we are reminded that clinical vigilance and high index of suspicion should lead to early cessation of natalizumab treatment in suspect individuals, diagnostic workup, and, if appropriate, institution of therapeutic plasma exchange with the intent to reverse the biological effects of this adhesion molecule inhibitor [Khatri *et al.* 2008]. Longer follow up, and additional clinical and MRI data will be crucial in determining the utility of plasma exchange and other acute interventions in these and future PML cases. For now, clinical vigilance

appears to be the most effective maneuver for early identification of suspected PML, thus underscoring the importance and efficacy of risk mitigation programs such as the TOUCH program for natalizumab and other future therapies that may carry significant risks.

So, where does this leave us? We believe that disease-modifying therapy in MS is very much in an accelerating state of flux, ushered in by natalizumab, in which highly effective therapies are finally coming within reach. Newer investigational agents, such as alemtuzumab, fingolimod, rituximab and others, while demonstrating encouraging efficacies may also have significant but uncommon adverse events. We must expect that as therapeutic efficacies significantly increase, that corresponding downside stakes will increase as well. The benefit–risk ratio remains, as it always has and will remain, the best metric against which physician and patient together may judge the appropriateness of a given treatment. Benefit is never guaranteed; risk is at best roughly estimated. We believe that natalizumab is an extremely effective treatment for relapsing MS, in which, based on best currently available information, efficacy continues to outweigh risk for the carefully selected patient [Thompson *et al.* 2008; Kappos *et al.* 2007]. Inadequate treatment of active MS has its own associated risks and ‘expense’ (loss of function, gainful employment, independence and quality of life). We anticipate the continued need for clinical vigilance while using natalizumab, as well as anticipate the need for new vigilance programs incorporating *in vitro* assays for monitoring immune physiology as new, highly effective MS therapies continue to be developed.

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