

Natalizumab for Moderate-to-Severe Crohn's Disease

Gerald W. Dryden, MD, MSPH
Associate Professor of Medicine
Division of Gastroenterology/Hepatology
Department of Medicine
University of Louisville School of Medicine

In January of 2008, the US Food and Drug Administration (FDA) announced approval of the $\alpha 4$ integrin receptor antagonist natalizumab (Tysabri, Elan/Biogen Idec) for the treatment of moderate-to-severe Crohn's disease (CD) in patients refractory to anti-tumor necrosis factor (TNF) biologic therapy. Natalizumab curbs T-cell-mediated inflammation in the gut through a novel pathway, blocking the $\alpha 4$ integrin receptor expressed on the T-cell surface and thus preventing passage of T cells through the gut's vascular endothelium. Natalizumab is also indicated for the treatment of certain forms of relapsing multiple sclerosis (MS).

The first significant trial of natalizumab in the CD population was a phase II trial published in the *New England Journal of Medicine* in 2003. This was followed by the placebo-controlled phase III ENACT I trial, designed to establish the efficacy of natalizumab for induction of CD remission and select adequate numbers of patients to evaluate maintenance treatment in the follow-up ENACT II trial. ENACT I demonstrated considerable response to natalizumab but statistical significance for the primary endpoint was confounded due to a high placebo response. However, post-hoc analysis of ENACT I patients with active disease, indicated by elevated levels of C-reactive protein (CRP), demonstrated a statistically significant rate of response (62% vs 37% in the placebo group). These results were reinforced in the ENCORE trial, which enrolled only patients with elevated CRP and again demonstrated significant response to natalizumab versus placebo in a prospective fashion.

Enrollment and follow-up of therapy in the CD studies had been completed when 2 cases of progressive multifocal leukoencephalopathy (PML) were identified among patients receiving natalizumab in combination with interferon- β -1a for treatment of MS. At this point, the manufacturers voluntarily recalled natalizumab from the market and ceased all clinical trials in order to screen all patients for signs of neurologic adverse effects. In the process of this screening, no other cases of PML were identified in MS patients and although one case was identified retrospectively in a CD patient with a history of infliximab

and azathioprine therapies and chronic leukopenia, none have been seen in any treatment group since. This screening information, along with the results of ENCORE and ENACT I and II, were submitted to the FDA and contributed to the re-approval of natalizumab for MS and subsequent approval for CD refractory to other forms of biologic therapy.

Patients taking natalizumab must also enroll in the Tysabri Outreach Unified Commitment to Health (TOUCH) registry. TOUCH enrollees are required to read a monograph on natalizumab safety and discuss it with their prescribing physician before receiving their first natalizumab infusion. After the initial infusion, patients fill out a questionnaire pertaining to neurologic side effects and undergo regular symptom-based screening to monitor for adverse events. Some physicians are also adopting a regimen of intermittent magnetic resonance imaging and routine laboratory studies to further monitor effects on the central nervous system.

Screening of patients for potential reactivation of JC virus (the cause of PML) presents a challenge, as the virus is latent in approximately 90% of the general population. Furthermore, some studies have shown that even reactivation of the virus does not directly lead to development of neurologic disease. Further investigation of this mechanism will be necessary in order to maximize the safety and future use of natalizumab. Other future research might focus on the use of natalizumab in the 40% of patients who are primary nonresponders to anti-TNF biologic therapy as well as patients with ulcerative colitis who are not responsive to anti-TNFs. The original development of natalizumab was done in a new-world primate model of ulcerative colitis, and it may prove particularly effective in this disease state.

Natalizumab has now been administered to over 21,000 patients with MS and 6,300 of them have taken it for over 1 year, with no additional cases of PML reported. In the setting of patients who have failed anti-TNF therapy, natalizumab thus presents a viable option. Patients who have been fully informed regarding natalizumab's risk/benefit profile versus that of other biologic therapies should partner with their physicians to determine their next steps in the course of treatment.

Suggested Reading

- Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med*. 2003;348:24-32.
Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2005;353:1912-1925.
Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE trial. *Gastroenterology*. 2007;132:1672-1683.

