

Natalizumab reduces relapse and disability in relapsing multiple sclerosis

Clinical question Is natalizumab safe and effective for the treatment of relapsing multiple sclerosis?

Bottom line Natalizumab reduces the likelihood of relapse and progression of disability in patients with relapsing multiple sclerosis (RMS). Although no cases of progressive multifocal leukoencephalopathy (PML) were seen in this study, a meta-analysis estimates the risk at approximately 1 per 1,000 patients treated for 18 months.

Synopsis Natalizumab is a selective adhesion-molecule inhibitor that is thought to block binding of leukocytes to vascular cells in the brain, thereby attenuating the inflammatory response seen in RMS. However, it has been linked to PML, a fatal and rapidly progressive neurodegenerative condition. In this study, 942 patients were randomly assigned (allocation concealed) in a 2:1 ratio to receive either natalizumab 300mg by intravenous infusion every four weeks or placebo. Relapses were assessed by a neurologist blinded to treatment assignment and could be treated by high-dose corticosteroids. Patients underwent magnetic resonance imaging (MRI) at baseline and after one year and two years. Groups were balanced at the start of the study and analysis was by intention to treat. Approximately 9 per cent in each group withdrew from the study, but half these patients continued to undergo regular monitoring. After two years, the cumulative probability of progression of disability was lower in the natalizumab group (17 per cent vs 29 per cent; $P < 0.001$; number needed to treat [NNT] 9). The probability of relapse was also decreased (0.26 vs 0.81 relapses per patient per year; $P < 0.001$). There were also fewer new or enlarging lesions detected by MRI in the natalizumab group; the

percentage of patients remaining relapse free at one (77 per cent vs 56 per cent; NNT 5) and two years (67 per cent vs 41 per cent; NNT 4) was lower in the natalizumab group. There was no difference between groups in the risk of infection and no cases of PML were detected. The only adverse events more common in the natalizumab group were fatigue (27 per cent vs 21 per cent) and allergic reaction (9 per cent vs 4 per cent). Patients in this study were excluded if they were taking interferon. A second study found similar benefits in a group of 1,171 randomised to natalizumab plus interferon or interferon alone for up to two years, although two developed PML (*New England Journal of Medicine* 2006;354:911–23). A third study compiled data from 3,417 patients who had received natalizumab in clinical trials and concluded that the overall risk of PML was 1 per 1,000 patients treated for 18 months (95 per cent confidence interval 0.2–2.8 per 1,000) (*ibid*, pp924–33).

Level of evidence 1b (individual randomised controlled trial with narrow confidence interval)

Funding Industry

Reference Polman CH, O'Connor PW, Havrdova E, et al, for the AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *New England Journal of Medicine* 2006;354:899–910.

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