Expert Opinion

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Is natalizumab a breakthrough in the treatment of multiple sclerosis?

Evaluation of: [1] MILLER DH, KHAN OA, SHEREMATA WA *et al.*: A controlled trial of natalizumab for relapsing multiple sclerosis. *N. Engl. J. Med*. (2003) **348**:15-23.

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In patients with either relapsing-remitting or secondary-progressive multiple sclerosis, there were fewer new lesions/patient with natalizumab (0.7 and 1.1 with natalizumab 3 and 6 mg/kg every 28 days, respectively) than in the placebo group (9.6 new lesions/patient) over 6 months. There were also fewer relapses in the natalizumab groups than the placebo group. However, there were no changes in the Expanded Disability Status Scale scores in any of the groups. Natalizumab was well-tolerated. Thus, the initial results with natalizumab treatment over 6 months in multiple sclerosis are encouraging.

Keywords: multiple sclerosis, natalizumab

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1. Introduction

Multiple sclerosis (MS) is a leading cause of chronic neurological disability, especially in young adults. Although the use of IFNs to prevent the progression of MS has been studied for 20 years, their use has remained controversial as the effectiveness of IFNs is limited and they are also costly. A recent systematic review concluded that the recombinant IFNs slightly reduced the number of MS patients who have exacerbations during the first year of treatment [2]. However, the clinical effect of IFNs beyond 1 year is uncertain [2]. Thus, the need for pharmacotherapy, to slow the disease progression and reduce the disability, remains.

MS is a chronic inflammatory disease of the nervous system in which a T cell-mediated inflammatory process is associated with the destruction of the myelin sheaths. These lesions may involve lymphocytes and monocytes, which gain access to the brain parenchyma from the circulation after adhering to vascular endothelial cells, in the area of the inflammation. The glycoprotein-$\alpha_4\beta_1$ integrin is expressed on the surface of lymphocytes and monocytes and mediates cell adhesion and trans-endothelial migration. Experimental evidence showed that an antibody against α_4-integrin reduced inflammation and signs of disease activity in an animal model of MS [3].

Natalizumab is a humanised, monoclonal antibody derived from murine monoclonal antibodies raised against human α_4-integrin. A preliminary clinical trial has indicated that short-term treatment with natalizumab may reduce the number of new active lesions in patients with active relapsing-remitting or secondary-progressive MS [4]. As only 72 patients were enrolled in this preliminary trial, and natalizumab was only infused on two occasions [4], larger, longer-term clinical trials of natalizumab were indicated. The larger, longer controlled International Natalizumab Multiple Sclerosis Trial is the subject of this evaluation.

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2. Methods and results [1]

The randomised, double-blind trial was performed in 26 clinical centres in the US, Canada and the UK and enrolled 213 patients. The patients had either relapsing-remitting or secondary-progressive MS, had at least two relapses within the previous 2 years and had a minimum of three lesions on a T_2-weighted magnetic resonance imaging (MRI) of the brain. The patients also had to have a baseline score on the Kurtzke Expanded disability Status Scale (EDSS) of 2 – 6.5 [5]. This score is of functional system grades with the systems being pyramidal, cerebella, brain stem, sensory, bowel and bladder, visual, cerebral and other, on a scale of 0 – 10, with the score increasing with severity.

At baseline, the patients were predominantly female, 144 and 69 had relapsing-remitting and secondary-progressive MS, respectively; with a mean EDDS of 4.3. The patients all had MS for a mean of ≥ 10 years with three relapses in the past 2 years. Patients received an infusion of natalizumab 3 or 6 mg/kg i.v. or placebo, every 28 days for 6 months. Patients receiving natalizumab 3 and 6 mg/kg had > 80 and ~ 90% saturation of α_4-integrin receptors on peripheral-blood leukocytes, respectively.

Brain lesions in MS can be detected with MRI and new lesions with features of inflammation can be detected with gadolinium-enhanced T_1-weighted MRI. These procedures were performed 1 month before randomisation, immediately before each treatment and 1, 3 and 6 months after the last treatment. The primary outcome measure was the number of new gadolinium-enhancing lesions over the 6-month treatment period. There were 9.6 new lesions/patient compared to 0.7 and 1.1 new lesions/patient in the natalizumab 3 and 6 mg/kg groups, respectively ($p < 0.001$ for both groups); there was no significant difference between the two natalizumab groups. Natalizumab was effective in both relapsing-remitting and secondary-progressive MS. In the relapsing-remitting group, there were 12.1, 0.6 and 0.6 new lesions/patient, and in the secondary-progressive group, there were 5.4, 1.0 and 2.0 lesions/patient in the placebo, natalizumab 3 and 6 mg/kg groups, respectively. The secondary MRI outcomes were the number of persistent enhancing lesions, the volume of enhancing lesions, the number of new active lesions and the number of scans showing one or more new enhancing lesions, and these were all much less in the natalizumab groups than the placebo group.

There were fewer relapses in the natalizumab groups than the placebo group, either as reported by the patient or the neurologist. The patients reported the number of relapses to be 36 (in 27 of 71), 18 (in 13 of 68) and 15 (in 14 of 74) of those in the placebo and the natalizumab 3 and 6 mg group; respectively. The neurologists reported relapses in 15, 3 and 8, in the placebo and the natalizumab 3 and 6 mg group; respectively. Treatment with natalizumab was also associated with a reduction in the use of the permitted corticosteroid treatment (methylprednisolone 1 g/day i.v. for 3 or 5 days). Thus, methylprednisolone was used in 22 of 27 (81%), 5 of 13 (38%) and 7 of 14 (50%) of patients assigned to the placebo, and the natalizumab 3 and 6 mg group with relapses, respectively. This suggests that the relapses which occurred during natalizumab treatment may have been less severe than those which occurred without treatment.

The benefits of natalizumab do not persist after the treatment ceased. Thus, after treatment with natalizumab was discontinued, the number of relapses observed 9 – 12 months after the 6-month treatment commenced was similar in each group.

Along a visual-analogue scale (VAS), patients marked a point along a 100 mm line that reflected their assessment of overall well-being. The placebo-group reported a 1.38 mm worsening, whereas the natalizumab 3 and 6 mg groups marked a 9.49 and 6.21 mm improvement, respectively. However, there were no changes in the EDDS scores in any of the groups.

Adverse effects were monitored during, and for 6 months after the infusion. Natalizumab increased the total white cell counts. Binding antibodies against natalizumab developed in 15 patients. Similar numbers of patients in each group had adverse effects.

3. Discussion

The authors suggest that natalizumab is more effective than the IFNs or glatiramer acetate (copolymer-1, Copaxone®; Teva Pharmaceutical Industries Ltd.). Thus, in the present study, the reduction in the formation of lesions was ~ 90% with both doses of natalizumab, whereas a reduction of 50 – 80 and 30% has been reported with the IFNs and glatiramer acetate, respectively [6].

4. Expert opinion

4.1. Disability

One of the disappointing aspects of this trial was that although the patients had fewer relapses with natalizumab, this did not translate into an improvement in the EDDS over 6 months. However, there was a small improvement in the VAS. This improvement in the VAS may just reflect the decreased number of relapses.

In Prevention of Relapses and Disability by IFN-β_{1a} Subcutaneously in Multiple Sclerosis (PRISMS), the EDDS increased gradually in placebo- but not IFN-treated patients, so that there was a small significant difference after 2 years [7]. It will be of interest to ascertain whether a longer treatment with natalizumab has any effect on the EDDS.

Cognitive function was not measured in the International Natalizumab Multiple Sclerosis Trial. The cognitive domains most commonly affected in MS are information processing and verbal and visual memory. IFN-β_{1a}, but not IFN-β_b or glatiramer acetate, has been shown to improve information processing and learning/memory in neuropsychological testing [8]. The effects of natalizumab on

cognitive function have not been tested so far, and should be included in future studies.

4.2. Is the effect sustained?

One of the problems with the IFNs is that their beneficial effect in MS is not sustained. Thus, in the PRISMS-4 trial (the extension of the PRISM trial from 2 – 4 years) the effectiveness of IFN-β_{1a} reduced with time [9]. Persistent neutralising antibodies developed in 14 – 24% of patients, and this may explain the reduced effectiveness [9]. It will be of interest to ascertain whether the effects of natalizumab are sustained.

4.3. Combination treatment

The IFNs, glatiramer acetate and natalizumab, have different mechanisms of action in MS. IFN-β acts through cell-surface receptors in order to mobilise transcription factors which, in turn modifies gene expression [10]. The protein products of IFN-β are responsible for its observed antiviral, antiproliferative and anti-inflammatory actions [10]. Glatiramer acetate is a mixture of synthetic polypeptides composed of four amino acids. Glatiramer acetate inhibits T cell responses by competing with the myelin basic protein, for binding sites on the MHC class II molecules [10]. As these agents have different mechanisms of action to natalizumab, their effects in MS could be additive and this should be tested.

4.4. Is natalizumab a breakthrough in the treatment of multiple sclerosis?

The initial results with natalizumab treatment over 6 months in MS are encouraging. However, this benefit needs to be tested and shown to continue with long-term treatment before we consider natalizumab to be a breakthrough in the treatment of MS.

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