A meta-analysis on the efficacy and tolerability of natalizumab in relapsing multiple sclerosis

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CRD summary
The review concluded that available data on the efficacy and safety of natalizumab were insufficient to reach a convincing conclusion. The review had some methodological problems, but the authors’ conclusions are suitably cautious and appear appropriate.

Authors’ objectives
To assess the effectiveness and tolerability of natalizumab in relapsing multiple sclerosis (MS).

Searching
PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1966 to October 2008 for articles in English. Search terms were reported. Abstracts presented at meetings were searched. Reference lists of included trials were searched.

Study selection
Controlled trials that assessed the efficacy and/or tolerability of natalizumab compared with placebo for the treatment of MS were eligible for inclusion. Key efficacy outcomes included mean change in Expanded Disability Status Scale, number of patients with at least one relapse and number of patients with at least one new gadolinium (Gd) enhancing lesions. Tolerability outcomes included any adverse events, serious adverse events, death and withdrawals due to adverse events.

The included trials evaluated natalizumab (dose ranged from 1mg/kg to 6mg/kg) compared with placebo in patients with relapsing remitting MS or secondary progressive MS. Patients’ mean age ranged from 36 to 44 years. Duration of treatment varied from 24 to 48 weeks.

Three reviewers independently selected studies. Disagreements were resolved by consensus.

Assessment of study quality
Quality was assessed using the Jadad five-point scale of randomisation, blinding and withdrawals/drop-outs. Trials that scored at least 3 out of 5 were deemed high quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data on efficacy and tolerability outcomes were used to calculate relative risks (RRs) and 95% confidence intervals (CIs).

It appeared that three reviewers were involved in data extraction and disagreements were resolved by consensus.

Methods of synthesis
Pooled relative risks, together with 95% CIs, were calculated using a fixed-effect or random-effects meta-analysis. Statistical heterogeneity was assessed using the Cochran Q test. L’Abbé plots were used to explore the effects of heterogeneity. Publication bias was assessed by funnel plot analysis.

Results of the review
Four trials (n=1,407 patients) were included in the review. Study sample size ranged from 72 to 942 patients. The
quality of the included trials was generally high: three trials scored at least 4 out of 5 and one trial scored 3 out of 5.

Funnel plot analysis revealed a degree of asymmetry, which indicated potential for publication bias.

**Effectiveness:** Compared with placebo, natalizumab at a dose of 3mg/kg or 6mg/kg or 300mg every four weeks had a statistically significantly lower risk of at least one relapse (RR 0.50, 95% CI 0.42 to 0.61; two trials); there was no evidence of statistical heterogeneity for this analysis. When all doses of natalizumab were compared with placebo, there was no statistically significant difference in the risk of at least one relapse (RR 0.70, 95% CI 0.42 to 1.17; four trials). There was no statistically significant difference between natalizumab compared with placebo in terms of at least one new Gd-enhancing lesion (RR 0.22, 95% CI 0.05 to 1.01; two trials). There was evidence of statistical heterogeneity for both of these analysis (Q test p<0.01).

**Tolerability:** Compared with placebo, natalizumab had a statistically significantly higher risk of serious adverse events (RR 0.39, 95% CI 0.29 to 0.52; two trials). There was no statistically significant difference between natalizumab and placebo in terms of any adverse events (RR 0.99, 95% CI 0.96 to 1.01; four trials) and withdrawal due to adverse events (RR 1.43, 95% CI 0.68 to 3.02; two trials). There was no evidence of statistical heterogeneity in any of the tolerability analyses.

**Authors’ conclusions**
Available data on the efficacy and safety of natalizumab were insufficient to reach a convincing conclusion.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant databases were searched. Publication bias was assessed and funnel plot analysis revealed a degree of asymmetry, which indicated potential for bias. There was potential for language bias as only English-language articles were included. Three reviewers undertook study selection and data extraction; it was unclear how many reviewers were involved in quality assessment. The included trials were generally high quality. None of the trials used the same dosing regimen. Trials were combined using meta-analysis and heterogeneity was explored, which appeared appropriate.

The review had some methodological problems, but the authors’ conclusions were suitably cautious and appeared appropriate.

**Implications of the review for practice and research**
**Practice:** The authors stated that it seemed that use of 3mg/kg or 6mg/kg every four weeks was the best method of administration of natalizumab for preventing relapsing MS and occurrence of new Gd-enhancing lesions.

**Research:** The authors stated that further clinical trials were needed to obtain more conclusive results regarding the effectiveness and tolerability of natalizumab.

**Funding**
National Science Foundation.

**Bibliographic details**

**DOI**
10.5114/aoms.2010.13901

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by CRD

MeSH
Antibodies, Monoclonal; Humans; Multiple Sclerosis, Relapsing-Remitting; Remission Induction

AccessionNumber
12010003998

Date bibliographic record published
04/08/2010

Date abstract record published
26/01/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.