

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

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Abstract

Introduction: Natalizumab is a new humanized monoclonal antibody used in multiple sclerosis (MS). The aim of this meta-analysis was to evaluate the efficacy and tolerability of this drug in relapsing MS. PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies that investigated the efficacy and/or tolerability of natalizumab in MS. Data were collected from 1966 to 2008 (up to October).

Material and methods: The search terms were: “multiple sclerosis” or “MS” and “natalizumab”. “Mean change in Expanded Disability Status Scale (EDSS)”, “number of patients with at least one relapse”, and “number of patients with at least one new gadolinium (Gd)-enhancing lesion” were the key outcomes of interest for assessment of efficacy. “Any adverse events”, “serious adverse events”, “death”, and “withdrawal because of adverse events” were the key outcomes for tolerability. Among existing trials, four randomized placebo controlled clinical trials met our criteria and were included.

Results: Pooled relative risk for at least one relapse in four trials including all doses was 0.7, with a non-significant RR (95% CI: 0.42-1.17, $p = 0.17$). Summary RR for at least one relapse in two trials in which doses of 3 mg/kg or 6 mg/kg or 300 mg every 4 weeks were administered gave a value of 0.5 as a significant RR (95% CI: 0.42-0.61, $p < 0.0001$). The summary RR for at least one new Gd-enhancing lesion was 0.22, a non-significant RR (95% CI: 0.05-1.01, $p = 0.051$). Three deaths were reported in the natalizumab group. Comparing adverse events between natalizumab and placebo yielded a non-significant RR of 0.99 (95% CI: 0.96-1.01, $p = 0.34$) for any adverse events ($n = 3$), and a significant RR of 0.39 (95% CI: 0.29-0.52, $p < 0.0001$) for serious adverse events ($n = 2$). The summary RR for withdrawal due to adverse events by natalizumab vs. placebo therapy between two trials was 1.43, a non-significant RR (95% CI: 0.68-3.02, $p = 0.35$).

Conclusions: It seems that using 3 or 6 mg/kg every 4 weeks is the best method of administration of natalizumab for preventing relapse and occurrence of new Gd-enhancing lesions. The current data on the efficacy and safety of natalizumab are insufficient to reach a convincing conclusion and thus further clinical trials are still needed.

Key words: relapsing multiple sclerosis, natalizumab, efficacy, adverse events, withdrawal, meta-analysis.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system. Although the exact aetiology of MS remains unclear, it is likely caused by dysregulation of the immune system leading to injury of the nervous system which is triggered through a multifactorial pathway of genetic predisposition and environmental triggers (e.g. geographic latitude, vitamin D deficiency, viruses, and smoking) [1, 2]. With an age onset of 20-40, overall incidence rate of MS is 3.6 cases per 100,000 person-years in women and 2.0 in men [3].

Several therapeutic options are available for MS including interferon beta, glatiramer acetate, immunomodulators, mitoxantrone, and monoclonal antibodies (MAbs). The MAbs, as monospecific antibodies against certain pro inflammatory/inflammatory molecules, are currently used in many autoimmune disorders and have shown great potential for treatment of MS [4].

The $\alpha 4 \beta 1$ integrin is a cell adhesion molecule on the surface of lymphocytes and monocytes that mediates adherence and migration of leukocytes through the blood brain barrier. Natalizumab, a humanized monoclonal antibody, binds to $\alpha 4$ integrins and inhibits the integrin-induced inflammatory pathway [5, 6].

Following Food and Drug Administration (FDA) approval of natalizumab for treatment of MS in November 2004, it was withdrawn from the market in February 2005 because two patients who received natalizumab in combination with interferon- $\beta 1a$ developed progressive multifocal leukoencephalopathy (PML) with one death [7, 8]. Natalizumab was conditionally re-approved in June 2006 after no additional cases of PML were reported. Current guidelines recommend reserving natalizumab for patients with aggressive initial presentation or refractory to other therapies. In addition, use of natalizumab in combination with interferon is discouraged [9].

Until this time, no meta-analysis on the efficacy and/or tolerability of natalizumab in relapsing MS has been conducted. In the present work, by evaluating all randomized controlled trials a meta-analysis was conducted to reach a better conclusion about the efficacy and tolerability of this new promising medication for MS.

Material and methods

Data sources

PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for studies investigated the efficacy and/or tolerability of natalizumab in multiple sclerosis. Data were collected from 1966 to 2008 (up to October). The search terms were: "multiple sclerosis" or "MS"

and "natalizumab". The language was restricted to English. The reference list from retrieved articles was also reviewed for additional applicable studies.

Study selection

Controlled trials investigating the efficacy and/or tolerability of natalizumab in patients with MS were considered. "Mean change in Expanded Disability Status Scale (EDSS)", "number of patients with at least one relapse", and "number of patients with at least one new gadolinium (Gd)-enhancing lesion" were the key outcomes of interest for assessment of efficacy. "Any adverse events", "serious adverse events", "death", and "withdrawal because of adverse events" were the key outcomes for tolerability. We evaluated all published studies as well as abstracts presented at meetings. Three reviewers independently examined the title and abstract of each article to eliminate duplicates, reviews, case studies, and uncontrolled trials. Trials were disqualified if they were not placebo-controlled or their outcomes did not consider efficacy or tolerability. The reviewers independently extracted data on patients' characteristics, therapeutic regimens, dosage, trial duration, and outcome measures. Disagreements, if any, were resolved by consensus.

Assessment of trial quality

Jadad score, which evaluates studies based on their description of randomization, blinding, and dropouts (withdrawals), was used to assess the methodological quality of the trials [10]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis

Data from selected studies were extracted in the form of 2×2 tables. All included studies were weighted and pooled. The data were analysed using StatsDirect (2.7.2). Relative risk (RR) and 95% confidence intervals (95% CI) were calculated using Mantel-Haenszel and DerSimonian-Laird methods. The Cochran Q test was used to test for heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was demonstrated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plots were used as an indicator for publication bias.

Results

The electronic searches yielded 1547 items: 241 from PubMed, 20 from Cochrane Central, 446 from Web of Science, and 840 from Scopus. Of those,

9 trials were scrutinized in full text. Five reports were considered ineligible while 4 trials [11-14] were included in the analysis (Figure 1). All 4 trials received a Jadad score of 3 or more in assessment of trial quality (Table I). Patients' characteristics, type of MS, mean EDSS before trial, dosage of natalizumab, and duration of treatment/follow-up for each study are reported in Table II. This meta-analysis included 1407 patients with relapsing MS randomized to receive either natalizumab or placebo. All trials included in the current meta-analysis were randomized and double blinded and patients were diagnosed with relapsing MS according to EDSS score and magnetic resonance imaging (MRI) results.

Efficacy

Pooled RR for at least 1 relapse in 4 trials including all doses [11-14] was 0.7 with 95% CI of 0.42 to 1.17 and a non-significant RR ($p = 0.17$, Figure 2A). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($p = 0.0065$, Figure 2B) and could not be combined; thus, the random effects for individual and summary of RR were applied. Regression of normalized effect versus precision for all included studies for relapse among natalizumab vs. placebo therapy was 2.02 (95% CI = -5.47 to 9.51, $p = 0.37$), and Kendall's test on standardized effect vs. variance indicated tau = 0.67, $p = 0.33$ (Figure 2C).

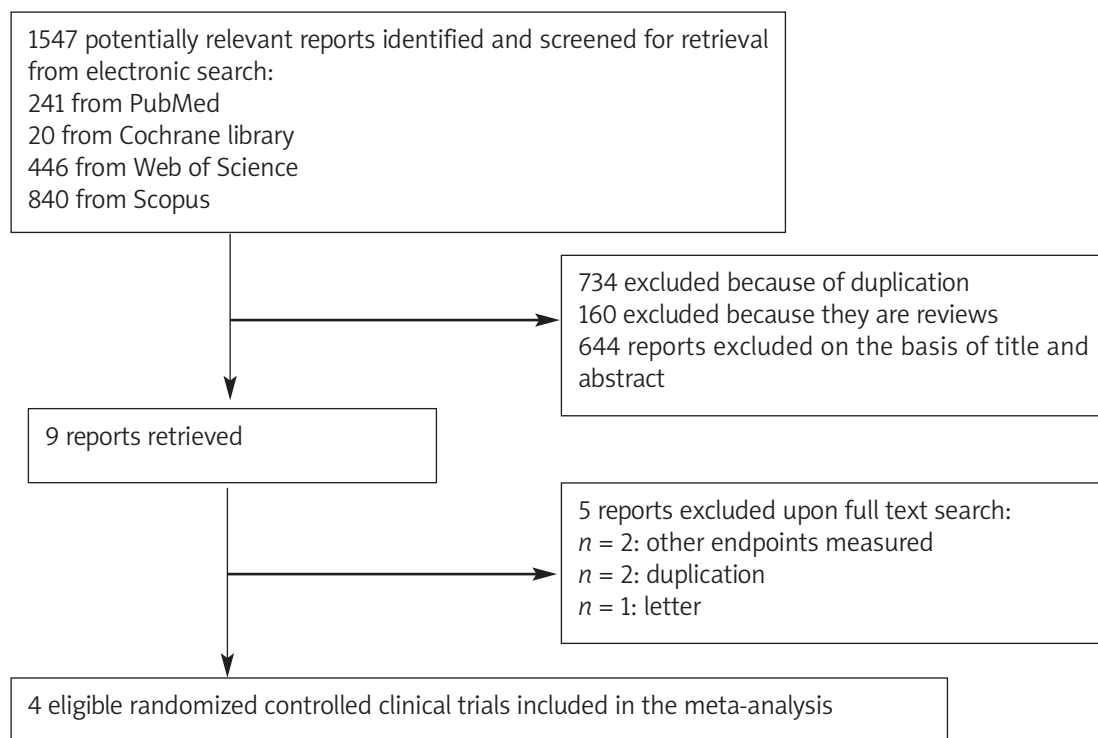


Figure 1. Flow diagram of the study selection process

Table I. Jadad quality score of randomized controlled trial included in the meta-analysis

Study	Factors and Jadad score			Total Jadad score
	Randomization	Blinding	Withdrawals and dropouts	
Polman <i>et al.</i> , 2006	2	2	1	5
O'Connor <i>et al.</i> , 2004	1	2	1	4
Miller <i>et al.</i> , 2003	2	1	0	3
Tubridy <i>et al.</i> , 1999	1	2	1	4

Table II. Characteristics of papers included in the meta-analysis

Study	Mean age	Sex (No.)		Type of MS	EDSS		Dosage of natalizumab	Duration of treatment/follow-up [weeks]
		Female	Male		Natalizumab	Placebo		
Polman <i>et al.</i> , 2006	36	660	282	RRMS	2.3 ±1.2	2.3 ±1.2	300 mg every 4 weeks	48
O'Connor <i>et al.</i> , 2004	39.5	147	33	RRMS, SPMS	1 mg: 4.5 3 mg: 4.3	4.5	Single infusion of 1 mg/kg or 3 mg/kg	45
Miller <i>et al.</i> , 2003	43.9	152	61	RRMS, SPMS	3 mg: 4.2 6 mg: 4.3	4.4	3 mg/kg or 6 mg/kg every 4 weeks	24
Tubridy <i>et al.</i> , 1999	40.4	46	26	RRMS, SPMS	4.9	4.7	2 infusions of 3 mg/kg 4 weeks apart	24

MS – multiple sclerosis, EDSS – Expanded Disability Status Scale, RRMS – relapsing remitting multiple sclerosis, SPMS – secondary progressive multiple sclerosis

Summary RR for at least 1 relapse in 2 trials in which 3 mg/kg or 6 mg/kg or 300 mg every 4 weeks were administered for therapy [11, 13] was

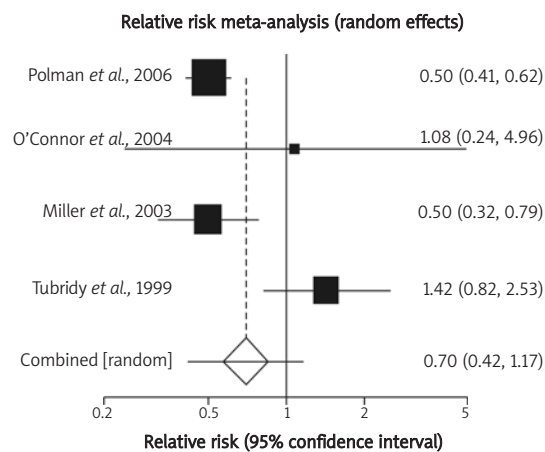


Figure 2A. Individual and pooled relative risk for the outcome of “at least one relapse” in the studies considering natalizumab vs. placebo therapy in all doses

0.5 with a 95% CI of 0.42-0.61, a significant RR ($p < 0.0001$, Figure 3A). The Cochrane Q test for heterogeneity indicated that the studies are homogenous ($p = 0.98$, Figure 3B) and could be combined but because of few included studies, the random effects for individual and summary of RR were applied. Regression of normalized effect vs. precision for all included studies for clinical response among natalizumab vs. placebo therapy could not be calculated because of too few strata.

The summary RR for at least 1 new Gd-enhancing lesion in 2 trials [11, 13] was 0.22 with a 95% CI of 0.05-1.01 and a non-significant RR ($p = 0.051$, Figure 4A). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous ($p < 0.0001$, Figure 4B) and could not be combined; thus the random effects for individual and summary of RR were applied. Regression of normalized effect vs. precision for all included studies for clinical response among natalizumab vs. placebo therapy could not be calculated because of too few strata.

Mean change in EDSS was reported in 3 trials [11, 12, 14]; but only 1 trial [12] reports standard

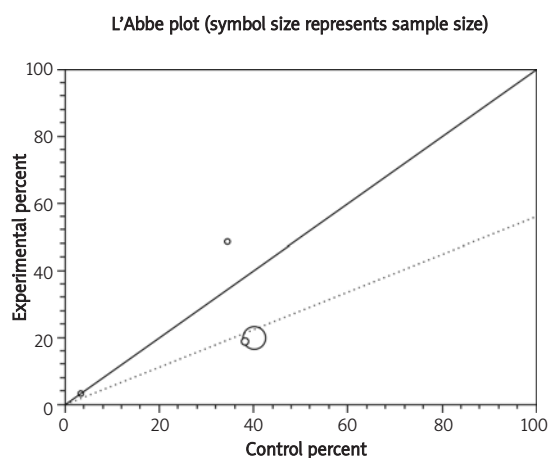


Figure 2B. Heterogeneity indicators for the outcome of “at least one relapse” in the studies considering natalizumab vs. placebo therapy in all doses

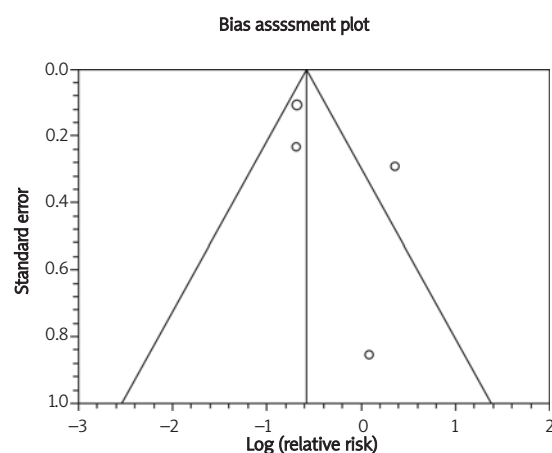


Figure 2C. Publication bias indicators for the outcome of “at least one relapse” in the studies considering natalizumab vs. placebo therapy in all doses

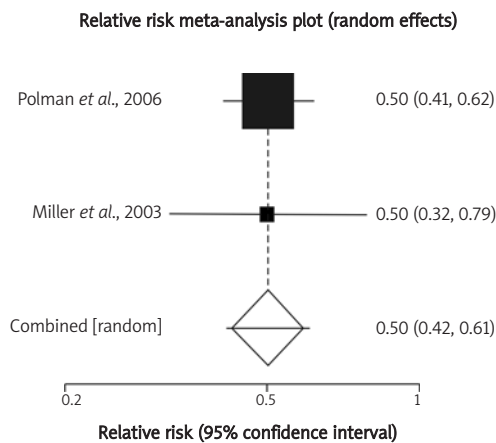


Figure 3A. Individual and pooled relative risk for the outcome of “at least one relapse” in the studies considering natalizumab vs. placebo therapy in doses of 3 or 6 mg/kg or 300 mg every 4 weeks

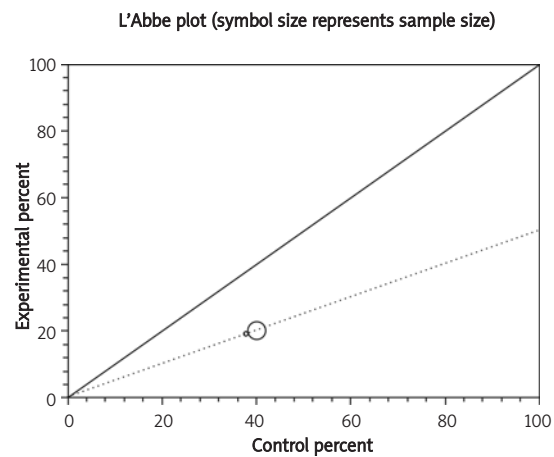


Figure 3B. Heterogeneity indicators for the outcome of “at least one relapse” in the studies considering natalizumab vs. placebo therapy in doses of 3 or 6 mg/kg or 300 mg every 4 weeks

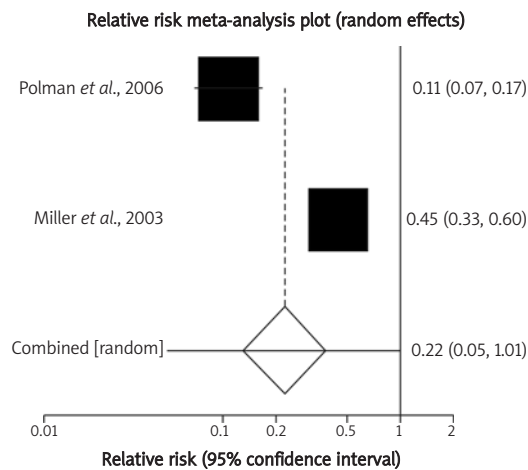


Figure 4A. Individual and pooled relative risk for the outcome of “at least one new Gd-enhancing lesion” in the studies considering natalizumab vs. placebo therapy

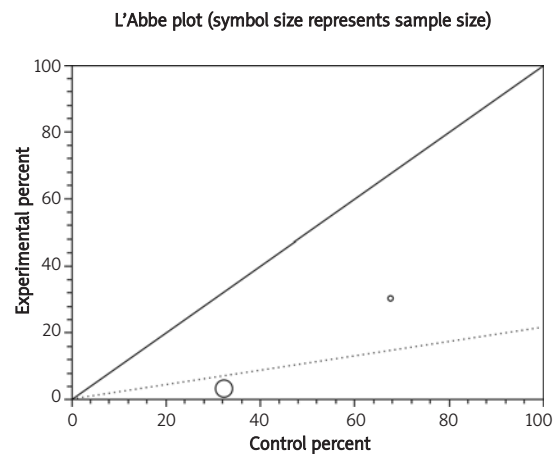


Figure 4B. Heterogeneity indicators for the outcome of “at least one new Gd-enhancing lesion” in the studies considering natalizumab vs. placebo therapy

Table III. Outcomes

Study	Mean change in EDSS		No. of patients with at least one relapse		No. of patients with at least one new Gd-enhancing lesion	
	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo
Polman <i>et al.</i> , 2006	–	–	126/627	126/315	22/627	102/315
O'Connor <i>et al.</i> , 2004	1 mg: –1.5 ±1.5 3 mg: –1.3 ±1.4	–1.5 ±1.5	4/117	2/63	–	–
Miller <i>et al.</i> , 2003	3 mg: –0.14 6 mg: –0.03	+0.03	27/142	27/71	43/142	48/71
Tubridy <i>et al.</i> , 1999	–0.04	+0.02	18/37	12/35	–	–

deviation of the mean (Table III), leaving us with insufficient data to pool the results.

Tolerability

Table IV shows the number of patients with any adverse events, serious adverse events, and withdrawal because of adverse events in both the natalizumab group and the placebo group in each trial. Type of serious and common adverse events, and cause of death are demonstrated in Table V. As shown, 3 deaths have been reported from 2 trials [11, 13]. In Polman's trial [13], 2 deaths occurred during the study, both in the natalizumab group. One patient, who died of malignant melanoma, had a history of malignant melanoma and had noted a new lesion at the time of receiving the first dose of natalizumab; he had received a total of 5 doses of natalizumab before receiving a confirmed diagnosis. A second patient died of alcohol

intoxication after having received 25 doses of natalizumab. Another death was reported in Miller's study [11] because of pleural carcinomatosis complicated by haemothorax.

The summary RR for any adverse events of natalizumab vs. placebo therapy among 3 trials [12-14] was 0.99 with a 95% CI of 0.96-1.01, indicating a non-significant RR for natalizumab administration ($p = 0.34$, Figure 5A). The Cochrane Q test for heterogeneity indicated that the studies are not significantly heterogeneous ($p = 0.29$, Figure 5B) and the fixed effects for individual and summary of RR were applied. Regression of normalized effect vs. precision for all included studies for any adverse events among natalizumab vs. placebo therapy could not be calculated because of too few strata.

The summary RR for serious adverse events of natalizumab vs. placebo therapy in 2 trials [11, 13] was 0.39 with a 95% CI of 0.29-0.52, indicating

Table IV. Adverse events

Study	Any adverse events		Serious adverse events		Death		Withdrawal because of adverse events	
	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo
Polman <i>et al.</i> , 2006	596/627	300/312	56/627	75/312	2/627	0/312	19/627	6/312
O'Connor <i>et al.</i> , 2004	106/117	56/63	–	–	–	–	–	–
Miller <i>et al.</i> , 2003	–	–	8/142	7/71	0/142	1/71	7/142	3/71
Tubridy <i>et al.</i> , 1999	32/37	34/35	–	–	–	–	–	–

Table V. Type of adverse events

Study	Type of serious adverse events		Type of common adverse events		Cause of death	
	Natalizumab	Placebo	Natalizumab	Placebo	Natalizumab	Placebo
Polman <i>et al.</i> , 2006,	relapse of multiple sclerosis cholelithiasis, need for rehabilitation therapy	relapse of multiple sclerosis, cholelithiasis need for rehabilitation therapy	headache, fatigue, urinary tract infection	headache, fatigue, urinary tract infection	malignant melanoma, alcohol intoxication	–
O'Connor <i>et al.</i> , 2004	–	–	Headache, pharyngitis, nausea	headache, pharyngitis, dizziness, back pain	–	–
Miller <i>et al.</i> , 2003	anaphylactoid reaction, serum sickness	serum sickness	headache, infection, pharyngitis	headache, accidental injury, infection, myasthenia	–	pleural carcinomatosis

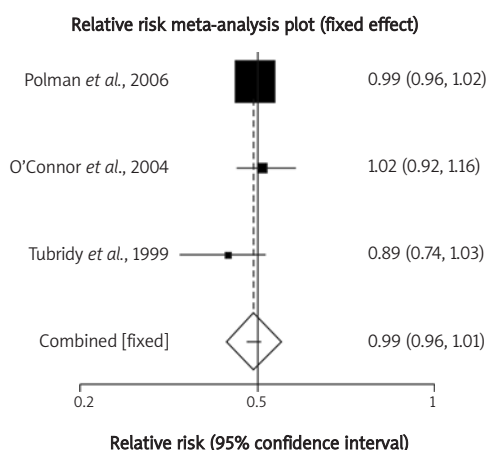


Figure 5A. Individual and pooled relative risk for the outcome of “any adverse events” in the studies considering natalizumab vs. placebo therapy

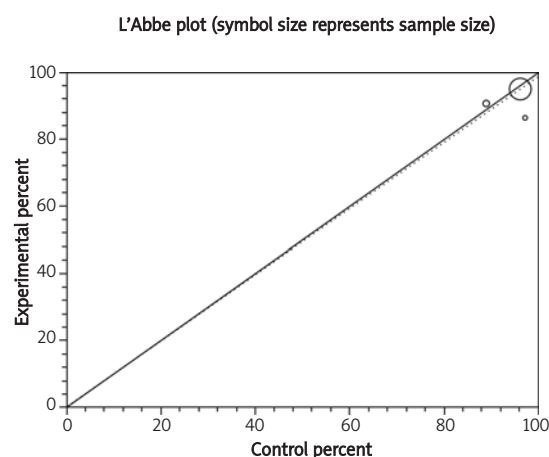


Figure 5B. Heterogeneity indicators for the outcome of “any adverse events” in the studies considering natalizumab vs. placebo therapy

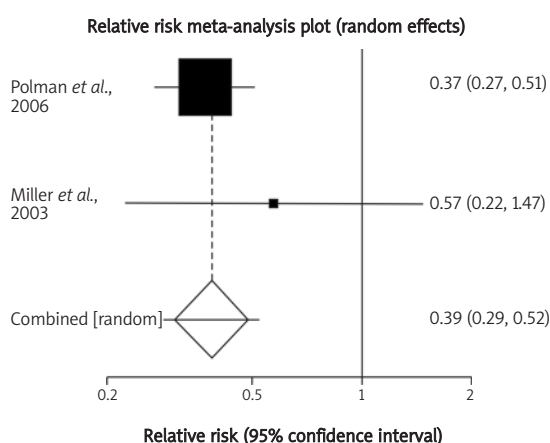


Figure 6A. Individual and pooled relative risk for the outcome of “serious adverse events” in the studies considering natalizumab vs. placebo therapy

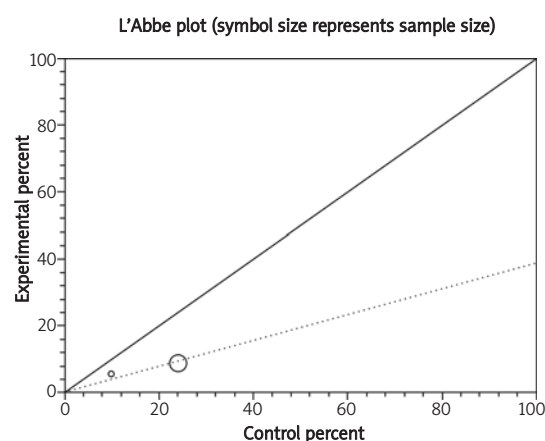


Figure 6B. Heterogeneity indicators for the outcome of “serious adverse events” in the studies considering natalizumab vs. placebo therapy

a significant RR for natalizumab administration ($p < 0.0001$, Figure 6A). The Cochrane Q test for heterogeneity indicated that the studies are homogeneous ($p = 0.41$, Figure 6B) but because of few included studies, the random effects for individual and summary of RR were applied. Regression of normalized effect vs. precision for all included studies for any adverse events among natalizumab vs. placebo therapy could not be calculated because of too few strata.

The summary RR for withdrawal due to adverse events by natalizumab vs. placebo therapy in two trials [11, 13] was 1.43 with a 95% CI of 0.68-3.02, indicating a non-significant RR for natalizumab administration ($p = 0.35$, Figure 7A). The Cochrane

Q test for heterogeneity indicated that the studies are homogeneous ($p = 0.7131$, Figure 7B) and the random effects for individual and summary of RR were applied because of few included studies. Regression of normalized effect vs. precision for all included studies for any adverse events in natalizumab vs. placebo therapy could not be calculated because of too few strata.

Discussion

In the present study, the efficacy and tolerability of natalizumab were evaluated for the first time by meta-analysis technique. The results demonstrated non-priority of natalizumab over placebo in

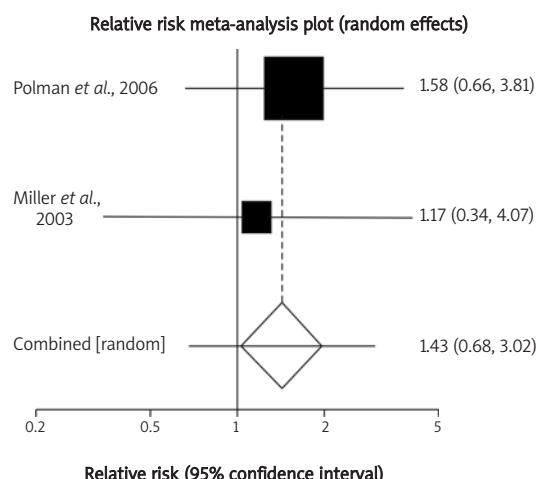


Figure 7A. Individual and pooled relative risk for the outcome of “withdrawal due to adverse events” in the studies considering natalizumab vs. placebo therapy

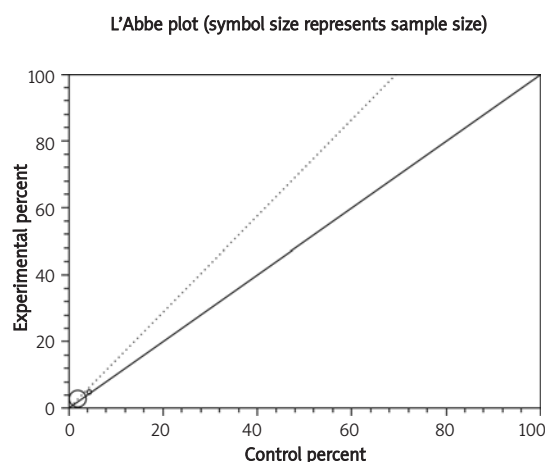


Figure 7B. Heterogeneity indicators for the outcome of “withdrawal due to adverse events” in the studies considering natalizumab vs. placebo therapy

preventing relapse or occurrence of new Gd-enhancing lesions.

Since different drug regimens were administered to the patients in the included trials, only two trials were selected which had similar drug regimens and thus the analysis for these two trials was repeated [11, 13]. The results of this analysis showed that natalizumab was effective in preventing relapse and occurrence of new Gd-enhancing lesions when administered in 3 or 6 mg/kg doses every weeks. As shown in Figures 3A and 2A, the regimen of 3 or 6 mg/kg every 4 weeks seems the most appropriate because of the 50% reduction in relapse rate. In fact, this dose has also been recommended by the last reported guidelines from the National Institute for Health and Clinical Excellence (NICE, UK) and the TOUCH Natalizumab prescribing programme for MS.

Contrast-enhanced MRI is a sensitive method for detecting active lesions. Gd-enhancement is a marker for blood brain barrier breakdown and histologically correlates with the inflammatory phase of lesion development. New lesions in MS are defined as new enhancements in areas that had not been seen in a previous scan [15]. As explained in the introduction, PML is a serious adverse effect reported from patients who received natalizumab, but in the present meta-analysis there was no report of PML from natalizumab. There were two deaths reported in one of the included studies [13] in this meta-analysis but it seems they were not related to natalizumab. As shown in Table V, there was no significant difference between natalizumab and placebo in terms of serious and common adverse events.

According to the NICE guidelines, natalizumab is mostly recommended for the treatment of relapsing-remitting multiple sclerosis (RRMS), although it can be an option for other kinds of MS and it is recommended to continue with it until the clinicians consider it appropriate to stop.

Regarding the updated review of Consensus Reports related to current basic and escalating immunomodulatory treatments in MS, the indication and application of natalizumab should preferably be handled in an MS centre. In addition, it should be administered as monotherapy only in patients with a normal differential blood count with approval of exclusion for infections [16].

In conclusion, it seems that the best method of administration of natalizumab in patients with relapsing MS is 3 or 6 mg/kg every 4 weeks. Current data on the efficacy and safety of natalizumab seem to be insufficient and further clinical trials are needed to obtain more conclusive results [17].

Acknowledgments

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