

# Clinical efficacy issues in the treatment of multiple sclerosis: update of natalizumab

Francesco Patti  
Angelo Pappalardo

Multiple Sclerosis Center, University of Catania, Catania, Italy; Physical Medicine and Rehabilitation Unit, Hospital of Acireale, Catania, Italy

**Abstract:** Multiple sclerosis is a frequent neurologic disease, which causes sensory impairment, fatigue, cognitive deficits, imbalance, loss of mobility, spasticity, and bladder and bowel dysfunction. Several new therapies have been introduced in the past decade, but additional drugs are needed to slow disease progression and reduce disability. Natalizumab (NA) is an  $\alpha 4$  integrin antagonist, effective in decreasing the development of brain lesions in experimental models and in several studies of patients with MS. Six randomized controlled trials of NA in MS have been published in the last 10 years. Overall, 2,688 relapsing-remitting MS subjects have been enrolled in these studies. Hence, there are already sufficient data to draw some conclusions about the effectiveness of NA in the treatment of MS, although for definitive considerations it would be reasonable to wait for the observational phase IV studies of clinical practice to complete. Moreover, the medical community is concerned with the safety of NA, particularly with the risk of developing progressive multifocal leukoencephalopathy while on NA therapy. From the analyses of the six cases, it seems that the overall risk is around 1/1,000 and could increase with the number of NA infusions.

**Keywords:** multiple sclerosis, disease-modifying drugs, natalizumab, progressive multifocal leukoencephalopathy

## Background

Multiple sclerosis (MS) is a leading cause of neurologic disability in young and middle-aged patients. The impact of the disease on daily living can be highly disabling because the pathological process may affect many functional systems. Patients suffer from a variety of neurological symptoms as fatigue, spasticity, bladder, bowel and sexual dysfunction, sensory loss, ataxia, or cognitive failure.<sup>1,2</sup> But above all, people with MS experience psychologic distress and social troubles, which could negatively impact their quality of life (QoL) if combined.<sup>3,4</sup> One of the main causes of stress is the unpredictable and bizarre course of the disease, which affects patients and caregivers alike.

In the last 20 years, the introduction of the disease-modifying drugs (DMDs) such as interferon- $\beta$  (IFN $\beta$ ) and glatiramer acetate (GA) in relapsing-remitting MS (RRMS) and more recently in people with clinically isolated syndromes (CIS) has aroused broadly hopeful expectations, mainly focused on their efficacy in slowing down the progression of disease and reducing frequency and severity of relapse.<sup>5-8</sup> Unfortunately, IFN $\beta$  and GA are only partially effective and most patients with MS have breakthrough disease activity despite therapy with these medications.<sup>5-8</sup>

Other medication or therapeutic strategies have been tried in patients with MS. Mitoxantrone (MIT) is the only immunosuppressive drug approved for the treatment of worsening forms of RRMS and for progressive-relapsing MS (PRMS) or

Correspondence: Francesco Patti  
Department of Neurology,  
Multiple Sclerosis Center,  
Via Santa Sofia 78, 95123 Catania,  
Policlinico Università Catania, Italy  
Tel +39 095 3782620  
Fax +39 095 3782832  
Email patti@unict.it

secondary-progressive MS (SPMS), but its potential cardiac toxicity must be taken into account.<sup>9,10</sup> To avoid or minimize this serious adverse event, induction therapy with MIT followed by an immunomodulating agent was proposed. A short course of MIT followed by IFN $\beta$  or GA was found to be safe and effective, with an early and sustained decrease in magnetic resonance imaging (MRI) disease activity.<sup>11,12</sup>

A combination of the two classes of recognized first-line treatment, a IFN $\beta$  and GA, is currently under evaluation in a large phase III trial.<sup>13</sup> None of the combination studies performed with IFN $\beta$  to date have pointed out unequivocal evidence of benefit, including combinations with statins and azathioprine.<sup>14</sup>

In addition, new drugs have been developed. Among them, natalizumab (NA) is an interesting therapy in patients with breakthrough disease, especially for those in whom DMDs were ineffective or not well tolerated.

In this review, we highlight the clinical efficacy and safety profile of NA as well as the impact of MS on patients' QoL.

## Introduction

Natalizumab (NA; Tysabri<sup>®</sup> Biogen Idec, Cambridge, MA, USA and Elan Pharmaceuticals, Gainesville, GA, USA) is a recombinant humanized monoclonal antibody, derived from a murine monoclonal antibody, targeted against the glycoprotein  $\alpha 4$  integrin, also called a very late antigen 4 (VLA-4). This molecule is expressed on the surface of all circulating leukocytes such as lymphocytes and monocytes and has the function to mediate the cell adhesion and transendothelial migration.<sup>15</sup> Adhesion molecules are involved in inflammatory demyelination as they enhance systemic immune responses into the target tissue.<sup>16</sup> Cytokines may play a role in upregulating the expressions of these molecules.

In MS, circulating leukocytes enter the central nervous system (CNS) and produce inflammation and myelin damage. Prevention of leukocyte infiltration may be obtained by an antibody against VLA-4.

First efficacy evidence of antibodies against  $\alpha 4$  integrin in prevention of leukocyte infiltration was observed in experimental autoimmune encephalomyelitis (EAE), an inflammatory condition of the CNS used as animal model of MS.<sup>17</sup> Subsequently, Kent and colleagues demonstrated that the blockage of VLA-4 suppressed clinical and pathological features of EAE in the guinea pig.<sup>18</sup>

## Placebo-controlled studies in humans

The study of the clinical use of NA in MS began with a small, short-term, placebo-controlled study. Patients were

treated twice with NA, 3 mg/kg at weeks 0 and 4. Follow up lasted for 24 months. The treated group showed significantly fewer new active nuclear MRI (NMR) lesions and fewer new enhancing lesions than the placebo group.<sup>19</sup> Several years later, in a broader controlled double-blind trial on 213 patients with RRMS or relapsing SPMS, NA was administered at two different doses (3 or 6 mg/kg) every 28 days for six months. Patients under active treatment showed marked reduction in the mean number of new gadolinium-enhancing lesions (0.7 per patient in the group given 3 mg, 1.1 in the group given 6 mg) in comparison with the placebo group (9.6 per patient). Additionally, both NA-treated groups reported fewer relapses and an improvement in general well being. Most frequent adverse events were headache, urinary tract infection, and muscle weakness.<sup>20</sup>

A randomized trial with NA was also carried out in patients with acute MS relapses.<sup>21</sup> A single dose of NA (1 or 3 mg/kg) or placebo were administered just after the onset of an exacerbation in 180 patients. There was no difference in Expanded Disability Status Scale (EDSS) score variation over time between treatment and placebo groups, but both treated groups showed a significant decrease in gadolinium-enhancing lesion volume when compared with placebo. Overall, NA was well tolerated; the most frequent side effects were headache, pharyngitis, dizziness, and nausea. The percentages of patients with side effects were similar between the two different dose-treated groups.

In the GLANCE trial, 110 patients, who were treated with GA for at least one year and who had experienced at least one exacerbation, were randomized to receive either GA plus NA or GA plus placebo. The primary end-point was the rate of new active lesion on MRI. Patients treated with GA plus NA reported a 74% reduction in new gadolinium-enhancing T1 lesions and a 62% reduction in new or enlarging T2 lesions. No significant adverse events were observed in patients treated with combination therapy.<sup>22</sup>

Following the GLANCE trial, two phase III, randomized, double-blind, placebo-controlled trials, AFFIRM and SENTINEL, were executed. In the AFFIRM study,<sup>23</sup> Tysabri<sup>®</sup> (NA); administered to 627 patients with RRMS at a dose of 300 mg every four weeks for more than two years, produced a reduction of sustained progression of disability by 42%. Moreover, the rate of clinical relapse and the accumulation of new or enlarging hyperintense NMR lesions decreased by 68% and by 83%, respectively. The treated group reported more frequently than placebo fatigue and allergic reaction; serious hypersensitivity reactions occurred in eight patients. Two patients in the NA group died during the study. The former

had already a diagnosis of malignant melanoma and had already noted a new skin lesion when the first dose of NA was administered. On the whole, five doses of NA were injected before the patients received a confirmed diagnosis. The latter died of alcohol intoxication after having received 25 doses of NA. Nevertheless, the authors concluded that NA monotherapy had an excellent safety and tolerability profile in addition to the significant reduction of disability progression and occurrence of clinical relapse.

Unfortunately, the enthusiasm for the safety of NA was dramatically dampened with the results of the SENTINEL study.<sup>24</sup> In this study there were two cases of progressive multifocal leukoencephalopathy (PML), one of which was fatal. Despite these adverse events, the clinical and NMR outcomes had not been unfavorable. NA was given to 1,171 RRMS patients at a dose of 300 mg, in combination with IFN $\beta$ -1a. These patients had had at least one exacerbation despite the IFN $\beta$  therapy, during the 12-month period before the randomization. Combination therapy determined a 24% reduction of relative risk of sustained disability progression and a lower annualized rate of relapse over a two-year period in comparison with IFN $\beta$ -1a alone. Besides, combination therapy produced fewer new or enlarging lesions on T2-weighted NMR.

Subsequently, the incidence and clinical effects of antibodies that developed over two years of NA treatment among patients included in the AFFIRM and SENTINEL studies was reported. In the AFFIRM study, antibodies were found in 57 of 625 (9%) patients, of whom 20 (3%) were transiently positive and 37 (6%) were persistently positive. Patients with persistent positive antibody showed a significant loss of clinical efficacy as assessed by disability progression, relapse rate, and MRI in comparison with antibody-negative patients. Similar results were obtained in SENTINEL except with regard to disability progression and lack of significant differences among persistently antibody-positive and antibody-negative subjects.<sup>25</sup> The same trouble had been present during IFN $\beta$  therapy, in which the presence of neutralizing antibodies (Nab) reduced or abolished bioavailability in a relevant percentage of patients.<sup>26</sup>

These findings suggested the opportunity to investigate NA antibody during immunomodulating treatment in those patients with suboptimal clinical response.

## NA in gastroenterology

NA had been used in people with Crohn's disease (CD). The pathogenesis of CD involves persistent recruitment of leukocytes into gut tissue, with resultant inflammation.

Several studies have suggested that NA may be effective for the treatment of active CD.<sup>27-29</sup> Two controlled trials were conducted to test NA as induction and maintenance therapy in CD. The first trial, known as ENACT-1, included 905 patients, of whom 724 were randomly assigned to receive 300 mg of NA. In the second trial (ENACT-2) which included 339 patients who were responders to NA, 168 were randomly re-assigned to receive NA. In ENACT-1, two patients treated with NA died, the former from asphyxiation due to an occupational accident, the latter from complication of surgery due to a severe exacerbation of CD. In ENACT-2, one patient died from PML associated with the John Cunningham virus; one patient developed a basal-cell carcinoma of the skin; influenza and influenza-like disease occurred more frequently in the NA group than in placebo group and finally, there was one report each of varicella pneumonia and cytomegalovirus hepatitis, both in the NA-treated group.<sup>30</sup>

## The dilemma of safety

At this point there was a pause for reflection and it was decided to retest the profile of safety and tolerability. Thus, in February 2005, NA was withdrawn from the market. All NA-treated patients (n = 3,417) were re-examined. Of 44 patients who were identified with clinical findings of possible PML, 43 were successively ruled out. Data on cerebrospinal fluid testing and follow-up MRI of the remaining patients were not available. The authors concluded that the risk of PML in patients treated with NA is roughly 1 in 1,000, but the risk associated with longer treatment remained to be determined.<sup>31</sup>

Following these findings and based on the recommendation of an advisory committee, NA was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in people with intensely active RRMS, who were not responding to IFN $\beta$  therapy or in patients who experienced faster disability progression, even if not previously treated with IFN $\beta$ . Nevertheless, the question of the safety of NA is anything but clarified. At the FDA hearing for market re-approval, several cases of unusual infections in patients treated with NA were reported<sup>32</sup> (Table 1). The role of NA in determining these infections, if in whole or in part, is not yet clear. This raises doubt whether NA may compromise cell-mediated immunity. And moreover, it enhances the prudence to initiate NA treatment in combination with other immunosuppressant. Further research in larger cohorts and for a longer time should clarify the above issues. For these purposes, a large-scale post-registration study (the TYGRIS study) is ongoing.

In the course of 2008 and 2009, information on new cases of PML became available. To date (July 2009), a 10th

**Table 1** Opportunistic infections in the natalizumab-treated patients

Infections	No. of cases
Viral meningitis and encephalitis	2 (one fatal)
Acute cytomegalovirus	2
Pulmonary aspergillosis	2
Cryptosporidial gastroenteritis	1
<i>Pneumocystis carinii</i> pneumonia	1
Varicella pneumonia	1
Mycobacterium avium complex pneumonia	1
<i>Burkholderia cepacia</i> pneumonia	1

confirmed case of PML has occurred among patients with MS who had used NA. However, it appears that when PML is detected and treated early, outcome is generally improved. In conclusion, it is important that patients taking NA and their doctors become more vigilant in monitoring for any occurrence of new, unusual symptoms that might indicate PML.<sup>33</sup> Typical symptoms associated with PML progress over days to weeks and can include progressive weakness on one side of the body, disturbances of vision, cognitive deficits, and personality changes. Because of the risk of PML, Tysabri® is available in the US only through the TOUCH (Tysabri® Outreach Unified Commitment to Health) prescribing program. TOUCH is a restricted distribution program focused on safety and minimizing the risk of PML.<sup>34</sup>

## Risk-benefit and cost-effectiveness

Several reports have sought to quantify the risk and benefits of NA in RRMS using quality-adjusted life years (QALY) as a metric, which gives a single index score for each state of health (full health = 1, death = 0).

The most pressing question was to verify whether the beneficial health effects of NA on reducing relapses and slowing down disease progression overcame the negative effects of PML on QALY. Dorsey observed that, even after increasing the current estimated risk of PML by 10, the net health effects of NA are clearly positive.<sup>35</sup> Over the first two years of NA therapy, the negative health effects from PML were small (loss of 0.001 QALY) in comparison with the positive effects on relapse and disability gained (0.033 QALY).

Very recently, long-term health changes in NA-treated patients were compared with the health profiles modeled for a natural history cohort and with IFN $\beta$ -1a-treated patients. The natural history cohort accumulated 8.70 QALY over the 20-year time horizon. NA produced a further 0.80 QALY gained for a total of 9.50 QALY, while IFN $\beta$ -1a resulted in an additional 0.42 QALY for a total of 9.12 QALY gained<sup>36</sup>

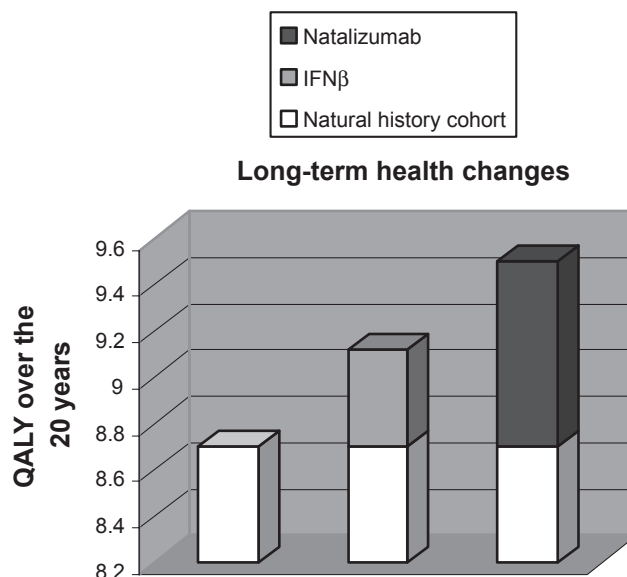
(Figure 1). On these grounds, a more than sevenfold increase in risk of PML is necessary to diminish NA health gain below that of IFN $\beta$ -1a.<sup>36</sup>

The cost-effectiveness of NA was estimated in comparison with IFN $\beta$ , GA, and supportive care. The incremental cost-effectiveness ratios (ICERs), calculated for the base case, was found to be £2,300 per QALY for NA compared with IFN $\beta$ , £2,000 per QALY for NA versus GA, £8,200 per QALY for NA versus supportive care. The authors deduced that NA is likely to be a cost-effective therapy for patients with highly active RRMS.<sup>37</sup> In the same way, Kobelt and colleagues explained that treatment with NA was less expensive and more effective than treatment with other available current DMDs. Taking into account only health care costs, the cost per QALY gained with NA was found to be €38,145.<sup>38</sup>

## Recent evidence

Post-marketing observational reports have clearly demonstrated the relative safety and tolerability of NA. In a recent county-based surveillance program on 909 patients, the most common adverse events were allergic reactions and usually mild infections. Drug inefficacy, adverse events and detection of anti-natalizumab antibody were the most frequent causes of NA therapy suspension, while no other cases of death or major side effects were described.<sup>39</sup>

In the past two years, there have been published other reports, some of which highlighting beneficial effects of NA. Balcer and colleagues examined the effects of NA on visual



**Figure 1** Long-term health changes.

**Abbreviations:** IFN, interferon; QALY, quality-adjusted life years.

function in the two randomized clinical trials, AFFIRM and SENTINEL, by means of low-contrast letter acuity. The risk of clinical significant visual loss at the lowest contrast level was reduced in the NA-treated groups by 35% in AFFIRM and by 28% in SENTINEL, while mean changes in vision scores worsened in non-NA groups.<sup>40</sup>

Recently, Havrdova and colleagues reported on post-hoc analyses of data from the AFFIRM study to determine the effects of NA in comparison with placebo on the proportion of patients who were free of disease activity over two years: 383 (64%) of 596 patients taking NA and 117 (39%) of 301 taking placebo were free of clinical disease activity, and 342 (58.5%) of 593 and 42 (14%) of 296 of placebo group were free of radiological disease activity.<sup>41</sup>

Despite the favorable clinical effects of NA, there are also a few concerns the overall effects of NA. The occurrence of early relapses after the first dose of NA in active MS patients was reported by Centonze and colleagues in seven of 35 patients who had had at least two clinical relapses during a 12-month therapy with other immunomodulatory drugs. The exacerbations were mild and achieved their peak of severity within 18–30 hours after NA administration. However, all patients recovered spontaneously or after a short course of intravenous high dose steroid injection.<sup>42</sup>

Vellinga and colleagues described a post-withdrawal rebound increase in T2 lesional activity in NA-treated MS patients.<sup>43</sup> At variance with this study, O'Connor and colleagues demonstrated that there was not evidence of rebound increase in MRI.<sup>44</sup> In Vellinga and colleagues' study, NA had been discontinued when cases of PML were observed and patients underwent safety MRI before the reintroduction on NA. Some of them showed a considerable number of new T2 lesions, developed in the 15-month interval between the suspension and the reintroduction of NA.<sup>43</sup>

Stüve and colleagues evaluated immune activity in the blood and spinal fluid, relapse rates, disease progression and MRI scans 14 months after the cessation of NA administration. These authors found that at 14 months, most were stable, with no new clinical disease activity, MRI activity or immune activity.<sup>45</sup> Similarly, Schiess and Calabresi suggested that stopping Tysabri® after increasing the number of drug administrations was not associated with rebound syndrome, whereas stopping the drug after only a few doses could cause disease worsening.<sup>46</sup>

Little is known on the use of NA in pediatric MS. Huppke and colleagues reported the safety and the effectiveness of NA in three pediatric RRMS patients who had failed to

immunomodulatory therapy. NA was given at a dosage of 3 to 5 mg/kg for 15 months; no other exacerbation occurred and QoL significantly improved.<sup>47</sup>

## Effects of NA on health-related quality of life

In the last 10 years, several authors detected the relationship between DMDs and health-related QoL (HRQoL). This field of research has assumed a broad importance given the high expectations from treatment with DMDs and its relative frequent side effects which could substantially influence the HRQoL of patients and caregivers. Furthermore, the intrinsic nature of the disease and the known differences of what is more important for patients and physicians led many neurologists to include the use of scales assessing the personal perception of the disease in their clinical practice.<sup>48</sup> These scales measure QoL and reflect the patients' personal point of view of the "illness". Neurologists should also incorporate QoL measurement instruments such as the Short Form-36 Health Survey (SF-36), Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54), Sickness Impact profile with the Expanded Disability Status Scale,<sup>49</sup> Multiple Sclerosis Functional Composite Measure,<sup>50</sup> and neuropsychological tests for cognitive impairment.<sup>51</sup>

There are very few reports of the impact of NA on HRQoL in patients with MS. The largest data were collected from 2.113 patients enrolled in both AFFIRM and SENTINEL studies. HRQoL was investigated through the SF-36 and a single-item subject global assessment visual analog scale. NA significantly improved SF-36 physical component summary (PCS) and mental component summary (MCS) scores at week 104 in AFFIRM. PCS changes resulted significantly improved by week 24 and in all successive examinations. Higher change scores on the PCS and MCS were obtained at all post-baseline time points for patients treated with NA, while placebo-treated patients had worsening scores at five of the six time points. In SENTINEL, patients treated with NA plus IFN $\beta$  showed higher PCS scores at weeks 52 and 104. NA-treated patients in both studies were more likely to experience clinically important improvement and less likely to experience clinically important deterioration on the SF-36 PCS.<sup>52</sup>

Therefore, it seems NA therapy could determine a beneficial effect on both psychological and physical profiles. The improvement of QoL undoubtedly would lead to coping better with the challenges of a chronic disease as MS. Nevertheless, this point must be interpreted with caution, considering the previous analyses on the effects

of IFN $\beta$  therapies on MS patients' QoL, which provided conflicting evidence. These studies have taught us that QoL can be affected by several demographic, social, and clinical variables such as age, education, employment, disability, depression, and adverse treatment events.

Similar to what was observed in MS patients, HRQoL of CD patients benefited from NA treatment. The Inflammatory Bowel Disease Questionnaire and the SF-36 scores of patients who responded to NA induction remained stable, but worsened in those patients randomized to receive placebo.<sup>53</sup>

## Conclusion

The introduction of Tysabri<sup>®</sup> on the market for the treatment of people with MS was firstly associated with the enthusiasm of patients and clinicians for a drug at least eight-fold more effective than previous DMDs. These first years of NA use in clinical practice raised the question of safety. PML is considered a serious problem associated with NA therapy. We do not know if there is a cumulative dose of NA before PML is provoked. It seems from the analyses of the 10 available cases that the overall risk is around 1 in 1,000 (there are more than 50,000 people under treatment with NA worldwide) which could increase with the number of NA infusions. The risk of cardiotoxicity and leukemia increases with higher doses of mitoxantrone. In the same way, the risk of definitive amenorrhea or cystitis increases with higher doses of cyclophosphamide, which is sometimes used as rescue therapy. These considerations tend to limit the use of NA in the case of MS. However, we think that the risk/benefit ratio favors treating patients with NA. Moreover, the evidence of PML in patients treated with other biologic drugs such as infliximab, etanercept, and rituximab have taught clinicians to recognize and diagnose earlier PML and manage it properly. The use of plasma exchange and the proper use of steroids are reported as effective and safe. It should be emphasized that the introduction on the market of this new drug and the possible future medications for treating MS patients has deeply changed the role and the attitude of treating physicians in clinical practice who should consider safety first and efficacy second.

We think that the possible skepticism and safety concerns raised by the "new era" of treating MS could be considered as reassuring for both clinicians and patients, if neurologists change their habits and properly approach the new challenge.

## Disclosures

The authors report no conflicts of interest in this work.

## References

- Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study: I. Clinical course and disability. *Brain*. 1989;112:133–146.
- Lyon-Caen O, Jouvent R, Hauser S, et al. Cognitive function in recent-onset demyelinating diseases. *Arch Neurol*. 1986;43:1138–1141.
- Rudick RA, Miller D, Clough JD, Gragg LA, Farmer RG. Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. *Arch Neurol*. 1992;49(12):1237–1242.
- Benito-León J, Morales JM, Rivera-Navarro J, Mitchell A. A review about the impact of multiple sclerosis on health-related quality of life. *Disab Rehabil*. 2003;25(23):1291–1303.
- The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I: clinical results of a multicenter randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655–661.
- Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM; the Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon beta-1a for disease progression in relapsing-remitting multiple sclerosis. *Ann Neurol*. 1996;39:285–294.
- Johnson KP, Brooks BR, Cohen JA, et al. Copolymer I reduces relapse rate and improve disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter double-blind placebo controlled trial. *Neurology*. 1995;45:1268–1276.
- Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet*. 1998;352:1498–1504.
- Clerico M, Rivoiro C, Contessa G, Viglietti D, Durelli L. The therapy of multiple sclerosis with immune-modulating or immunosuppressive drug. A critical evaluation based upon evidence based parameters and published systematic reviews. *Clin Neurol Neurosurg*. 2008;110: 878–885.
- Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:1332–1338.
- Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. *J Neurol Neurosurg Psychiatry*. 2008;79(1):52–56.
- Vollmer T, Campagnolo D, Panitch P, Bar-Or A, Arnold D. Reductions in MRI Disease activity and relapse rates observed after induction of short-term immunosuppression with mitoxantrone followed by long-term glatiramer acetate (GA) are maintained at 24 months in patients with relapsing remitting multiple sclerosis (RRMS). *Neurology*. 2007;68(Suppl 1):A279.
- Deutsch F, Arnold DL. Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis. *Mult Scler*. 2008;14: 663–670.
- Golg R. Combination therapies in multiple sclerosis. *J Neurol*. 2008;255(Suppl 1):51–60.
- Hynes RO. Integrins: a family of cell surface receptors. *Cell*. 1987;48:549–554.
- French-Constant C. Pathogenesis of multiple sclerosis. *Lancet*. 1994;343:271–275.
- Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. *Nature*. 1992; 356(6364):63–66.
- Kent SJ, Karlik SJ, Cannon C, et al. A monoclonal antibody to alpha 4 integrin suppresses and reverses active experimental allergic encephalomyelitis. *J Neuroimmunol*. 1995;58(1):1–10.
- Tubridy N, Behan PO, Capildeo R; UK Antegren Study Group. The effect of anti- $\alpha 4$  integrin antibody on brain lesion activity in MS. *Neurology*. 1999;53:466–472.

20. 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.
21. O'Connor PW, Goodman A, Willmer-Hulme AJ; the Natalizumab Multiple Sclerosis Trial Group. Randomized multicenter trial of natalizumab in acute MS relapses Clinical and MRI effects. *Neurology.* 2004;62:2038–2043.
22. Goodman AD, Rossman HS, Bar-Or A, et al. GLANCE: Results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology.* 2009;72(9):806–812.
23. Polman CH, O'Connor PW, Havrdova E, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2006;354:899–910.
24. Rudick RA, Stuart WH, Calabresi PA, et al; SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med.* 2006;354:911–923.
25. Calabresi PA, Giovannoni G, Confavreux C, et al; AFFIRM and SENTINEL Investigators. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology.* 2007;69:1391–1403.
26. Bertolotto A, Gilli F, Sala A, et al. Persistent neutralizing antibodies abolish the interferon beta bioavailability in MS patients. *Neurology.* 2003;60:634–639.
27. Sandborn WJ, Yednock TA. Novel approaches to treating inflammatory bowel disease: targeting alpha-4 integrin. *Am J Gastroenterol.* 2003;98:2372–2382.
28. Gordon FH, Lai CW, Hamilton MI, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. *Gastroenterology.* 2001;121:268–274.
29. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. *N Engl J Med.* 2003;348:24–32.
30. 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.
31. Yousry TA, Major EO, Ryschewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med.* 2006;354:924–933.
32. Center for Drug Evaluation and Research (CDER). Peripheral and Central Nervous System Drugs Advisory Committee; FDA Advisory Hearing, March 7–8, 2006. Available at: <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4208S1-Slide-Index.htm>. Accessed on August 14, 2009.
33. National Multiple Sclerosis Society Research Bulletin. Update on Tysabri and PML. June 30, 2009. Available from <http://www.nationalmssociety.org/news/news-detail/>. Accessed on July 10, 2009.
34. Bozie C, Belcher G, Kim R, et al. Natalizumab in patients with relapsing-remitting multiple sclerosis: updated utilization and safety results including TOUCH and TYGRIS. Seattle, WA: 61st annual Meeting of American Academy of Neurology; April 25–May 2 2009.
35. Dorsey ER, Thompson JP, Noyes K, et al. Quantifying the risks and benefits of natalizumab in relapsing multiple sclerosis. *Neurology.* 2007;68:1524–1528.
36. Thompson JP, Noyes K, Dorsey ER, et al. Quantitative risk-benefit analysis of natalizumab. *Neurology.* 2008;71:357–364.
37. Gani R, Giovannoni G, Bates D, et al. Cost-effectiveness analyses of natalizumab compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics.* 2008;26(7):617–627.
38. Kobelt G, Berg J, Lindgren P, et al. Modeling the cost-effectiveness of a new treatment for MS (natalizumab) compared with current standard practice in Sweden. *Mult Scler.* 2008;14:679–690.
39. Mancardi GL, Amato MP, D'Alessandro R, et al. Natalizumab: a country-based surveillance program. *Neurol Sci.* 2008;29: S235–S237.
40. Balcer LJ, Galetta SL, Calabresi PA, et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology.* 2007;68:1299–1304.
41. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol.* 2009;8(3):254–260.
42. Centonze D, Furlan R, Gasperini C, et al. Early relapses after the first dose of natalizumab in active multiple sclerosis patients. *Mult Scler.* 2008;14:1137–1138.
43. Vellinga MM, Castelijns JA, Barkhof F, et al. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS. *Neurology.* 2008;70:1150–1151.
44. O'Connor PW, Goodman A, Kappos L, et al. Results of clinical and magnetic resonance imaging analyses following cessation of natalizumab dosing in patients with multiple sclerosis. Madrid, Spain: 22nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis; Sept 29, 2006.
45. Stüve O, Cravens PD, Frohman EM, et al. Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. *Neurology.* 2009;72:396–401.
46. National Multiple Sclerosis Society. Details: No rebound in those who stopped taking tysabri after extended exposure. Feb 10, 2009. Available from: <http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=814>. Accessed July 10, 2009.
47. Huppke P, Stark W, Zürcher C, Huppke B, Brück W, Gärtner J. Natalizumab use in pediatric multiple sclerosis patients. *Arch Neurol.* 2008;65(12):1655–1658.
48. Rothwell PM, McDowell Z, Wong CK, Dorman PJ. Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessment of disability in multiple sclerosis. *BMJ.* 1997;314:1580–1583.
49. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11): 1444–1452.
50. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler.* 1999;5(4): 244–250.
51. Patti F. Cognitive impairment in multiple sclerosis. *Mult Scler.* 2009;15(1):2–8.
52. Rudick RA, Miller D, Hass S, et al; AFFIRM and SENTINEL Investigators. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol.* 2007;62(4):335–346.
53. Feagan BG, Sandborn WJ, Hass S, Niecko T, White J. Health-related quality of life during natalizumab maintenance therapy for Crohn's disease. *Am J Gastroenterol.* 2007;102(12):2737–2746.

### ClinicoEconomics and Outcomes Research

## Publish your work in this journal

ClinicoEconomics & Outcomes Research is an international, peer-reviewed open-access journal focusing on Health Technology Assessment, Pharmacoeconomics and Outcomes Research in the areas of diagnosis, medical devices, and clinical, surgical and pharmacological intervention. The economic impact of health policy and health systems

Submit your manuscript here: <http://www.dovepress.com/clinicoeconomics-and-outcomes-research-journal>

Dovepress

organization also constitute important areas of coverage. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.