

Assessment: The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review)

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology



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ABSTRACT

The clinical and radiologic impact of natalizumab (Tysabri) as therapy for multiple sclerosis (MS) is assessed. On the basis of Class I evidence, natalizumab has been demonstrated to reduce measures of disease activity and to improve measures of disease severity in patients with relapsing-remitting (RR) MS (Level A). The relative efficacy of natalizumab compared to current disease-modifying therapies cannot be defined accurately (Level U). Similarly, the value of natalizumab in the treatment of secondary progressive (SP) MS is unknown (Level U). The value of combination therapy using natalizumab and interferon in the treatment of RRMS is also unknown (Level U). There is an increased risk of developing progressive multifocal leukoencephalopathy (PML) in natalizumab-treated patients (Level A for combination therapy, Level C for monotherapy) and possibly an increased risk of other opportunistic infections (Level C). The PML risk in a pooled clinical trial cohort has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this figure could change in either direction with more experience with the drug. *Neurology*® 2008;71:766-773

GLOSSARY

CAM = cellular adhesion molecule; **EDSS** = Expanded Disability Status Scale; **FDA** = Food and Drug Administration; **Gd** = gadolinium; **MAD** = mucosal addressin; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **RCT** = randomized controlled trial; **RR** = relapsing-remitting; **SP** = secondary progressive; **WBC** = white blood cell.

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by injury to the myelin sheaths, oligodendrocytes, gray matter, and, to a lesser extent, the axons.¹⁻³ There is considerable evidence indicating that autoreactive T-cells proliferate, cross the blood-brain barrier, and enter the CNS under the influence of cellular adhesion molecules (CAMs) and pro-inflammatory cytokines.^{4,5} In addition to T-cells, other mononuclear cells (macrophages and B-cells) are also present in acute MS lesions. In chronic MS lesions, by contrast, active inflammation is less conspicuous and lesions are characterized by gliosis and by a variable degree of axonal loss.

Evaluation of the effectiveness of different therapies in MS requires a consideration of which outcome measures are relevant to the prevention or

postponement of long-term disability (both physical and cognitive). Because disability in MS evolves over many years and because clinical trials only study patients for short periods (typically 6 months to 3 years), assessments of efficacy must be based on short-term surrogate measures. However, it is unknown which (if any) of these short-term surrogates correlates with long-term disability. Consequently, most trials have relied upon a combination of measures to assess disease activity and severity. Disease activity can be assessed with both clinical measures (e.g., the annualized attack rate, the time to first relapse, or the probability of being relapse-free for some period of time) and MRI measures (e.g., gadolinium [Gd]-enhancing lesions, the number of new T2 lesions, or a combination of the two). Dis-

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ease severity is generally assessed clinically using the Expanded Disability Status Scale (EDSS), either as a one-point increase in the scale that is sustained for at least 3 or 6 months, or as a categorical change in the scale from baseline to the end of the trial.⁶ MRI disease severity is typically assessed by the total volume (burden) of disease seen on T2-weighted scans, although there is considerable interest in the use of other measures such as cerebral (brain) atrophy or the volume of hypointense lesions seen on T1-weighted images (T1-black holes), which may have a closer relationship to neurologic disability than the less-specific T2 lesions.

Natalizumab (Tysabri) is a humanized monoclonal antibody that binds to the $\alpha 4$ subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins which are expressed (among other places) on the surface of activated T-cells. This interaction blocks the binding of these activated lymphocytes to their endothelial receptors (vascular cellular adhesion molecule or VCAM-1 and mucosal addressin [MAD] CAM-1), which is an important step in T-cell transmigration through the blood-brain barrier and into the CNS.⁷⁻¹¹ Natalizumab may also suppress ongoing inflammatory reactions by inhibiting the binding of $\alpha 4$ -positive leukocytes to osteopontin and fibronectin.⁷⁻¹¹ The blockage of this interaction results in a profound decrease (relative to non-treated patients with MS) in the number of white blood cells (WBCs) within the CSF, including CD4+ and CD8+ T-lymphocytes, CD19+ B-lymphocytes, and CD138+ plasma cells.^{12,13} Moreover, this profound suppression of WBCs in the CSF can persist for at least 6 months after discontinuation of natalizumab.¹² On the basis of an early smaller clinical trial,^{14,15} which showed a promising therapeutic response to natalizumab over 6 months in a group of patients with MS, two large studies in RRMS were launched at essentially the same time. The preliminary results of these two trials were the basis of the initial expedited Food and Drug Administration (FDA) approval of natalizumab for relapsing forms of MS in November 2004. Very shortly after this approval, progressive multifocal leukoencephalopathy (PML) was discovered in two of the study patients, which led to a market suspension of this agent in February 2005. In June 2006, on the basis of the complete data from these two trials, the FDA reapproved natalizumab for use in patients with MS with a “black box” warning about the risk of PML. Moreover, because of the PML risk (and despite clear evidence of natalizumab’s effi-

cacy early in the course of MS), the FDA recommended that its use be restricted to selected patients with relapsing disease, such as those who have failed to respond to or tolerate other disease-modifying therapies, or those who present with a particularly aggressive initial disease course. This assessment evaluates the effectiveness and safety of natalizumab in the treatment of MS and, specifically, addresses the following six clinical questions:

1. Does treatment with natalizumab reduce disease activity in RRMS by clinical and MRI measures?
2. Does treatment with natalizumab reduce disease severity in RRMS by clinical and MRI measures?
3. How does the efficacy of natalizumab compare with currently available disease-modifying therapies?
4. Is natalizumab effective in other clinical types of MS such as SPMS?
5. In patients with RRMS, does the combination of natalizumab with other disease-modifying therapies improve efficacy?
6. In patients with MS, how safe is natalizumab, either alone or in combination with other immunomodulating agents?

DESCRIPTION OF THE ANALYTIC PROCESS

The MEDLINE and EMBASE databases (1966 to present) were searched in October 2006 under the terms natalizumab and MS and the reference lists of identified articles were reviewed. These searches identified 316 articles. Only articles reporting results from controlled clinical trials in humans were included in this assessment. Panel members reviewed the abstracts. Twelve articles, relating to five randomized controlled trials (RCTs), met our inclusion criteria.¹²⁻²³ In addition, a sixth RCT (the GLANCE trial comparing the combination of natalizumab and glatiramer acetate to glatiramer acetate alone) had sufficient data presented for classification.²⁴ Each panel member read each article and classified the level of evidence for the clinical trials according to the system used by the American Academy of Neurology for therapeutic interventions (available as supplemental data on the *Neurology*[®] Web site at www.neurology.org).

ANALYSIS OF EVIDENCE

Question 1: Does treatment with natalizumab reduce disease activity in RRMS by clinical and MRI measures? Of the six Class I studies, three trials looked primarily at MRI outcomes and demonstrated that natalizumab significantly reduced MRI activity mea-

Table 1 Outcome and classification of the randomized controlled trials of natalizumab in MS*

Study	Class of study	Size	Natalizumab dosage [†]	Clinical activity	MRI activity	Clinical severity	MRI severity	Study population
UK Study Group ⁴	I	72	3 mg/kg q 4 wk (×2)	NR	‡	NR	NR	RRMS
Phase II Trial ^{15, 17}	I	213	3 or 6 mg/kg q 4 wk (×6)	§	‡	NR	NR	RRMS SPMS
Natalizumab Study Group ¹⁶	I	110	1 or 3 mg/kg (one dose)	NR	‡	NR	NR	RRMS
GLANCE Trial ²⁴	I	180	300 mg [¶] q 4 wk (×6)	NS	§	NR	NR	RRMS
AFFIRM Trial ²⁰	I	942	300 mg q 4 wk (120 wk)	‡	‡	‡	‡	RRMS
SENTINEL Trial ²¹	I	1,171	300 mg [¶] q 4 wk (120 wk)	‡	‡	‡	‡	RRMS

*Clinical activity was assessed by attack rate or attack-free status. MRI activity was assessed by gadolinium enhancement, new T2 lesions, or both. Clinical severity was assessed by confirmed Expanded Disability Status Scale progression. MRI severity was assessed by total T2 volume (burden) of disease.

[†]q 4 wk means administered every 4 weeks. Number of doses or trial duration in parentheses.

[‡]Significant ($p < 0.01$); [§]marginally significant ($p = 0.01-0.05$).

[¶]In combination with GA 20 mg SC qd.

^{||}In combination with IFN β 1a 30 mcg IM qw.

MS = multiple sclerosis; RR = relapsing-remitting; NR = not reported or not studied; SP = secondary progressive; NS = not significant.

tures compared to placebo alone or to placebo in combination with other disease-modifying agents.^{16,18,26} Three additional RCTs studied both clinical and MRI outcomes.^{17,19,22-24} Two compared natalizumab to placebo^{15,17,20,22} and the other studied the combination of natalizumab and IFN β -1a (Avonex) 30 μ g per week IM compared to IFN β -1a alone.²¹

The dose of natalizumab varied somewhat among the six RCTs (table 1). In the large Phase III placebo-controlled trial, the AFFIRM Trial,^{20,22} patients had mild disability and were entered relatively early in their disease course. In the large Phase III trial studying combination therapy, the SENTINEL Trial,²¹ patients were at somewhat later disease duration and had breakthrough activity while on IFN β -1a therapy. In the Phase II trial, which included both RRMS and SPMS patients,^{15,17} the disability at baseline and disease duration were considerably greater (mean EDSS = 4.2–4.4; mean duration = 10.2–13.1 years). All three of these natalizumab trials^{15,17,20-22} showed a significant benefit of treatment (as evaluated by a relative-risk comparison) on both clinical and MRI measures of disease activity defined earlier (tables 2 and 3), with MRI activity being suppressed by 80–90% and clinical activity being reduced by 50–70%.

Question 2: Does treatment with natalizumab reduce disease severity in RRMS by clinical and MRI measures? In both of the 2-year Class I trials in which disease severity was measured,²⁰⁻²² there was a significant benefit of treatment on both clinical and MRI measures of disease severity defined earlier (tables 2 and 3).

Question 3: How does the efficacy of natalizumab compare with currently available disease-modifying therapies? To determine the true relative efficacy of different agents requires a randomized head-to-head

study, in which both number needed to treat (NNT) and relative risk methods would provide equivalent answers. In cross-trial comparisons, however, these two methods of analysis often lead to disparate answers (tables 2 and 3) and neither, by itself, is a reliable measure of comparative efficacy.

Natalizumab was demonstrated to have a therapeutic benefit ($p < 0.001$) with respect to each of the four principal outcomes currently used in MS clinical trials (table 1). Moreover, the effect size and statistical significance for natalizumab on each of these outcomes (measured as the relative risk ratio) are generally larger using this agent than those reported using any of the other currently available therapies,²⁵⁻³⁵ especially with respect to clinically based outcomes (table 2). However, using an NNT analysis, which is the inverse of the absolute difference between the two treatment arms and thus emphasizes absolute treatment effects rather than the relative effects, the apparent comparative value of natalizumab is altered (table 3). Consequently, the magnitude of any advantage of natalizumab therapy over current agents cannot be defined accurately on the basis of current data.

Moreover, patients recruited into placebo-controlled trials today will tend to have less advanced MS when compared to patients who entered earlier trials. This is because most clinicians tend to steer patients with more aggressive RRMS away from trials that include a placebo arm. When the pivotal trials of other agents were conducted 15–20 years ago, when no proven therapies existed, such patients were encouraged to participate in placebo-controlled trials. In addition, because disease-modifying therapy seems to be more effective early in the disease course,³⁶⁻³⁸ these differences in the patient

Table 2 Relative effect sizes and statistical significances of the main 2-year outcomes (placebo-controlled trials) for the different Food and Drug Administration approved therapies in relapsing-remitting multiple sclerosis

Dose, route, and schedule	Baseline EDSS	Disease duration, y [†]	Pre-study attack rate, mean/y	Placebo attack rate, mean/y	Clinical measures [*]		MRI measures [*]		
					Attack rate, mean [‡]	Progression	New T2 lesions	Gd+ or CU lesions	Burden of disease
IFNβ-1a, 30 μg, IM, qw ^{28,29}	2.4	6.5	1.2	0.8	-18% [§]	-37% [§]	-36% [¶]	-42% [§]	-4% (NS)
IFNβ-1a, SC, 44 μg tiw ^{32,33}	2.5	5.3	1.5	1.3 [#]	-32%	-30% [§]	-78%	-88%	-15%
IFNβ-1b, 250 μg, SC, qod ²⁵⁻²⁷	2.9	3.9	1.7	1.3 [#]	-34%	-29% (NS)	-83% [¶]	NR	-17%
GA 20 mg, SC, qd ^{30,31**}	2.6	6.9	1.5	0.8	-29% [¶]	-12% (NS)	-38% [¶]	-33% [¶]	-8% [¶]
MTX 12 mg/m ² , IV, q 3 mo ^{34,35**}	4.5	9.6	1.3	0.6	-42%	-75% [§]	-79% [§]	-79% (NS)	NR
NTZ 300 mg, IV, q 4 wk ²⁰	2.3	5.0	1.5	0.7	-68%	-42%	-83%	-92%	-18%

*Relative risk reductions (or increases) have been calculated by dividing the reported rates in the treated group (intent-to-treat analysis) by the comparable rates in the placebo group, except for MRI disease burden, which was calculated as the difference in the median % change between the treated and placebo groups. Original citations are available from several published reviews.⁴⁻⁶ Progression = 1 point Expanded Disability Status Scale (EDSS) progression, sustained for 3 months (in the IFNβ-1a 30 μg qw trial this change was sustained for 6 months; in the IFNβ-1b trial this was over 3 years). Different studies measured these MRI measures differently making comparisons difficult (numbers for new T2 and Gd+ represent the best case scenario for each trial); new T2, Gd+, or CU = new T2, gadolinium enhanced, or combined unique lesions.

[†]Mean duration. Measured from diagnosis in the IFNβ-1b trial rather than from symptom onset; reported as median in the natalizumab trial.

[‡]Annualized attack rate difference vs placebo.

[§]p ≤ 0.05; [¶]p ≤ 0.01; ^{||}p ≤ 0.001.

[#]Definition of on study relapse did not require fulfillment of predefined criteria of change in neurologic scores.

**MRI measures from 9 month frequent MRI study.³¹

**Study included mainly secondary progressive MS population.

IFNβ = interferon beta; IM = intramuscular; qw = once per week; NS = not significant; SC = subcutaneous; tiw = three times per week; qod = every other day; nr = not reported; GA = glatiramer acetate; MTX = mitoxantrone; NTZ = natalizumab; q 3 mo = once every 3 months.

Table 3 NNT^{*} values based on efficacy 2-year outcome data for the IFNβs, GA, and natalizumab in RRMS^{20, 25-33}

Outcome	IFN beta-1b (250 μg qod)	IFN beta-1a (30 μg qw)	GA (20 mg qd)	IFN beta-1a (22 μg tiw)	IFN beta-1a (44 μg tiw)	Natalizumab (300 mg q4w)
Relapse count						
Annualized rate [†]	2 (2-5)	7 (4-100)	4 [‡]	3 (2-5)	2 (2-5)	2 (1-6)
Relapse free (%)						
1 year	NR	NR	16(5-∞) [§]	7 (4-16)	4 (3-8)	5 (4-7)
2 years [†]	7 (4-23)	9 (4-∞) [§]	15 (6-∞)	10 (6-51)	6 (4-11)	4 (3-5)
Progression free (%)	13 (6-∞)	8 (4-38)	33 (7-∞)	12 (5-∞)	9 (5-53)	8 (6-17)
T1 (Gd) lesion count						
Annualized rate	NR	1.4 [‡]	0.09 [‡]	0.11 [¶]	0.11 [¶]	0.91 [‡]
No T2 active scans (%)	5 (3-11)	NR	NR	9 (6-26)	4 (3-7)	2 (2-3)
No T1 active scans (%)	NR	8 (4-70)	14 (5-∞) [¶]	4 (2-8) [¶]	3 (2-6) [¶]	4 (3-5)

*NNT values are rounded to the nearest integer (except for T1 [Gd] lesion counts); CIs are in parentheses.

[†]NNT per year based on annualized rate over 2 years.

[‡]The 95% CI of the differences in annualized relapse rate between Copaxone and placebo is (-0.02 to 0.31); therefore, the 95% CI of the NNT cannot be calculated, although the point estimate is 4.

[§]9-month data.

[¶]Applies to "all subjects as randomized" analysis set. A total of 43% did not complete the study because of its early termination. NNT for the subset (57%) completing 2 years on study.

^{||}Calculated from the median.

^{||}12-month data.

NNT = number of patients needed to treat to obtain benefit; IFN = interferon; GA = glatiramer acetate; RRMS = relapsing-remitting multiple sclerosis; qod = every other day; qw = once weekly; qd = once daily; tiw = three times weekly; q4w = once every 4 weeks; nr = not reported.

populations studied may tend to overestimate the difference between current and novel therapies in cross-trial comparisons. Finally, because it is unclear which of our current short-term surrogate outcomes are the most valid predictors of long-term disability, it is impossible to know which, if any, outcome or outcomes to emphasize in any such comparisons (tables 2 and 3).

Question 4: Is natalizumab effective in other clinical types of MS such as SPMS? The only available evidence for the use of natalizumab in forms of MS other than RRMS is derived from the moderately sized Phase II study,¹⁵ which included patients with either RRMS or SPMS. This study reported a benefit on measures of disease activity (both clinical and MRI) in the combined group, but did not analyze the two subgroups separately.

Question 5: In patients with RRMS, does the combination of natalizumab with other disease-modifying therapies improve efficacy? The optimal method to determine the value of combination therapy is a three-armed trial, in which both agents are studied alone and in combination. No such study is available. The SENTINEL trial included only two arms: one group received interferon-beta 1a and the other interferon-beta 1a plus natalizumab, so it is impossible to determine the value of combination therapy compared to natalizumab alone.

This uncertainty underscores the importance of avoiding any conclusions regarding the efficacy of natalizumab combination therapies until sufficient data from three-armed clinical trials are available to properly assess both the efficacy and long-term safety of such regimens.

Question 6: In patients with MS, how safe is natalizumab, either alone or in combination with other immune modulating agents? In all six RCTs, the therapeutic benefits of natalizumab were associated with few notable side effects for up to 2 years of treatment. Nevertheless, 2–9% of patients in the AFFIRM and SENTINEL trials had an allergic or other hypersensitivity reaction to natalizumab and in 1%, which included rare anaphylactoid reactions, these were considered serious by the investigators.^{20–22} Also, approximately 6% of patients developed persistent binding antibodies to the natalizumab molecule, and in these patients the therapeutic effect of natalizumab seemed to be neutralized completely.^{20–22}

Despite such encouraging safety results, there are reasons for caution. After the completion of the SENTINEL trial, two patients (both in the arm receiving combined natalizumab and IFN β -1a therapy) developed PML, one of whom died.^{18,19} The other remains severely disabled. In reviewing the previous experience with natalizumab in Crohn disease,

a third postmortem case of PML was identified in a patient who had received natalizumab alone.³⁹ This patient, however, previously received other immunosuppressive agents (in addition to natalizumab) and was still mildly lymphopenic at the time natalizumab was restarted prior to the development of PML. The basis for PML in these patients is unclear. However, the possibility that concurrent immunosuppression (either from IFN β or otherwise) contributes to the development of PML in patients on natalizumab cannot be excluded. It is also possible that the risk of PML is due to natalizumab alone and that this risk may increase with greater time on therapy. There may be individual risk factors for PML in patients treated with natalizumab which are yet unidentified. Extensive studies on stored serum samples from the patients who participated in these two clinical trials failed to reveal viremia in two of the three patients prior to the onset of clinical symptoms of PML. Imaging features of MS and PML overlap to some degree, especially early in the course. Consequently, prospective monitoring for PML prior to the appearance of clinical manifestations may not be possible or reliable.

Finally, although there was not a statistical excess of either opportunistic infections or malignancies in the natalizumab-treated patients, the possibility that these potential complications of therapy may emerge as larger numbers of patients are treated for longer periods of time cannot be excluded at present. At the FDA hearing for market reapproval,⁴⁰ several unusual infections were reported to have occurred in patients receiving natalizumab (either for Crohn disease or for MS). These included two cases of viral meningitis and encephalitis (one fatal), two cases of acute cytomegalovirus, pulmonary aspergillosis, and one case each of cryptosporidial gastroenteritis, *Pneumocystis carinii* pneumonia, varicella pneumonia, mycobacterium avium intracellulare complex pneumonia, and *Burkholderia cepacia* pneumonia.⁴⁰ Whether natalizumab was responsible, in whole or in part, for these complications is unknown because most of them occurred in the setting of concomitant immunosuppressive or immunomodulatory treatments and/or intercurrent illnesses. Nevertheless, these observations raise concern about whether patients treated with natalizumab might have compromised cell-mediated immunity and certainly warrant caution in combining natalizumab with other immune therapeutic agents. Further experience in a much larger patient population for a longer time period may provide a more definitive answer regarding long-term safety of natalizumab.

Similarly, despite the fact that Yousry et al.²³ have estimated the risk of PML as 1 per 1,000 patients

treated for an average of 17.9 months (95% CI: 0.2 to 2.8 per 1,000), this figure probably provides an incomplete estimate of the actual risk. For example, if concomitant IFN β therapy predisposes to PML, the risk for patients on natalizumab monotherapy may be much lower. By contrast, if this complication can occur with natalizumab alone, the risk will re-emerge and may increase with increased exposure time to therapy.

Another confounding factor is that patients treated in the future with natalizumab may not be comparable to the populations studied in the clinical trials. Under current FDA recommendations, future patients treated with natalizumab will have failed to tolerate or respond adequately to IFN β or glatiramer acetate. In such patients, the disease duration may be longer and the disability level greater at the time of treatment initiation than was the case in the large pivotal trials and, consequently, such patients may be generally less responsive to immune-modulating therapies (including natalizumab) than patients who are treatment-naïve.³⁶⁻³⁸ In assessing the risks and benefits of therapy for individual patients, it must be considered that natalizumab is still a partially effective therapy with very rare but potentially fatal complications, and that MS is typically a nonfatal disease with other therapeutic options not associated with PML. Finally, as with any of the currently available disease-modifying therapies, the treatment decision in an individual patient must be tempered by an understanding that the disease activity and disease severity measures used as outcomes in clinical trials have an uncertain relationship with long-term disability, that some patients may experience unacceptable side effects to therapy, and that certain patients with MS, even without specific therapy, will have a relatively benign disease course.

CONCLUSIONS

1. Natalizumab reduces measures of disease activity such as clinical relapse rate, Gd-enhancement, and new and enlarging T2 lesions in patients with relapsing MS (Class I studies, Level A).

2. Natalizumab improves measures of disease severity such as the EDSS progression rate and the T2-hyperintense and T1-hypointense lesion burden seen on MRI in patients with relapsing MS (Class I studies, Level A).

3. The relative efficacy of natalizumab compared to other available disease-modifying therapies is unknown (Level U).

4. The value of natalizumab in the treatment of SPMS is unknown (Level U).

5. The SENTINEL trial provides evidence for the value of adding natalizumab to patients already re-

ceiving IFN β -1a, 30 μ g, IM once weekly (one Class I study, Level B). It provides no information either about the value of adding IFN β therapy to patients already receiving natalizumab in the treatment of RRMS or about the value of continuing IFN β therapy once natalizumab therapy is started (Level U).

6. There is an increased risk of developing PML in natalizumab-treated patients (Level A for combination therapy, Level C for monotherapy). The two cases seen in MS were treated with a combination of natalizumab and IFN β -1a, but the fact that PML occurred only with combination therapy may be a chance development. There may also be an increased risk of other opportunistic infections (Level C). On the basis of clinical trial data, the PML risk has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this estimate could change in either direction with more patient-years of exposure.

Since the development of this guideline, two cases of PML have been reported in patients receiving natalizumab monotherapy, one of whom had never previously received any immunomodulatory or immunosuppressive treatment. This observation indicates that natalizumab, by itself, is a risk factor for PML. However, the evidence has not been formally reviewed by TTA.

RECOMMENDATIONS

1. Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML, it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course. This recommendation is very similar to that of the FDA.

2. Similarly, because combination therapy with IFN β and natalizumab may increase the risk of PML, it should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. The true risk of PML in patients receiving natalizumab monotherapy needs to be established in large longitudinal postmarketing surveys of patients on treatment for several years. A large-scale postregistration study (the TYGRIS study) is now under way to address this issue.

2. It is currently possible to monitor a patient's specific cellular immunity to JC virus. If such a test were commercially available, studies to determine its value in predicting the risk of developing PML would be strongly recommended.

3. Testing to assess different dosing regimens to improve efficacy and/or reduce risk should be done.

4. Assessment of the safety and efficacy of combinations of treatments should be made.

5. Study of ways to reverse immediately the effects of natalizumab if PML or other serious side effects occur should be done.

6. Head-to-head comparative studies are needed to define the relative value and safety of natalizumab, both compared to our current therapies and to those under development.

7. The effectiveness of natalizumab in other disease types of MS such as SPMS needs to be studied.

DISCLOSURE

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DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Subcommittee of the American Academy of Neurology**

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