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REVIEW ARTICLE

Natalizumab for relapsing-remitting multiple sclerosis

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Abstract
Introduction: Natalizumab is a monoclonal antibody that inhibits leukocyte migration across the blood-brain barrier and has been approved for the treatment of relapsing-remitting multiple sclerosis.
Objective: To provide a review and update of the pharmacological and therapeutic characteristics of natalizumab, with special emphasis on the most recently published data on the efficacy, effectiveness and safety of this drug.
Development: Several randomized clinical trials in patients with relapsing forms of multiple sclerosis have demonstrated that natalizumab substantially reduces clinical and radiological disease activity. Post hoc analysis of phase III clinical trials and the results of post-approval observational studies indicate that natalizumab significantly increases the proportion of patients with complete clinical and radiological response and is effective in patients with highly active forms of multiple sclerosis and suboptimal response to other treatments. Like other monoclonal antibodies, natalizumab can cause hypersensitivity reactions, which are severe in 1%of patients. Other adverse effects are generally mild or infrequent. Nevertheless, several cases of progressive multifocal leukoencephalopathy have been detected in patients treated with natalizumab monotherapy. The risk of this severe complication seems to increase with the number of doses administered.
Conclusion: Natalizumab has a favourable risk-benefit ratio in the treatment of relapsing-remitting multiple sclerosis. However, because of the potential risk of progressive multifocal leukoencephalopathy, patients must be carefully selected and specific protocols must be followed during the drug's administration.

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PALABRAS CLAVE
Esclerosis múltiple;
Natalizumab;
Anticuerpo monoclonal;
Ensayo clínico;
Leucoencefalopatía multifocal progresiva

Natalizumab para la esclerosis múltiple remitente-recurrente

Resumen
Introducción: Natalizumab es un anticuerpo monoclonal inhibidor de la migración leucocitaria a través de la barrera hematoencefálica, autorizado para el tratamiento de la esclerosis múltiple remitente-recurrente.
Objetivo: Realizar una revisión y actualización de los aspectos farmacológicos y terapéuticos de natalizumab, con especial énfasis en los datos de eficacia, efectividad y seguridad publicados más recientemente.
Desarrollo: Varios ensayos clínicos aleatorizados en pacientes con formas recurrentes de esclerosis múltiple han demostrado que natalizumab reduce considerablemente la actividad clínica y radiológica de la enfermedad. El análisis post hoc de ensayos clínicos fase III y los resultados de estudios observacionales postautorización indican que natalizumab incrementa significativamente la proporción de pacientes con respuesta clínica y radiológica completa, y que es eficaz en aquellos con formas muy activas de esclerosis múltiple y con respuesta subóptima a otras terapias. Al igual que otros anticuerpos monoclonales, natalizumab puede causar reacciones de hipersensibilidad, siendo graves en el 1% de los pacientes. Otros efectos adversos de natalizumab son en general leves o poco frecuentes. No obstante, se han detectado varios casos de leucoencefalopatía multifocal progresiva en pacientes tratados con natalizumab en monoterapia. El riesgo de esta grave complicación parece incrementarse con el número de dosis recibidas.
Conclusión: Natalizumab ha demostrado una relación beneficio-riesgo favorable en el tratamiento de la esclerosis múltiple remitente-recurrente. El riesgo potencial de leucoencefalopatía multifocal progresiva, sin embargo, obliga a la selección cuidadosa de los pacientes y a seguir protocolos de actuación específicos durante su administración.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) that affects some 2.5 million people worldwide.[1] It has a very high socioeconomic impact, largely due to the prolonged length of the illness, with the highest incidence in young adults and the resulting early loss of productivity, and the cost of the treatments and multidisciplinary care required by patients.[2] MS usually debuts in the third or fourth decade of life with a relapsing clinical course, subsequently evolving toward a chronic condition characterized by the sustained progression of the resulting disability.[1] Studies examining the natural course of MS reveal that approximately 50% of all patients require help in walking 15 years after diagnosis, and that the median time to reaching a high degree of disability is some 30 years.[3]

The objective of any therapy seeking to modify MS is to reduce the frequency and severity of relapse, and to prevent or delay evolution toward a progressive phase. The evidence available suggests that MS is a disease with an autoimmune aetiology and, in line with this concept, its treatment has until now been based on the use of immunomodulating drugs such as interferon β (IFNβ) or glatiramer acetate (GA).[4] Despite the important therapeutic advance that the introduction of these drugs represented in the mid-nineties, they are only partially efficacious and their effects on the long term prognosis has yet to be resolved.[5] One decade later, the incorporation of natalizumab (Tysabri®; Biogen Idec, Inc., Elan Pharmaceuticals, Inc.) into the treatment armamentarium for MS constitutes another significant step forward. Natalizumab is a monoclonal antibody that keeps leukocytes from migrating across the blood-brain barrier. This drug has proven to have a good benefit-risk ratio in MS patients, reducing the frequency of outbreaks, the progression of disability, and the lesions quantified by neuroimaging. This review represents an update on the pharmacological and treatment aspects of natalizumab in the treatment of MS, focusing on the most recently published clinical efficacy and safety data.

Mechanism of action

Current hypotheses sustain that a core event in the pathogenesis of MS is the activation of auto-reactive T lymphocytes in the periphery that, after proliferating and crossing the blood-brain barrier, trigger a cascade of inflammatory events in the CNS culminating in axonal demyelination and damage.[1] The migration of leukocytes across the blood-brain barrier requires the interaction between adhesion molecules expressed on the cell surface, such as selectins and integrins, and their endothelial receptors. In particular, the combination of the high affinity between $\alpha 4\beta 1$ integrin and the vascular cell adhesion molecule-1 (VCAM-1) allows the cells to come to a stop on

the vascular endothelium and initiate transendothelial migration.[6]

Natalizumab, a humanized monoclonal antibody with an IgG4 structure, is a selective adhesion molecule inhibitor that recognizes and binds specifically to the α4 subunit of α4β1 integrin.[7] This drug blocks the binding that takes place between the endothelial VCAM-1 and the α4β1 integrin expressed on the surface of activated T lymphocytes and other mononuclear leukocytes, keeping them from adhering to the endothelium, preventing cell migration and recruitment toward the parenchyma, and the subsequent inflammatory activity in the CNS.[8] It has also been suggested that natalizumab might have immunomodulating effects by inhibiting interaction between α4β1 integrin and molecules of the extracellular matrix, such as fibronectin or osteopontin, or by decreasing the number of dendritic cells and class II CMH expression in the perivascular spaces of the CNS.[7,9]

Pharmacokinetics

When doses of between 1 and 3 mg/kg of natalizumab are administered to healthy volunteers or to MS patients, drug concentrations are detectable in blood for 3 to 8 weeks.[10,11] After a single dose, peak serum concentrations are reached slowly, over the course of 1 or 2 hours following administration, despite the fact that the drug is distributed mainly in the vascular system and hardly diffuses to the tissues.[12] The concentration in blood slowly goes down and takes between 1 and 2 weeks to fall to half, maintaining elevated levels of α4 integrin saturation during this time.[10,13,14] Permanence in blood increases by increasing the dose and, thereby, justifies the dosage chosen in phase III clinical trials and approved by regulatory agencies, namely 300 mg administered intravenously (i.v.) every 4 weeks. The pharmacokinetic parameters of natalizumab are similar in patients with MS following the administration of repeated 300-mg doses: the serum elimination half life is 11±4 days; serum clearance is 16±5 mL/h, and the distribution volume is 5.7±1.9 L.[11,12]

Although no pharmacokinetic studies have been conducted in patients with kidney or liver failure, the data available do not indicate the need to modify dosing of natalizumab in these cases. Its pharmacokinetics also appear to remain unaltered when administered together with other drugs.[11,12,15] However, the presence of anti-natalizumab antibodies can treble the drug's rate of plasma clearance, lowering its concentration in blood to values that compromise its therapeutic efficacy.[12]

With the usual treatment schedule in patients with MS, the saturation of α4 integrin is greater than 70% 4 weeks after the last dose of natalizumab. If the administration of the drug is suspended, its plasma concentrations and biological effects can persist for up to 12 weeks.[14,16] For this reason, if its elimination must be speeded up, measures such as plasmaphoresis should be used. This decreases natalizumab plasma concentrations by 92% after 3 exchanges of 1.5 plasma volumes. However, the α4 integrin saturation may not decrease in parallel. Five exchanges of 1.5 plasma volumes every other day would be needed to lower natalizumab concentrations to below 1 μg/mL and α4 integrin saturation to less than 50% in 95% of patients.[14]

Clinical Trials

Natalizumab's efficacy in the treatment of MS has been evaluated in six randomized, placebo-controlled, double-blind clinical trials that have included a total of 2,688 patients; 1,567 of whom were given natalizumab.[13,17-21] Four of these trials were phase II and 2 were phase III. The patients evaluated had been diagnosed with Relapsing-Remitting MS (RRMS), although the diagnosis of secondary progressive MS was also accepted as an inclusion criterion in the phase III trials.

The design and results of the phase II trials are summarized in table 1. The main objective of 3 of these studies was to evaluate the efficacy of natalizumab in monotherapy or in combination with the standard GA treatment on disease activity determined by means of cerebral magnetic resonance imaging (MRI).[17-19] A fourth study examined the hypothesis that treatment with natalizumab during the acute phase of a relapse can speed up the patient's clinical recovery.[13] All together, the results obtained provided convincing evidence for the first time that a selective α4 integrin monoclonal antibody inhibitor was a potentially efficacious, well-tolerated alternative in the treatment of MS, which justified carrying out phase III clinical trials to confirm natalizumab's clinical efficacy and safety.

Phase III Clinical Trials

The 2 phase III trials in which natalizumab was evaluated for the treatment of RRMS, designated by the acronyms AFFIRM and SENTINEL, had a similar design.[20,21] Both included patients with an expanded disability scale score (EDSS) of 0 to 5.0, lesions on the cerebral MRI that were compatible with MS, and who had presented at least one relapse in the preceding 12 months. The protocol of the SENTINEL study, as an additional criterion, also required prior treatment with IFNβ-1a for at least 12 months before randomization.[21] In both trials the efficacy and safety of 300 mg of natalizumab administered i.v. every 4 weeks were compared to placebo. In the SENTINEL study all participants also received treatment with IFNβ-1a at a dose of 30 μg administered intramuscularly every week.[21] The primary objectives differentiated two pre-established timepoints in the two trials. The first primary objective was to evaluate whether, after 1 year of treatment, the frequency of relapses in the natalizumab group was less than in the placebo group. At the 2-year timepoint, coinciding with the end of treatment, the primary objective consisted of comparing the accumulated likelihood of sustained progression of the disability between study groups, defined as an increase of at least 1.0 points on the EDSS scale maintained for 12 weeks for the patients with a baseline score ≥ 1.0, or a sustained increase of at least 1.5 points over the course of 12 weeks when the baseline score was 0.

The results of both trials are summarized in table 2. The original plan had included an interim analysis of the first endpoint once the data from the first 900 patient-years evaluated in the AFFIRM study and 1,200 patient-years in the SENTINEL study were available.[20,21] At that time, the patients treated with natalizumab in the 2 trials exhibited

Table 1 Phase II randomized clinical trials of natalizumab for the treatment of multiple sclerosis

Author (year)	Study	Inclusion criteria	Treatment	N	Results for primary endpoints
Tubridy et al. (1999) [17]	Efficacy of natalizumab on disease activity evaluated by MRI in patients with RRMS and SPMS	Ages 18-55 years, EDSS 2-7, ≥ 2 relapses in the previous 18 months, > 4 weeks since last relapse	Natalizumab 3 mg/kg i.v. or placebo (1:1), 2 doses administered at weeks 0 and 4	72	Mean accumulated number of new active lesions on cerebral MRI between weeks 1 and 12 of the study: 1.8 for natalizumab 3 mg/kg, 3.6 for placebo (p<0.042)
Miller et al. (2003)[18]	Efficacy of natalizumab on disease activity evaluated by MRI in patients with RRMS and SPMS	Ages 18-65 years, EDSS 2-6.5, ≥ 2 relapses in the previous 2 years, ≥ 3 lesions in T2 on the cerebral MRI	Natalizumab 3 mg/kg i.v., natalizumab 6 mg/kg i.v. or placebo (1:1:1), every 4 weeks for 6 months	213	Mean number of new Gd+ lesions on cerebral MRI during treatment period: 0.7 for natalizumab 3 mg/kg, 1.1 for natalizumab 6 mg/kg, 9.6 for placebo (p<0.001)
O'Connor et al. (2004) [13]	Clinical efficacy of natalizumab in patients with RRMS and SPMS during the acute phase of relapse	Ages 18-65 years, EDSS 0-5.5, clinical stability over the previous ≥ 30 days, symptoms of relapse of > 24 h, but < 96 h, EDSS > 3 during relapse	Natalizumab 1 mg/kg i.v., natalizumab 3 mg/kg i.v. or placebo (1:1:1), single dose	180	Comparison of the mean change on the EDSS during the first week of treatment between both study groups: no differences were seen between natalizumab and placebo
Goodman et al. (2009) [19]	Efficacy of natalizumab combined with GA on radiological activity of the disease in patients with RRMS and SPMS	Ages 18-55 years, EDSS 0-5, treatment with GA for ≥ 12 months, ≥ 1 relapse in the preceding 12 months	Natalizumab 300 mg i.v. or placebo (1:1) every 4 weeks, in addition to GA 20 mg s.c. daily, for ≤ 24 weeks	110	Rate of formation of new active lesions during the treatment period: 0.03 for natalizumab 300 mg and GA 20 mg, 0.11 for placebo and GA (p<0.031)

GA: glatiramer acetate; EDSS: expanded disability status scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondarily progressive multiple sclerosis; i.v.: intravenous; MRI: magnetic resonance imaging; s.c.: subcutaneous.

a relative decrease in the yearly frequency of relapses versus placebo of 68 and 54%, respectively (p<0.001). This difference was maintained when all the first-year data were analyzed (65 and 53%; p<0.001) and at the end of the second year of the study (68 and 55%; p≤0.001). The frequency of relapses was similar in both trials, despite the fact that in the SENTINEL study, all the participants received IFNβ-1a. The proportion of relapse-free patients during the 2 years in the AFFIRM and SENTINEL studies was 67 and 54% in the natalizumab groups, as compared to 41 and 32% in the placebo groups, relatively (p<0.001). The second primary endpoint, the accumulated likelihood of progression of disability at the 2-year endpoint, was also significantly less in the natalizumab groups, with hazard ratios of 0.58 and 0.76, which represents a decrease of 42 and 24% in the risk of progression of disability versus placebo.[20,21]

Although the results of the cerebral MRI findings were a secondary endpoint, in both natalizumab trials, there were 83% fewer new or growing hyperintense lesions in T2-weighted sequences versus placebo (p<0.001), and between 89 and the 92% fewer gadolinium-enhancing lesions in T1-weighted sequences (p<0.001) after 2 years of treatment.[20,21] In the AFFIRM study, treatment with natalizumab was also associated with a decrease of 76% in the number of new hypointense lesions in T1-weighted sequences with respect to the placebo group (p<0.001).[22] Likewise, the volume of lesions in T2-weighted sequences fell by 9.4% in the natalizumab group and increased by 8.8% in the placebo group (p<0.001).[22] These data suggest a sustained and relevant effect of treatment with natalizumab in the prevention of the appearance of new lesions in patients with RRMS.

A *post hoc* analysis in patients from the AFFIRM study evaluated the capacity of natalizumab to achieve a full clinical and radiological response.[23] The absence of clinical activity of disease was defined as having no relapse and no progression of disability over the 12 weeks. The absence of radiological activity was defined as the absence of gadolinium-enhancing lesions in T1-weighted sequences and of new or growing hyperintense lesions in T2-weighted sequences of MRI. The absence of disease activity was defined as the absence of both variables. A significantly

Table 2 Phase II randomized clinical trials of natalizumab for the treatment of multiple sclerosis

Trial (author, year)	N	Inclusion criteria	Treatment (duration)	Clinical and radiological objectives	Results	
					Natalizumab	Placebo
AFFIRM (Polman et al., 2006)	942	Ages 18-50 years, EDSS 0-5, lesions on MRI consistent with MS, ≥ 1 relapse in the previous 12 months	Natalizumab 300 mg i.v. or placebo (1:1) every 4 weeks (116 weeks)	Relapse rate in the first year (95%CI)[a]	0.27 (0.21-0.33)	0.78 (0.64-0.94)
				Accumulated likelihood of progression of disability at 2 years[b]	17%	29%
				Number of new/growing lesions in T2 at 2 years (mean ± SD)	1.9 ± 9.2	11.0 ± 15.7
				Number of Gd+ lesions at 2 years (mean ± SD)	0.1 ± 1.4	1.2 ± 3.9
SENTINEL (Rudick et al., 2006)	1,171	Ages 18-55 years, EDSS 0-5, lesions on MRI consistent with MS, ≥ 1 relapse in the previous 12 months, treatment with IFNβ-1a ≥ 12 months	Natalizumab 300 mg i.v. or placebo (1:1) every 4 weeks, in addition to IFNβ-1a 30 μg i.m. every week (116 weeks)	Relapse rate in the first year (95%CI)	0.38 (0.32-0.45)	0.81 (0.72-0.92)
				Accumulated likelihood of progression of disability at 2 years[b]	23%	29%
				Number of new/growing lesions in T2 at 2 years (mean ± SD)	0.9 ± 2.1	5.4 ± 8.7
				Number of Gd+ lesions at 2 years (mean ± SD)	0.1 ± 0.6	0.9 ± 3.2

SD: standard deviation; EDSS: expanded disability status scale; RRMS: relapsing-remitting multiple sclerosis; CI: confidence interval; IFNβ-1a: interferon β-1a; i.v.: intravenous; i.m.: intramuscular; MRI: magnetic resonance imaging.

$p<0.001$ for all comparisons except accumulated likelihood of progression of disability at 2 years in the SENTINEL study ($p=0.02$).

[a] Primary endpoint first year.

[b] Primary endpoint second year.

larger proportion of patients treated with natalizumab was found to be free of clinical activity (64 versus 39%; p<0.0001), free of radiological activity (58 versus 14%; p<0.0001), and free of disease activity (37 versus 7%; p<0.0001) compared to the placebo group during the 2-year study period.[23]

Another study carried out a *post hoc* analysis of response to natalizumab treatment in the patients from the AFFIRM and SENTINEL studies with highly active RRMS, defined by 2 or more relapses in the year preceding the study and the presence of at least 1 gadolinium-enhancing lesion in T1-weighted sequences in an MRI scan performed prior to randomization.[24] In the patients with highly active RRMS who participated in the AFFIRM study, natalizumab lowered the accumulated risk of progression of disability confirmed at 24 weeks by 64% versus placebo (p=0.008), while the annualized relapse rate was reduced by 81% (p<0.001) during the 2 years of treatment. In the SENTINEL study, the combined natalizumab and IFNβ-1a therapy also lowered the accumulated risk of progression of disability confirmed at 24 weeks by 58% versus IFNβ-1a and placebo (p=0.038) and the annualized rate of relapse, by 76%(p<0.001) in the same type of patient.[24] Despite the fact that it was a subgroup analysis, the data derived from this study suggest that natalizumab is efficacious in highly active forms of the disease.

Posterior analyses of the effect of natalizumab on other pre-established tertiary objectives have been published. Visual function, not specifically related to episodes of optical neuritis, is an important measure of disability in MS patients. In the AFFIRM and SENTINEL studies, visual acuity was examined every 12 weeks by means of the Sloan optotype. Natalizumab lowered the risk of clinically relevant loss of low contrast vision (predefined as a reduction of 2 lines on the optotype) by 28 and 35%, respectively, versus the control groups.[25]

Health-related quality of life (HRQoL) analyses provide a global, subjective assessment of the effect of treatment on the patient's health status. In the AFFIRM and SENTINEL studies a rigorous analysis of HRQoL was performed by means of the SF-36 Health Questionnaire and a visual analogue scale (VAS) of overall well-being, which were evaluated prior to beginning treatment and at weeks 24, 52, and 104.[26] In the AFFIRM study, treatment with natalizumab was associated with an improvement on the dimensions of physical function and mental health of the SF-36 Questionnaire at week 104 versus baseline, in comparison with the placebo group. An improvement was also seen on the physical function dimension at all the remaining timepoints evaluated. In the SENTINEL study, this parameter was also significantly better at weeks 52 and 104 in the natalizumab treatment group. Likewise, the changes on the VAS were favourable for natalizumab in the AFFIRM study. These data suggest that treatment with this drug may be associated with an improvement in HRQoL of patients with MS.[26]

Observational studies

Phase III clinical trials proved natalizumab's considerable efficacy in decreasing clinical and radiological activity in patients with RRMS. Nevertheless, due to reports of cases of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab, the treatment indications approved by the European Medicines Agency (EMA) restrict its use to patients with highly active RRMS despite treatment with IFNβ and those who have serious, rapidly evolving forms of RRMS. No clinical trial has specifically addressed the efficacy of natalizumab as second line therapy in patients with sub-optimal response to IFNβ or GA, or in aggressive forms of RRMS. In this regard, post-authorization observational studies conducted in several European centres provide relevant information with respect to the use of natalizumab in the conditions for which it has been approved.[27-31] These studies indicate that natalizumab is used as second line treatment in between 88 and 94% of patients. All in all, and despite their methodological limitations, the data published suggest that natalizumab is effective in patients who exhibit a sub-optimal response to other drugs during at least the first year of treatment, with a degree of therapeutic benefit similar to that observed in the randomized clinical trials (table 3).[27-29,31]

Immunogenicity of natalizumab

Similarly to what is seen with other peptidic therapeutic agents, natalizumab can induce the formation of anti-natalizumab antibodies during its administration. In the AFFIRM and SENTINEL studies, the presence of anti-natalizumab antibodies was determined by ELISA every 12 weeks during the 2 years of treatment.[32] A patient was defined as being persistently positive if they had a concentration of antibodies ≥ 0.5 μg/mL on two or more determinations performed at an interval of no less than 6 weeks. In the AFFIRM study, natalizumab induced the formation of antibodies in 9% of the patients: 6% were persistently positive and 3% were temporarily positive (a single positive determination). In the SENTINEL study, 6% of the patients were persistently positive and 5% were temporarily positive. In most cases (88-96%), antibodies were detected for the first time within the first 12 weeks of treatment. In both trials, the existence of anti-natalizumab antibodies was related to a decrease in serum concentration of natalizumab. The presence of persistent antibodies was associated with decreased clinical and radiological efficacy of natalizumab. In the temporarily positive patients, natalizumab reached its full efficacy after approximately 6 months following treatment initiation, the time at which antibodies became negative.[32]

Tolerance and safety

In general, natalizumab was well tolerated in the clinical trials. In 1,617 patients with MS treated with natalizumab in placebo-controlled clinical trials, for a maximum of two years, 5.8% of the patients treated with natalizumab and 4.8% of those treated with placebo presented adverse events that required treatment withdrawal. Hypersensitivity reactions were the most common reason for discontinuing treatment.[12] More than forty-three percent (43.5%) of the

Table 3 Post-authorization observational studies of natalizumab for the treatment of multiple sclerosis

	Oturai et al. (2009) [27]	Outteryck et al. (2010) [28]	Putzki et al. (2009) [29]	Putzki et al. (2010) [31]
Number of patients	234	384	97	85
Mean age (years)	39.5	3811	36.5	37.3
Duration of disease (years)	8	7	8	≈ 6
Baseline EDSS	4	4	3.5	3
ARR previous year	2.53	2.19	2.3	2,0
First Line (%)	6	6	6	12
Second Line (%)	94	94	94	88
Mean follow-up (months)	11.3	8.3	19.3	18.4
ARR first year	0.68	0.59[a]	0.2	0.3
No relapses (%)	63	60[a]	80	79
No progression (%)	91	—	90	93

EDSS: expanded disability status scale; ARR: annualized rate of relapses.
First Line: percentage of patients treated with natalizumab as first treatment option; second line: percentage of patients previously treated with other disease-modifying drugs.
[a]Percentage of patients with at least 12 months of follow-up (n=127).

patients treated with natalizumab reported adverse drug reactions (placebo, 39.6%). The adverse events reported with natalizumab with an incidence of 0.5% higher than placebo were: headache, dizziness, vomiting, nausea, arthralgias, urinary tract infection, nasopharyngitis, tremors, fever, fatigue, hives, and hypersensitivity reactions.[33]

Reactions to infusion

In placebo-controlled clinical trials, reaction to infusion was defined as any adverse event occurring either during the 1-hour infusion or during the hour following infusion. These reactions were seen in 24% of the patients treated with natalizumab in monotherapy and in 18% of the subjects who received placebo (p=0.04).[20] Most of these reactions merely required symptomatic treatment and were not cause for treatment discontinuation; they were serious in less than 1% of the cases.[15,20] The most common reactions to infusion reported in patients treated with natalizumab were headache, dizziness, nausea, tremors, and hives.[12]

Hypersensitivity reactions

In the AFFIRM study, adverse events reported as hypersensitivity reactions occurred in 4% of natalizumab-treated patients. Five (0.8%) of the reactions were deemed to be serious systemic reactions (anaphylactic or anaphylactoid reactions).[20] Hypersensitivity reactions generally take place during the infusion of natalizumab or during the following hour, and usually manifest as hives with or without other symptoms. The risk of presenting these reactions is greater during the first months of treatment, with the highest risk period being between the first and seventh infusions, above all, during the second infusion.[33,34] The risk also appears to be greater in patients who have been re-exposed to natalizumab after a short, initial exposure (1 or 2 doses) and after a prolonged period (3 or more months) without treatment.[33] When it occurs, this type of reaction appears to respond well to treatment with adrenaline, antihistamines, and corticosteroids.[34] The drug must be permanently discontinued in patients who have presented a hypersensitivity reaction.[33]

In the phase III clinical trials, a higher incidence of reactions to infusion and hypersensitivity were detected in patients with persistently positive anti-natalizumab antibodies. In the AFFIRM study, hypersensitivity reactions presented in 46% of the patients with persistently positive antibodies, in 15% of patients with temporarily positive antibodies, and in 0.7% of the patients without antibodies. However, no predictions can be made concerning which patients with persistently positive antibodies will develop hypersensitivity.

Although most hypersensitivity reactions occur within the first 2 h following natalizumab infusion, delayed hypersensitivity reactions can also appear a few hours and up to several days after administration.[35-37] These reactions also tend to present during the first months of treatment, and are clinically similar to serum-sickness-type reaction, which poses the possibility of a type III hypersensitivity mechanism. Usual symptoms include fever, headache, neck pain, pruritus, general malaise, and joint pain. It would be necessary to suspend treatment in patients with delayed reactions and anti-natalizumab antibodies. Some authors are of the opinion that, if no antibodies are detected, pre-treatment with antihistamines and corticosteroids and decreasing infusion rate might be enough to control symptoms.[36,38]

Altered laboratory test results

Treatment with natalizumab is associated with an increase in plasma concentrations of lymphocytes, monocytes, eosinophils, and basophils. This effect is consistent with natalizumab's mechanism of action, which decreases cell migration outside the bloodstream. In fact, no increase of neutrophils, which does not express $\alpha 4$ integrin, is seen.

This effect does not appear to be associated with any clinical manifestation and is reversible once treatment is withdrawn.[33]

No significant differences were seen regarding the elevation of hepatic enzymes between the natalizumab-treated groups and the placebo group in phase III clinical trials. However, several cases of clinically relevant liver damage have been reported in patients treated with natalizumab, reappearing in some of them after re-administration. The EMA has evidence of at least 29 cases of liver damage, of which two-thirds were considered serious. This agency recommends constant liver function monitoring and withdrawal of treatment in the case of significant reactions.[39]

Neoplasms

No appreciable differences were detected in the incidence of neoplasms in patients treated with natalizumab in comparison to those who received placebo in the randomized clinical trials. Furthermore, the incidence of the neoplasms that were observed, such as breast cancer or basal cell carcinoma, did not exceed the rates expected in the general population. In the AFFIRM study, one patient with a history of malignant melanoma died as a result of a metastatic melanoma.[20] In the post-authorization phase another two cases of melanoma were reported in patients treated with natalizumab.[40] One case of primary cerebral lymphoma after receiving 21 doses of natalizumab has also been reported in a 40-year old patient who had previously been treated with azathioprine.[41] There is another report of a 30-year-old patient in whom treatment with natalizumab may have affected the growth of a primary cerebral lymphoma.[42] Nevertheless, the data currently available do not suffice to determine whether the drug can increase the risk of melanoma or primary cerebral lymphoma, or modify their course.

Infections

According to data from the phase III clinical trials, natalizumab does not increase the overall risk of infections in comparison to placebo. In these studies, the infection rate was approximately 1.5 per patient-year in both groups and the nature of the infections was similar. A slight, non-significant increase was seen in the incidence of pneumonia and urinary tract infections in the patients who received natalizumab, including one case of diarrhoea due to *Cryptosporidium*, an opportunistic infection. Except for PML, no other opportunistic infections were seen during the clinical trials in MS patients. A case of ocular toxoplasmosis has recently been published in a 28-year old patient, as well as one case of serious cutaneous candidiasis in a 61-year-old female, both of which occurred after the eleventh dose of natalizumab.[43,44]

Infections due to the varicella-zoster virus and the herpes simplex virus were seen in the clinical trials at a slightly greater rate in individuals treated with natalizumab versus placebo. Serious cases have been reported, including herpetic meningitis and another fatal case of herpetic encephalitis during the post-authorization period.[12] Therefore, although no relationship has been demonstrated between the risk of opportunistic infections or infections due to the herpes virus and natalizumab, care should be taken and the appearance of these infections in treated individuals watched for.

Progressive Multifocal Leukoencephalopathy

The SENTINEL study was suspended in February, 2005, shortly prior to its end date, as a result of 2 reports of PML in patients who had been receiving natalizumab in combination with IFNβ-1a.[45,46] Subsequently, another case of PML was reported in a patient treated with natalizumab for Crohn's disease.[47] These facts led to the withdrawal of the drug by the laboratory responsible for its marketing, which had been authorized 3 months earlier in the United States.[48] A comprehensive review was then undertaken of the patients who had been treated with natalizumab until that time to rule out other possible causes for PML. The analysis included 3,389 participants in clinical trials, of whom 3,117 had received natalizumab and 273 placebo. The physicians who had administered natalizumab to close to 7,000 patients between November, 2004, and February 2005, after the product had been authorized were also contacted. No new cases were found and the incidence of PML was estimated to be 1 case for every 1,000 patients exposed to a mean of 18 doses monthly of natalizumab.[49] Based on these results, in June, 2006, the reintroduction of natalizumab was reintroduced for the treatment of RRMS in the United States and Europe.

Between June, 2006, and January, 2010, close to 66,000 patients received at least 1 dose of natalizumab around the world. During this period, 31 new cases of PML have been confirmed associated with the use of natalizumab in monotherapy in the United States and Europe; of the new cases, 23 involved patients treated for more than 2 years.[50,51] The analysis of the data available suggests that the risk of PML increases as the number of doses received increases and that the accumulated rate of PML is 0.8 cases for every 1,000 patients treated with 12 or more doses of natalizumab, and 1.3 cases for every 1,000 patients treated with 24 doses or more.[51] The magnitude of the risk in patients who have received 36 doses or more cannot currently be established.

PML is a demyelinating disease of the CNS caused by a lytic infection of the oligodendrocytes by the JC virus, which is polyomavirus ubiquitous in humans. In developed countries, between 70 and 90% of all adults have detectable antibodies against the JC virus. Primary infection takes place at young ages and is typically asymptomatic, although the mechanisms of transmission are not clearly understood.[52,53] Subsequently, the virus remains quiescent in the kidneys, lymph organs, and possibly, in the CNS.[54,55] PML typically appears when the immune system is compromised and it has been postulated that it occurs as a consequence of the reactivation of the latent JC virus or due to an adaptive mutation that fosters infection of the CNS.[53,56,57]

Clinically, PML is characterized by sub-acute onset of neurological deficits, including cognitive, visual, and motor disorders. The MRI scan of the brain generally reveals bilateral, asymmetric sub-cortical lesions on the brainstem and cerebellum, hypointense in T2-weighted sequences and

FLAIR, without enhancement after the administration of contrast and without significant mass effect. In an appropriate clinical and radiological context, the diagnosis is clearly supported by PCR detection of DNA from the JC virus in the cerebrospinal fluid, with an approximate sensitivity of 80% and specificity exceeding 95%.[54,56,58] This test may begin by being negative, and in case of diagnostic suspicion, it is recommended that the test be repeated.[53,59]

The bases of the causal relation between exposure to natalizumab and PML are not known. On the other hand, the anti-migratory effect of natalizumab on T lymphocytes might interfere with the mechanisms of immune surveillance in the CNS, thereby allowing infection by the JC virus;[60] on the other hand, natalizumab increases the number of B and pre-B lymphocytes[61] in the bloodstream and of CD34+ haematopoietic progenitor cells,[62,63] which may act as a reservoir for the JC virus and facilitate its dissemination toward the CNS.[53,64-66]

There is currently no method for estimating the individual risk of PML or predicting its development.[66,67] Hence, it is critical for patients with MS treated with natalizumab to be closely monitored clinically to detect the possible appearance of PML early on. Moreover, a reference MRI scan of the brain should be available prior to beginning treatment and it should be repeated annually.[33,50] On the other hand, MS and PML are diseases that cause similar clinical and radiological alterations and an in-depth algorithm has been elaborated as a guide to the diagnostic evaluation of natalizumab-treated MS patients who present new neurological symptoms or when existing symptoms get worse (references 16 and 59).

There is no treatment for PML with proven efficacy, and the disease generally progresses to death, with the mean survival being 6 months.[68] Prior experience indicates that immune reconstitution is associated with better prognosis.[54,69] Consequently, this is considered a priority aim in the treatment of PML and, in patients who receive natalizumab, it is essential that the drug be withdrawn if PML is suspected. Since the biological effects of natalizumab may last for months, plasmaphoresis is one method to accelerate its elimination.[14] However, as previously explained, the efficacy of plasma exchange may be limited due to natalizumab's high affinity for α4 integrin, which could cause sustained immunosuppression despite having eliminated the drug from the circulation.

It is important to point out that the discontinuation of natalizumab in patients with MS and PML can be associated with an immune reconstitution inflammatory syndrome (IRIS) that can cause a serious worsening of the patient's status.[45,51,70] According to recent data, many patients in whom natalizumab was withdrawn due to PML and who underwent plasmaphoresis or immunoadsorption developed IRIS days to weeks after the procedure.[51] In these cases, steroid treatment may be considered to foster patient recovery.[70,71]

Effect of treatment withdrawal

The AFFIRM study carried out an analysis of disease activity after discontinuation of treatment in 51 patients treated with natalizumab and 27 who received placebo. In the natalizumab group, disease activity returned to levels comparable to pre-treatment levels without any rebound effect taken as an increase in disease activity compared to this period. Furthermore, patients treated with natalizumab did not get any worse than those who received placebo.[20] A later study investigated disease activity after treatment discontinuation in 23 participants from the AFFIRM and SENTINEL studies who had received a median of 30 doses of natalizumab, with clinical and radiological stability during 14 months of follow-up.[60,72] Finally, recent data regarding the follow-up of 946 participants in clinical trials support the idea that, after withdrawing prolonged treatment with natalizumab, disease activity returns to pre-treatment levels, but no higher, after 4 months.[73]

However, another study has suggested the existence of a radiological rebound effect, defined as an increase in the number of active lesions in T2-weighted sequences versus pre-treatment.[74] For some authors, this discrepancy may be due to the fact that, in the study in question, the rebound effect occurred mainly at the expense of patients who had received short treatment schedules (mean of 2 doses).[38,75] Nevertheless, a series of 7 patients has recently been described as receiving between 7 and 14 doses of natalizumab and in these, 3 months after treatment withdrawal, an altered mental state or fatigue was detected, without focal symptoms and with multiple gadolinium-enhancing lesions on the cerebral MRI (mean: 14; range: 8 to 21). Treatment with corticosteroids resulted in clinical and radiological resolution. The authors suggest that this phenomenon might be due to restitution of the lymphocytic flow in the CNS and propose the name CIRIS (CNS IRIS).[76] As a result, more studies are needed to establish the risk of a possible rebound effect after withdrawal of treatment with natalizumab and its relation with the number of doses administered.

Conclusion

Natalizumab is the first monoclonal antibody and the first selective inhibitor of leukocyte migration available for the treatment of MS. Several randomized, placebo-controlled clinical trials have demonstrated that natalizumab considerably reduces disease activity and improves the parameters of severity in patients with RRMS. Additional studies suggest that this drug is effective in the treatment of patients with suboptimal response to other immunomodulating treatments, and in patients with highly active forms of RRMS. It would be of great interest to have comparative data regarding natalizumab's efficacy versus other available treatment options, so as to be able to assess both efficacy and risk in relative terms. Nevertheless, in the absence of such studies, the data available are very favourable for natalizumab. As with other recombinant peptidic agents, natalizumab can induce the formation of specific persistent antibodies. This immunogenic reaction is associated with a loss of the drug's efficacy and increases the risk of hypersensitivity reactions. The incidence of other adverse effects is low. However, the appearance of several cases of PML in patients treated with natalizumab and other monoclonal antibodies indicates that the development of new drugs with more selective and possibly more efficacious

mechanisms of action may also be accompanied by an increased risk of potentially serious adverse effects, which mandates careful patient selection and the observance of specific action protocols.

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