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BRIEF REPORT

Assessment of the effectiveness and safety of natalizumab for treating relapsing-remitting multiple sclerosis☆

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KEYWORDS
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Abstract
Objective: Assessing the effectiveness and safety of natalizumab for treating relapsing-remitting multiple sclerosis in a tertiary hospital.
Method: Observational, prospective study of adult patients treated with natalizumab from May 2007 until February 2009. Treatment: 300 mg natalizumab every four weeks. Response criteria: assessment of disease progression, appearance of flare-ups and assessment of magnetic resonance images. Adverse reactions during treatment with natalizumab were recorded.
Results: Thirty patients (73%female); average age 34±8.4 years; mean baseline EDSS 3.4±1.3; number of flare-ups in the past year 2.1±1.2. Treatment was discontinued in five patients, due to refusal in one case, ineffectiveness in two cases and anaphylaxis in the other two cases. Fourteen patients completed one year of treatment with satisfactory results. A lower EDSS score by 36%, 47%, 31%, 54%and 28%was obtained at 3, 6, 9, 12 and 15 months of treatment respectively. The prevalence of relapse-free patients was 94%, 76%and 54%at 3, 6 and 12 months. MRI imaging studies in 11 patients one year after they began treatment showed no new lesions. Two patients suffered severe anaphylactic shock and another one had an outbreak of urticaria. The presence of neutralising antibodies was the reason for suspending treatment in 6.6%of the patients.
Conclusions: The treatment's effectiveness and safety in our patient group suggest that natalizumab is a treatment for refractory patients or those with aggressive types of multiple sclerosis, although we do not yet know about its long-term effects and the evolution of the appearance of neutralising antibodies.

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PALABRAS CLAVE
Natalizumab;
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Evaluación de la efectividad y la seguridad del natalizumab en el tratamiento de la esclerosis múltiple remitente recidivante

Resumen
Objetivo: Evaluar la efectividad y la seguridad del natalizumab en el tratamiento de la esclerosis múltiple remitente recidivante en un hospital de tercer nivel.
Método: Estudio observacional, prospectivo, de los pacientes adultos tratados con natalizumab desde mayo de 2007 hasta febrero de 2009. Tratamiento: natalizumab 300 mg cada cuatro semanas. Criterio de respuesta: valoración de la progresión de la enfermedad, aparición de brotes y evaluación de imágenes mediante resonancia magnética. Se han recogido las reacciones adversas durante el tratamiento con natalizumab.
Resultados: Treinta pacientes (el 73%eran mujeres); promedio de edad: 34 ± 8,4 años; escala expandida del estado de discapacidad medio basal: 3,4 ± 1,3, y número de brotes en el último año: 2,1 ± 1,2. Cinco pacientes suspendieron el tratamiento, uno por abandono del tratamiento, dos por ineficacia y dos por reacciones anafilácticas. Catorce pacientes completaron un año de tratamiento con resultados satisfactorios. Se obtuvieron reducciones de la escala expandida del estado de discapacidad del 36, el 47, el 31, el 54 y el 28%a los 3, los 6, los 9, los 12 y los 15 meses de tratamiento, respectivamente. La prevalencia de pacientes libres de recidiva fue del 94, el 76 y el 54%a los 3, los 6 y los 12 meses, respectivamente. Las imágenes de resonancia magnética al año de tratamiento correspondientes a 11 pacientes no mostraron nuevas lesiones. Dos pacientes sufrieron reacciones anafilácticas graves y otro sufrió una reacción urticarial. Un 6,6%de los pacientes presentó anticuerpos neutralizantes que motivaron la suspensión del tratamiento.
Conclusiones: La efectividad y la seguridad obtenidas en nuestros pacientes sugieren que el natalizumab constituye una alternativa para los pacientes refractarios o con formas agresivas de esclerosis múltiple, aunque falta conocer los efectos a largo plazo y la evolución de la aparición de anticuerpos neutralizantes.

Introduction

Multiple sclerosis (MS) is a recurrent chronic disabling neurological disease of the central nervous system (CNS). The lesions tend to be multiple and are distributed throughout the CNS.[1] MS is characterised by the development of inflammatory lesions in the brain and spinal cord, giving rise to areas of demyelination and axonal degeneration. Flare-ups or relapses are episodes of acute neurological dysfunction of at least 24 hours, although they sometimes evolves over days, and it take weeks to stabilise and subside.[2]

The Kurtzke Expanded Disability Status Scale (EDSS) is used to measure the progress of the disease, and scores dysfunction on a scale from 0 (absence of disability) to 10 (death), with intervals of 0.5. Magnetic resonance imaging (MRI) is an important advance that is used to rule out other diseases and establish the criteria for dissemination in space and time. The gadolinium-enhanced T1-weighted scan shows that the disease is active (rupture points in the blood-brain barrier can be observed) and the T2-weighted scan of hyperintense lesions allow for the assessment of the patient's lesion load.

Initial therapy is commonly based on interferon beta and/or glatiramer. Mitoxantrone, cyclophosphamide, intravenous corticosteroids and natalizumab are used for patients with relapsing-remitting multiple sclerosis (RRMS).

Natalizumab is a monoclonal antibody that blocks alpha 4 beta 1 integrin, an adhesion molecule that is expressed on the lymphocyte surface in a process necessary for the migration of peripheral blood lymphocytes into the CNS. Natalizumab is indicated for disease-modifying treatment in monotherapy for very active RRMS in patients with high disease activity despite treatment with interferon beta. It is also indicated for patients with rapidly evolving severe RRMS. Its use is contraindicated in combination with other drugs, and the possibility of pre-existing immunosuppression must be ruled out. In addition, a previous monitoring programme must be followed.[3,4] The aim of this study is to evaluate natalizumab effectiveness and safety in adult patients with RRMS in a tertiary hospital.

Method

Observational prospective study of adult patients with RRMS treated with natalizumab in a tertiary hospital from May 2007 to February 2009. Patients selected were those who had aggressive and rapidly evolving MS and had been unsuccessfully treated with conventional immunomodulatory

treatments. Demographic, diagnostic and clinical data was collected and stored in a database used in the daily practice for the monitoring of patients undergoing treatment with natalizumab. All treatments with natalizumab were approved by the *Comité Asesor para la Esclerosis Múltiple* (advisory committee for multiple sclerosis) of the regional health agency of Valencia in accordance with specific criteria. The efficacy of the treatment was monitored using the following clinical criteria: 1) patient's disability status using the EDSS at three, six, nine and twelve months; 2) decrease in the number of flare-ups or relapses during treatment; 3) evaluation of MRI images: gadolinium-enhanced T1-weighted images of lesions and T2-weighted images of hyperintense lesions.

Adverse reactions during the treatment were recorded along with the presence of neutralising antibodies (anti-natalizumab antibodies).

Results

The demographic and clinical characteristics of the patients are shown in Table 1. Thirty patients (73%women) received at least one dose of natalizumab during the study period (interval: 1-22). Patients were treated previously with conventional immunomodulatory drugs, 97%of the patients using one of the three interferon beta drugs, 37%using glatiramer acetate and 17%using mitoxantrone. Some 26% used three different types of drugs. One patient started treatment with natalizumab when he presented with an aggressively evolving inflammatory process. The patient responded satisfactorily until treatment was discontinued (patient left the country). MRI images were taken of all patients and these images confirmed MS lesions (lesions in characteristic plaques) before starting treatment with natalizumab and the appropriate regular controls. Patient immunocompetence was confirmed before starting the treatment. The presence of IgG in cerebrospinal fluid was observed in 25 patients, a characteristic finding for patients with MS, which confirms the inflammatory nature of the disease. Of the 30 patients, five discontinued treatment. One withdrew from treatment (the patient left the country) although the patient received eight cycles with good response and tolerance. Two patients discontinued treatment due to ineffectiveness and two for anaphylactic reactions in the second infusion. Fourteen patients completed one year of treatment with satisfactory results. The response to treatment measured using the EDSS and the appearance of flare-ups is shown in Table 2. Reductions were achieved in the EDSS, by 36%, 47%, 31%, 54%and 28% at three, six, nine, twelve and fifteen months of treatment, respectively. The prevalence of relapse-free patients was 94%, 76%and 54%at three, six and twelve months,

Table 1 Demographic and baseline clinical characteristics of patients in the study (n=30)

Characteristic		
Age, years (mean, SD, 95%CI)	33 (8.4) (16.2-49.8)	
Years from diagnosis l) (median, interva	9 (14-41)	
Age at diagnosis (mean, SD, 95%CI)	25 (7.1) (10.8-39.2)	
EDSS at the start of treatment		
	1-1.5	3
	2-2.5	5
	3-3.5	14
	4-5	5
	>5	3
Flare-ups over the last year		
	1	11
	2	11
	3	5
	>3	3

CI indicates confidence interval; EDSS, Expanded Disability Status Scale; SD, standard deviation.

Table 2 Effectiveness results (disability and flare-ups)

Characteristic	Value	No. of patients evaluated
EDSS, 3 months	2-2.5	10
n=27	3-3.5	7
	4-5	3
	>5	1
EDSS, 6 months	1-1.5	1
n=17	2-2.5	8
	3-3.5	6
	4-5	1
	>5	1
EDSS, 9 months	1-1.5	1
n=13	2-2.5	6
	3-3.5	5
	4-5	1
EDSS, 12 months	0	1
n=11	1-1.5	1
	2-2.5	5
	3-3.5	3
	>5	1
EDSS, 15 months	1-1.5	1
n=9	2-2.5	3
	3-3.5	4
	>5	1
No. of flare-ups, 3 months	No flare-ups	19
n=21	1	2
No. of flare-ups, 6 months	No flare-ups	13
n=17	1	4
No. of flare-ups, 12 months	No flare-ups	6
n=11	1	5

EDSS indicates Expanded Disability Status Scale.

respectively. The MRI images at one year corresponding to 11 patients did not show new lesions (gadolinium-enhanced lesions).

Two patients suffered severe anaphylactic reactions that required the permanent cessation of treatment. Another patient had an outbreak of urticaria requiring premedication with methylprednisolone, but which did not lead to the discontinuation of treatment. As for the appearance of anti-natalizumab antibodies, they were initially detected in three patients (10%). One of these patients showed ineffectiveness, another had a severe anaphylactic reaction in the second infusion, and the third patient continued with a good response since the antibodies disappeared after a few weeks. This meant that anti-natalizumab antibodies persisted in 6.6% of the patients.

Discussion

Natalizumab has a different mechanism of action, which makes it an alternative for patients refractory to conventional treatments. The patients studied were refractory to immunomodulatory drugs and had rapidly evolving RRMS,[4] which made them eligible for treatment with natalizumab, complying with the criteria of the NICE guidelines for natalizumab in RRMS.[4]

Two large clinical trials have shown the effectiveness of natalizumab in RRMS,[5,6] and although no trials have compared natalizumab against standard treatment, indirect analyses have been performed on natalizumab and interferon beta and glatiramer acetate that show favourable results for natalizumab.[4] Data on the efficacy and safety of natalizumab was compared, which was obtained from the AFFIRM clinical trial and from the systematic reviews for interferon beta and glatiramer. Natalizumab was associated with a statistically significant reduction in relapse rates, compared to interferon beta and glatiramer. There were no statistically significant differences in side effects between natalizumab and glatiramer. However, when compared with interferon beta, natalizumab showed a lower risk of flu-like reactions. In terms of efficacy, measured through MRI images, the AFFIRM trial concluded that natalizumab prevented the formation of new lesions.[7]

Data on the effectiveness achieved in our patients is promising, although the data should be regarded with caution since there were few patients who completed one year of treatment (response data is available for 11 patients). Natalizumab improved disability rates and reduced the number of flare-ups in tested patients, although the percentage of relapse-free patients decreased over months. This was not due to the diminishing effectiveness of natalizumab but rather to the lower number of patients tested. One patient's EDSS did not decline due to flare-ups prior to treatment with natalizumab which left unrecoverable sequelae.

After the FDA approved the use of natalizumab, three cases of progressive multifocal leukoencephalopathy (PML) were reported that caused the withdrawal of this drug two years after its initial marketing. PML is a severe demyelinating CNS disease that is caused by the reactivation of the JC polyomavirus in an immunosuppression context. After a study of the available safety and efficacy data, and once the risks had been assessed, the EMEA once again approved natalizumab for RRMS patients who had been unsuccessfully treated with interferon beta or were intolerant to it, and for those who had rapidly evolving aggressive forms of the disease. The manufacturing laboratory placed a warning in its datasheet that the possibility of pre-existing immunosuppression must be ruled out before starting therapy with natalizumab. It also warns against concomitant use of other immunosuppressive drugs and recommends having a recent MRI scan made so as to confirm the absence of lesions suggesting PML.[3]

In August 2008, the *Agencia Española de Medicamentos y Productos Sanitarios* (Spanish agency of drugs and healthcare products) issued an alert stating that the detection of a case of PML in Europe (not in Spain) did not change the risk-benefit of the drug under current authorised conditions. The alert also indicated how to avoid the development of PML.[8]

In terms of toxicity, two patients suffered severe adverse reactions related to the infusion, which resulted in the discontinuation of treatment (in one of these patients, the presence of anti-natalizumab antibodies was confirmed), but no patient experienced PML. Yoursy et al assessed the risk of suffering from PML in more than 3000 patients treated with natalizumab over an average of 17 months. Only three cases that were already previously known were confirmed as PML despite having studied suspicious cases. They therefore concluded that the risk of suffering PML was 1 in 1000 treated patients.[9] Other authors analysed the benefit of natalizumab compared to interferon beta-1a, assessing the reduction in relapses, the progression of the disease and risk of PML. They concluded that both drugs have similar benefits for MS patients and that the benefit obtained from natalizumab exceeded the risk of PML.[10] In patients previously treated with other immunomodulatory therapies, one must rigorously evaluate the patient's immune status before starting the administration of natalizumab to minimise the risk of developing opportunistic infections, including PML.[11]

In clinical trials, 10% of patients had anti-natalizumab antibodies, which persisted in 6% (positive in a new analysis performed at a minimum interval of six weeks). In our study, the data was similar since neutralising antibodies were initially detected in three patients but it was the cause of ineffectiveness and/or toxicity requiring the discontinuation of treatment in only two of them (6.6%).

The main limitations of this study were the limited number of patients assessed and, since this was an observational study, that the effectiveness and safety could not be adequately established due to the lack of a reference control group.

In conclusion, the effectiveness and safety achieved in these patients suggests that natalizumab can be used as an alternative treatment for refractory patients or for those suffering from aggressive MS. However, long-term effects and emergence of neutralising antibodies during treatment are yet to be properly assessed.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Ibarra O, Adévol M, Castillo I, Mora O, Ais A, Lovato E. Farmacoterapia ambulatoria: Farmacoterapia de la esclerosis múltiple. Curso de formación en farmacoterapia SEFH. Madrid: Aran; 2006.
2. García Merino JA, Blasco Quilez MR. Tratamiento farmacológico de la esclerosis múltiple. Inf Ter Sist Nac Salud. 2007;31:111-7.
3. Ficha técnica de Tysabri® [accessed 2009 Apr 6]. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tysabri/H-603-PI-es.pdf.
4. National Institute for Health and Clinical Excellence NICE. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. Technology Appraisal Guidance No. 127; 2007. Available from: www.nice.org.uk.
5. Polman C, O'Connor P, Havrdova E, Hutchinson M, Kappos L, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899-910.
6. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911-23.
7. Miller DH, Soon D, Fernando KT, MacManus DG, Barker GJ, Yousry TA, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology. 2007;68:1390-401.
8. Alerta del 14 de agosto de 2008 de la Agencia Española del Medicamento y Productos Sanitarios [accessed 2009 Jun 6]. Available from: http://www.agemed.es/actividad/alertas/usoHumano/seguridad/home.htm.
9. Yousry TA, Habil M, Major EO, Ryschkewitsch C, Fahle G, Fischer S, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006;354:924-33.
10. Dorsey ER, Thompson JP, Noyes K, Dick AW, Holloway RG, Schwid SR, et al. Quantifying the risk and benefits of natalizumab in relapsing multiple sclerosis. Neurology. 2007; 68:1524-8.
11. Gold R, Jawad A, Millar DH, Henderson DC, Fassas A, Fierz W, et al. Expert opinion: Guidelines for the use of natalizumab in multiple sclerosis patients previously treated with immunomodulating therapies. J Neuroimmunology. 2007;187: 156-8.