Natalizumab-related anaphylactoid reactions in MS patients are associated with HLA class II alleles

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ABSTRACT

Objectives: We aimed to investigate potential associations between human leukocyte antigen (HLA) class I and class II alleles and the development of anaphylactic/anaphylactoid reactions in patients with multiple sclerosis (MS) treated with natalizumab.

Methods: HLA class I and II genotyping was performed in patients with MS who experienced anaphylactic/anaphylactoid reactions and in patients who did not develop infusion-related allergic reactions following natalizumab administration.

Results: A total of 119 patients with MS from 3 different cohorts were included in the study: 54 with natalizumab-related anaphylactic/anaphylactoid reactions and 65 without allergic reactions. HLA-DRB1*13 and HLA-DRB1*14 alleles were significantly increased in patients who developed anaphylactic/anaphylactoid reactions ($p_{M-H} = 3 \times 10^{-7}$; odds ratio $[OR]_{M-H} = 8.96$, 95% confidence interval $[CI] = 3.40-23.64$), with a positive predictive value (PPV) of 82%. In contrast, the HLA-DRB1*15 allele was significantly more represented in patients who did not develop anaphylactic/anaphylactoid reactions to natalizumab ($p_{M-H} = 6 \times 10^{-4}$; $OR_{M-H} = 0.2$, 95% CI = 0.08–0.50), with a PPV of 81%.

Conclusions: HLA-DRB1 genotyping before natalizumab treatment may help neurologists to identify patients with MS at risk for developing serious systemic hypersensitivity reactions associated with natalizumab administration. *Neurol Neuroimmunol Neuroinflamm* 2014;1:e47; doi: 10.1212/NXI.000000000000047

GLOSSARY

CI = confidence interval; **HLA** = human leukocyte antigen; **MS** = multiple sclerosis; **NPV** = negative predictive value; **OR** = odds ratio; **PPV** = positive predictive value.

Similar to other biological agents, natalizumab, a highly effective therapy for multiple sclerosis (MS), can induce infusion-related hypersensitivity reactions. These reactions typically occur within 2 hours after infusion, with a peak at the second infusion, and range from urticaria, allergic dermatitis, and hives to more serious anaphylactic/anaphylactoid reactions in which treatment should be discontinued.[1] The incidence of systemic hypersensitivity reactions classified as anaphylactoid or anaphylactic was reported to be 0.8% in the AFFIRM trial[2] and ranged between 1.0% and 3.8% in more recent observational studies.[3–6]

An important number of drug hypersensitivity reactions are known to be mediated through interactions with human leukocyte antigen (HLA) molecules encoded within the major histocompatibility complex.[7] Based on this, in the present study we investigated whether the

development of anaphylactic/anaphylactoid reactions in patients with MS treated with natalizumab was associated with particular HLA class I and class II alleles.

METHODS Patients and HLA typing. Inclusion criteria were patients with MS treated with natalizumab who developed anaphylactic/anaphylactoid reactions within 2 hours after infusion between the second and eleventh administrations of natalizumab, which motivated natalizumab suspension. Patients fulfilled the clinical criteria for the diagnosis of anaphylaxis promulgated in the World Allergy Organization anaphylaxis guidelines.[8] Patients with MS who did not develop anaphylactic/anaphylactoid reactions during natalizumab infusions were used as controls.

Genomic DNA was extracted from peripheral blood samples using standard methods. HLA genotyping was performed by means of the PCR-SSOP Luminex method using Lifecodes *HLA-A*, *HLA-B*, *HLA-DRB1*, and *HLA-DQB* typing kits (Immucor Gamma Transplant Diagnostics, Inc., Heppignies,- Belgium) according to the manufacturer's instructions.

Statistical analysis. Statistical analysis was performed by using the SPSS 17.0 package (SPSS Inc., Chicago, IL). Comparisons of groups were analyzed using the χ^2 test of a Fisher exact test (when expected values were below 5). To calculate combined odds ratios (ORs) and 95% confidence intervals (CIs), we used the Cochran-Mantel-Haenszel method implemented in Review Manager RevMan v. 5.0 (The Nordic Cochrane Centre, Copenhagen, Denmark). *p* values <0.05 were considered statistically significant. The Der Simonian and Laird random effects model was used according to the results of the tests of heterogeneity. A sensitivity analysis was performed to test the relative influence of each study on the results. Studies were sequentially dropped, and the effect on the change in the overall degree of heterogeneity was determined.

Standard protocol approvals, registrations, and patient consents. The study was approved by the corresponding local ethics committees, and all patients gave their informed consent.

RESULTS A total of 119 patients with MS belonging to 3 different cohorts (French, n = 63; Spanish, n = 48;

German, n = 8) were included in the study. A summary of demographic and main clinical characteristics of patients with MS who participated in the study is shown in table 1. Information on anti-natalizumab antibodies was available for 27 (50%) of the 54 patients with MS who developed infusion-related anaphylactic/anaphylactoid reactions, and 22 patients (81.5%) were positive for anti-natalizumab antibodies.

Tables e-1, e-2, and e-3 summarize the distribution of HLA alleles in all the patients with MS included in the study. The frequency of carriers of the *HLA-DRB1*13* and *HLA-DRB1*14* alleles (the latter in almost complete linkage disequilibrium with *HLA-DQB1*05:03*) was significantly increased in patients who experienced anaphylactoid reactions compared to patients who did not develop drug-related allergic reactions (28/54 [52.0%] vs 6/65 [10.5%]; $p_{M-H} = 3 \times 10^{-7}$; OR_{M-H} [95% CI] = 8.96 [3.40–23.64]) (figure). In contrast, as depicted in the figure, the frequency of carriers of the *HLA-DRB1*15* allele (in almost complete linkage disequilibrium with *HLA-DQB1*06:02*) was significantly increased in the group of patients without allergic reactions to natalizumab compared to patients who developed anaphylactoid reactions (7/54 [13.0%] vs 29/65 [44.8%]; $p_{M-H} = 6 \times 10^{-4}$; OR_{M-H} [95% CI] = 0.2 [0.08–0.50]). In the European population, the frequencies of the *HLA-DRB1*15* and *HLA-DRB1*13/*14* alleles are 14% each.

Most probably these risk and protective HLA class II alleles conformed ancestral haplotypes with class I alleles, since the *HLA-DRB1*13* and *HLA-DRB1*14* alleles were frequently accompanied by *HLA-A*24*, and the *HLA-DRB1*15* allele by *HLA-A*03* or *HLA-B*07* (see tables e-2 and e-3). Nonetheless, the HLA class II alleles remained the best associated markers of

Table 1	Summary of demographic and baseline clinical characteristics of patients with MS treated with natalizumab included in the study					
	France		**Spain**		**Germany**	
Characteristics	AR	No AR	AR	No AR	AR	No AR
N	33	30	16	32	5	3
Age, y[a]	35.8 (6.3)	37.5 (9.0)	35.8 (8.3)	38.1 (7.1)	33.4 (4.8)	37.7 (8.7)
Female/male (% women)	30/3 (90.9)	21/9 (70.0)	12/4 (75.0)	23/9 (71.9)	4/1 (80.0)	2/1 (66.7)
Duration of disease, y[a]	8.9 (7.0)	10.2 (6.2)	8.7 (2.6)	11.7 (6.7)	7.8 (3.2)	6.7 (4.5)
EDSS score[b]	3.1 (1.5-4.0)	3.8 (3.0-5.0)	3.3 (2.0-4.4)	3.3 (2.0-4.0)	2.0 (1.5-2.5)	2.5 (2.0-3.0)
No. of relapses[c]	2.0 (1.0)	2.2 (1.0)	1.7 (0.9)	1.5 (1.0)	4.5 (0.7)	2.5 (2.1)

Abbreviations: AR = anaphylactic/anaphylactoid reaction; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.
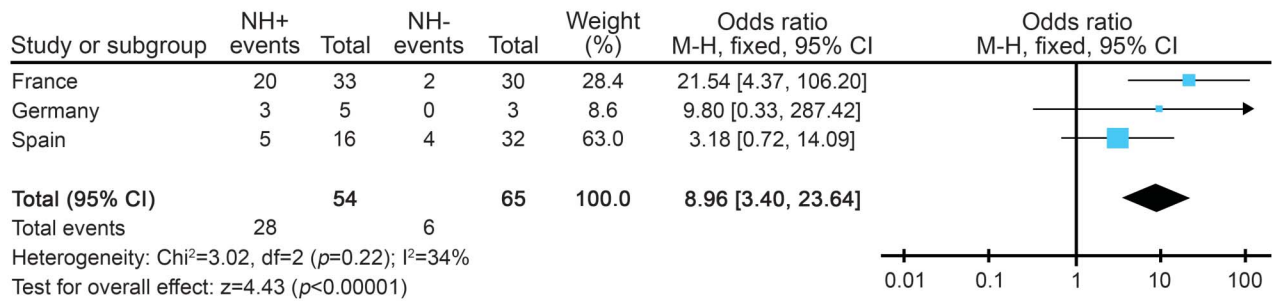Data are expressed as mean (SD) unless otherwise stated.
[a] Refers to age and disease duration at treatment onset.
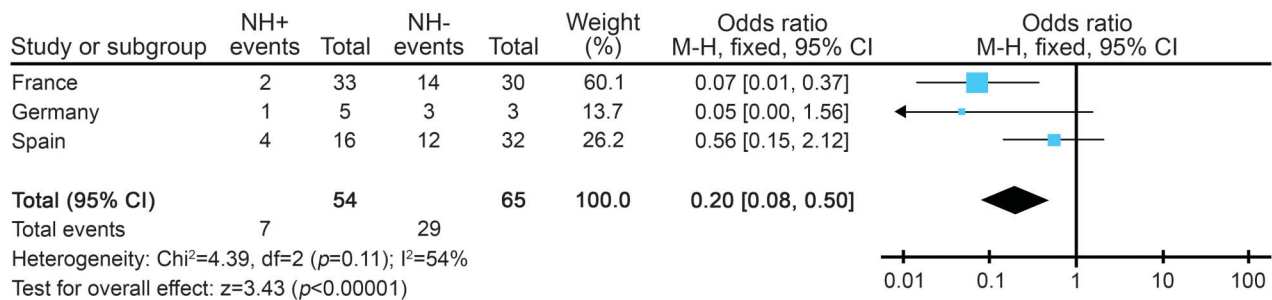[b] Data are expressed as mean (interquartile range).
[c] Refers to the number of relapses in the year before treatment onset. For the Germany cohort, information on relapses and EDSS is missing in 5 and 3 patients, respectively.

Meta-analysis showing the influence of *HLA-DRB1*13/*14* (A) and *HLA-DRB1*15* (B) in the development of anaphylactic/anaphylactoid reactions to natalizumab in the different study cohorts. Forest plots showing the overall data and data after eliminating heterogeneity by removing the Spanish cohort. CI = confidence interval; HLA = human leukocyte antigen; HN+/HN− = patients who developed and did not develop anaphylactic/anaphylactoid reactions, respectively; M–H = Mantel-Haenszel.

anaphylactic/anaphylactoid reactions to natalizumab, conferring the following positive and negative predictive values (PPV/NPV): PPV = 0.82/NPV = 0.69 for the *HLA-DRB1*13* and *14*, and PPV = 0.81/NPV = 0.57 for the *HLA-DRB1*15*.

DISCUSSION Two types of infusion-related hypersensitivity reactions have been described in patients with MS treated with natalizumab: type I allergic reactions, which usually occur within 2 hours after infusion,[1] and type III hypersensitivity reactions, which typically develop during several days.[9] Type I hypersensitivity reactions include serious systemic anaphylactic/anaphylactoid, with an incidence that has been reported to be near 4% in some observational studies.[3,6] When these hypersensitivity reactions are present, administration of natalizumab must be discontinued and patients should not be retreated.

Aiming to identify patients at risk for developing anaphylactic/anaphylactoid reactions to natalizumab, we performed HLA typing for class I and class II alleles in patients with MS from 3 different cohorts who were treated with natalizumab. The selection of the HLA region as the main target for genotyping was based on current evidence in the literature demonstrating significant associations between HLA and predisposition to adverse drug reactions.[7] Drug hypersensitivity reactions are supposed to be mediated by inappropriate T-cell activation, and the key proteins implicated in these responses are the HLA molecules. Several models have been proposed to explain the mechanisms whereby small synthetic compounds are recognized by T cells in an HLA-dependent manner, including the hapten/prohapten model, the altered peptide repertoire model, and the p-i model (pharmacologic interaction of drugs with immune receptors).[10] Examples of drug-induced hypersensitivity reactions influenced by the HLA are the reactions to the reverse-transcriptase inhibitor abacavir and the xanthine oxidase inhibitor allopurinol, which are mediated by HLA class I alleles, and the reactions to the reverse-transcriptase inhibitor

nevirapine and the first-line anticonvulsant carbamazepine, which are mediated by both HLA class I and class II alleles.[7,10]

Patients with MS carrying *HLA-DRB1*13* and *HLA-DRB1*14* alleles were at higher risk for developing natalizumab-related anaphylactic/anaphylactoid reactions compared to patients without allergic reactions, with an OR of 9 and a PPV of 82%. On the other hand, the *HLA-DRB1*15* allele, which is known to be the main genetic risk for MS, had a protective effect on the development of anaphylactic/anaphylactoid reactions, with an OR of 0.2 and a PPV of 81%.

Neutralizing antibodies against natalizumab are usually present in patients having type I hypersensitivity reactions.[11] In our study, 81% of the patients with MS who experienced anaphylactic/anaphylactoid reactions were positive for anti-natalizumab antibodies.

Based on these results, genotyping for the *HLA-DRB1* gene may be incorporated into clinical practice before initiating treatment with natalizumab to identify MS patients with increased (or decreased) risk for developing serious hypersensitivity reactions following IV administration of natalizumab. We suggest that patients with MS and *HLA-DRB1*13* and *HLA-DRB1*14* alleles be strictly monitored during natalizumab administration, maintaining a high index of suspicion for hypersensitivity reactions.

AUTHOR CONTRIBUTIONS

B. de la Hera: HLA genotyping, manuscript revision, statistical analysis and interpretation of the data. E. Urcelay: manuscript drafting and revision, study concept and design, contribution of patients and clinical data, statistical analysis and interpretation of the data. D. Brassat: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. A. Chan: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. A. Vidal-Jordana: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. A. Salmen: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. L.M. Villar: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. J.C. Álvarez-Cermeño: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. G. Izquierdo: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. O. Fernández: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. B. Oliver: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. A. Saiz: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. J.R. Ara: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. A.G. Vigo: HLA genotyping, manuscript revision, statistical analysis and interpretation of the data. R. Arroyo: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. V. Meca: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. S. Malhotra: manuscript drafting and revision, analysis and interpretation of the data. N. Fissolo: manuscript drafting and revision, analysis and interpretation of the data. A. Horga: manuscript revision, contribution of patients and clinical data. X. Montalban: manuscript revision, contribution of patients and clinical data, analysis and interpretation of the data. M. Comabella: manuscript drafting and revision, study concept and design, analysis and interpretation of the data, study supervision.

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