The genetics of natalizumab hypersensitivity

One learns to itch where one can scratch

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Many of the immune therapies that are currently approved or in development for patients with multiple sclerosis (MS) are potentially immunogenic recombinant proteins. Some of these proteins have amino acid substitutions, while others may differ from their endogenous counterparts by posttranslational modifications. Recombinant antibodies, including natalizumab, also induce immune responses that render them inactive and that cause some recipients to display a variety of symptoms that are discussed below. Even with the development of technologies that allow the development of fully humanized monoclonal antibodies, their immunogenicity could not be fully abolished.

With regard to immune responses to natalizumab, 2 curious phenomena can be discerned: (1) their incidence has substantially increased as the agent made its way through clinical development, and (2) the phenotype of hypersensitivity sensations is ill-defined.

The publication of an initial small placebo-controlled trial with natalizumab does not mention hypersensitivity reaction to natalizumab at all. Subsequently, several immune-related adverse events were reported in a phase 2 clinical trial. One out of 68 patients in the 3 mg/kg body weight natalizumab treatment group experienced an anaphylactoid reaction with urticaria and bronchospasm. In addition, there were 3 reports of serum sickness, one in each natalizumab treatment group and one in the placebo group. It is interesting that all 3 of these events occurred at a single study site. In one of the phase 3 trials (AFFIRM), 4% of natalizumab recipients had hypersensitivity reactions, including urticaria or generalized urticaria, allergic dermatitis, hypersensitivity, and 5 patients with anaphylactic or anaphylactoid reactions. The majority of reactions occurred on the second infusion. In the second phase 3 trial (SENTINEL), 1.9% of patients assigned a combination therapy of 2 potentially recombinant immunogenic proteins, natalizumab and interferon β-1a (Avonex), had a hypersensitivity reaction, 8 of which were isolated cases of urticaria. Despite the mostly benign outcomes from these hypersensitivity reactions, neurologists would like to be able to predict which of their patients is at risk. If a diagnostic test existed, a decision might be made to monitor these individuals more closely or to initiate another pharmacotherapy.

In the current issue of Neurology® Neuroimmunology & Neuroinflammation, de la Hera et al. investigated potential associations between human leukocyte antigen (HLA) class I and class II alleles and the development of anaphylactic or anaphylactoid reactions in patients with MS treated with natalizumab. A total of 54 patients with natalizumab-related anaphylactic or anaphylactoid reactions and 65 patients without allergic reactions recruited at 3 sites were included in the study. Information on anti-natalizumab idiopathic neutralizing antibodies (Nabs) that are frequently associated with infusion reactions was available in only half of the 54 patients with MS who developed infusion-related anaphylactic or anaphylactoid reactions, and 81.5% of patients were seropositive. There is no information on the antibody status of the other 65 patients. Overall, this lack of data makes the results of this study difficult to interpret.

A definition for anaphylactoid reactions is not provided, but anaphylaxis is described as a severe, potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance. The authors show that HLA-DRB1*13 and HLA-DRB1*14 alleles are significantly increased in patients who developed anaphylactic or anaphylactoid reactions. In contrast, the HLA-DRB1*15 allele is significantly more represented in patients who did not develop these reactions. The sample size was too small to address the question of whether those alleles
Hypersensitivity reactions to natalizumab are rare and usually not life-threatening. Many of these reactions are related to Nabs to natalizumab, which can easily be detected by standardized assays. Even if the findings of the study are replicated in an independent cohort and further studies elucidate the immunologic background that leads to the generation of anti-natalizumab Nabs, it seems unlikely that predictive genetic testing will ever become routine clinical practice.

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