Successful desensitization to natalizumab in a skin test - positive patient: a case report

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Key words
Desensitization, hypersensitivity reaction, monoclonal antibody, natalizumab.

Summary
Relevant interest has been focused on rapid desensitization for drug hypersensitivity and on its use for reactions to monoclonal antibodies. Natalizumab is a highly effective therapy for multiple sclerosis but its use can be limited by hypersensitivity reactions. Herein we present a case of a 36-year-old male patient with multiple sclerosis who started natalizumab therapy due to rapid neurological deterioration. During the second infusion he developed a reaction involving urticaria, erythema and angioedema. Natalizumab sensitization was demonstrated by a positive result on the intradermal test. The anti-natalizumab IgG neutralizing antibody assay was negative. Lacking any alternative, equally effective treatment, he underwent a rapid intravenous desensitization protocol. Desensitization was successfully repeated eleven times and the patient's neurological conditions improved and remained stable after one year. This case demonstrates that rapid desensitization is a safe and effective procedure in the treatment of natalizumab hypersensitivity.

Introduction
Natalizumab is a humanized monoclonal antibody against the cellular adhesion molecule α4-integrin which is highly effective in multiple sclerosis (MS) therapy. In a pivotal clinical trial hypersensitivity reactions occurred in about 4% of the patients leading to discontinuation of the therapy and persistent serum anti-natalizumab antibodies appeared in up to 6% of patients, closely associated with an increase in infusion-related adverse events and an almost complete loss of effectiveness (1, 2). Delayed, serum sickness-like, type III reactions associated with early formation of neutralizing antibodies were also described (3). Delayed infusion reactions, clinically resembling a serum sickness reaction, can also occur in anti natalizumab antibody-negative patients (4).

To date, only one case of IgE-mediated hypersensitivity reaction to natalizumab has been described. It was diagnosed by means of a positive result on the intradermal test, by the detection in serum of specific IgE to natalizumab, and by immunoblot studies (5). In case of drug induced hypersensitivity reactions, desensitization protocols can be applied to induce a state of tolerance to the culprit drug in patients in whom alternatives are not available or are less effective (6). Since the tolerant state is temporary, for treatments with interval infusion like biologics, the procedure must be repeated for every new course and rapid protocols have been developed. Candidate patients for rapid desensitization to monoclonal antibodies include those who present type I hypersensitivity, mast cell/IgE-dependent reactions, and those who present anaphylactoid reactions during the in-
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fusion or shortly afterwards. The symptoms include pruritus, flushing, urticaria, angioedema, respiratory and gastrointestinal distress, hypotension and shock (7). Herein we describe a case of immediate hypersensitivity reaction to natalizumab in a patient with skin test positivity who successfully underwent rapid desensitization.

Case report

A 36-year-old male patient with MS started natalizumab therapy due to rapid neurological deterioration, in spite of immune modulating treatments expended in the previous years. During the second natalizumab infusion he developed a hypersensitivity reaction with urticaria, erythema and angioedema. Prompt interruption of the infusion and intravenous steroid treatment resolved the reaction. The anti-natalizumab IgG neutralizing antibody assay was negative. His medical history was negative for allergic diseases and spontaneous urticaria. The total IgE level was 698 IU/mL. Skin prick test with a battery of common inhaled allergens (ALK-Abelló) was negative. Two months after the reaction, a skin prick test with natalizumab solution (3 mg/mL) was performed and yielded negative results. We then performed the intradermal test starting by injecting 0.03 mL of a 1:1000 dilution of the natalizumab solution (0.003 mg/mL) prepared with saline and obtained a positive result. Then we proceeded to inject ten-fold diluted solutions obtaining a positive reaction until a 10-6 dilution. Histamine at 10 mg/dl was used as positive control for skin prick test. Saline was the negative control for the intradermal test. Reactions were considered positive when the size of the initial wheal increased by 3 mm or greater in diameter after 15-20 min and was associated with a flare (8). Skin prick test and intradermal test with 1:1000 dilution of natalizumab solution were performed in five not exposed subjects with negative results. Lacking any alternative treatment with similar clinical efficacy, in order to continue natalizumab administration, we adapted a rapid desensitization protocol previously used for other monoclonal antibodies (9). Three solutions were delivered in 12 consecutive steps, each step increasing the rate of drug administration by 2-2.5 fold (Tab. 1). To reach the target dose (300 mg), the remainder of solutions 1 and 2 was infused at the end in order not to modify the twelve step incremental dosing. This protocol allowed us to avoid preparing an exceeding dose of drug. Premedication with chlorpheniramine (10 mg) and ranitidine (50 mg) was administered intravenously 20 minutes before the initiation of the protocol. Three days after the first desensitization we repeated the intradermal test for natalizumab and the result was still positive. Desensitization was completed successfully eleven times at monthly intervals. A skin reaction occurred at the final step of the first infusion, less severe than the previous one. The infusion was stopped and the reaction was treated with histamine H1 blockers and corticosteroids. After resolution, the desensitization was completed by lengthening the step before the one at which the reaction occurred, and the highest rate of infusion of the final step was reduced to 60 ml/h. During the following infusions, two other skin reactions occurred at the final step. They were milder than the first one and resolved with histamine H1 blockers. No reactions occurred during the last six desensitizations. After the first infusion the patients neurological conditions significantly improved and remained stable over the time.

Discussion

Hypersensitivity reactions to natalizumab are a growing problem because of the high level of efficacy of this novel biologic agent in the therapy of relapsing-remitting MS, particularly for patients, as the one described here, resistant to multiple treatment regimens. Recently, induction of tolerance to natalizumab was reported in 3 patients (10). To our knowledge, this is the first report of desensitization to natalizumab in a skin test positive patient. Although the detection in serum of specific IgE to natalizumab has not been performed, the positivity of the intradermal test, also at very high dilutions, suggests that an IgE-mediated mechanism could be responsible for the reaction. An association with anti-natalizumab neutralizing antibodies was excluded. The absence of neutralizing anti-natalizumab antibodies should be verified before desensitization, as they are associated with a substantial reduction in the efficacy, altering the benefit-risk profile of the procedure (2, 10).
the possibility of a reaction must be kept in mind at each desensitization. However, as previously shown for other monoclonal antibodies (9), reactions during desensitization were less severe than the initial one. They occurred at the final step of the desensitization regimen. The treatment of the reaction and a modification of the protocol with a lengthening of the final step permitted the completion of the desensitization.

The efficacy of treatment of underlying diseases should be studied after applying desensitization protocols (6). The present case shows that the rapid desensitization protocol did not alter the efficacy of natalizumab. The treatment led to a significant clinical improvement that was sustained after one year.

In conclusion, in the case of immediate hypersensitivity reaction to natalizumab, the skin test and the IgG neutralizing antibody assay are useful to help understand the underlying mechanism and to define the indication to desensitization when an alternative treatment is not available. The present case shows that a patient with an immediate hypersensitivity reaction to natalizumab and skin test positivity can be safely and effectively treated by rapid desensitization.

References

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