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Mult Scler published online 28 May 2012
DOI: 10.1177/1352458512448269

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Desensitization to natalizumab: clinical and immunological observations

We have written these brief observations with reference to the paper by Camacho-Halili et al.¹ regarding desensitization for hypersensitivity reactions (HRs) during natalizumab (NZB) therapy.

Our single case report presents some differences from American cases such as evaluation of allergic reaction and administration of the therapy.

HRs occur in 4% of NZB-treated multiple sclerosis (MS) patients and result in the definitive discontinuation of therapy.² Our 36-year-old male MS patient, who previously underwent disease-modifying therapy (DMT), shifted to NZB because of rapid neurological deterioration. During his last year of DMT he showed a mild itchy erythema with an IgE value of 590 KU/I. A skin prick test with a battery of common inhalant allergens was negative.

The first NZB infusion was carried out without any problems. During the second NZB infusion, an HR with diffuse rash, facial angioedema and itch (grade II severity reaction, CTCAE, 2010)³ required immediate discontinuation of NZB. Intravenous anti-H2 and steroids were administered and the problem resolved. Successive anti-NZB IgG neutralizing antibody determination was negative.

Allergological evaluation was performed by skin prick and intradermal testing according to standardized procedures⁴ and to reported experience during therapy with monoclonal antibodies.^{5,6} Skin prick test with NZB solution (3 mg/l) was negative. The intradermal test was performed by first injecting 0.03 ml of a 1:1000 dilution (0.003 mg/ml) with saline and obtained a positive result up to a 10⁻⁶ dilution. Skin prick tests and intradermal tests with a 1:1000 dilution of NZB solution were performed on five non-exposed subjects. Negative results were observed.

We then adopted a desensitization protocol from Brennan's experience⁴ but during the first three desensitizations, two HRs occurred consisting of mild itching rash (grade I severity). To avoid HR recurrence, we decreased the infusion rate from 80 to 60 ml/h in the last step (12°) of the following administrations. No further HRs occurred. The HRs were

always associated with a total IgE value >600 KU/l. Progressive reduction of total IgE level was observed in the successive desensitizations.

Based on our experience, we underline that in order to diagnose an IgE-mediated mechanism of the reaction, both the prick test and the intradermal test must be performed since the latter is more sensitive. Detection of specific IgE to NZB could be the confirmatory proof. Moreover, slowing the infusion rate, reducing the critical mass of antigen load and the massive formation of IgE–Ag–mast cell complexes, can ensure the success of desensitization.

Summarizing, we suggest:

- classification of the reaction by multiple tests (prick test, intradermal test, specific IgE);
- slowing the infusion rate in case of HR during desensitization.

Finally, the relationship between total IgE levels and the occurrence of allergic events that we observed in our patient is interesting, since total IgE levels could predict specific IgE production⁷ and because IgE antibody concentration and specific activity affect effector cell degranulation.⁸ Therefore, a progressive reduction of total IgE levels could be linked to a successful desensitization.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflicts of interest in preparing this article.

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