



Letter

Successful desensitization to natalizumab using a 1-solution protocol

Natalizumab is a humanized IgG4 monoclonal antibody against the α_4 -subunit of integrin $\alpha_4\beta_1$ (VLA4 [very late antigen 4]), which is expressed on activated T cells. Antagonism of this target is thought to interfere with leukocyte adhesion to the vascular wall, thereby interfering with leukocyte trafficking across the blood brain barrier and reducing the inflammation within the central nervous system. Natalizumab is indicated for the treatment of relapsing-remitting multiple sclerosis.

Most common adverse events related to natalizumab are nausea, headache, and fatigue. Progressive multifocal leukoencephalopathy is the more severe complication of natalizumab therapy. It is a debilitating and often fatal neurologic condition caused by infection of the brain by JC virus.¹

Both immediate and delayed reactions to this drug has been described.^{2,3} Mechanisms of these reactions are not completely elucidated, but some immediate reactions fulfill criteria to be managed as type 1 allergic reactions. Desensitization to this agent has also been described in at least 4 patients, using the 3-solution protocol described by Castells et al.⁴ We present a case report of an immediate reaction to natalizumab managed by desensitization using a 1-solution protocol.

A 39-year-old nonatopic woman and with no prior history of drug reactions was referred to our drug allergy unit for adverse reaction to natalizumab. She had been diagnosed with relapsing-remitting multiple sclerosis at the age of 22 years and had been undergoing natalizumab therapy (300 mg intravenously per month) for 36 months. In the last session, she presented with itching and generalized urticaria at the end of the infusion. She received treatment with dexchlorpheniramine and hydrocortisone, 100 mg, with completed recovery.

Skin prick testing with natalizumab was performed at 20 mg/mL and intradermal testing at 0.02, 0.2, and 2 mg/mL, with negative results. Antinatalizumab IgG antibody test results were negative, total IgE level was 2.19 IU/mL, and basal tryptase level was 3.65 μ g/L.

Desensitization procedure was programmed with the 1-solution protocol that is used in our hospital for chemotherapy agents and monoclonal antibodies.⁵ One vial of 300 mg/15 mL of natalizumab was diluted in 100 mL of saline serum. Infusion was initiated at 5 mL/h and stepped up at 15-minute intervals to 10, 25, 50, 75, and 100 mL/h until the complete volume was administered. Premedication with dexchlorpheniramine, 6 mg, and ranitidine, 50 mg, intravenously was administered 30 minutes before beginning the procedure.

Desensitization was performed in our allergy unit by an allergist and nurse trained in desensitization. In the first procedure, the patient presented with mild rash on her back and arms 20 minutes after the infusion was finished. It was resolved

with dexchlorpheniramine. For the following sessions, we added aspirin (200 mg orally on breakfast since the day before) and cetirizine (10 mg every 12 hours since 3 days before the procedure) to the premedication. No other changes in the desensitization protocol were made. Natalizumab was administered 2 more times with excellent tolerance, but the neurologist advised stopping the treatment because she had 3 risk factors for progressive multifocal leukoencephalopathy: she had been undergoing natalizumab therapy for more than 36 months, she had JC virus infection (index, 2.36), and she had received prior treatment with interferon beta.

Hypersensitivity and/or infusion reactions were described in the natalizumab clinical trials. Both immediate and delayed reactions were previously described. A total of 9% of patients in the natalizumab arm of AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Relapsing Multiple Sclerosis) study² presented with some type of infusion-related reaction, including urticaria, pruritus, or flushing. These reactions were more frequent in patients who had antinatalizumab antibodies. These antibodies are associated with reduced clinical efficacy and infusion-related reactions. The SENTINEL (Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing-Relapsing Multiple Sclerosis) study found a similar association.⁶

There are reports of mild or moderate delayed reactions that have been successfully treated with steroids and reduction of infusion rate.³ Camacho-Halili et al⁷ described 3 patients with immediate reaction who were desensitized using a 3-solution, 15-step protocol. No patients presented with antinatalizumab antibodies, and skin prick test results were negative in 2 patients and borderline in 1 patient. All 3 patients received 60 mg of prednisone as premedication. A single case report by Bignardi et al⁸ reported a positive intradermal test result for natalizumab. A 36-year-old, male, atopic patient received 11 natalizumab doses using a 3-solution, 12-step protocol. He had mild reaction in the last step of the first 3 desensitizations. In this case only antihistamines and ranitidine were used as premedication. After the first reaction, the protocol was modified by lengthening the step before the one at which the reaction occurred and reducing the final rate of infusion.

Our patient received a more rapid 1-solution protocol, which has been used in our hospital in more than 50 oncologic patients with good results.⁵ Most desensitization protocols for parenteral drugs use 3 or more solutions to induce tolerance. However, Hong et al⁹ reported, in their 2012 review, that 1 patient was successfully desensitized to cetuximab using a 1-solution protocol similar to ours. Another series of 12 patients desensitized with a 1-solution protocol has been recently described for antineoplastic agents.¹⁰ Besides this, in the series by Brennan et al¹¹ of 105 desensitizations to monoclonal antibodies using Castells 3-bag, 12-step protocol, almost all reactions occurred with the last solution (70% in the last step). In addition, they

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.10.009>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

did not report any reaction in the first 7 steps of the protocol, including solution 1 and 3 first steps of solutions 2.¹¹ Our patient reaction occurred after finishing the last step.

We tried to avoid premedication with corticosteroids if possible because these patients are undergoing immunosuppressant treatment and they receive frequent steroids bolus to treat relapses. The use of aspirin as premedication to prevent skin symptoms is well documented for chemotherapy agents and monoclonal antibodies.¹² It is thought to work by using aspirin ability to suppress the production of prostaglandins. In our patient, aspirin allowed the readministration of the drug with the same protocol, with no reactions and avoiding corticosteroids. In conclusion, we present a rapid and safe protocol that allowed natalizumab therapy to be continued.

Eva Pérez-Rodríguez, MD*

Miguel Ángel Hernández-Pérez, MD†

Juan Antonio Martínez-Tadeo, MD*

*Service of Allergy and Clinical Immunology
Nuestra Señora de la Candelaria University Hospital
Santa Cruz de Tenerife, Spain

†Service of Neurology
Multiple Sclerosis Unit
Nuestra Señora de la Candelaria University Hospital
Santa Cruz de Tenerife, Spain
evperrod@gobiernodecanarias.org

References

- [1] Fernandez O. Best practice in the use of natalizumab in multiple sclerosis. *Ther Adv Neurol Disord*. 2013;6:69–79.
- [2] Polman CH, O'Connor PW, Havrdova E, et al. A randomized placebo controlled trial for of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354:899–910.
- [3] Hellwig K, Schimrig S, Fischer M, et al. Allergic and non allergic infusion reactions during natalizumab therapy. *Arch Neurol*. 2008;65:656–658.
- [4] Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122:574–580.
- [5] Pérez-Rodríguez E, Martínez-Tadeo JA, Pérez-Rodríguez N, et al. Desensitization to antineoplastic drugs: experience of 225 procedures in 51 patient. *Allergy*. 2016;71(suppl 102):146.
- [6] Vennegoor A, Rispens T, Strijbis E, et al. Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis. *Mult Scler*. 2012;19:593–600.
- [7] Camacho-Halili M, George R, Gottesman M, Davis-Lorton M. An approach to natalizumab hypersensitivity: a case series of induction of tolerance. *Mult Scler*. 2011;17:250–253.
- [8] Bignardi D, Ribizzi G, Voltolini S, Serrati C, Troise C. Successful desensitization to natalizumab in a skin test- positive patient: a case report. *Eur Ann Allergy Clin Immunol*. 2012;44:26–29.
- [9] Hong D, Bankova L, Cahill KN, Kyin T, Castells M. Allergy to monoclonal antibodies: cutting edge desensitization methods for cutting edge therapies. *Expert Rev Clin Immunol*. 2012;8:43–54.
- [10] Vidal C, Méndez-Brea P, López-Freire S, et al. A modified protocol for rapid desensitization to chemotherapy agents. *J Allergy Clin Immunol Pract*. 2016;4:1003–1005.
- [11] Brennan PJ, Rodríguez Bouza T, Ida Fsu F, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol*. 2009;124:1259–1266.
- [12] Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol*. 2009;102:155–160.