
Rapid Desensitization to Adalimumab Is Associated With Decreased Basophil Sensitivity

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Adalimumab is a fully human recombinant monoclonal antibody against TNF- α that is used mainly in inflammatory diseases such as Crohn disease and ulcerative colitis. Immediate hypersensitivity reactions to this molecule have been reported and may be local or systemic, ranging from pruritus to anaphylaxis [1]. Rapid subcutaneous desensitization to adalimumab has been undertaken by several teams and appears to be an effective management approach, especially in patients with no obvious alternative therapeutic options [2-5]. Rapid drug desensitization protocols for patients who experience hypersensitivity reactions consist of incremental, step-by-step administration of the full therapeutic doses of the eliciting drug [6]. Despite the absence of consensus on the appropriate protocol, particularly for subcutaneous drugs, the few cases reported in literature validate the concept. Here, we report that successful desensitization to adalimumab in 2 patients is associated with a decrease in basophil sensitivity, which we monitored using the basophil activation test (BAT).

Patient #1 was a 30-year-old woman with severe Crohn disease diagnosed 12 years ago. She experienced severe urticarial lesions at the injection site within 1 hour of the first injection of adalimumab (40 mg). This was a new course after a 6-year interruption of treatment (colectomy surgery, pregnancy). Patient #2 was a 38-year-old woman with severe ulcerative colitis diagnosed 10 years ago. She reported urticarial lesions at the injection site within 1 hour of the fifth injection of adalimumab (40 mg). For both patients, the results of prick testing with adalimumab were negative (100 mg/mL), although intradermal testing at 1:1000 (injection of 0.02 mL of

a 0.1 mg/mL solution) was positive at 20 minutes, suggesting IgE-mediated sensitization. Both patients were referred to the dermatology department to undergo rapid desensitization to adalimumab. Given the lack of consensus on rapid drug desensitization, protocols were established in line with the severity of the initial reactions in these patients. On the first day, patient #1 underwent a 9-step desensitization protocol, with administration of the drug at 30-minute intervals, until a cumulative dose of 54.3 mg was reached (0.005 mg, 0.05 mg, 0.5 mg, 1.25 mg, 2.50 mg, 5 mg, 10 mg, 15 mg, and 20 mg). This protocol was repeated every week, decreasing the number of injections to reach only 1 injection of the therapeutic dose (40 mg) at visit #10. Patient #2 underwent a 9-step protocol on the first day (0.005 mg, 0.05 mg, 0.5 mg, 1.25 mg, 2.5 mg, 5 mg, 5 mg, 10 mg, and 15 mg, every 30 minutes) until a cumulative dose of 39.30 mg was reached. The protocol was repeated every 2 weeks, again decreasing the number of injections to 1 injection (40 mg) at visit #12, and tolerance was good.

We report the performance of BAT in the assessment of the allergic nature of reactions to adalimumab (Supplementary file) using the 2 most common markers of activation/degranulation, namely, CD203c and CD63. Before the beginning of the desensitization protocol, BAT with adalimumab was strongly positive in both patients, according to the maximal percentage of activated basophils (ie, CDmax, which is related to basophil reactivity). We validated the specificity of this *in vitro* reaction

by testing 4 patients treated with adalimumab and found that tolerance was good in all 4 cases. All 4 patients had a negative BAT result for adalimumab (Supplementary file). Another parameter of BAT, CDsens, was recently reported to be correlated with basophil sensitivity [7-9]. CDsens is defined as $1/LC_{50} \times 100$, where LC_{50} is the lowest concentration of allergen enabling 50% of maximum activation of basophils. We therefore investigated CDsens during the rapid desensitization protocol to adalimumab in both patients. BAT was repeated 3 times (visits 1, 2, and 3 for patient #1, ie, before the protocol, at 3 weeks and 6 weeks after the beginning; and visits 1, 3, and 5 for patient #2, ie, before the protocol, at 6 weeks and 10 weeks after the beginning) (Figure). Despite the increasing clinical tolerance to adalimumab, BAT remained strongly positive. Indeed, CDmax remained constant (Figure) for both patients based on both markers (CD63 and CD203c), suggesting stable reactivity of basophils to adalimumab. However, we observed a reduction in CDsens with the 2basophil activation/degranulation markers, thus reflecting decreased sensitivity of the basophils in both patients. To our knowledge, this is the first demonstration that rapid drug desensitization is associated with modifications in basophils, displaying a higher activation threshold over the course of the injections.

The pathophysiological mechanisms associated with rapid drug desensitization remain unclear. *In vitro* experiments and *in vivo* mouse models have shown that increasing doses of an antigen lead to prolonged hyporesponsiveness to the triggering

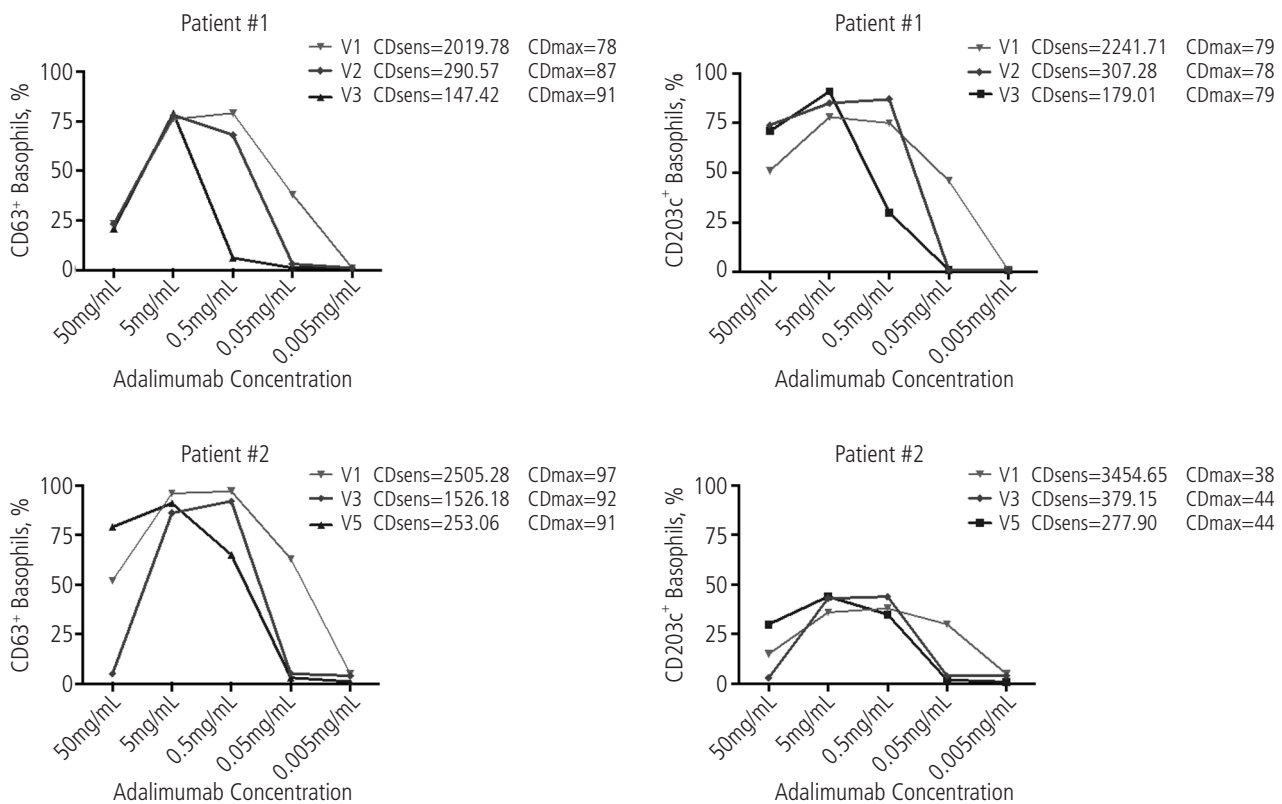


Figure. Basophil activation test enabling monitoring of rapid desensitization to adalimumab. Results of BAT for the 2 study patients expressed as CD63 (left) and CD203c (right) during the rapid desensitization protocol (at V1, V2, and V3 for patient #1 and V1, V3, and V5 for patient #2). CDsens and CDmax are specified for each test.

dose of the desensitizing antigen [6]. Recently, BAT was shown to be a potential biomarker for rapid drug desensitization, and Giavina-Bianchi et al [10] demonstrated that BAT remains positive upon sequential injection of the drug. Here, we show that, despite the stability of CDmax, rapid drug desensitization is associated with a decrease in CDsens, demonstrating for the first time an *in vivo* impact of such protocols on the sensitivity of human basophils. These exciting preliminary data must be confirmed in larger studies and will help to improve our understanding of the immunological mechanisms associated with the clinical success of rapid drug desensitization.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Singh S, Pardi DS. Update on anti-tumor necrosis factor agents in Crohn disease. *Gastroenterol Clin North Am*. 2014;43:457-78.
2. Bavbek S, Ataman Ş, Akıncı A, Castells M. Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients. *J Allergy Clin Immunol Pract*. 2015;3:629-32.
3. Gutiérrez Fernández D, Foncubierta Fernández A, Anguita Carazo JL, Fernández Meléndez S, Fernández Anguita MJ, Medina Varo F. Adalimumab desensitization protocol in a patient with a generalized urticarial reaction and angioedema following adalimumab administration. *J Investig Allergol Clin Immunol*. 2014;24:273-5.
4. Rodríguez-Jiménez B, Domínguez-Ortega J, González-Herrada C, Kindelan-Recarte C, Loribo-Bueno P, Garrido-Peño N. Successful adalimumab desensitization after generalized urticaria and rhinitis. *J Investig Allergol Clin Immunol*. 2009;19:246-7.
5. Quercia O, Emiliani F, Foschi FG, Stefanini GF. Adalimumab desensitization after anaphylactic reaction. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2011;106:547-8.
6. Castells Guitart MC. Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. *J Investig Allergol Clin Immunol*. 2014;24:72-9.
7. Johansson SGO, Nopp A, van Hage M, Olofsson N, Lundahl J, Wehlin L, et al. Passive IgE-sensitization by blood transfusion. *Allergy*. 2005;60:1192-9.
8. Chapuis A, Thevenot J, Coutant F, Messaoudi K, Michaud E, Pereira B, et al. Ara h 2 basophil activation test does not predict clinical reactivity to peanut. *J Allergy Clin Immunol Pract*. 2018;6:1772-4.
9. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol*. 2015;135:179-86.
10. Giavina-Bianchi P, Galvão VR, Picard M, Caiado J, Castells MC. Basophil Activation Test is a Relevant Biomarker of the Outcome of Rapid Desensitization in Platinum Compounds-Allergy. *J Allergy Clin Immunol Pract*. 2017;5:728-36.

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