Rapid Desensitization to Adalimumab Is Associated With Decreased Basophil Sensitivity

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Abstract: Rapid subcutaneous desensitization to adalimumab has been reported to be an effective management option. Monitoring this protocol using basophil activation test, we report here that desensitization is associated with a decrease of basophil sensitivity.

Key words: adalimumab, rapid desensitization, basophil activation test, CDsenS
Adalimumab is a fully human recombinant monoclonal antibody against TNF-α, largely used in inflammatory diseases, such as Crohn disease or ulcerative colitis. Immediate hypersensitivity reactions to this molecule have been described, either local or systemic, ranging from pruritus to anaphylaxis (1). Rapid subcutaneous desensitization to adalimumab has been reported by several teams, and appears to be an effective management option, especially in patients without other obvious therapeutic options (2–5). Rapid drug desensitization protocols consist in administrating, in the patients who experienced hypersensitivity reactions, full therapeutic doses of eliciting drug, in an incremental manner, step by step (6). Despite no precise consensus exists today concerning the protocol to use, particularly for sub-cutaneous drugs, the sparse cases reported in literature validate the concept. Here, we report that successful desensitization to adalimumab of two patients is associated with a decrease of the basophil sensitivity, that we have monitored using basophil activation test (BAT).

The patient #1 is a 30 years old woman, who presents a severe Crohn disease, diagnosed 12 years ago. She experienced severe urticarial lesions at the injection site within one hour of the first injection of adalimumab. This was a new course after a 6-year interruption of treatment (colectomy surgery, pregnancy). The patient #2 is a 38 years old woman, suffering from a severe ulcerative colitis, diagnosed 10 years ago. She reported urticarial lesions at the injection site within one hour of the fifth injection of adalimumab. For both patients, prick tests to adalimumab were negative but intradermal test at the concentration of 1:1000 was positive at 20 min, suggesting an IgE sensitization. These two patients were addressed to the dermatology unit to benefit from rapid desensitization protocols to adalimumab. Given the lack of consensus on rapid drug desensitization, protocols have been established in line with the severity of inaugural reactions in these two patients. Patient #1 received for her first cure day a nine-step desensitization protocol, every 30 minutes reaching a cumulative dose of 54,3mg (respectively: 0,005mg, 0,05mg, 0,5mg, 1,25mg, 2,50mg, 5mg, 10mg, 15mg and 20mg). This protocol was repeated every week, decreasing the number of injections to reach only one injection (40 mg) at the visit #10. Patient #2 beneficiated from a nine-step protocol for the first day (0,005mg, 0,05mg, 0,5mg, 1,25mg, 2,5mg, 5mg, 10mg and 15mg) with a cumulative dose of 39,30 mg. The protocol was repeated every two weeks, decreasing there again the number of injections to one injection (40 mg), at the visit #12 with a good tolerance.

We first report the performance of BAT in the assessment of allergic nature of the reaction (Fig. 1A), using the two most commonly used markers of activation/degranulation: CD203c and CD63. Before the beginning of the desensitization protocol, BAT to adalimumab were indeed strongly positive in both patients, according to the maximal percentage of activated basophil (i.e. CDmax, related to basophil reactivity). We validated the specificity of this in vitro reaction by testing four patients treated with adalimumab with a good tolerance. They all display
negative BAT to adalimumab (Fig. 1A). Recently, another parameter of basophil activation test, the CDsens, was described to be correlated to basophil sensitivity (7,8). CDsens is defined as 1/LC50 x 100, where LC50 is the lowest concentration of allergen giving 50% of the maximum activation of basophils. We thus interested ourselves to investigate CDsens along the rapid desensitization protocol to adalimumab in the two patients. We thus repeated basophil activation testing three times (visits 1, 2 and 3 for the patient #1, i.e. before the protocol, at 3 weeks and 6 weeks after the beginning; and visits 1, 3 and 5 for the patient #2, i.e. before the protocol, at 6 weeks and 10 weeks after the beginning) (Fig. 1B). The first finding was, despite the increasing clinical tolerance to adalimumab, BAT remains strongly positive. Indeed, CDmax remain constant, for both patients, using both marker (CD63 or CD203c). However, we observed a diminution of the CDsens parameter, reflecting a diminution of the sensitivity of the basophils, in both patients, with the two basophil activation/degranulation markers. To our knowledge, this is the first demonstration that rapid drug desensitization is associated with modifications on basophils, displaying a higher activation threshold along the injections.

Pathophysiological mechanisms associated to rapid drug desensitization are not fully understood today. In vitro experiments and in vivo mouse models have shown that increasing doses of an antigen lead to prolonged hyporesponsiveness to triggering dose of the desensitizing antigen (6). Recently, BAT has been shown to be a potential biomarker for rapid drug desensitization, and Giavina-Bianchi et al. have demonstrated that BAT remains positive upon sequential injection of drug (9). Here we show that, despite the stability of CDmax, rapid drug desensitization is associated to a decrease of CDsens, demonstrating for the first time an impact in vivo of such protocols on the sensitivity of human basophils. These preliminary exciting data have now to be confirmed on larger studies, and will help to a better understanding of immunological mechanisms associated to the clinical success of rapid drug desensitization.
References:


Figure legend:

Fig. 1: Basophil activation test allows monitoring of rapid desensitization to adalimumab. A. Results of basophil activation test (BAT) to adalimumab, expressed in percentage of maximal activation (CDmax), either using CD63 (left) or CD203c (right), for the two patients (P#1 and P#2) and 4 controls tolerating adalimumab (C#1, C#2, C#3 and C#4). B. Results of BAT for the two patients (up and down), expressed in CD63 (left) and CD203c (right), along the rapid desensitization protocol (at V1, V2 and V3 for the patient #1 and V1, V3 and V5 for the patient #2). CDsens is precised for each test.
A. CD max (CD63) (%) vs. Adalimumab concentration

B. Patient #1
- V1 CD\text{sens}=2019.78
- V2 CD\text{sens}=290.57
- V3 CD\text{sens}=147.42

Patient #2
- V1 CD\text{sens}=3454.65
- V3 CD\text{sens}=379.15
- V5 CD\text{sens}=277.90