

A New Pediatric Protocol for Rapid Desensitization to Monoclonal Antibodies

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Established Facts

- Hypersensitivity reactions to chemotherapeutic agents and monoclonal antibodies are common and may limit further therapeutic options.
- Drug desensitization aims to induce a temporary clinical tolerance to drug antigens.

Novel Insights

- Clinical success was demonstrated of a new protocol of rapid desensitization in a patient affected by ulcerative colitis who had developed anaphylaxis to infliximab.
- Rapid desensitization to monoclonal antibodies with a standardized 13-step protocol is safe and effective in a pediatric patient.

Key Words

Drug desensitization · Infliximab · Ulcerative colitis · Hypersensitivity reactions

Abstract

Monoclonal antibodies are important therapeutic tools, but their usefulness may be limited when patients experience acute hypersensitivity reactions. Patients reporting a history of adverse allergic reaction are likely to discontinue their therapeutic protocol or be switched to an alternative drug, which is sometimes less effective than that originally prescribed. Drug desensitization has proven to be a highly effective strategy to readminister a drug in a patient who has

experienced a hypersensitivity reaction. It involves forcing the patient's immune system to accept and tolerate the allergen. Nevertheless, such a procedure is still empiric for monoclonal antibodies and not common in the pediatric population. The aim of our study is to demonstrate the clinical success of a new protocol of rapid desensitization to infliximab in a pediatric patient affected by ulcerative colitis, who developed an anaphylaxis to the drug. We used a protocol of rapid desensitization consisting of 13 steps, with the first being 1/1,000,000 of the cumulative and total dose. Such a protocol has proven to be able to induce a temporary tolerance to infliximab, allowing the patient to achieve complete control of his disease.

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Introduction

Monoclonal antibodies (mAbs) are rapidly becoming a standard therapy in the treatment of several diseases. For the most part they are well tolerated. However, a subset of patients may experience hypersensitivity reactions (HSRs) following the administration of these drugs. The symptoms of HSRs range from mild (fever, rash, pruritus) to severe, including severe life-threatening anaphylaxis. Reactions may occur at the first dose or after repeated exposure. Skin tests with the offending agent may be negative, suggesting that the mechanism of the reported reaction is not necessarily IgE dependent. HSRs represent a treatment impediment that may nevertheless be bypassed through desensitization. In fact, such a technique allows a patient to temporarily 'tolerate' a medication that has previously induced a HSR.

Case Report

A 14-year-old patient affected by a severe form of ulcerative colitis (UC) experienced an anaphylactic reaction involving the skin and the respiratory system at the third treatment with infliximab, 15 min after the start of therapy. The administered dose was of 5 mg of infliximab per kg (total dose 250 mg). After the first reaction, the patient underwent an allergy workup. Skin tests to infliximab (skin prick test at 10 mg/ml and intradermal test at 1 mg/ml) were negative, while a provocation test to the drug was positive 6 min after the administration of the first dose (2.5 mg, 0.1% of the total dose; fig. 1). The patient developed an anaphylactic reaction, similar to the original one. The reaction included dyspnea, bronchospasm and angioedema of the face. After the reaction, tryptase levels were normal, while histamine levels had doubled compared to basal (0.9 ng/ml before and 1.96 ng/ml after the provocation test). We also tested the patient's serum, performing a basophil activation test (BAT). BAT is a procedure used to diagnose immediate-type hypersensitivity. It allows the evaluation of the activation of basophils upon allergen stimulation. The activation response may be measured at a single-cell level by using fluorochrome-bound mAbs to the specific activation markers CD63 and CD203c. When a patient experiences a reaction, basophil degranulation makes CD63 and CD203c appear on the cell surface [1]. For the BAT procedure, we used fresh whole blood and the drug concentrations were 10 mg/ml with three dilutions: 1:5, 1:25 and 1:125. Negative results were obtained for the first and the second concentrations, while a borderline result was obtained for the 1:125 dilution.

In our patient, we established that desensitization was the only way to reintroduce the culprit drug. We used a 13-step protocol in which the final cumulative dose of infliximab was 250 mg, and the first was 1/1,000,000 of the total dose. We tripled the dose at each step, every 15 min (table 1). Rapid desensitization was not interrupted by any adverse reactions and the patient tolerated the drug. He has already received his treatment three times since we introduced this new protocol, and each time he undergoes the protocol to tolerate the drug without experiencing any adverse symptoms.

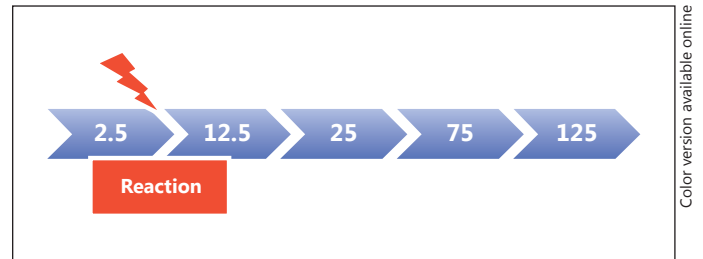


Fig. 1. Doses for the infliximab oral provocation test, in milligrams. The provocation test to the drug was positive 6 min after the first dose (2.5 mg, 0.1% of the total dose).

Table 1. Rapid desensitization protocol to induce infliximab tolerance in our patient

Infusion number	Dose administered, mg	% of therapeutic dose
1	0.00025	1/10 ⁶
2	0.00075	3/10 ⁶
3	0.0025	1/10 ⁵
4	0.0075	3/10 ⁵
5	0.025	1/10 ⁴
6	0.075	3/10 ⁴
7	0.25	1/10 ³
8	0.75	3/10 ³
9	2.5	1/10 ²
10	7.5	3/10 ²
11	25	1/10
12	75	3/10
13	140	1/2

We used a 13-step protocol in which the first dose was 1/1,000,000 of the total dose. The dose was tripled at each step, every 15 min. The rate of administration was 12.5 mg/h.

Discussion

HSRs to chemotherapeutic drugs, including mAbs, may require the discontinuation of the provoking medication, thereby raising a dilemma for the caregiver since further use could precipitate a severe and even fatal allergic reaction, but alternative drugs might be poorly tolerated or much less effective compared with the preferred agent [2, 3]. Infliximab is a chimeric IgG1k mAb that binds with high affinity and specificity both to the soluble form and to the membrane-bound TNF- α . Infliximab is used both for induction and maintenance of remission in Crohn's disease, and in the treatment of UC. Desensitiza-

Table 2. Desensitization regimens for infliximab allergy: different protocols of infliximab desensitization

Study	Protocols of infliximab desensitization	Patients, n	Outcome
Puchner et al. [5] (2001)	11-step protocol First dose: Patient 1: 0.002 mg Patient 2: 0.003 mg Final dose: Patient 1: 80 mg Patient 2: 160 mg Infusion rate: the dose was doubled every 15 min Time period: 4 h	2	Successful desensitization
Duburque et al. [17] (2006)	11-step protocol Solution 1: dilution of 2×10^{-3} mg/ml/kg in the first 4 steps Solution 2: dilution of 0.2 mg/ml/kg in the remaining 7 steps Infusion rate: every 15 min Time period: 2 h 45 min	14	7 patients (50%) achieved a complete remission
Brennan et al. [2] (2009)	12-step, three-bag protocol First dose: 0.0118 mg Final dose: 553,609 mg Infusion rate: every 15 min Solution 1: 0.024 mg/ml Solution 2: 0.24 mg/ml Solution 3: 2.38 mg/ml Time period: 5 h 40 min	23	Successful desensitization HRs during 29% of the desensitizations: 27 mild reactions 1 moderate reaction 2 severe reactions

tion may be performed in cases of HSRs to infliximab [4, 5]. Drug desensitization is defined as the induction of a temporary state of tolerance to a drug, which may be maintained only through continuous administration of the medication responsible for the HSR. Increasing doses of the implicated drug are administered over a short period of time, until the therapeutic dose is achieved and tolerated [6, 7].

In UC corticosteroids are effective for short-term treatment, but up to 45% of pediatric patients develop corticosteroid dependence in the subsequent year, which puts them at risk for corticosteroid-free inactive disease at 12 months [8]. Infliximab is safe and effective, inducing a response at week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy [9–12]. Unfortunately, repeated use of the medication has been associated with the development of immediate and delayed HSRs, and may limit the utility of this medication over time. Acute reactions constitute the most common type of reaction observed with TNF- α inhibitors [13, 14]. For acute infusion reac-

tions, several desensitization protocols have been successfully applied [15]. Protocols vary in the duration taken to achieve a therapeutic dose, ranging from a few hours to several weeks [16, 17] (table 2). The Brigham and Women's Hospital Rapid Drug Desensitization Program (BWH) devised a 12- to 20-step standard protocol based on an in vitro mouse mast cell model, in which unresponsiveness to a triggering antigen dose was achieved by delivering doubling doses of antigen at fixed time intervals starting at 1/1,000 of the final dose [18]. The most commonly used protocol has 12 steps, using three solutions at escalating rates. Patients who have had severe anaphylactic reactions to the agent of choice or who have reacted early in the standard 12-step desensitization may experience fewer symptoms if desensitized using a 16-step protocol, which adds another bag containing 1/1,000th of the full dose. The use of a 16-step (four bags) or a 20-step (five bags) protocol is reserved for high-risk patients. It was also observed that 70% of reactions during desensitization occurred during the 12th and final step of the standard 12-step protocol [1].

Mast cells and possibly basophils are supposedly the cell targets for rapid desensitization. Once mast cells and basophils are sensitized with specific IgE to medications, exposure to the allergen medication can cause the sudden systemic release of inflammatory mediators from activated mast cells, leading to anaphylaxis. We considered anaphylaxis as a rapid reaction suggesting allergy and affecting at least 2 different organs (for example, urticaria and bronchospasm) with or without hypotension. Hypotension was defined as a decrease of 30%, or as a 30-mm Hg lowering of systolic blood pressure when compared to normal values [19]. Rapid drug desensitization is a process by which mast cells are rendered hyporesponsive to a medication allergen by providing a temporary state of tolerance for drug hypersensitive patients, protecting them from anaphylaxis [20]. Three nonmutually exclusive hypotheses explaining how rapid drug desensitization might impair mast cell activation have been articulated: (1) depletion of activating signal transduction components such as syk kinase, (2) subthreshold depletion of mediators and (3) internalization of FcεRI through progressive cross-linking at a low antigen concentration [21–23]. The release of granule mediators such as β-hexosaminidase and the metabolism of arachidonic acid products such as prostaglandins and leukotrienes were inhibited by desensitization.

The case report we described reflects a typical systemic immediate adverse reaction to the drug. Symptoms occurred within the first 30 min after the medicament intake [24] and the provocation test was positive 6 min after administration of the first dose. Nevertheless, we should rule out the possibility of an IgE-mediated HSR, since tryptase levels did not increase after the reaction. Moreover, skin prick tests with infliximab resulted negative. The borderline BAT result obtained at the 1:125 dilution did not allow us to reach a conclusion for the reaction experienced by the patient. It has to be underlined, however, that BAT results cannot be considered as specific and sensitive enough to reach a firm diagnosis, and we ran the test primarily for research purposes.

Therefore, we suppose that the child's reaction to infliximab was IgG mediated. It has recently been highlighted that a high percentage of patients who had an acute infusion reaction (defined as a reaction occurring within 1 h of infusion initiation) were found to have positive IgG antibodies to infliximab [13]. In the literature there are a few studies showing that all the biological agents, such as infliximab, have the ability to induce the development of specific antidrug antibodies that are mostly represented by the IgG isotype [25]. On the whole, even though we believe in an IgG-mediated reaction, we cannot rule out the possibility of a nonallergic form of hypersensitivity, such as a nonspecific histamine release. In fact, while the tryptase values did not change, histamine levels increased after the reaction [26].

The protocol used for our patient has already been used at the Montpellier University Hospital in France to induce the tolerance of patients to a chemotherapeutic drug, such as docetaxel, with success in most cases [27]. Using the same protocol, we validated it in pediatrics as well by demonstrating that we were able to induce temporary tolerance to infliximab in a case with a previous HSR to the mAb. Unlike other desensitization protocols in which the final dose is often much more important than the previous one, our protocol shows an approximately 3-fold dose increase with each step. We believe that this could be helpful in preventing HSRs that may occur when the final dose is administered. Our protocol for infliximab still needs to be further tested, but it is currently the first available protocol for desensitization to mAbs reported in the literature. Therefore, our DSS schedule may represent a possible new approach to mAbs hypersensitivity, even in pediatrics.

Disclosure Statement

No conflict of interest to declare.

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