

Effective Desensitization to Tocilizumab in Delayed Hypersensitivity Reaction

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Keywords

Tocilizumab · Desensitization · Delayed hypersensitivity

Abstract

We present tocilizumab desensitization of a 47-year-old woman affected by rheumatoid arthritis with full body delayed erythematous urticarial reaction. Skin test for tocilizumab gave cutaneous reaction after 6 h at 20 mg/mL. The schedule of desensitization was then adapted for non-immediate reaction. We prepared a desensitization procedure reaching the cumulative dose of 516 mg in 5 weeks. After 6 months, the repetition of skin tests had a negative result, with demonstration of tolerance induction. Today the patient has good control of the disease. © 2018 S. Karger AG, Basel

Background

Rheumatoid arthritis daily therapy needs 3 major strategies: symptomatic drugs (NSAIDs-corticosteroids); disease-modifying anti-rheumatic drugs

(DMARDs; methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine); and biological drugs (Bdmards).

In the recent years, biological therapy has completely changed rheumatoid arthritis treatment. Many employed drugs are tumor necrosis factor (TNF) inhibitors such as infliximab, etanercept, adalimumab, golimumab, certolizumab.

Tocilizumab is an interleukin 6 receptor inhibitor and it is the drug of choice in rheumatoid arthritis, usually applied in combination with methotrexate, if other DMARDs and TNF alpha blockers have proven to be ineffective or have not been tolerated [1]. It can be used as a monotherapy for patients who do not tolerate methotrexate. The drug slows down the progression of the disease and can improve physical function of patients.

On the other hand, a clinical problem in biological therapy may be the onset of drug-induced immunogenicity. The host immune system can generate autoantibodies to the drug; this kind of adverse reaction can reduce the clinical effects of the drug and enhance the side effects. This mechanism caused inefficacy of the therapy in 40% of cases [2].

Table 1. Desensitization schedule

Week	Weekly dose, mg	Steps	Incremental dose, mg	Cumulative dose, mg
1	8.8	2	0.8+8	8.8
2	28	2	8+20	36.8
3	80	2	40+40	116.8
4	160	2	80+80	276.8
5	240	3	80+80+80	516.8
8	560	1	560	
12	560	1	560	

Biologicals drugs can elicit IgE-mediated immediate reaction or not-immediate reactions [3–5].

We can observe the following: acute infusion reactions, delayed infusion reactions, and injection site reactions.

Acute infusion reactions include mainly cutaneous symptoms, but anaphylaxis may occur. In some cases, patients may display fever or myalgia.

Delayed reactions usually occur within the first 2 weeks after the administration with symptoms like exanthems, fever, urticaria, arthralgia, myalgia, and itching. Injection site reactions are characterized by erythema, swelling, itching, or infiltrated claque.

Recently the diagnosis of allergic reactions was standardized for etanercept and adalimumab by the identification of non-irritant concentration (NIC) for skin tests [6]. Finally, NIC for tocilizumab skin test was observed [7].

We also found experiences about rapid desensitization for etanercept and adalimumab and 2 cases for tocilizumab [8–9], but in literature only case reports about desensitization in not-immediate reactions exist, and it does not exist in any case for tocilizumab.

Case Report

We present the clinical case of a 47-year-old woman affected by rheumatoid arthritis. In 2008, she was diagnosed with rheumatoid arthritis. Then, she underwent DMARDs therapy with hydroxychloroquine, and later salazopyrine, with poor clinical response.

In 2011, the patient begins MTX that suspends after a few months for a rise in transaminases concentration in the bloodstream; in 2012, she experienced low tolerance and poor clinical response with leflunomide.

Because of the persistence of the disease activity (Disease Activity Score: DAS 28 score >5.1) in 2013, the patient began biological therapy with infliximab at a dose of 3 mg/kg preceded by pre-med-

ication (prednisone 20 mg IV, paracetamol 500 mg, and oral antihistamine H1).

After 8 days, she developed erythematous urticarial reaction which was widespread in the full body.

One month after the resolution of dermatitis, the patient underwent therapy with tocilizumab 8 mg/Kg with premedication (methylprednisolone 20 mg, paracetamol 500 mg, cetirizine 20 mg).

In this occasion, the patient had a clear improvement of arthritis with DAS 28 score <2.6.

The month after that, the patient received a second infusion of tocilizumab 8 mg/Kg, with premedication.

Eight days later, the patient had developed also underarm and gluteus dermatitis after tocilizumab therapy. The erythematous urticarial reaction was widespread in the full body.

So, after allergist consultation, the patient undergoes skin test for tocilizumab with 4 healthy controls (in 2013, the NIC for the drug was not present in the literature [7]).

The patient had cutaneous reaction after 6 h at 20 mg/mL (NIC) The skin test was negative at this concentration in 4 healthy controls.

The schedule of desensitization was adapted for non-immediate reaction.

Desensitization Procedure

We prepared a weekly scheme with premedication (steroids, antihistamine, acetaminophen; Table 1).

We reached the cumulative dose of 516 mg in 5 weeks.

In the second month, we administered the dose of 560 mg in 2 steps in a day, with premedication.

In the third month, we administered a single dose of 560 mg with premedication and we continued monthly for 3 months, stopping premedication in the 4th month.

The patient then continues the therapy monthly with 560 mg of tocilizumab.

After 6 months, the repetition of skin tests had a negative result, with demonstration of tolerance induction.

Today the patient received this treatment with a good control of the disease (DAS 28 <2.6) and without allergic side effects.

Discussion

Several biological agents have been introduced into the drug market and more are emerging. Unfortunately, they may occasionally induce complete cellular and humoral immune responses, the main clinical consequences of which are drug hypersensitivity and loss of treatment response. Procedures for management of biological agents-induced reactions, including de-

sensitization, are becoming available in the clinical setting.

The knowledge of desensitization procedures may be useful to increase the safety profile of these drugs.

Hypersensitivity to tocilizumab is not rare. There is a need for allergological tests *in vivo* and *in vitro*.

This study is the first in the literature regarding desensitization for tocilizumab in case of non-immediate reactions.

Statement of Ethics

The patient have given his informed written consent and the study protocol was approved by the ethics committee.

Disclosure Statement

The authors of the present article declare that they have no conflicts of interest

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