

Successful rapid tocilizumab desensitization in a patient with Still disease

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Clinical Implication

- We report a rapid desensitization procedure for tocilizumab in a case of refractory adolescent onset Still disease. Our observation suggests that graded tocilizumab administration is feasible and allows its delivery after hypersensitivity reaction.

TO THE EDITOR:

Still disease is frequently refractory to standard therapy. Tocilizumab, an anti-IL-6 receptor antibody, has demonstrated efficacy and safety in a series of Still disease.¹ We report the case of a 16-year-old girl admitted to our department for the treatment of a refractory Still disease with pulmonary involvement. In 2009, the patient was evaluated for the abrupt onset of fever, arthritis, pharyngitis, and a maculopapular rash with hepatosplenomegaly and diffuse adenopathy. Results of blood tests revealed an increased blood ferritin concentration with an increased glycosylated fraction of ferritin. Hematologic, infectious, and autoimmune disorders were excluded, and the diagnosis of Still disease was given.

Despite high-dose corticosteroids, methotrexate, and anakinra, she still had arthralgia with uncontrolled inflammation. She developed an interstitial pneumonitis with diffuse interlobular thickening, ground-glass opacities, and pleural effusion with precapillary pulmonary hypertension. After a collegial discussion, it was decided to introduce tocilizumab as a treatment for Still disease. Clinical and biologic improvement was observed after the first infusion, with reduced pain, reduced C-reactive protein level, and decreased glycosylated fraction of ferritin.

The second infusion was performed 4 weeks later. Unfortunately, 10 minutes after the initiation of the second infusion, the patient experienced grade 2 hypersensitivity, according to the World Allergy Organization grading system,² with nausea, tachycardia, pruritus, urticaria, and angioedema with mouth edema. Tocilizumab was interrupted. All the symptoms disappeared a few hours after stopping the infusion. Anakinra was reintroduced in association with azathioprine, but the disease was not controlled.

Skin prick testing with tocilizumab, at the concentration of 4.8 mg/mL, was positive. The diameter of the wheal was 6 mm, and the diameter of the erythema was 11 mm. A positive reaction was defined as a wheal with a diameter at least 3 mm larger than produced by the negative control (diluent). A histamine skin prick test, at the concentration of 10 mg/mL, was used as a positive control. Skin prick tests performed in 8 controls with 4.8 mg/mL tocilizumab were uniformly negative. Due to the severity

TABLE I. A 5-step rapid desensitization protocol for tocilizumab

Concentration (mg/mL)	Rate of infusion (mL/h)	Time (min)	Volume infused (mL)	Dose administered at this step (mg)	Cumulative dose (mg)
4.8	8	0	4	20	20
4.8	17	30	8	40	60
4.8	33	60	17	80	140
4.8	58	90	29	140	280
4.8	83	120	42	200	480

of the symptoms, the failure of alternative treatments, and the efficacy of tocilizumab, we decided to perform a rapid desensitization procedure for tocilizumab. Written informed consent was obtained. The patient was premedicated 1 hour before the perfusion with 5 mg dexchlorpheniramine and 60 mg methylprednisolone as previously described.³ Tocilizumab (8 mg/kg [ie, 480 mg]) was given intravenously with a 5-step rapid desensitization protocol within 150 minutes (Table I). The first dose was 20 mg (4.1% of the total dose). There was no incident during the desensitization procedure. Every 3 weeks, perfusions were given with the same protocol, with an excellent tolerance. Unfortunately, she presented a severe recurrence of Still disease and tocilizumab was definitively stopped for failure to control the disease.

Still disease is a rare systemic inflammatory disorder of unknown etiology. It typically manifests as a triad of symptoms that include high-spiking fever, a characteristic rash, arthritis, and increased concentration of acute-phase reactants, including serum ferritin. Pleuritis is the most common pulmonary manifestation. Pathogenesis remains unclear. However, cytokine-mediated inflammation may be responsible for the features of the disease, and a role for IL-6 has been suggested.⁴ Analysis of recent data suggests that tocilizumab may have some efficacy in the treatment of refractory Still disease¹ and adult-onset Still disease.⁵ Tocilizumab usually is well tolerated, with transient neutropenia, mild and transient elevated transaminases, hyperlipidemia, and acute infusion reaction being rarely reported. Anaphylaxis is unusual, being reported in 0.13% of the patients in a recent Japanese series.⁶

To our knowledge, this is the first reported case of successful rapid tocilizumab desensitization. Because of the grade 2 hypersensitivity symptoms, tocilizumab was given with an higher starting dose than those reported in the protocols published by Castells et al.⁷ For higher hypersensitivity grades, we suggest to begin with lower doses (1 mg/mL). Rapid desensitization, by using the divided incremental steps protocol under medical supervision, is an effective tool for the safe administration of vital drugs in patients sensitized to induce a state of tolerance.⁷ Our observation suggests that graded tocilizumab administration is feasible and allows the delivery of tocilizumab after hypersensitivity reaction when there are no alternative therapeutics.

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