Hypersensitivity reactions to tocilizumab: role of skin tests in diagnosis

Sr., Tocilizumab (TCZ) is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody that binds to circulating soluble IL-6R and membrane-expressed IL-6R. This inhibits IL-6 binding to both forms of IL-6R and blocks the pro-inflammatory effects of IL-6 [1]. TCZ is approved in Europe and the USA for the treatment of moderate to severe RA in adult patients who have responded inadequately or been intolerant to previous therapy with one or more DMARDs or TNF inhibitors [1]. The most common adverse reactions to TCZ are infections and gastrointestinal symptoms [2]. However, increased therapeutic use of this monoclonal antibody in RA has disclosed other side effects.

Recently, delayed hypersensitivity reactions to TCZ have been described. These were analysed by means of skin biopsies, showing CD4+ T cells as well as eosinophil infiltration in the upper dermis [3, 4]. Among hypersensitivity reactions, anaphylaxis has also been reported [5]. Thus it is important to define simple and reliable diagnostic tests for patients who have experienced hypersensitivity reactions to TCZ. Our aims were to analyse the frequency of hypersensitivity reactions in patients treated with TCZ and to evaluate the role of skin tests in the diagnosis. In the Clinical Immunology and Rheumatology Units of Pisa University, 72 patients were treated with TCZ during 2005–13. Among them, we studied five patients [four females, one male; mean age 50 years (s.d. 10.79, range 31–62)] with hypersensitivity reactions to TCZ defined as previously reported [6]. Written consent was obtained from the patients according to the Declaration of Helsinki. The Ethics Committee of the University Hospital, Pisa approved the study. Commercial TCZ was used for skin prick tests (SPTs) (0.2, 2 and 20 mg/ml) and intradermal tests (IDTs) (0.002, 0.02, 0.2, 2 and 20 mg/ml). These concentrations were found to be non-irritant in 10 healthy subjects. A wheal area ≥3 mm was considered positive compared with the negative control (saline solution). Histamine was used as a positive control. SPT results were evaluated after 15 min and IDT after 20 min. Anti-histamine treatment was discontinued 5 days before testing and steroids 10 days. The patients were evaluated 15–72 months after the reaction.

Among the 72 patients treated, 20 discontinued TCZ treatment: 7 for the development of side effects, 7 for inefficacy, 5 for hypersensitivity reactions and 1 for remission of the disease; 1 patient died for unrelated reason. Among the five patients with hypersensitivity reactions, four experienced anaphylaxis and one pruritus. All the reactions were classified as immediate (within 20 min of the infusion). According to the grade, one of the reactions was mild, one was moderate and three were severe. Before starting TCZ, all the patients were treated with DMARDs and biologic agents. Patients’ demographic and clinical characteristics are reported in Table 1. TCZ was tested in all the patients who developed hypersensitivity reactions and in three patients who discontinued the treatment for inefficacy. Positive reactions to TCZ were observed by IDT in three of the four patients who developed anaphylaxis (Table 1). Interestingly, the three patients with positive tests experienced anaphylaxis after the second infusion. Among the five patients with hypersensitivity reactions to TCZ, one had a previous hypersensitivity reaction to adalimumab and one to anakinra. In contrast, the three patients who discontinued the treatment for inefficacy had negative results. The only patient with anaphylaxis that had a negative result for the skin test was tested 3 years after the last infusion.

In this study we report our experience with hypersensitivity reactions to TCZ in systemic autoimmune diseases and evaluate the potential role of skin tests in the diagnosis of these reactions. No reaction was observed at the first infusion and all the reactions were observed within 20 min, suggesting an IgE-mediated mechanism and previous sensitization to this agent. Such a mechanism was proved by positivity of the IDT in three of four patients who experienced anaphylaxis. Of interest, a previous history of atopy had no predictive value for the development of any type of hypersensitivity reaction to this agent. Anaphylaxis and urticaria are the clinical manifestations of mast cell degranulation due to IgE-mediated or non-IgE-mediated mechanisms [7] in drug hypersensitivity. The two mast cell activation pathways can be differentiated, identifying IgE specific for the culprit drug. This has been investigated recently in the case of anti-TNF-α agents [8]. Detection of IgE anti-infliximab has been reported [8], even if the assay has not yet been validated. An assay proposed for the detection of IgE to TCZ has not shown any positive results in the nine patients who developed anaphylaxis to TCZ [9]. To the best of our knowledge, this is the first report of in vivo skin testing for the diagnosis of immediate reactions to TCZ. Skin tests still represent a useful tool for identifying mast cell-sensitizing specific IgE [10]. In fact, a correlation between serological IgE positivity and IDT results has recently been reported in patients with reactions to infliximab. On the basis of our findings, we suggest that skin tests to TCZ might be a simple and
Skin tests to tocilizumab might be a simple and sensitive tool for the diagnosis of IgE-mediated hypersensitivity reactions.

**Rheumatology key message**

- Skin tests to tocilizumab might be a simple and sensitive tool for the diagnosis of IgE-mediated hypersensitivity reactions.

**Disclosure statement:** The authors have declared no conflicts of interest.

**Valeria Rocchi¹, Ilaria Puxeddu¹, Giuseppe Cataldo¹, Isabella Del Corso¹, Antonio Tavoni¹, Laura Bazzichi², Stefano Bombardieri² and Paola Migliorini¹**

¹Clinical Immunology and Allergy Unit and ²Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.

Accepted 12 March 2014

Correspondence to: Paola Migliorini, Clinical Immunology and Allergy Unit, Department of Clinical and Experimental Medicine, Via Roma 67, 56126 Pisa, Italy.

E-mail: paola.migliorini@med.unipi.it

**References**


Rheumatology 2014;53:1529–1530
doi:10.1093/rheumatology/keu008
Advance Access publication 7 March 2014

Tocilizumab-induced leucocytoclastic vasculitis in a patient with rheumatoid arthritis

SIR, Biologic agents are widely used for the treatment of RA in today’s treat-to-target era [1]. Although their safety and efficacy are acceptable, autoimmune adverse events associated with biologics have increasingly been reported. According to the BIOGEAS Study Group [2], vasculitis and SLE are the most frequent autoimmune diseases induced by biologics, and most reports were associated with anti-TNF agents. Among 139 cases of vasculitis, 137 cases were related to anti-TNF agents, except for 1 case related to rituximab and 1 to abatacept. Cutaneous involvement is most frequent, and leucocytoclastic vasculitis has been reported only with anti-TNF agents [3]. We report the first case of tocilizumab-induced leucocytoclastic vasculitis in a patient with RA. Written informed consent for publication of this case was obtained from the patient.

A 62-year-old Japanese woman had been suffering from seropositive RA for 23 years. She had a history of treatment with infliximab for 5 years, but this was switched to etanercept because of secondary failure, and etanercept was switched to tocilizumab because of primary failure. Subsequently she was treated with tocilizumab 8 mg/kg/month, MTX 4 mg/week and prednisolone 3 mg/day for 2.5 years, and low disease activity was achieved.

In April 2013 she presented with abdominal pain and arthralgia with a low-grade fever. Three weeks later she noticed the emergence of multiple palpable purpura on her forearms, buttocks, thighs and lower extremities (Fig. 1A). Most of her proximal interphalangeal joints were swollen and the 28-joint DAS (DAS28) increased to 5.98. ESR increased to 38 mm in the first hour (normal value <16 mm in women) and CRP was 5.35 mg/dl (normal value <0.3 mg/dl). Platelet count, renal function and urinalysis were normal. Serum IgG, IgA and IgM levels and complement factors (CH50, C3 and C4) were within normal limits. Serum anti-streptolysin O was negative. ANA and ANCA were negative. Circulating immunocomplex and cryoglobulin were absent. Upper gastrointestinal endoscopy showed normal gastric mucosa, and faecal occult blood testing was negative. Skin biopsy of the purpura of the lower legs revealed leucocytoclastic vasculitis with granulocyte invasion to small vessel walls in the dermis, nucleus disruption and extravasation of erythrocytes (Fig. 1B). Immunofluorescent staining did not show IgA deposition.

According to the 1990 ACR criteria, Henoch–Schoenlein purpura can be diagnosed from clinical and pathological findings even when lacking IgA deposition. However, this case did not fulfill the definition of IgA vasculitis of the 2012 Revised International Chapel Hill Consensus Conference classification. We diagnosed this case as leucocytoclastic vasculitis.

The cause of the leucocytoclastic vasculitis was difficult to ascertain because no agents were newly administered before this episode. We considered the possibility of tocilizumab-induced leucocytoclastic vasculitis and discontinued the administration of tocilizumab. Subsequently palpable purpura rapidly disappeared, so we concluded that leucocytoclastic vasculitis was induced by tocilizumab. Because of sustained arthritis and abdominal pain,