Are Biosimilars of Biologics the Same as the Reference Drug in Terms of Allergy? Selective Allergy to Tocilizumab Biosimilar

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Tocilizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody against the interleukin 6 receptor. It was the first monoclonal antibody approved for treating rheumatoid arthritis (RA) in Europe. It is administered to adult patients with moderate-to-severe RA who have responded inadequately to previous therapy with 1 or more disease-modifying antirheumatic drugs or tumor necrosis factor (TNF) inhibitors [1,2].

Monoclonal antibodies generate a growing economic burden for health care budgets. Biosimilars are biological drugs whose mechanism of action is close to that of a previously approved drug (reference drug), with demonstrated equivalent efficacy and comparable safety, immunogenicity, and pharmacokinetic profiles but with a significant cost-saving [1]. In 2022, the first tocilizumab biosimilar was approved by the European Medicines Agency (EMA).

We present the case of a 60-year-old woman with a previous history of glaucoma and RA. In August 2023, she started treatment with subcutaneous (SC) tocilizumab 162 mg weekly owing to clinically inadequate control of her RA with conventional treatment. She tolerated the drug well. Three months later, her treatment was changed to tocilizumab biosimilar 162 mg SC weekly to save costs. She developed an immediate hypersensitivity skin reaction to the first dose. This manifested as an intensely itchy wheal at the injection site approximately 1 hour after the injection. The wheal disappeared in about 5-6 days with no additional treatment needed and no residual lesion. With the following weekly injections, the wheal at the injection site grew progressively in size. After 16 doses of tocilizumab biosimilar (over 4 months), treatment was switched back to reference tocilizumab, with no skin reactions and good tolerance of subsequent doses. The reaction was reported to the EMA. The patient gave her consent for the publication of this case report.

The allergology study was undertaken 2 months later and involved skin tests with tocilizumab biosimilar 20 mg/mL following previous recommendations on dose and dilutions [2]. The result of a prick test (1/1) was negative. An intradermal test (IDT) (1/1) was immediately positive (eliciting a wheal of 12×10 mm in 10 minutes). A subsequent IDT (1/10) yielded a positive result (wheal of 10×9 mm). Therefore, the solution was diluted to 1/100, which also yielded a positive result (wheal of 9×8 mm). A negative result was recorded in the IDT (1/1) in 4 controls (2 atopic and 2 nonatopic). The results of the patient's IDTs are shown in Supplementary Figure 1. As the patient continued treatment with reference tocilizumab SC and showed good tolerance, IDT was performed with this agent. A basophil activation test (BAT) (BasoFlowEx, Exbio) was also performed with reference tocilizumab and biosimilar according to the manufacturer's instructions. Briefly, the BAT was carried out with the patient's blood sample and the blood from a nonatopic healthy control. The basophil population was defined as $SSC^{low}/CD203c^{+}$ by flow cytometry. The results are expressed as the stimulation index (SI), which was calculated as the ratio of the percentage of activated basophils ($SSC^{low}/CD203c^{+}/CD63^{+}$ cells) with various drugs to unstimulated basophils (negative control). Remarkably, the percentage of activated basophils after contact with the drug was required to be ≥5% for the result to be considered positive. Similarly, according to previous studies, an SI value had to be ≥2 to be considered positive. Dose-response curves were constructed using 6×10-fold concentrations (from 1/1 to 1/100 000), starting at 20 mg/mL in 1X phosphate-buffered saline (Figure). A cross-linking anti-IgE antibody mixed with a stimulating peptide, N-formyl-Met-Leu-Phe, was used as a positive control. A marked dose-response curve was observed

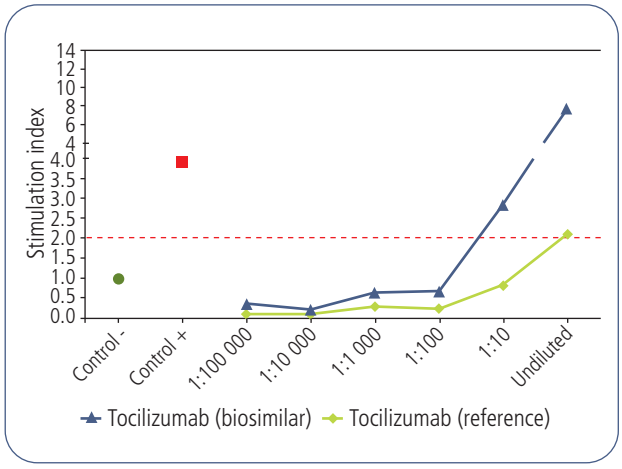

Figure. Basophil activation test with tocilizumab biosimilar (*Tyenne*) and reference tocilizumab (*Actemra*) using 6×10-fold concentrations of the drug, starting at 20 mg/mL in 1X phosphate-buffered saline and increasing up to 1:100 000. Unstimulated cells were used as a negative control; a cross-linking anti-IgE antibody mixed with N-formyl-Met-Leu-Phe was used as a positive control. The population of activated basophils was defined as $SSC^{low}/CD203c^{+}/CD63^{+}$ by flow cytometry. The results are expressed as the stimulation index, calculated as the ratio of the percentage of activated basophils with different drugs to the percentage of unstimulated cells (negative control).

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for tocilizumab biosimilar, with a maximum basophil activation of 36.4% (SI, 7.82), which was approximately double that of the positive control (Figure). Even though a small response was observed with the reference drug (9.8%; SI, 2.1), this was significantly lower than the SI of 4 from the positive control and was therefore considered negative. The positive BAT and IDT results with tocilizumab biosimilar provide in vitro and in vivo confirmation of sensitization.

Hypersensitivity reactions associated with tocilizumab have been reported [2,3]. Most are immediate. Anaphylactic reactions are also frequent and are estimated to affect 0.1%-0.7% of patients in clinical trials [3]. Isolated cases of delayed hypersensitivity reaction to tocilizumab infusion have been reported and involve mainly erythroderma [4], eosinophilic papular skin rash [5], and vasculitis [6,7]. However, no allergy work-up was performed in any of the abovementioned studies. Another isolated case of successful desensitization to tocilizumab has also been published [8].

No demonstrated cases of allergy to tocilizumab biosimilar with good tolerance to reference tocilizumab have been published. Most excipients in both drugs were similar, except for hydrochloric acid (E507) and sodium hydroxide (E524), which were present in the biosimilar but not in the reference product. The patient's glaucoma is currently being treated with daily eye drops, which she tolerates well. The excipients include hydrochloric acid or sodium hydroxide. Moreover, multiple eye drops (frequently containing hydrochloric acid and/or sodium hydroxide) administered to the patient in periodic ophthalmological check-ups did not induce an allergic reaction. Although we were unable to analyze these excipients in a skin test and thus rule out allergy, the patient has tolerated them in other drugs, indicating that the possibility of allergy is low. The immunological mechanism involved in the allergic reaction remains unclear. Although biosimilars closely resemble the reference drug in terms of efficacy, safety, immunogenicity, and pharmacokinetic profile, structural differences between both drugs may be observed.

Biosimilars of several monoclonal antibodies have been approved in the last few years. Only 1 other case of suspected allergy to a biosimilar with good tolerance to the reference drug has been published, in this case with rituximab. Despite a suggestive systemic allergic reaction after the rituximab infusion, no allergy work-up was performed [9]. Curiously, the biosimilar hypersensitivity reactions to both rituximab biosimilar [9] and tocilizumab biosimilar reported in this manuscript developed after the first injection. Other hypersensitivity reactions to reference tocilizumab [4,5] and other biologics [3] have been reported after the first infusion, suggesting that sensitization is via a route other than the drug administered.

In conclusion, this is the first case of demonstrated allergy to a monoclonal antibody biosimilar (confirmed by a suggestive skin allergy reaction and positive IDT and BAT results) with tolerance to the reference drug after the allergic reaction.

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Conflicts of Interest

Dr Betancor was supported by a Rio Hortega Research Contract from Instituto Carlos III, Ministry of Science. Dr Barroso has received fees for lectures from Roxall and manuscript support from Sanofi outside the submitted work. Dr Valverde has received fees for lectures from GSK and participates on an advisory board for Organon outside the submitted work. Dr Sastre reports grants and personal fees from Sanofi, GSK, Novartis, AstraZeneca, Mundipharma, and Faes Farma outside the submitted work. Dr del Pozo reports personal fees and others from Sanofi, AstraZeneca, GSK outside the submitted work. The remaining authors declare that they have no conflicts of interest.

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