

# A Patient with Local Hypersensitivity Reactions to Three TNF- $\alpha$ Inhibitors and Local/Systemic Hypersensitivity Reactions to Tocilizumab: Desensitization to Tocilizumab

Üç TNF- $\alpha$  İnhibitörü ile Lokal ve Tosilizumab ile Lokal/Sistemik Aşırı Duyarlılık Reaksiyonu Gelişen Bir Hasta: Tosilizumab ile Desensitizasyon

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## Abstract

Tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors are effective alternatives for chronic inflammatory diseases. They are generally well tolerated; however, they may lead to the immediate/delayed local or systemic hypersensitivity reactions (HSR). Tocilizumab is a monoclonal antibody against interleukin 6 receptors. It is given both via intravenous (IV) and subcutaneous (SC) routes and there are limited data reporting that the overall injection and/or infusion reaction rate to tocilizumab is estimated as 7-8%. Cross-reactivity between either TNF- $\alpha$  inhibitors or tocilizumab is not expected. However, we herein present an unusual case of a patient who reacted with local injection site reactions (ISRs) to three TNF- $\alpha$  inhibitors, adalimumab, etanercept, and golimumab. The patient then reacted with ISR and anaphylaxis to SC and IV tocilizumab, respectively. Skin prick tests with all biologicals were negative but positive in early readings of intradermal testing. After all, tocilizumab was successfully administered via rapid drug desensitization.

**Key Words:** TNF- $\alpha$  Inhibitors, Tocilizumab, Local Hypersensitivity Reactions, Anaphylaxis, Desensitization

## Öz

Tümör nekroz faktör-alfa (TNF- $\alpha$ ) inhibitörleri, kronik enflamatuvar hastalıklar için etkili alternatiflerdir. Genellikle iyi tolere edilirler, ancak erken/geç tip lokal veya sistemik aşırı duyarlılık reaksiyonlarına (ADR) yol açabilirler. Tosilizumab, interlökin-6 reseptörlerine karşı bir monoklonal antikordur. Hem intravenöz (İV) hem de subkütan (SK) yolla verilir ve sınırlı sayıda çalışmada tosilizumab ilişkili enjeksiyon ve/veya infüzyon reaksiyon oranının %7-8 olduğu bildirilmiştir. TNF- $\alpha$  inhibitörleri veya tosilizumab arasında çapraz reaktivite beklenmemektedir. Ancak biz burada olağan dışı bir olgu olan üç TNF- $\alpha$  inhibitörü, adalimumab, etanercept ve golimumab, ile lokal enjeksiyon yeri reaksiyonu gelişen bir hasta sunduk. Hastada daha sonra SK ve İV tosilizumab ile sırasıyla lokal enjeksiyon yeri reaksiyonu ve anafilaksi gelişti. Tüm biyolojik ajanlarla yapılan deri prick testleri negatif, intradermal testlerin erken okumaları pozitif. Bununla birlikte tosilizumab hızlı ilaç desensitizasyon yoluyla başarıyla uygulandı.

**Anahtar Kelimeler:** TNF- $\alpha$  İnhibitörleri, Tosilizumab, Lokal Aşırı Duyarlılık Reaksiyonu, Anafilaksi, Desensitizasyon

## Introduction

Tumor necrosis factor-alpha (TNF- $\alpha$ ) inhibitors are valid alternatives in the treatment of multiple rheumatologic conditions. Five TNF- $\alpha$  inhibitors namely infliximab, adalimumab,

etanercept, golimumab, and certolizumab are currently available (1). TNF- $\alpha$  inhibitors are generally well tolerated but may cause immediate/delayed local or systemic hypersensitivity reactions (HSRs), which can be life-threatening (2,3). The most common reactions with subcutaneous (SC) TNF- $\alpha$  inhibitors are local

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injection site reactions (ISRs) (2,3). In clinical trials, ISRs have been reported in up to 37%, 30%, and 16% of the etanercept, adalimumab, and golimumab-treated patients, respectively. These reactions were immediate or delayed and generally mild-to-moderate in severity (2,3).

Tocilizumab is a humanized monoclonal antibody against interleukin 6 receptors. It is administered both via intravenous (IV) and SC routes. Limited data report that HSR rates are estimated as 0.1%–0.7%, and the overall injection and/or infusion reaction rate is estimated as 7–8% with tocilizumab (4).

Cross-reactivity of TNF- $\alpha$  inhibitors with each others or with tocilizumab is not expected. However, herein we present an unusual case of a patient who reacted with ISRs to three TNF- $\alpha$  inhibitors, adalimumab, etanercept, and golimumab. The patient then reacted with ISR and anaphylaxis to SC and IV tocilizumab, respectively. Fortunately, tocilizumab was successfully administered via rapid drug desensitization (RDD).

## Case Report

A 28-year-old woman with a twelve-year history of rheumatoid arthritis, having received hydroxychloroquine, oral steroid, methotrexate, leflunomide, and sulfasalazine without significant benefit, was switched to 50 mg etanercept SC injections weekly, in 2014. After the 2<sup>nd</sup> injection, she developed local swelling, pruritus, and redness 5 cm in diameter within one hour, progressing to 10 cm and 20 cm in diameter after the 3<sup>rd</sup> and 4<sup>th</sup> injections.

She was then started on 40 mg/0.8 mL adalimumab SC injections, twice monthly, in 2016. The 2<sup>nd</sup> and the 3<sup>rd</sup> injections of adalimumab resulted in pruritus, redness, and swelling 5 cm and 10 cm in diameter, respectively, at the site of injection within 5 minutes. The 5<sup>th</sup> injection resulted in a local reaction covering the whole upper thigh.

She was then switched to 50 mg/0.5 mL SC golimumab, monthly, in September 2017, but she developed pruritus, redness, and swelling 5 cm and 8 cm in diameter, respectively, at the site of injection within 5 minutes after the 2<sup>nd</sup> and 3<sup>rd</sup> injection. After the 4<sup>th</sup> injection, redness and swelling reached 10 cm in diameter. She denied having systemic reactions with any of these TNF- $\alpha$  inhibitors.

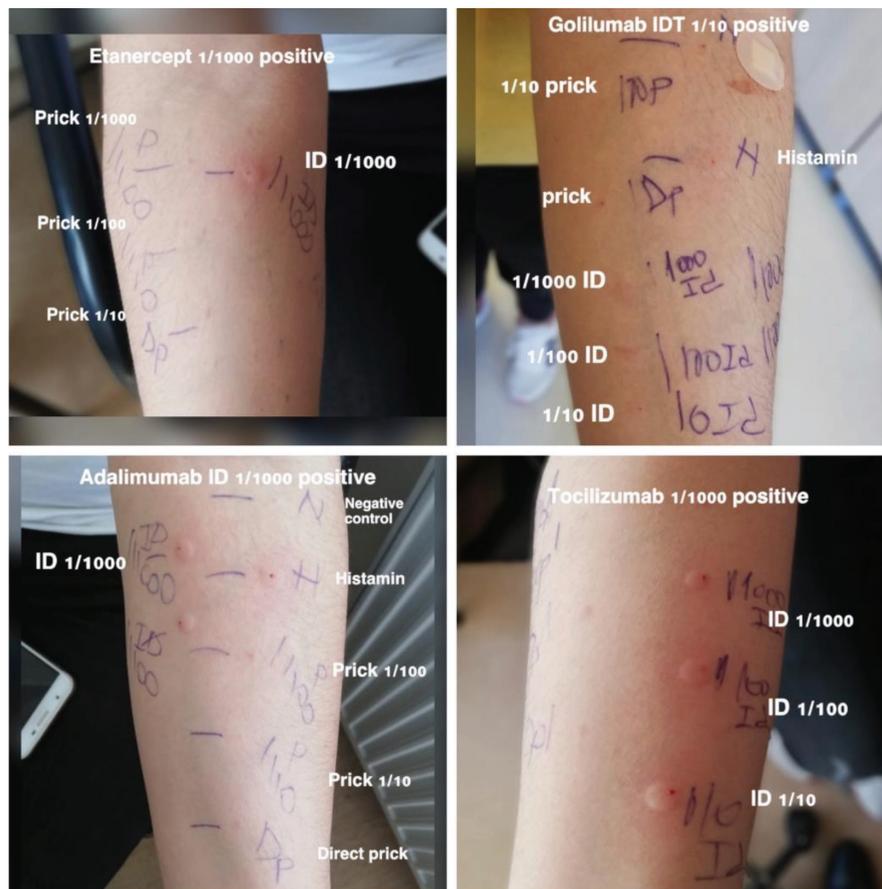
In March 2018, 560 mg IV infusion monthly of tocilizumab was prescribed. She responded well to tocilizumab during 12 infusions, and then switched to 162 mg/0.9 mL tocilizumab SC weekly. After the 2<sup>nd</sup> and 3<sup>rd</sup> injection, tocilizumab resulted in local pruritus, redness, and swelling less than 5 cm and between 5–10 cm in diameter, respectively, within 5 minutes. After the 4<sup>th</sup> injection, redness, and swelling reached more than 20 cm in diameter prompting drug discontinuation. Then, tocilizumab was changed to monthly infusion, but during the 1<sup>st</sup> infusion,

she developed facial and uvular swelling, mild dyspnea, urticaria, pruritus, a 30 mmHg fall in systolic blood pressure (from 120/80 mmHg to 90/60 mmHg), tachycardia without loss of consciousness, which required IV methylprednisolone (100 mg) and antihistaminic (pheniramine 45.5 mg), fluid support, and she recovered within 20 minutes. After discharge, intermittent urticaria relapsed for a month despite using antihistamines.

Reported non-irritant doses of TNF- $\alpha$  inhibitors and tocilizumab were used for prick (PT) and intradermal testing (IDT) (2,5). A wheal diameter of 3 mm or more than the negative control was considered positive for PT and when the size of the initial wheal increases by 3 mm or greater in diameter associated with a flare was considered positive for IDT. All were negative in prick tests but were positive in early reading of 1/1000 dilutions of IDTs except golimumab, which was positive in 1:10 dilutions (Table 1) (Figure 1). All readings at 24, 48, and 72 hours were negative. Serum anti-drug antibodies (ADA), including ADA-IgE for all culprit drugs were included into the allergology tests. The patient was negative for non-isotype-specific (Theradiag, Paris, France) and for IgE (ImmunoCAP assay, Thermo Scientific-Phadia, Sweden), anti-etanercept, adalimumab, golimumab, and tocilizumab antibodies.

## Discussion

The mechanism underlying ISRs to SC-administered biologics remains unclear. In studies with TNF- $\alpha$  inhibitors, most are thought to be T-lymphocyte-mediated delayed-type, but the underlying mechanism may be IgE-mediated, and continued treatment may not always be advisable (6). Prick and early reading IDT are important in diagnosing immediate systemic or local IgE-mediated HSRs. Accordingly, skin tests have been found positive in some patients with ISRs to TNF- $\alpha$  inhibitors (2). No data are available for ISRs to tocilizumab, but skin tests have been found positive in cases of IV tocilizumab-induced anaphylaxis (5,7,8) (Table 2). Our patient demonstrated positive immediate skin test reactivity to both TNF- $\alpha$  inhibitors and tocilizumab, which suggests IgE-mast cell involvement. Only one study reported two patients who developed HSR to 3 anti-TNFs including infliximab, adalimumab, and etanercept (3). One was positive on IDT only with infliximab. The second resulted positive to IDTs with all anti-TNFs. However, there was no serologic evaluation of these cases (3) (Table 2). Our patient reacted to three TNF- $\alpha$  inhibitors with ISRs that developed after repeated administrations and showed positivity on IDTs, suggesting a sensitization phase and IgE involvement to each agent. Interestingly, the patient reacted to repeated tocilizumab administration, first as ISR via the SC route, followed by anaphylaxis with the IV route. Besides repeated administration, positive IDT also supported an IgE-mediated reaction to tocilizumab. It remains unknown why the serologic evaluation



**Figure 1:** Positivity on early readings intradermal tests to etanercept, golimumab, adalimumab, tocilizumab

**Table 1: Skin test data**

	Concentration	Direct prick test	Intradermal test	
Etanercept	50 mg/mL	Negative	1/1000	OD:8x8 mm ED:20x20 mm
Adalimumab	40 mg/0.8 mL	Negative	1/1000	OD:9x9 mm ED:15x15 mm
Golimumab	50 mg/0.5 mL	Negative	1/10	OD:5x5 mm ED:6x6 mm
Tocilizumab	20 mg/mL	Negative	1/1000	OD:5x5 mm ED:8x8 mm

OD: Edema diameter; ED: Erythema diameter

was negative in our patient. Perhaps the long-time interval between the reactions and the serum sampling ranging from 5 months to 2 years for TNF- $\alpha$  inhibitors and to 3 months for tocilizumab led to the negativity of assays. Another possibility is that skin testing may have been more sensitive than *in vitro* tests.

If there is no valid alternative in the event of an immediate HSR, RDD is effective and safe (2,9). There are case reports of IgE-mediated ISRs induced by TNF- $\alpha$  inhibitors, but very limited data with successful desensitizations with tocilizumab

(2). A patient with tocilizumab-induced anaphylaxis had prick-test positivity and was desensitized successfully (7). A 15-year-old male with systemic juvenile arthritis developed pruritus, maculopapular rash, angioedema, and dyspnea after a 2<sup>nd</sup> dose of tocilizumab. He was positive on IDT with 1/1 concentration and desensitized with a classic 12-step RDD (8). We successfully used the classic 12-step protocol during tocilizumab desensitization (8,10).

In conclusion, we present a patient with ISRs to three TNF- $\alpha$  inhibitors and ISR/anaphylaxis to tocilizumab. She was skin-

**Table 2: Details of reported cases with hypersensitivity reactions to different TNF- $\alpha$  inhibitors or tocilizumab**

Ref no	Patients	Diseases	Drugs	Clinical presentation	Skin tests/serology	Management (desensitization/change of the treatment)
3	Patient 1	Autoimmune disease (detailed information is not available)	Infliximab, Etanercept Adalimumab	Anaphylaxis with infliximab and large local reactions with etanercept and adalimumab	IDT: (+) with three TNF- $\alpha$ inhibitors	No information
3	Patient 2	Autoimmune disease (detailed information is not available)	Infliximab, Etanercept Adalimumab	U/AO	IDT: (+) with infliximab (-) skin test with etanercept/ adalimumab	No information
5	Patient 3	FMF	Canakinumab	U	(-)	Continue treatment with premedication
5	Patient 4	Polyarticular juvenile idiopathic arthritis	Tocilizumab	Anaphylaxis	Not available	Desensitization, successful
5	Patient 5	Systemic juvenile idiopathic arthritis	Tocilizumab	Anaphylaxis	IDT: (+)	Discontinued
5	Patient 6	Granulomatosis with polyangiitis	Rituximab	Anaphylaxis	IDT: (+)	Desensitization, successful
5	Patient 7	SLE	Rituximab	Anaphylaxis	Not available	Discontinued
5	Patient 8	Polyarticular juvenile idiopathic arthritis	Tocilizumab	Anaphylaxis	IDT: (+)	Discontinued
7	Patient 9	Still disease	Tocilizumab	U/AO	SPT: (+)	Desensitization, successful
8	Patient 10	Systemic juvenile idiopathic arthritis	Tocilizumab	Anaphylaxis	IDT: (+)	Desensitization, successful

IDT: Intradermal test, SPT: Skin prick test, U/AO: Urticaria/angioedema, FMF: Familial Mediterranean fever, SLE: Systemic lupus erythematosus

test positive to these drugs and was successfully desensitized to tocilizumab.

### Ethics

**Informed Consent:** Written informed consent for the publication of this report was obtained from the patient by the corresponding author.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: B.Ö.Ö., N.O.A., Concept: S.B., Design: S.B., Data Collection or Processing: E.E.G., Analysis or Interpretation: F.N., A.V., Literature Search: B.Ö.Ö., N.O.A., Writing: B.Ö.Ö., N.O.A., E.E.G., S.B.

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