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CASE REPORT

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Successful Desensitization with Ixekizumab in a Patient with a History of Multiple Biological Agent Allergy

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ABSTRACT

Biological agents, widely used in the treatment of oncologic, immunologic, and rheumatologic diseases, have long-term effects in reducing mortality rates and disease burden. Targeted biological agents are of great importance due to their higher efficacy and lower side effects. For patients with a history of hypersensitivity reactions or at risk of developing such reactions to these agents, drug desensitization is considered an appropriate treatment option.

In this case report, Ixekizumab was successfully administered to a 53-year-old female patient with a history of allergies to several biological agents through desensitization. The drug was given without premedication, using three different solutions in a 7-step protocol over 90 minutes. This process was successful despite the patient's previous hypersensitivity reaction to Ixekizumab.

Keywords: Desensitization, ixekizumab, hypersensitivity, biological agents

INTRODUCTION

Biological agents include cytokines, monoclonal antibodies, and fusion proteins. They are targeted therapeutic drugs used in the treatment of lymphoma, leukemia, breast cancer, lung cancer, gastric cancer, malignant melanoma, rheumatologic diseases, urticaria, asthma, atopic dermatitis, allergic bronchopulmonary aspergillosis, eosinophilic granulomatous polyangiitis, inflammatory bowel diseases, psoriasis, multiple sclerosis, etc. Infusion-related reactions, cytokine release syndrome, hypersensitivity reactions (early-late type), immunodeficiency, autoimmunity, allergic/atopic diseases, cross-reaction with normal cells (e.g. acne formation due to Panitumumab) and non-immunological side effects (e.g., major depression due to interferons) may be observed due to biologics, which have become widespread since the early 2000s. In addition, anaphylaxis cases have been described due to Polysorbate 80 used in the stabilization of drug emulsions, and the other additives such as mannitol, albumin, latex, papain, trometamol may also have antigenic potential (1).

Serum tryptase levels should be measured 30-120 minutes after the reaction to differentiate anaphylaxis from infusion-related reactions and cytokine release syndrome. Symptoms indicating the severity of organ involvement such as cardiovascular symptoms are associated with high tryptase levels and should suggest mast cell activation syndromes, especially systemic mastocytosis . However, in some cases of anaphylaxis, tryptase levels may also be in the normal range.

Since mast cells do not respond transiently to allergens for up to 4 weeks, skin tests should be postponed until 4-6 weeks after the allergic reaction. Except for adalimumab, infliximab, omalizumab and etanercept, biologics do not yet have a standardized skin test dose (2,3).

Desensitization is the process of starting with small doses of the drug to which the patient is allergic and increasing the doses at certain time intervals so that the patient can tolerate this drug. If the biological agent is the first-line treatment option and there is no alternative, desensitization can be considered by an experienced Allergist.

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Table I: Active and auxiliary substances of biological agents for which the patient has a history of HSRs.

Trade Name	Active substance	Auxiliary substances
Humira® (AbbVie, USA)	Adalimumab	Mannitol, Polysorbate 80
Simponi® (Merck Sharp Dohme, USA)	Golimumab	Sorbitol, L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate-80
Verxant® (Novartis, Switzerland)	Secukinumab	Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate-80
Enbrel® (Pfizer, Belgium)	Etanercept	Mannitol, sucrose, trometamol, tromatamol HCl
Copellor® (Eli and Lily Company, USA)	Ixekizumab	Sodium citrate dihydrate, anhydrous citric acid, sodium chloride, Polysorbate 80

The patient's consent was obtained and patient information is presented.

CASE

A 53-year-old woman with psoriatic arthritis was admitted to our outpatient clinic with a history of allergic reactions to many biological agents and most recently pruritus and urticarial rashes after subcutaneous injection of Ixekizumab (Copellor®).

Her medical history included palpitations and shortness of breath 15 minutes after Adalimumab (Humira®) administration. Within minutes after the administration of Golimumab (Simponi®), urticarial rashes and pruritus occurred and the treatment was discontinued. Palpitations, urticaria and high blood pressure 5 minutes after Secukinumab (Verxant®) administration. Swelling of the hands and compartment syndrome due to swelling 1 hour after administration of etanercept (Enbrel®). Due to HSRs related to all these treatments, the patient's treatment was continued without biologic agents for a while. Pain control was attempted with NSAIDs and oral corticosteroids. However, when symptom control could not be achieved, it was decided by the Rheumatologist to start Ixekizumab (Copellor®). Itching and urticarial rash developed 5 minutes after the administration of Ixekizumab.

Except for Etanercept, all of the biologic agents for which the patient had a previous history of drug allergy contained polysorbate 80 (E433) as an excipient (Table I). The same excipient was also present in Ixekizumab.

Skin prick test (80 mg/ml) and intradermal tests with Ixekizumab were performed at dilutions of 1/1000, 1/100, and 1/10. Skin prick test and intradermal tests were negative. For exclusion of excipient allergy, skin prick test and intradermal tests (1/100, 1/10 dilutions) were performed with methylprednisolone acetate (Prednol®) containing polysorbate 80 and dexamethasone (Dekort®) without polysorbate 80. Skin tests were negative.

Table II: Ixekizumab desensitization protocol.

Step	Dose (mg)	Concentration (mg/mL)	Volume (mL)
1	1.6	1/10	0.2
2	2.4	1/10	0.3
3	4	1/10	0.5
4	12	1/1	0.15
5	16	1/1	0.20
6	20	1/1	0.25
7	24	1/1	0.30
Total	80		1.9

Ixekizumab was administered in 90 minutes with a 7-step protocol with 3 solutions without premedication (Table II). No allergic reaction was observed during the first desensitization and subsequent administrations.

DISCUSSION

Ixekizumab is a humanized monoclonal antibody in the Immunoglobulin G4 structure targeting Interleukin-17A (IL-17A). IL-17A is produced by T helper 17 cells and is involved in neutrophil apoptosis, inflammatory cytokine release, and triggering psoriasis-induced angiogenesis. It was found to be more effective than Etanercept in the treatment of psoriatic plaques. Side effects observed with Ixekizumab include injection site reactions, upper respiratory tract symptoms, nausea, and fungal infections. Cases of Ixekizumab-associated angioedema and urticaria have been reported in <0.1% of clinical trials, but no anaphylaxis events have been reported.

So far, we found 3 cases in the literature in which desensitization with Ixekizumab was performed (4). These cases were switched to Ixekizumab in 3 cases of non-response to previous biological agents. In addition, we found urticaria after Ixekizumab switch in a patient who was previously unresponsive to Adalimumab in the literature (5). However, our case differs from the other cases because of a history of multiple biologic agent allergy.

In this case, we wanted to emphasize that desensitization is a successful option in patients who develop allergic reactions to biologic agents but in whom it is not appropriate to start an alternative drug to the biologic agent.

Conflict of Interest

No conflict of interest.

Funding

There are no sources of funding to declare.

Ethical Approval

Informed consent was obtained from the patient who agreed to take part in the study. Ethical approval is not required at our institution to publish an anonymous case report.

Author Contributions

Concept: **Fatma Terzioglu Sahin, Seyma Ozden,** Design: **Seyma Ozden, Ismet Bulut,** Data collection or processing: **Fatma Terzioglu Sahin, Seyma Ozden, Ismet Bulut,** Analysis or Interpretation: **Seyma Ozden, Ismet Bulut**, Literature search: **Seyma Ozden, Ismet Bulut,** Writing: **Fatma Terzioglu Sahin, Seyma Ozden, Ismet Bulut,** Approval: **Fatma Terzioglu Sahin, Seyma Ozden, Ismet Bulut.**

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