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Successful subcutaneous desensitization in a patient with systemic reaction due to ixekizumab

Desensibilización subcutánea administrada con éxito en un paciente con reacción sistémica por ixekizumab.

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Abstract

Background: Ixekizumab is a high-affinity IgG4 monoclonal humanized antibody useful for the treatment of ankylosing spondylitis. Benign skin reactions are a common adverse event with ixekizumab but systemic hypersensitivity reactions are much more unusual.

Case report: We describe the case of a 54-female patient with HLAB27+ spondyloarthritis. Treatment with ixekizumab 80 mg subcutaneous (containing polysorbate) was prescribed. The patient experienced immediate severe dyspnea, skin erythema and flushing. Intradermal test (0.8 mg/ml) was clearly positive in the immediate reading. The patient was planned to undergo ixekizumab desensitization according to an 8-step protocol with good tolerance.

Conclusion: We report a patient with HLAB27+ spondyloarthritis treated with ixekizumab who developed a systemic IgE-mediated reaction. A successful and easy to perform subcutaneous desensitization protocol is described.

Keywords: Hypersensitivity; Ixekizumab; Systemic reaction; Skin test; Desensitization protocol.

Resumen

Antecedentes: Ixekizumab es un anticuerpo monoclonal humanizado IgG4 de alta afinidad para el tratamiento de pacientes con espondilitis anquilosante. Las reacciones cutáneas benignas son un evento adverso común en pacientes que reciben ixekizumab; no obstante, las reacciones de hipersensibilidad sistémica son excepcionales.

Reporte de caso: Paciente femenina de 54 años con espondiloartritis HLAB27+. Se indicó tratamiento con ixekizumab, en dosis de 80 mg por vía subcutánea (contiene polisorbato), y de inmediato experimentó disnea severa, eritema cutáneo y enrojecimiento. La prueba intradérmica (0.8 mg/mL) resultó positiva en la lectura inmediata. Se planificó desensibilización con ixekizumab, según el protocolo de 8 pasos con buena tolerancia.

Conclusión: La desensibilización por vía subcutánea con ixekizumab fue exitosa y fácil de realizar.

Palabras clave: Hipersensibilidad; Ixekizumab; Reacción sistémica; Prueba cutánea; Protocolo de desensibilización.

BACKGROUND

Ixekizumab is a high-affinity IgG4 monoclonal humanized antibody that selectively targets interleukin 17A and 17A/F, indicated, among others, for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.[1]

Benign skin reactions are a common adverse event with ixekizumab but systemic hypersensitivity reactions are much more unusual. According to a recent meta-analysis including 17 clinical trials and near 7000 patients, only 28 cases of serious allergic reactions or hypersensitivity have been reported (0.2 patient-year of exposure), none of them confirmed as anaphylaxis after medical review.[2]

CASE REPORT

We describe the case of a 54-female patient with HLAB27+ spondyloarthritis (axial and peripheral pattern) resistant to multiple systemic previous treatments like corticosteroids, metothrexate, adalimumab and etarnecept. Because of the partial response to the mentioned drugs, the negative effect on the patient's quality of life and the severity and potential future consequences of the basal disease, treatment with ixekizumab 80 mg subcutaneous (containing polysorbate 80 as excipient) was prescribed following the approved schedule: 160 mg (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. 20 minutes after first administration, the patient developed an extensive local reaction at the injection site with pruritus, redness and swelling (>10cm) treated with intravenous corticosteroids with good response, disappearing in 30 minutes without residual lesions. This injection site reaction increased steadily till fifth administration, after which the patient also experienced immediate severe dyspnea, skin erythema and flushing (grade 3 anaphylaxis)[3] treated with epinephrine, intravenous corticosteroids, antihistamines and inhaled bronchodilators resulting in remission in 20 minutes. Ixekixumab was changed by Infliximab and the patient was referred to our outpatient clinic for assessment.

The medical history of the patient did not show any relevant allergic antecedent except an intermittent rhinoconjunctivitis and asthma with sensitization to house dust mites, as well as grass and olive pollens, currently well controlled with as needed treatment. The patient maintained the usual symptomatic treatment with non-sedating antihistamines, topical nasal corticosteroids and antihistamine eye drops. Skin tests were performed 2 months after the reaction to avoid false-negative results using concentrations (1:1 to 1:100) of ixekizumab diluted in saline fluid prepared by the Pharmacy Department. Skin prick test (SPT) result with ixekizumab (80 mg/ml) was doubtful whereas intradermal test (0.8 mg/ml) was clearly positive in the immediate reading with a swelling size of 12 x 12 mm. As control, intradermal tests (IDT) in ten healthy controls were performed, all of them with negative results. Skin tests (SPT and IDT) with Polysorbate 80 undiluted were negative. Serum total IgE level was 130 UI/ml, as expected in an atopic patient, whereas levels of Triptase and Interleukin-6 were normal (5.9 mg/l and 2.77 pg/mL respectively).

Despite the severity of the reaction, the rheumatologist, due to the unresponsiveness of previous drugs and the development of important side effects with Infliximab, considered that the patient should continue receiving Ixekizumab. So, after written informed consent was obtained, the patient was planned to undergo ixekizumab desensitization according to an 8-step protocol with a total duration of 1 hour and 45 minutes to reach a total dose of 80 mg (**Table 1**). We chose this protocol over others (Jimenez et al, 3 solutions and 7 steps) because we considered it safer, starting with a lower initial dose but being fast and effective at the same time.[4] The procedure was carried out in the outpatient medical infusion center. Doses were subcutaneously administered in different places of the same arm every 15 minutes. Premedication with Ebastine 20 mg, AAS 300 mg and Montelukast 10 mg orally as

Table 1. Eight-Step ixekizumab desensitization protocol

Step	Solution (mg/mL)	Time (min)	Volume (mL)	Dose (mg)	Accumulated dose (mg)
1	0.08 (D)	0	0.1	0.008	0.008
2	0.8 (C)	15	0.1	0.08	0.088
3	8 (B)	30	0.1	0.8	0.888
4	16 (A)	45	0.1	1.6	2.488
5	80	60	0.06	4.8	7.288
6	80	75	0.16	12.8	20.088
7	80	90	0.32	25.6	45.688
8	80	105	0.43	34.31	79.998

well as Metilpredinosolone 40 mg intravenously were administered one hour before de procedure.[5]

One hour after the last shot, the patient presented only redness at the site of the highest dose injection that resolved in few minutes spontaneously. Due to its good tolerance, 2 weeks later, a much faster protocol (2 doses of 40 mg separated by 30 minutes) was used without any adverse effect. So, for the third administration, the full dose was administered also without incidences.

Flow cytometry-based basophil activation test (BAT) was performed before and after desensitization. Basophis were identified by IgE expression on the cell surface and CD63 antigen expression was analyzed on IgE^{high} basophils in human heparinized whole blood after stimulation with ixekizumab. The BAT result was positive in the patient (**Figure 1**) with a percentage of basophils ($SSC\text{-}A^{low}/IgE^{high}$) stimulated with ixekizumab of 52% before desensitization, percentage decreasing to 15,5% after the procedure. BAT with ixekizumab was also carried out in a control patient treated with this drug but without previous hypersensitivity reactions, with negative result (data not shown).

Ethics aspects

The study did not collate any personal data that can identify the patient and informed consent was signed. The study was performed considering the prevailing regulations of good clinical practice and personal data privacy. The authors declare that they have not received financing for this study.

DISCUSSION

To our knowledge, this is the first case of desensitization with ixekizumab reported in a patient with systemic immediate hypersensitivity, as shown by the positivity of the skin test and BAT. Previously, only Jimenez et al pub-

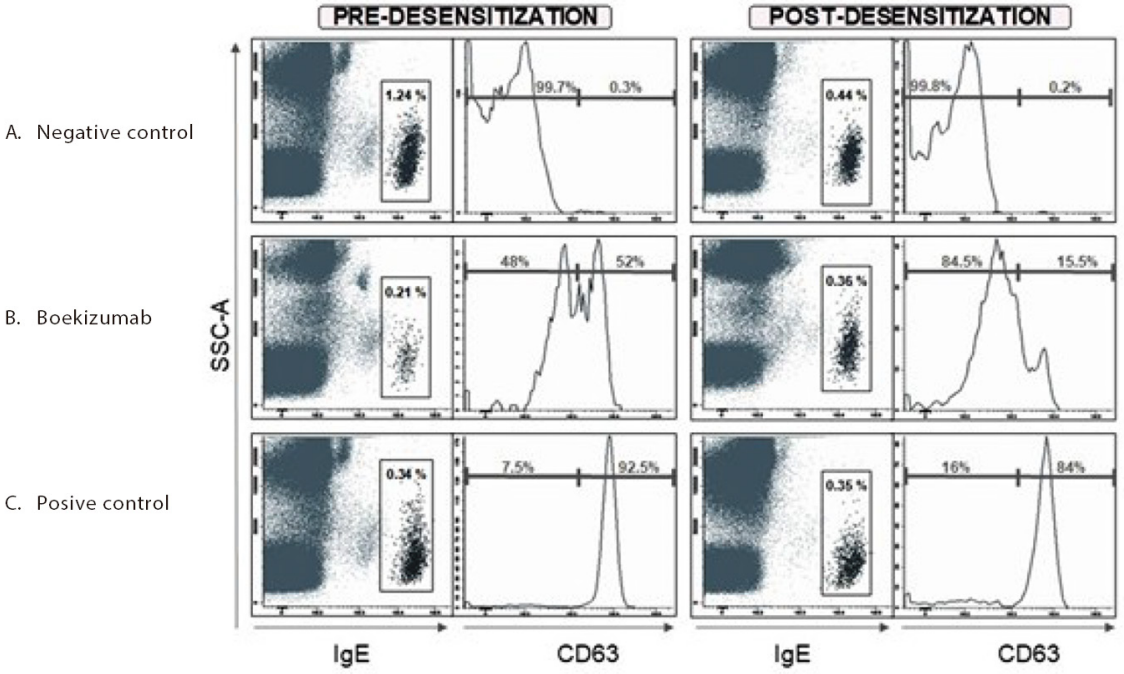

Figure 1. Basophil activation test result pre- and post-desensitization. **A)** As negative control, background basophil activated with buffer was only 0.3% and 0.25% respectively**. B)** The percentage of activated basophils stimulated with ixekizumab was 52%, decreasing to 15.5% after desensitization. **C)** As positive control, basophil activation with chemotactic peptide N-formyl-Met-Leu-Phe was 92.5% and only slightly decreased to 84% after desensitization.

lished another successful desensitization with the same drug, performed in a younger woman affected by plaque psoriasis who developed injection site reactions due to an IgE mediated mechanism, only shown by skin tests.[6]

It´s not possible to know if the first local site reactions suffered by the patient were caused by a non-specific mechanism or by an immediate hypersensitivity. However, the size of the swelling, the accompanying symptoms and the steadily increasing with the following shots, make plausible to think that we were in the second scenery, and in this case, we could argue about when the sensitization took place. In fact, hypersensitivity reactions with the first administration of other biological agents like adalimumab and etarnecept have been reported,[7] not knowing the right moment of drug sensitization.

CONCLUSIONS

Our 8-step protocol desensitization to ixekizumab was safe and effective enabling the patient to maintain the best therapeutical option for her. Our experience may be helpful for similar clinical cases where the therapeutic options are very limited and a disabling condition such axial spondyloarthritis is present, whenever a positive risk/ benefit took place and an informed consent were obtained.

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Conflict of interest statement

The authors report no proprietary or commercial interest in any product mentioned, concept discussed or personal relationships with other people or organizations that could influence their workhand conclusions in this article.

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REFERENCES

1. Pharmacoeconomic Review Report: Ixekizumab (Taltz): (Eli Lilly Canada Inc.): Indication: For the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 May. PMID: 33237678.
2. Griffiths CEM, Gooderham M, Colombel JF, Terui T, et al. Safety of Ixekizumab in Adult Patients with Moderate-to-Severe Psoriasis: Data from 17 Clinical Trials with Over 18,000 Patient-Years of Exposure. Dermatol Ther (Heidelb) 2022; 12 (6): 1431-1446. doi: 10.1007/s13555-022-00743-9.
3. Muraro A, Worm M, Alviani C, Cardona V, et al; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy 2022; 77 (2): 357-377. doi: 10.1111/all.15032.
4. de la Varga-Martínez R, Gutiérrez-Fernández D, Foncubierta-Fernández A, Andrés-García JA, et al. Rapid subcutaneous desensitization for treatment of hypersensitivity reactions to etanercept in two patients with positive basophil activation test. Allergol Int 2017; 66 (2): 357-359. doi: 10.1016/j.alit.2016.09.002.
5. ALMuhizi F, De Las Vecillas-Sanchez L, Gilbert L, Copaescu AM, et al. Premedication Protocols to Prevent Hypersensitivity Reactions to Chemotherapy: a Literature Review. Clin Rev Allergy Immunol 2022; 62 (3): 534-547. doi: 10.1007/s12016-022-08932-2.
6. Jimenez RB, Vera DG, Rivera-Díaz R, Cortijo-Cascajares S, et al. Successful subcutaneous desensitization in a patient with allergy to ixekizumab. J Allergy Clin Immunol Pract 2018; 6 (5): 1761-1762. doi: 10.1016/j.jaip.2017.12.036.
7. Bavbek S, Ataman Ş, Akıncı A, Castells M. Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients. J Allergy Clin Immunol Pract 2015; 3 (4): 629-32. doi: 10.1016/j.jaip.2015.01.009.