Case Report

Asia Pacific Allergy

OPEN

Effective desensitization in an IgE-mediated hypersensitivity reaction to tocilizumab in neuromyelitis optica

Francisca Cunha[1,*], Pedro Alves[1], João Cardoso Lopes[1], Carmelita Ribeiro[1], and Ana Todo Bom[1,2]

ABSTRACT

Neuromyelitis optica is a rare, inflammatory autoimmune disease of the central nervous system. Tocilizumab is a humanized monoclonal antibody, which targets the inhibition of the interleukin-6 receptor, a mediator with an important role in the pathophysiological mechanism of neuromyelitis optica. Hypersensitivity reactions to tocilizumab are rare, but similar to other biological drugs can elicit a hypersensitivity reaction. The authors present a case of a 50-year-old female patient, with a neuromyelitis optica, with a severe reaction at the 6th cycle of treatment. The patient was referred to Drug Allergy Consultation, where she underwent tocilizumab skin tests: intradermal test 1/1,000 with a positive result. The patient was then proposed for drug desensitization, and, to date, the patient has undergone 22 desensitization cycles, all of which were uneventful. This case emphasizes the importance of trying to phenotype the hypersensitivity reactions to monoclonal antibodies, and therefore invest in an allergy workup to make the best decision for our patients.

Keywords: Desensitization protocol; IgE-mediated hypersensitivity; neuromyelitis optica; tocilizumab

1. Introduction

Classically known as Devic's disease [1], neuromyelitis optica (NMO) is a rare, chronic inflammatory autoimmune disease of the central nervous system [2, 3]. Predominantly, NMO affects the spinal cord and optic nerve [3].

Tocilizumab (TCZ) is a humanized monoclonal antibody that inhibits the interleukin-6 (IL-6) receptor, blocking IL-6´s proinflammatory activities, which have an important role in the pathophysiological mechanism of NMO [4]. Its effectiveness has been demonstrated in several autoimmune pathologies, with European Medicines Agency approval for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. However, only a few successful cases in the treatment of NMO have been described [5]. According to the literature, other treatments can be used in NMO, such as the classic immunosuppressive medications (azathioprine and mycophenolate mofetil) and other monoclonal antibodies with different targets (rituximab, eculizumab, satralizumab, and inebilizumab) [6].

With its increasing use, different types of adverse reactions have been reported to TCZ. The most common adverse reactions to TCZ are type A reactions, namely infections, gastrointestinal symptoms, headache, hypertension, increased liver enzymes, and injection site reactions [6]. Similar to other biological drugs, TCZ can elicit hypersensitivity reactions (HSR)—type I, cytokine-release, mixed, and type IV—that are estimated to occur in 0.7% of treated patients [7, 8]. In daily clinical practice, it is essential to recognize a hypersensitivity reaction and its severity. In anaphylaxis, accurate diagnosis and adequate and timely treatment are essential. Desensitization to a drug can be an "alternative" to the use of the drug indicated for the pathology in question.

2. Case report

Our patient is a 50-year-old female, without past allergies, diagnosed with NMO in 2020. The patient started treatment with TCZ in 2021. She underwent 5 uneventful treatment sessions with TCZ (400 mg), each lasting 2 hours—1 hour of infusion followed by another hour of surveillance. At the 6th cycle of treatment, approximately 15 to 30 minutes after the start of the TCZ infusion, she presented with a pruritic and erythematous maculopapular lesion, starting on the heels, and then proximally progressing and affecting the entire body's surface. Concomitantly, dizziness and hypotension were observed. No other symptoms were reported—angioedema, dyspnea, wheezing, oropharyngeal tightness, gastrointestinal symptoms, lipothymia, or syncope. The reaction was treated with intramuscular clemastine 2 mg and intravenous methylprednisolone 125 mg, with consequent symptoms resolution. The patient was then referred to our Drug Allergy Clinic, where she underwent, 8 weeks after the reaction, skin tests with TCZ (20 mg/mL): prick

[1]*Allergy and Clinical Immunology Department, Coimbra Hospitalar and University Center, Coimbra, Portugal,* [2]*Pathophysiology Institute, Faculty of Medicine, Coimbra University, Coimbra, Portugal*

**Correspondence to Francisca Cunha*

Allergy and Clinical Immunology Department, Coimbra Hospitalar and University Center, Praceta Prof. Mota Pinto 3000-075 Coimbra, Portugal.

Tel: +351-917-470-247.

Email: francisca.cunha.tavares@gmail.com

The authors declare that the clinical case has not been previously published, and isn't for publication consideration elsewhere. Written and oral informed consent from the patient was properly obtained.

Received: 25 January 2024; Accepted: 12 November 2024

Published online 13 January 2025

http://dx.doi.org/10.5415/apallergy.0000000000000170

testing at 1/100, 1/10, and 1/1 concentrations were negative; however, intradermal testing was positive at 1/1,000 (0.02 mg/mL) (Fig. 1). Prick tests with latex, positive (histamine chloridrate 10 mg/mL), and negative controls (saline solution) were also performed. The excipient Polysorbate-80, which is present in the drug's composition, was also tested, with negative results. In compliance with the 2002 Allergy recommendations for skin test diagnostic procedures, we then excluded irritant reactions by testing the intradermal 1/1,000 concentration in 10 nonexposed controls [9]. No reaction was observed in this group (the written and oral informed consents were obtained for controls). These results confirmed the diagnosis of an IgE-mediated hypersensitivity reaction to TCZ.

3. Desensitization procedure

Given the need to undergo treatment with TCZ, due to the high risk of NMO recurrence, the patient was then proposed for drug desensitization. Desensitization was carried out using a protocol of 11 steps and 3 bags with a cumulative dose of 400 mg (Table 1) [10–12], and antiallergic premedication. Taking into account the therapeutic cycles (6-week intervals) and TCZ's half-life, each treatment was carried out using a desensitization protocol. To date, the patient has undergone 22 desensitization cycles with TCZ, all of which were uneventful, and her clinical condition has progressed favorably.

4. Discussion

Biologicals are a crucial therapeutic resource in immunological, inflammatory, and oncological diseases, due to their selective targets. The widespread use of biological therapy in clinical practice is believed to have significantly contributed to an increase in the number of HSRs over the last few years [13]. According to the literature, TCZ provided a safe and effective treatment for NMO [14]. However, hypersensitivity to TCZ does not seem to be that rare, and skin testing has been shown to be useful for the diagnosis of type I and type IV phenotypes.

Given the description of the clinical case, we are facing a severe hypersensitivity reaction, anaphylaxis. The recommended treatment is adrenaline, although its administration was not carried out by the team that assisted the patient at the time of the reaction. The authors want to reinforce the importance of recognizing anaphylaxis and the need to administer the appropriate treatment, adrenaline.

In our case report, we were able to confirm an IgE-mediated hypersensitivity reaction (type I) using skin testing. This method has also proven to be useful in the confirmation of IgE-mediated

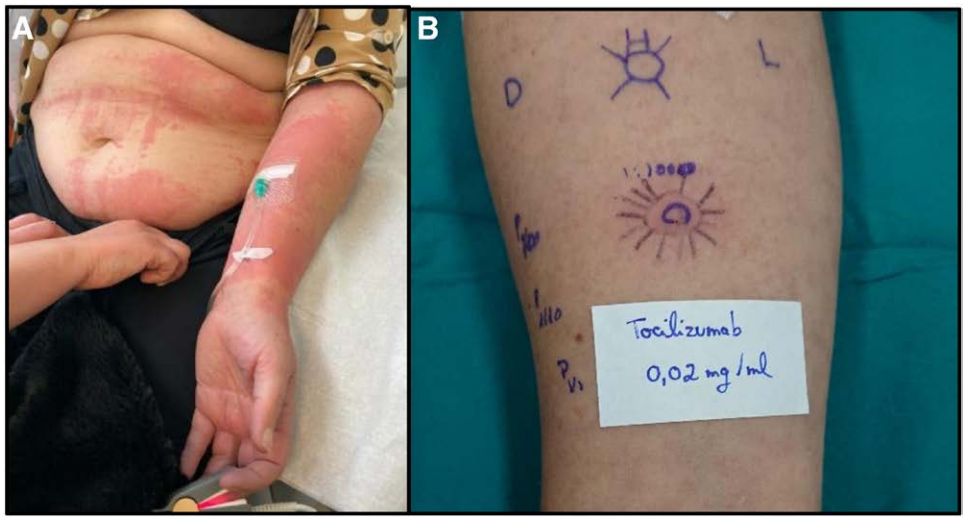

Figure 1. Clinical manifestations of the index reaction and results of skin test with tocilizumab. (A) Erythematous maculopapular lesions at the 6th cycle of tocilizumab. (B) Skin testing tocilizumab, with a positive test at the concentration of 0.02 mg/mL.

Table 1.

Tocilizumab desensitization protocol

Step	Bag	Infusion rate, mL/h	Time, min	Incremental dose, mg	Cumulative dose, mg
1	A	10	15	0.04	0.04
2	A	25	15	0.1	0.14
3	A	50	15	0.2	0.34
4	A/B	100	15	0.4	0.74
5	B	20	15	0.8	1.54
6	B	50	15	2	3.54
7	B/C	100	15	4	7.54
8	C	20	15	8	15.54
9	C	40	15	16	31.54
10	C	80	15	32	63.54
11	C	160	79	337	400

Solution A: 0.016 mg/mL. Solution B: 0.16 mg/mL. Solution C: 1.6 mg/mL.

hypersensitivity reactions, in risk stratification, severity prediction, and, at the same time, selection of a suitable therapeutic approach for the patient.

Weighing the risks and benefits, the patient underwent a desensitization protocol. That protocol was defined with the input of a multidisciplinary team and accompanied by close medical surveillance during all cycles of desensitization with TCZ. The desensitization was successful, with significant improvements in the clinical management of the patient's disease. To our knowledge, despite few published case reports of desensitization to TCZ in rheumatologic diseases, this is the first described case of TCZ desensitization in NMO. It also proposes nonirritating concentrations for skin testing, using negative controls.

We believe that it is necessary to increasingly try to phenotype the HSRs to monoclonal antibodies, and therefore invest in an allergy workup to make the best decision for our patients.

Conflicts of interest

The authors have no financial conflicts of interest.

Author contributions

Francisca Cunha: conceptualization of the work, drafting the work, writing, and editing. Pedro Alves and João Cardoso Lopes: conceptualization of the work, review, and editing. Carmelita Ribeiro: conceptualization of the work and supervision. Ana Todo Bom: supervision, validation, and review.

References

1. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999;53:1107-1114.
2. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-189.
3. Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. J Neuroinflammation 2021;18:208.
4. Tétu P, Hamelin A, Moguelet P, Barbaud A, Soria A. Management of hypersensitivity reactions to tocilizumab. Clin Exp Allergy 2018;48:749-752.
5. Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. Nat Rev Dis Primers 2020;6:85.
6. Giglhuber K, Berthele A. Adverse events in NMOSD therapy. Int J Mol Sci 2022;23:4154.
7. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. J Allergy Clin Immunol 2018;142:159-170.e2.
8. Galvão VR, Castells MC. Hypersensitivity to biological agents-updated diagnosis, management, and treatment. J Allergy Clin Immunol Pract 2015;3:175-85; quiz 186.
9. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.
10. Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am 2009;29:585-606.
11. Alvarez-Cuesta E, Madrigal-Burgaleta R, Broyles AD, Cuesta-Herranz J, Guzman-Melendez MA, Maciag MC, Phillips EJ, Trubiano JA, Wong JT, Ansotegui I; Steering Committee Authors. Standards for practical intravenous rapid drug desensitization & delabeling: a WAO committee statement. World Allergy Organ J 2022;15:100640.
12. Villarreal González R, González Díaz S, de Lira Quezada C, Macías Weinmann A, Acuña Ortega N. Desensibilización rápida a tocilizumab en artritis idiopática juvenil sistémica [Rapid desensitisation to tocilizumab in systemic idiopathic juvenile arthritis]. An Pediatr (Engl Ed) 2021;94:180-181.
13. Bavbek S, Pagani M, Alvarez-Cuesta E, Castells M, Dursun AB, Hamadi S, Madrigal-Burgaleta R, Sanchez-Sanchez S, Vultaggio A. Hypersensitivity reactions to biologicals: An EAACI position paper. Allergy 2022;77:39-54.
14. Du C, Zeng P, Han JR, Zhang TX, Jia D, Shi FD, Zhang C. Early initiation of tocilizumab treatment against moderate-to-severe myelitis in neuromyelitis optica spectrum disorder. Front Immunol 2021;12:660230.