ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Coexisting autoimmune diseases: an opportunity to associate immunobiologicals?

Coexistência de doenças autoimunes: oportunidade para a associação de imunobiológicos?

Isaac Teodoro Souza-e-Silva[1], Pablo Waldeck Gonçalves-de-Souza[1], Rossy Moreira Bastos-Junior[1], Sérgio Duarte Dortas-Junior[1], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

Autoimmune diseases can be safely treated in clinical practice with immunobiologicals. The simultaneous occurrence of multiple immune-mediated diseases in the same individual could require a combination of immunobiologicals to control symptoms and improve quality of life. We report the case of a patient with rheumatoid arthritis who was receiving etanercept and required additional omalizumab for chronic spontaneous urticaria.

Keywords: Urticaria, angioedema, omalizumab, etanercept, biological therapy.

RESUMO

O tratamento das doenças autoimunes com imunobiológicos é uma opção segura na prática clínica. A simultaneidade na ocorrência de doenças imunomediadas em um mesmo indivíduo pode determinar a necessidade da associação dos imunobiológicos para controle dos sintomas e melhora da qualidade de vida dos doentes. Relatamos o caso de uma paciente com artrite reumatoide em uso de etanercepte, que necessitou da associação de omalizumabe para o tratamento de urticária crônica espontânea.

Descritores: Urticária, angioedema, omalizumabe, etanercepte, terapia biológica.

Introduction

Immunobiological therapy aims at optimize the therapeutic management for several diseases. It has changed the course of several immunoallergic diseases, such as urticaria, atopic dermatitis, and asthma, as well as a number of rheumatological and other diseases. Immunobiologicals have been the subject of several studies in recent years. Their efficiency in disease control has restored quality of life for patients suffering from severe and persistent symptoms. Thus, patients with associated comorbidities may benefit from the combined use of immunobiologicals in their therapeutic plan.

In this article, we report the case of a rheumatoid arthritis patient being treated with etanercept who required associated omalizumab for chronic spontaneous urticaria (CSU). The treatment was effective and safe.

Case report

A 66-year-old woman with rheumatoid arthritis had been using subcutaneous etanercept (anti-tumor necrosis factor) 50 mg weekly for 10 years. The disease was under control, with no new joint complaints and improved morning stiffness. She reported being treated for systemic arterial hypertension with losartan, having a thyroidectomy in 1977 (no cause was reported), and having recovered from hepatitis C in 2018.

1. Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ), Immunology Service - Rio de Janeiro, RJ, Brazil.

Submitted Apr 21 2023, accepted June 12 2023.

Arq Asma Alerg Imunol. 2023;7(2):209-12.

http://dx.doi.org/10.5935/2526-5393.20230027-en

In January 2020, she began having wheals associated with angioedema, mainly on the face and feet, with no specific trigger (Figure 1). She used oral corticosteroids for exacerbations, in addition to first-generation antihistamines prescribed by a dermatologist. After evaluation by an immunologist, following current guidelines for chronic urticaria, the following tests were performed - complete blood count, erythrocyte sedimentation rate, C-reactive protein, total IgE, and antithyroperoxidase tests were performed (Table 1). Although she was prescribed second-generation antihistamines (even quadruple doses), she had no success controlling the disease (urticaria control test [UCT] = 0 and urticaria activity score over 7 days [UAS7] = 42). In February 2022, she started using omalizumab 300 mg every 4 weeks and a quadruple dose of loratadine 10 mg/day. The disease was completely controlled (UCT = 16, UAS7 = 0) within 1 week of the first omalizumab dose. In September 2022, the interval between applications was increased, but after 4 weeks itching and urticaria returned (UCT = 11 and UAS7 = 10). Treatment was again prescribed at a 4-week interval, and the patient has remained on omalizumab 300 mg/4 weeks associated with loratadine 10 mg without showing further symptoms (UCT = 16 and UAS7 = 0). Table 2 shows the patient's laboratory results before and after beginning omalizumab in association with etanercept, which remained unchanged and within normal limits. Although both etanercept and omalizumab have been proven safe, since this patient had a history of methotrexate use for rheumatoid arthritis and previous hepatitis C virus infection, it was decided to monitor her metabolic panel as directed in the etanercept package insert.

Table 1
Laboratory tests performed between 02/24/2020 and 03/24/2021

Complete blood count:	
Hgb 14 g/dL	
Htc 42%	
Leukogram 10,100 mm^3 (0/0/0/0/0/0/66/29/5)	
Plt: 321,000	
AntiTPO < 5.0 UI/mL	IgE total 324 UI/mL
CRP 10 mg/dL	ESR 5 mm in 1 hour

Hgb = hemoglobin, Htc = hematocrit, Plt = platelets, AntiTPO = anti-thyroperoxidase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

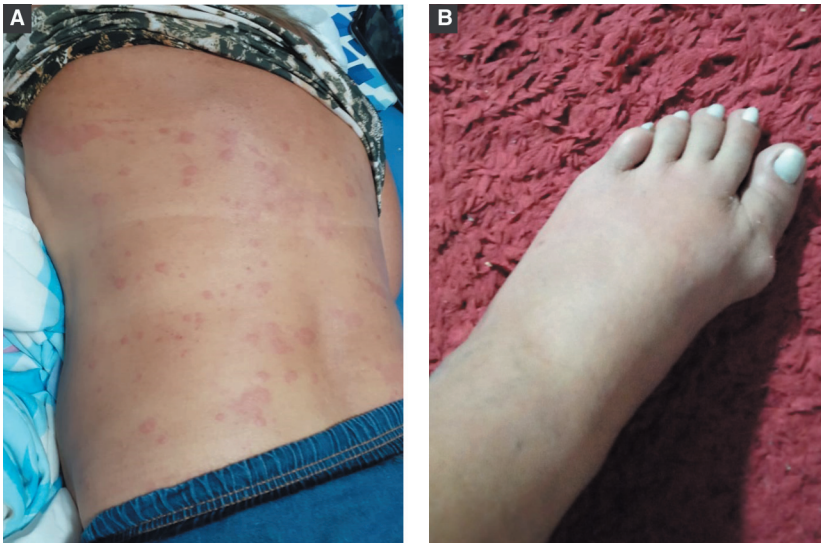

Figure 1
A) Patient's back with erythematous lesions due to chronic spontaneous urticaria.
B) Foot with erythematous lesions and hallux deformity characteristic of rheumatoid arthritis

Discussion

Urticaria is a debilitating disease that affects most patients entire bodies. CSU is characterized by episodes of urticaria and angioedema, or both, for > 6 weeks. Its pathophysiology is not fully understood, although tissue mast cell activation and inflammatory mediator release is the final common pathway of all forms of urticaria.[1] In addition to urticaria and angioedema, CSU is characterized by pruritus, which can be so intense that it incapacitates the patient.

Despite its low prevalence and complex etiology, in addition to its recurrent and unpredictable course, CSU can persist for years, with approximately 10% of patients presenting symptoms ≥ 5 years.[2] Women are more affected and the most affected age group is 20-40 years. Although its pathogenesis has not been fully elucidated, IgG-related autoimmunity and IgE-mediated autoallergy are the main mechanisms described in the literature.[3]

CSU is diagnosed through a detailed evaluation of the patient's clinical history and a physical examination to rule out other possible causes for the symptoms. No single specific diagnostic test has been developed.[4] Current guidelines recommend a complete blood count and erythrocyte sedimentation rate and/or C-reactive protein; specialists should order total and antithyroperoxidase IgE. The same guidelines recommend against extensive laboratory tests not guided by clinical history.[4]

CSU treatment is well established, aiming at complete symptom control so that patients can have a normal life.[4] The first line of treatment consists of monotherapy with daily doses of second-generation antihistamines; the dosage is dependent on the symptom, and can be even quadrupled to achieve complete control.[4]

In patients whose symptoms are refractory to quadruple monotherapy with second-generation antihistamines, association with omalizumab is indicated.[4] Omalizumab is a humanized anti-IgE monoclonal antibody that was initially used to treat severe allergic asthma. It selectively binds to circulating IgE, blocking its binding to mast cell and basophil receptors. Its effectiveness for CSU has been demonstrated in double-blind studies, as well as its safety for children > 12 years old, pregnant women, and patients with other diseases, such as cancer.[5]

It is indicated as an additional therapy for CSU (associated with second-generation antihistamines) in a subcutaneous dose of 300 mg every 4 weeks. The dose can be increased to 450 mg or 600 mg, and the time interval can be reduced to 2 weeks.

Etanercept blocks tumor necrosis factor, which is elevated in inflammatory diseases. It may be recommended for rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis. It effectively reduces symptoms and is safe for long-term use, for example, to treat children > 2 years of age with juvenile idiopathic arthritis.[6]

CSU has been associated with autoimmune, atopic, and psychiatric diseases. In a meta-analysis of 60 studies, the prevalence of organ-specific autoimmune diseases in patients with CSU was 27.5%, among which autoimmune thyroid diseases stood out.[2] However, no studies have clearly linked these diseases with CSU.

Table 2
Laboratory tests pre- and post-treatment with omalizumab

Date	ALP	ALT	AST	GGT	Urea	Creatinine	Htc
Dec 2020	115 U/L	27 U/L	29 U/L	33 mg/dL	1.1 mg/dL	14.6 mg/dL	45.1%
Apr 2022	123 U/L	21 U/L	28 U/L	33 mg/dL	1.0 mg/dL	14.9 mg/dL	47%

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transferase, Htc = hematocrit.

These associations highlight the need to study omalizumab in combination with other immunobiologicals; there are few reports in the literature about the concomitant use of omalizumab and other biologics. A case was reported of a male patient who received guselkumab for psoriasis and omalizumab for CSU over a period of 21 months with no clinically relevant adverse effects or drug interactions.[7] In another case report, a patient developed CSU while using adalimumab for psoriatic arthritis. Omalizumab was prescribed concomitantly with adalimumab for 24 weeks, after which it was discontinued due to complete control of urticaria.[8] A recent study evaluated the combined use of omalizumab with other biologics (adalimumab, ustekinumab, secukinumab, and ixekizumab) indicated for psoriasis or hidradenitis suppurativa in 31 patients. No adverse events were observed due to the association, as has been found in other studies. One patient had diarrhea 9 months after adding omalizumab to secukinumab, which was resolved after discontinuing secukinumab.[3]

The greatest challenge to using a combination of immunobiologicals is the high cost of treatment. However, it is important consider whether these costs are outweighed by the natural course of some autoimmune diseases in the long term.

The present case described a patient with comorbidities and an extensive and complex pathological history who, after careful analysis, received a safe treatment that changed the course of her diseases without any side effects. Her laboratory results remained unchanged throughout treatment (Table 2), clearly demonstrating the safety of the combined treatment.

Therapeutic advances in chronic autoimmune diseases have prolonged the lives of patients. In patients with multiple diseases, combined immunobiologicals are becoming increasingly common. The safety of concomitant immunobiologicals, as seen in this case, is extremely important. The study of such combinations and the establishment of consensus and norms for their use is fundamental, as it can radically change the course of diseases and improve quality of life. This case report stands out for demonstrating the safety of a combination of immunobiologicals that act on different inflammatory response pathways to control debilitating and difficult-to-control chronic diseases.

References

1. Gehlen B, Mousinho-Fernandes M, Argolo PN, Pereira GF, Kalil J, Motta AA, et al. Tratamento da UCE refratária aos anti-histamínicos e na impossibilidade do omalizumabe, nos adultos. Arq Asma Alerg Imunol. 2021;5(3):223-31.
2. Murdaca G, Paladin F, Borro M, Ricciardi L, Gangemi S. Prevalence of autoimmune and autoinflammatory diseases in chronic urticaria: pathogenetic, diagnostic and therapeutic implications. MDPI Biomedicines. 2023;11(2):410.
3. Koç Yıldırım S, Erbagcı E, Hapa A. Omalizumab treatment in combination with any other biologics: Is it really a safe duo? Australas J Dermatol. 2023;64(2):229-33.
4. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66.
5. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgereit T, Maurer M. How to Treat Patients with Chronic Spontaneous Urticaria with Omalizumab: Questions and Answers. J Allergy Clin Immunol Pract. 2020;8(1):113-24.
6. Pfizer. Bula Enbrel® etanercepte (Internet). Available at: https://www.pfizer.com.br/bulas/enbrel.
7. Karstarli Bakay OS, Kacar N. Combined treatment with omalizumab and secukinumab in a patient with chronic spontaneous urticaria and psoriasis. Dermatol Ther. 2022;35(9):e15638.
8. Diluvio L, Vollono L, Zangrilli A, Manfreda V, Prete MD, Massaro A, et al. Omalizumab and adalimumab: a winning couple. Immunotherapy. 2020;12(18):1287-92.

Abbreviations: RA = rheumatoid arthritis, anti-TPO = antithyroperoxidase, HCV = hepatitis C virus, CRP = C-reactive protein, UAS7 = urticaria activity score over 7 days, CSU = chronic spontaneous urticaria, UCT = urticaria control test, ESR = erythrocyte sedimentation rate.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Sérgio Duarte Dortas-Junior
E-mail: sdortasjr@gmail.com