www.jcimcr.org

JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 2

Tildrakizumab and omalizumab: An interlocking therapy for autoimmune conditions

Laura Diluvio*; Chiara Pensa; Arianna Piccolo; Caterina Lanna; Luca Bianchi; Elena Campione

Department of Dermatology, University of Rome Tor Vergata, Viale Oxford, 81 00133 Rome, Italy.

***Corresponding Authors: Laura Diluvio**

Dermatologic Unit, Policlinico Tor Vergata, Viale Oxford, 81 00133 Roma, Italy.

Tel: +65-6716-2000;

Email: lauradiluvio@yahoo.it

Received: Jun 21, 2021

Accepted: Jul 29, 2021

Published: Jul 31, 2021

Archived: www.jcimcr.org

Abstract

In Western countries the number of individuals suffering from an autoimmune condition is constantly growing and often patients suffering from autoimmune disease are susceptible to developing a second autoimmune disorder. We report a case of an adult female patient affected by psoriasis vulgaris and treated with tildrakizumab, a humanized monoclonal antibody targeting interleukin-23, who later developed chronic spontaneous urticaria and started omalizumab, a humanized antibody to IgE, showing a favorable outcome. We speculate that the two combined therapies have restored the cytokine balance bringing it towards tolerance and remission of the two pathologies. It is conceivable that tildrakizumab may have a synergic action with omalizumab in the treatment of urticaria in patients affected by both psoriasis and urticaria. Our case and the study of the mechanisms of action of the two drugs suggest how the two therapies can act with an interlocking mechanism in achieving the final therapeutic effect.

Keywords: Chronic spontaneous urticarial; dual biologic therapy; omalizumab; psoriasis; tildrakizumab.

Introduction

Psoriasis causes a long-lasting, inflammatory disease of skin and joints, characterized by the appearance of sharply demarcated erythematous and scaly plaques [1]. An augmented inflammation driven by the tumor necrosis factor-α/interleukin-23/interleukin-17 axis represents the major pathomechanism of disease. Furthermore, psoriasis is considered an autoimmune disease that manifests with autoreactive T cells and can coexist with other autoimmune diseases [2]. Chronic spontaneous Urticaria (CSU) represents a common skin disease easily distinguished by the presence of migrating pruritic wheals, angioedema, or both for at least six consecutive weeks. Evidence confirmed that CSU represents an autoimmune condition in up to 50% of cases, in which mast cells and T cells appear to play a key pathogenetic role [3]. Furthermore, according to the theory of "overlapping autoimmune diseases", patients suffering from autoimmune disease are susceptible to developing a second autoimmune disorder, as noted with chronic urticaria and insulin-dependent diabetes mellitus, rheumatoid arthritis, celiac disease, Graves' disease, vitiligo, pernicious anemia, Hashimoto's thyroiditis and psoriasis [4]. Over the last few years, biologics targeting the Il-23/Il-17 axis have marked significant therapeutic progress for psoriasis, but recent evidence has shown that these can also be beneficial in the case of recalcitrant CSU. We report a case of an adult female patient, previously affected by psoriasis and treated with tildrakizumab, a humanized IgG1 monoclonal antibody targeting interleukin-23, who developed

chronic spontaneous urticaria and started omalizumab, a humanized antibody to IgE, showing a favorable outcome. Our case and the study of the mechanisms of action of the two drugs suggest how the two therapies can act with an interlocking mechanism in achieving the final therapeutic effect.

Case report

A 35-year-old Caucasian female patient presented to our Dermatologic Unit with multiple episodes of urticaria (Figure 1a). Skin manifestations started insidiously approximately 2 years before and past medical history revealed psoriasis since the age of sixteen, hypothyroidism, insulin resistance, and primary lymphedema of the left lower limb. Her current medications included tildrakizumab since April 2020. Previous anti-psoriatic drugs included corticosteroids, narrow-band ultraviolet B therapy, cyclosporine, MTX and apremilast, all discontinued due to lack of effectiveness. Before starting tildrakizumab, her PASI was 25 and DLQI 15 (Figure 2a), after 12 weeks of therapy her PASI was 7 and DLQI 6. At week 24 the patient achieved complete remission of the psoriatic disease (Figure 2b). Complete blood count, electrophoresis, coagulation profile, liver and kidney function tests, thyroid and antibody function tests, antinuclear antibody test, extractable nuclear antigen panel, C1 esterase inhibitor test, C3-C4, diagnostic markers of viral hepatitises, HIV, erythrocyte sedimentation rate and parasitological testing were normal. An increased c-reactive protein blood test was observed (6.2 mg/L, normal range: 0-5), along with total serum IgE level (344 UI/ml, normal range: 0-87). Skin prick and patch tests were negative. Human Leukocyte Antigen (HLA) class I testing was also performed: HLA-A 2G:02P, 30:1P; HLA-B 13:02 P, 35:03P; HLA-C 06:02P, 12:03P, which has been linked to the development of psoriasis and psoriatic arthritis [5]. Omalizumab 300 mg as an add-on to H1-antihistamines (rupatadine) was administered by subcutaneous injection every 4 weeks for 6 months. Clinical assessment of weekly Urticaria Activity Score for 7 days (UAS-7) was performed at baseline, 12 and 24 weeks of treatment. A complete reset of the UAS-7, from 40 at baseline to 0 in weeks 12 and 24, was oserved (Figure 1b). Throughout the entire treatment with omalizumab, administering of tildrakizumab mg every other week was continued as indicated for psoriatic disease (100 mg at week 0, and 4, and every 12 weeks thereafter). No adverse effects were reported.

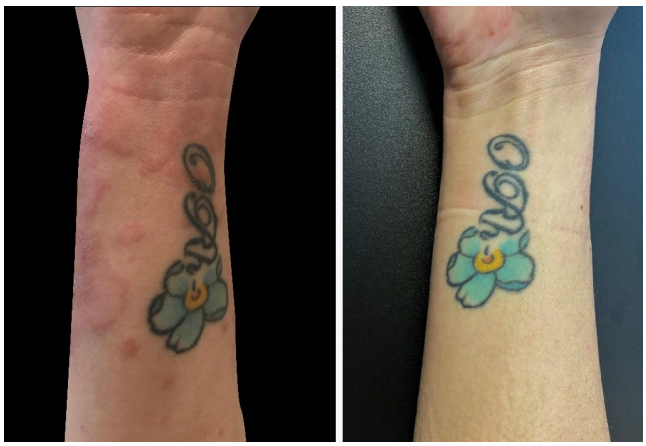

Figure 1: (A) chronic spontaneous urticaria affecting patient's wrist before administering omalizumab. **(B)** clearing of wheals 12 weeks after starting omalizumab.

Figure 2: (A) Psoriasis affecting patient's hands before administering tildrakizumab. **(B)** clearing of psoriasic lesions 24 weeks after starting tildrakizumab.

Discussion

Physicians are often reluctant to prescribe simultaneous biologic therapies because of safety hazards and nowadays very little data exist about combination therapy for psoriasis and CSU [6]. We report for the first time a case of a young female patient suffering from recalcitrant psoriasis and urticaria successfully treated with two concomitant biologics, tildrakizumab and omalizumab.

Omalizumab binds to free IgE, which lowers free IgE levels and causes FcεRI receptors on basophils and mast cells to be downregulated further preventing IgE-mediated histamine release and inflammation [7]. However, as concerns the safety of omalizumab in combination with a second biologic agent there were no statistically significant differences in the average number of infections per year and this drug can be used for patients affected by CSU with comorbid chronic inducible urticaria, with cancer, who receive other biologics or immunosuppressant drugs, or who are pregnant or want to become pregnant, or are breast-feeding [8]. Tildrakizumab is a high-affinity humanized IgG1 monoclonal antibody targeting interleukin-23 p19, recently approved for use in moderate to severe psoriasis [1]. The reSURFACE studies demonstrated the safety and tolerability of tildrakizumab, which allowed obtaining clinical efficacy in patients, who do not respond or who only partially respond to older-generation biologics [9]. Recently, IL-17A has been proved to be increased in the skin of CSU patients – both lesional or non-lesional skin biopsies compared with normal skin. Whether produced by CD4+ T cells and/or is truly produced by mast cells, IL-17A seems to play a major role in increasing the degranulation activity of skin mast cells in CSU [10]. Increasing reports of successfully treated CSU patients with anti-Il-17 were published recently, strengthening the concept that the TH-17 axis could be a proper candidate to be targeted in CSU [10]. The anti-IL-17A antibody had a slow onset of action, but treated patients remained free of other drugs during therapy [11]. By an argument similar to the one that led to increasing success in psoriasis treatment, we hypothesize that acting upstream in the IL-23/IL-17 cytokine pathway may be beneficial for CSU patients likewise. Tildrakizumab specifically blocks the p19 subunit of interleukin-23, thus inhibiting Th17 polyclonal expansion and

survival, which rely on Il-23 receptor activation [12]. Il-23/Il-17 axis plays a pivotal role in the development of autoimmune diseases, such as psoriasis, but it seems to be also implicated in the pathogenesis of urticaria. Indeed serum levels of IL-17 and IL-23 are increased in patients affected by chronic urticaria and positively correlated with the severity of the disease [13]. On the other hand, omalizumab could contribute to this mechanism of action by further reducing the number of circulating free IgE and, as suggested by Gadir, by increasing Treg cell activity due to the reversal of their Th2 cell-like program [14]. An increase in Treg cells could restore the balance between Th17/Treg, favoring the restoration of tolerance and the shutdown of autoimmunity. We hypothesize that the patient has been refractory to other therapies for psoriasis in the past due to the predominant role of IL-23 in her type of psoriasis: such high levels may also have induced the concomitant urticarial manifestation. The two combined therapies have restored the balance bringing the balance towards tolerance and therefore towards the remission of the two pathologies. It is therefore conceivable that tildrakizumab may have a synergic action with omalizumab in the treatment of urticaria in patients affected by both psoriasis and urticaria. This case supports both the efficacy and safety of tildrakizumab and omalizumab as dual biologic therapy of recalcitrant psoriasis and CSU, for their interaction on the Th17/Treg axis, possible point of union between the two pathologies.

Data availabity statement: Data available on request from the authors.

Ethical statement and informed consent statement: This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions: LD, CP, AP, CL, EC and LB were involved in direct management of the patient and were drafted the first manuscript and reviewed the literature. A.Z. supervised the manuscript drafting. All authors read and approved the final manuscript.

References

1. Banaszczyk K. Tildrakizumab in the treatment of psoriasis - literature review. Reumatologia. 2019; 57: 234-238.
2. Kumar B, Jain R, Sandhu K, Kaur I, Handa S. Epidemiology of childhood psoriasis: A study of 419 patients from northern India. Int J Dermatol. 2004; 43: 654–658.
3. Leznoff A, SussmanG L. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy ClinImmunol. 1989; 84: 66-71.
4. Kolkhir P, Borzova E, Grattan C, Asero R, Pogorelov D, et al. Autoimmune comorbidity in chronic spontaneous urticaria: A systematic review. Autoimmun Rev. 2017; 16: 1196-1208.
5. Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018; 178: 854-862.
6. Diluvio L, Vollono L, Zangrilli A et al. Omalizumab and adalimumab: A winning couple. Immunotherapy. 2020; 12: 1287-1292.
7. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy. 2017; 72: 519– 533.
8. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, ButtgereitT, et al. How to Treat Patients with Chronic Spontaneous Urticaria with Omalizumab: Questions and Answers. J Allergy ClinImmunol Pract. 2020 ; 8: 113-124.
9. KimballAB, PappKA, ReichK et al. Efficacy and safety of tildrakizumab for plaque psoriasis with continuous dosing, treatment interruption, dose adjustments and switching from etanercept: results from phase III studies.Br J Dermatol. 2020; 182: 1359–1368.
10. Toubi E, Vadasz Z. The Emerging Role of IL-17 in the Immune-Pathogenesis of Chronic Spontaneous Urticaria. Immunotargets Ther. 2020; 22: 217-223.
11. Sabag DA, Matanes L, Bejar J, Sheffer H, Barzilai A, Church MK, et al. Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. ClinExp Allergy. 2020; 50: 799-804.
12. Leung S, Liu X, Fang L et al. The cytokine milieu in the interplay of pathogenic Th1/Th17 cells and regulatory T cells in autoimmune disease. Cell Mol Immunol. 2010; 7: 182–189.
13. Atwa MA, Emara AS, Youssef N, Bayoumy NM. Serum concentration of IL-17, IL-23 and TNF-α among patients with chronic spontaneous urticaria: Association with disease activity and autologous serum skin test. J Eur Acad Dermatol Venereol. 2014; 28: 469-474.
14. Abdel-Gadir A, Schneider L, Casini A, et al. Oral immunotherapy with omalizumab reverses the Th2 cell-like programme of regulatory T cells and restores their function. ClinExp Allergy. 2018; 48: 825-836.