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CASE REPORT

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Case of benralizumab-induced exacerbations of chronic spontaneous urticaria

Eli Magen[1,2] | **Irina Komarova**[1] | **Israel Magen**[3] | **Sofia Phirtskhalava**[3]

[1]Department of Medicine C, Clinical Immunology and Allergy Division, Barzilai University Medical Center, Ben-Gurion University of the Negev, Ashkelon, Israel

[2]Leumit Health Services, Tel Aviv-Yafo, Israel

[3]Tbilisi State Medical University, Tbilisi, Georgia

Correspondence
Eli Magen, Medicine C Department, Ben Gurion University of Negev, Barzilai University Medical Center, Ashkelon, Israel.
Email: allergologycom@gmail.com

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Abstract

The role of IL-5 in chronic spontaneous urticarial (CSU) is unclear. It may be that benralizumab is an important bidirectional modifier of CSU; that is, blocking IL-5 may improve CSU in some patients, but it is possible that it may worsen CSU in others.

KEYWORDS

benralizumab, chronic, exacerbation, induced, spontaneous, urticaria

1 | INTRODUCTION

The anti-interleukin-5 monoclonal IL-5- (IL-5) receptor-α antibody benralizumab is currently proposed as one of the drugs for the treatment of patients with severe chronic spontaneous urticaria (CSU).[1] The rationale for using targeted therapy against IL-5 in CSU is the eosinophilic infiltrates and the presence of IL-5 in CSU hives, suggesting that IL-5 plays a role in the pathophysiology of CSU.[1,2,3] Here, we report a patient with CSU and concurrent severe eosinophilic asthma in whom benralizumab exacerbated CSU. Type I hypersensitivity to benralizumab was ruled out by a negative skin prick and intradermal test. The underlying mechanism is not clear in this case, but type II hypersensitivity induction by benralizumab is considered.

2 | CASE PRESENTATION

A 59-year-old atopic man presented with severe asthma attacks. His medical history included nonseasonal allergic rhinitis and atopic asthma for 18 years and a concomitant CSU with a positive autologous serum skin test (ASST) that had persisted for 2 years.

His CSU was well controlled (UAS7 of 0–4) with the oral H1 antihistamine fexofenadine 180 mg (Telfast® Trima Ltd). The patient was also treated with high-dose inhaled corticosteroids (ICS) plus long-acting β-agonists (LABA) (budesonide and formoterol (Symbicort® Turbuhaler® 320/9 μg, AstraZeneca Israel) bid plus montelukast 10 mg qd (Singulair® Merck, Sharp & Dohme Israel) and high-dose administrations of the oral corticosteroid (OCS) prednisone 40 mg qd, but asthma was poorly controlled.

Israel Magen and Sofia Phirtskhalava Medical student.

Peripheral blood count showed a high level of eosinophils (9% – 823 cells/ml). Benralizumab was then started, indicated as additional maintenance therapy for severe eosinophilic asthma poorly controlled despite high-dose ICS plus LABA.[4]

Benralizumab 30 mg (Fasenra®, AstraZeneca Israel) was administered by subcutaneous injection every 4 weeks for the first three doses and every 8 weeks thereafter achieving excellent asthma control. The asthma control test (ACT) (0–25) was 11 before the start of benralizumab treatment and 21 after 4 weeks of benralizumab treatment. We also observed a significant reduction in the blood eosinophil count, which decreased to 2% – 128 cells/ml 2 months after the start of treatment. However, after 3 months, the patient began to suffer daily from severe attacks of urticarial rash and angioedema (UAS7–38). The dose of 180 mg fexofenadine was gradually increased to four times daily without significant benefit. Therefore, benralizumab was discontinued. Two weeks after discontinuation of benralizumab, the UAS7 score decreased from 32 to 6, and the fexofenadine dose was gradually reduced to one tablet per day.

However, 4 months after discontinuation of benralizumab, the patient began to suffer from frequent and severe asthma exacerbations (ACT decreased to 9). Because of the high efficacy of benralizumab in severe eosinophilic asthma, it was decided to resume this medication. Two weeks after resumption of treatment with benralizumab, the patient experienced a severe exacerbation of CSU with daily eruptions of a giant urticarial rash accompanied by symptomatic dermographism and angioedema attacks (UAS7 41), which required re-dosing of fenoxifenadine 180 mg to four times daily and four 3–4-day short-term treatments with high-dose OCS (prednisone 60 mg) within 2 months to control the disease. Two weeks after repeated discontinuation of benralizumab, there was a remarkable clinical improvement in CSU (UAS7–8). To rule out hypersensitivity to benralizumab, we administered prednisone 30 mg/day to the patient to control his hives for 5 days and discontinued the antihistamines. A skin prick test (SPT) and an intradermal test (IDT) with benralizumab were performed on the volar surface of his right arm 6 days after fenoxifenadine discontinuation. Both SPT and the IDT were negative, and the delayed IDT reading was also negative.

The use of medications, UAS7, pulmonary function tests, and asthma control tests, eosinophil and basophil granulocytes in peripheral blood during clinical observation of the patient are listed in Table 1.

3 | DISCUSSION

Three clinical scenarios should be considered when discussing this case. The first assumes that the observed exacerbation of CSU during benralizumab treatment was triggered by a specific hypersensitivity to the drug. In clinical trials, immediate IgE-mediated hypersensitivity reactions (including anaphylaxis) were observed in approximately 3% of patients treated with benralizumab.[5] Type I hypersensitivity reactions occur with humanized monoclonal antibodies whose immunogenicity is caused by the use of transgenic mouse cells that are unable to form human carbohydrate side chains.[6] The

TABLE 1 Medications, UAS7, pulmonary function, and asthma control tests, blood eosinophils, and basophils during clinical observation

	Baseline	4 weeks	12 weeks	28 weeks	30 weeks	32 weeks
ICS + LABA + LTA	+	+	+	+	+	+
Fexofenadine	180 mg/d	720 mg/d	720 mg/d	180 mg/d	720 mg/d	360 mg/d
Benralizumab	–	+	+	–	+	–
UAS7	4	38	32	6	41	8
FEV_1 (L) (1.8–4.5)	2.1	2.7	2.8	1.9	2.7	2.4
FEV_1 (% predicted) (75–125)	68	94	95	65	93	91
FEV_1%/FVC	71	85	87	68	84	82
Asthma control test, ACT (0–25)	11	21	NA	9	NA	NA
Eosinophils (% blood leucocytes) (0.6–4.2)	9	2	NA	11	NA	NA
Eosinophils (cells/μl blood) (50–330)	823	128	NA	898	NA	NA
Basophils, (% blood leucocytes) (0–1.2)	0.8	0.1	NA	0.9	NA	NA
Basophils, (cells/μl blood) (0–100)	49	10	NA	54	NA	NA

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β-agonists; LTA, leukotriene antagonist; UAS7, Urticaria Activity Score 7.

immunogenic region of benralizumab is its idiotype, but its afucosylated Fc region may also represent a novel structure for the immune system.[7]

In our patient, we did not observe clinical signs of immediate hypersensitivity reaction after benralizumab injections. Moreover, the CSU exacerbations in our case occurred very late after the initiation of benralizumab treatment, making a type I hypersensitivity reaction to the drug highly unlikely. Moreover, the absence of a positive local reaction to SPT and IDT was highly suggestive of the absence of IgE-mediated hypersensitivity to benralizumab.

The second clinical scenario could be that immunological dysregulation was triggered by benralizumab treatment targeting regulatory pathways linking natural killer (NK) cells, IL-15, and IL-21 cytokines and triggering type II hypersensitivity.[8] Due to the absence of the fucose molecule in the sugar component of the CH2 domain of the monoclonal antibody, benralizumab has remarkably high affinity for the FcγRIIIa receptor of NK cells and induces potent antibody-dependent cell-mediated cytotoxicity.[9] In addition, activated NK cells induce IFN-γ, TNF-α, GM-CSF, and MIP-1α production upon stimulation and contribute to mast cell and basophil activation.[10] The type hypersensitivity in CSU is thought to be mediated by IgG-induced ADCC against autoantigens (mainly IgG autoantibodies against FcεRI).[11]

The importance of this form of autoimmunity in patients with CSU in the pathogenesis of CSU is well recognized.[11,12]

Our patient with the positive ASST probably had an autoimmune form of CSU. Considering the observed marked basophil depletion after benralizumab treatment, we can additionally speculate that the decreased production of Th2 cytokines and the shifted Th1-type immunological balance associated with basophil depletion may also be related to the exacerbations of CSU.[13] It is interesting to note that the worsening of CSU in our patient occurred despite the reduction in peripheral blood eosinophil count and the associated improvement in asthma. This observation raises the possibility that the eosinophils did not contribute to the reported worsening of CSU in this case. This may argue against the idea that targeting IL-5 may be of therapeutic benefit in all CSU patients.

The third, immune complex formation, was hypothesized to explain some cases of paradoxical autoimmune side effects of mepolizumab therapy in severe eosinophilic asthma.[14] Similar autoimmune mechanisms related to immune complex formation may play a role in patients with paradoxical reactions to benralizumab treatment. The possibility of the formation of immune complexes against benralizumab in the blood, which then deposit in the vessel walls and activate the complement system, with the development of urticarial vasculitis (UV) should be considered. The urticarial wheals of UV persist for more than 24 h in most patients, sometimes up to 72 h, and are resistant to treatment with antihistamines.[15] Although UV mainly affects the skin, it can also affect other organ systems and lead to hypocomplementemia. It may occur in association with autoimmune diseases, drug reactions, infections, or malignancy.[16] Our patient had no systemic manifestations associated with UV (fever, musculoskeletal, renal, gastrointestinal, cardiac, or other manifestations of type III hypersensitivity) and no hypocomplementemia.

The patient refused skin biopsies, whereas the study of the histopathology of spontaneous urticarial lesions as well as those induced by ASST, as performed by other authors,[2] would have greatly facilitated the understanding of the immunopathology in this case.

Regrettably, we cannot perform noninvasive in vitro tests, such as the basophil activation assay or plasma histamine and leukotriene B4 levels, which could provide useful information in this case.

It is possible that benralizumab is an important bidirectional modifier of CSU, that is, blocking IL-5 may improve CSU in most patients, but it is also possible that it worsens CSU in some patients, as in our case.

AUTHOR CONTRIBUTIONS

Eli Magen contributed to acquisition of clinical data. Irina Komarova, Israel Magen, and Sofia Phirtskhalava were involved in analysis and interpretation of data and in drafting of the manuscript. Eli Magen revised it critically for important intellectual content. All authors gave final approval of the version to be published.

CONFLICT OF INTEREST

All authors have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Eli Magen https://orcid.org/0000-0002-7713-423X

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