Case Report

Simultaneous treatment with benralizumab and ustekinumab in a patient with severe asthma and ulcerative colitis

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ABSTRACT

The burden of autoimmune diseases is rising worldwide. The expansion of the population of patients eligible for severe asthma biological therapy we are seeing in clinical practice could lead to the simultaneous use of different monoclonal antibodies. We present the case of biological combination therapy with ustekinumab and benralizumab in a patient with ulcerative colitis and severe eosinophilic asthma. The patient, already undergoing biological treatment for colitis, began to suffer from uncontrolled severe asthma. Since benralizumab was administered, the patient has not experienced any exacerbations requiring oral corticosteroids, emergency department visits, or hospital admissions, and the control of asthma symptoms and respiratory function considerably improved. Twelve months after the initiation of the combination, both diseases are well controlled, without any side effects or blood test abnormalities. To our knowledge, this is one of the first reported cases of patients simultaneously receiving a combination of biological therapy for ulcerative colitis and asthma.

KEY WORDS: Asthma, biological therapy, combination therapy, ulcerative colitis

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INTRODUCTION

In the past few years, major advances in the understanding of the immune system and autoimmune diseases' pathogenesis led to the development of biological therapies, which allowed clinicians to better treat many immune-mediated inflammatory diseases. In severe asthma, biologics proved highly effective in reducing exacerbations, diminishing symptoms, and improving lung function.[1] Patients suffering from autoimmune diseases and treated with a biological agent may suffer from uncontrolled severe asthma and necessitate the prescription of an asthma-approved biological agent, thus requiring the simultaneous use of a second monoclonal antibody. We present the case of a patient with ulcerative colitis (UC) and severe eosinophilic asthma receiving a biological combination treatment with ustekinumab and benralizumab.

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CASE HISTORY

We report the case of a 61-year-old female diagnosed with Ulcerative Colitis in 2016. In 2021 she had started

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biological therapy with adalimumab because she was refractory to corticosteroids. Table 1 shows the medical history and medications of the patient, while Figure 1 summarizes the clinical course of the patient, including lab values, respiratory function tests, and questionnaire scores. In January 2023 she was referred to our severe asthma service. Despite ongoing treatments for asthma, the patient presented dyspnea on mild exertion and uncontrolled daily symptoms (wheezing, nightly cough causing nocturnal awakenings, high consumption of rescue medication) nasal congestion and postnasal drainage, and she had frequent exacerbations. She was prescribed oral prednisone courses 5 times in the previous 12 months from her primary physician, the last one just the month before the referral. The patient presented severe airway obstruction and inadequate control of her symptoms despite maximal inhaler therapy. She was diagnosed with severe uncontrolled eosinophilic asthma and based on her chronic corticosteroid usage and exacerbation history, she was a candidate to receive biological therapy. The patient was referred to an allergologist and a ENT specialist for a complete evaluation also in consideration of her sinonasal symptoms. Skin prick tests indicated no sensitization to pet dander, trees, grasses, and mold allergens. A fiberoptic nasal endoscopy was performed, with evidence of polypoid neoformations obstructing the right ostiomeatal complex, therefore a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) was made. Diagnostic endoscopy allows the formulation of disease severity scores, such as the Nasal Polyp Score (NPS). Her NPS was 2 points for the right nostril and 0 points for the left nostril. Polyposis was graded mild and medical therapy with Mometasone furoate as nasal corticosteroid spray was added to control symptoms before considering surgery. In March 2023 the patient was referred to the Inflammatory Bowel Diseases (IBDs) Unit, to assess the possibility of a simultaneous biological therapy for her UC and Severe Asthma. The decision was to suspend adalimumab and switch to ustekinumab, because the anti-TNF- α agent could have had a negative effect on asthma control determining again steroid dependence, although this time oral corticosteroids (OCS) courses were necessary to control asthma during exacerbations. In the choice of the biological agent switch, also the cardiovascular risk profile related to her arterial hypertension and her carotid artery stenosis played a significant role. Considering the IBD symptoms were controlled and the disease was in the clinical, laboratory, and endoscopic remission, it was decided to start a biological therapy for severe eosinophilic asthma before switching to the anti-IL12/23 biological agent. However, in April 2023 the patient experienced an asthma exacerbation requiring a course of OCS and antibiotic therapy, and the start of a biological therapy for asthma was delayed. In May 2023 the patient started ustekinumab therapy due to relapse of UC. Even if a biological therapy for asthma had not been administered yet, the relapse of IBD in the previous month determining bloody diarrhea, urgency, and abdominal pain required the anticipation of the switch to biological therapy. A single IV 260 mg induction dose was administered, to be followed by a subcutaneous maintenance 90 mg dose administered every 8 weeks. In June 2023, the patient came back to visit the severe asthma service. She still presented dyspnea on mild exertion, uncontrolled daily symptoms, nasal congestion, and postnasal drainage. Monoclonal antibodies are available for the treatment of severe asthma and CRSwNP target Type 2 inflammation. Considering the relevant history of eosinophilia, a biological agent with anti-eosinophilic activity was thought to be the most effective. In consideration of the favorable dosing schedule, to better detect any potential side effects deriving from the interaction or the simultaneous administration of the two monoclonal antibodies, she started benralizumab 30 mg,

Table 1: Medical history of the patient and home medications at the time of referral

Medical history	Home medications
The patient was diagnosed with asthma in 2011 and ulcerative colitis in 2016	Adalimumab 40 mg every two weeks
Arterial hypertension	Beclometasone/Formoterol 200 µg/6 µg inhaler two puffs two times per day
Steroid-induced diabetes	Tiotropium respimat inhaler two puffs daily
Carotid artery stenosis	Mesalazine
No history of smoking	Amlodipine
No relevant family history	Daily low-dose Aspirin
	Insulin therapy
	Statins
	Cetirizine (as needed)

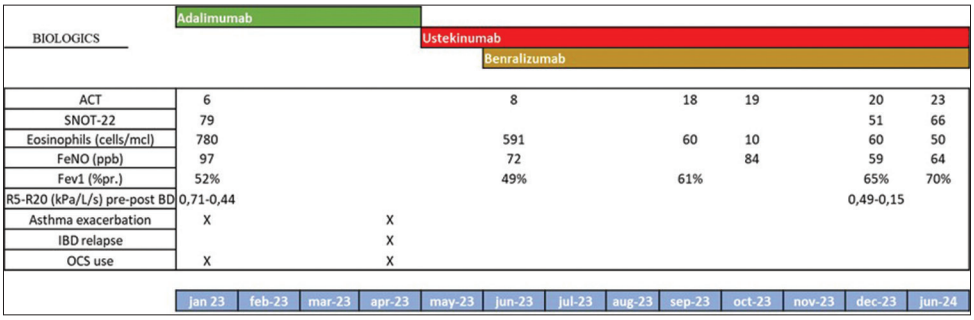

Figure 1: Clinical course of the patient. Asthma exacerbations were defined as acute events requiring OCS. IBD relapse was defined as acute worsening of gastrointestinal symptoms. ACT, asthma control test; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in one second; IBD, inflammatory bowel disease; OCS, oral corticosteroids; R5-R20, Resistance between 5 and 20 Hz as measured with impulse oscillometry, both before and after bronchodilation test; and SNOT-22, Sinonasal outcome test-22

administered by subcutaneous injection every 4 weeks for the first three doses and then every 8 weeks thereafter. In July the patient was evaluated again by the IBD unit. She had experienced improvement of intestinal symptoms, reporting 2–3 evacuations of formed stool per day, without blood or mucus. Abdominal pain resolved. In October 2023 the patient perceived a subjective increase in the amount of sputum, without any change in color or consistency. Sputum was analyzed and tested positive for *Aspergillus fumigatus*. Her primary physician prescribed a cycle of antibiotic therapy plus a mucolytic agent. The patient had never been febrile. Oral corticosteroids were not prescribed. Two weeks later the sputum was analyzed again and tested negative for any microbiologic agent. An HRCT of the lungs and blood tests were prescribed. CT scan showed no abnormal findings. Specific IgG, IgM, and IgE for Aspergillus were negative, as well as galactomannan and C reactive protein (CRP). The patient has been re-evaluated after 12 months since starting the biological therapies. Her IBD symptoms are well controlled. She reports 2-3 evacuations of formed stool per day, without blood or mucus, and any other symptoms such as abdominal pain, urgency, or tenesmus. No extraintestinal manifestations of the disease have been reported. She reports respiratory well-being (ACT 23 points), complaining only about nasal symptoms (rhinorrhea and subjective hyposmia). Therefore we decided to try to downgrade the inhaled therapy to beclometasone/formoterol 100 μg/6 μg inhaler two puffs two times per day and tiotropium respimat inhaler two puffs daily, while continuing the nasal corticosteroid spray at a maximal dose. Since asthma biological therapy was started, the patient has not experienced any exacerbations requiring OCS, emergency department visits, or hospital admissions, and the control of asthma symptoms and respiratory function considerably improved. Twelve months after the initiation of the biological combination therapy, both diseases are well controlled, without any side effects or blood test abnormalities. The patient is still receiving both therapies.

DISCUSSION

Increasing evidence has demonstrated that respiratory involvement is frequent in IBD patients.[2] A connection between IBD and obstructive lung disease (OLD) has long been reported, with bronchiectasis being the most frequent.[2] A recent cohort study highlighted that individuals with IBD both had a higher likelihood of pre-existing OLD and an increased risk of developing OLD compared to individuals without IBD.[3] In particular, female patients with UC have a higher prevalence of asthma, thus confirming the importance of considering respiratory symptoms when examining patients with manifest or suspected IBD and the need for a rapid pulmonologist evaluation for the administration of appropriate inhalation treatment.[4] The main pathogenic mechanisms of asthma inflammation are often categorized as T2-high and T2-low. T2-high endotype has an immune–inflammatory response driven by T helper type 2 (Th2) cells and type 2 innate lymphoid cells (ILC2) and mediated by type 2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, and include the allergic and non-allergic eosinophilic phenotypes.[5] Biomarkers, such as blood eosinophil count (BEC), total and specific IgE, and fractional exhaled nitric oxide (FeNO), can be used as indicators of type 2 asthma endotype.[6] Once asthma is phenotyped, the level of asthma control needs to be assessed, also through questionnaires such as the ACT, because it can guide the decision to increase the intensity of the therapy up to biological drugs, to control symptoms and reduce the risk of future exacerbations and adverse outcomes. To the best of our knowledge, this is one of the first cases of patients receiving concurrent biological therapy for UC and Asthma, specifically ustekinumab and benralizumab. Ustekinumab is a human immunoglobulin (Ig) G_1 kappa monoclonal antibody (mAb) that inhibits IL-12 and IL-23, cytokines that modulate lymphocyte function. The mAb binds to the p40 subunit common to IL-12 and IL-23 and prevents their interaction with the IL-12Rβ1 subunit of the IL-12 and IL-23 receptor complexes.[7] Benralizumab is a humanized IgG1k mAb that binds to IL-5Rα, preventing the interaction between IL-5 and its receptor. In addition, through its Fc constant region, Benralizumab binds to the FcγIIIRa receptor expressed by NK cells, thus inducing eosinophil apoptosis.[8] Only another patient, in the case series by Lommatzsch *et al*.,[9] received a combination for our same indications, i.e. severe asthma and UC, with the concurrent administration of Dupilumab and Vedolizumab for 26 months. It is not clear whether the anti-TNF-α biological agent exerted a negative influence on asthma inflammation and symptom control. The switch to ustekinumab was decided in agreement with the IBD unit after a multidisciplinary meeting, which is recommended by international guidelines.[10] Recent evidence in IBD highlighted that ustekinumab could be the preferred second-line agent in patients with prior anti-TNF alpha agents' exposure.[11] Regarding the cardiovascular risk profile of our patient, data from clinical trials and post-marketing safe reports did not observe an increased risk of acute arterial events, and no changes in the serum lipid levels were observed during treatment with ustekinumab.[12] In conclusion, the concurrent administration of ustekinumab and benralizumab had a good safety profile and was successful in treating both severe asthma and UC in our patients. The detection of A. Fumigatus in the sputum was interpreted as environmental contamination since all specific tests were negative and the detection was not confirmed again after two weeks of mucolytic treatment only. ABPA was therefore ruled out. The patient has been re-evaluated after 12 months since starting the biological therapies, and both diseases are well controlled, without any adverse event. The patient is going to be evaluated again in the following months, to observe whether nasal polyposis worsens or becomes uncontrolled under the current therapy. In this case, a biological switch could be considered. Still little is known about the concomitant use of more than one monoclonal antibody and the potential adverse effects deriving from

the combination. In these patients, regular clinical and laboratory monitoring of the patient as we did for this patient is recommended to early detect potential significant side effects, such as an increased risk of infection.

Declaration of patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Key messages

We describe case of biological combination therapy with ustekinumab and benralizumab. Severe asthma and Inflammatory Bowel Diseases, such as Ulcerative Colitis, have a high impact on quality of life, and the simultaneous administration of monoclonal antibodies could be required to control both diseases.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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