CASE REPORT

New onset severe ulcerative colitis following Ixekizumab therapy

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ABSTRACT

Ixekizumab is one of the three biologic agents including Secukinumab and Brodalumab that targets the Interleukin-17 (IL-17) pathway to reduce inflammation in psoriasis and ankylosing spondylitis. In this report we present the case of 42-year-old woman, who was diagnosed with psoriasis and psoriatic arthritis. One week after first administration of Ixekizumab, she developed diffuse abdominal pain, bloody diarrhea (7-8 stools/day) and fever. Following imaging (colonoscopy, computed tomography) and laboratory investigations, she was diagnosed with acute severe ulcerative colitis complicated with toxic megacolon. The medical treatment (first corticotherapy, then infliximab) has failed and the patient needed emergency colectomy. Based on the immunological mechanisms and the observation from other studies, Ixekizumab should be considered an etiology for new-onset inflammatory bowel disease.

KEYWORDS: Ixekizumab; psoriasis; ulcerative colitis; toxic megacolon; colectomy

INTRODUCTION

Interleukin-17 (IL-17) inhibitors (Ixekizumab, Secukinumab, Brodalumab) are biological agents approved for the treatment of ankylosing spondylitis, psoriasis and psoriatic arthritis [1]. New molecules (Bimekizumab) are on the pipeline for clinical practice [2]. Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody which selectively binds to IL-17 and prevents interaction with its receptor [3]. Immune-mediated inflammatory diseases, like psoriasis and inflammatory bowel disease (IBD), share the same pathogenic mechanisms involving IL-23, IL-17, Th17 and tumor necrosis factor (TNF), leading to the need for the same pharmacological treatments [4]. Anti-IL-17 inhibitors have proven efficacy in the treatment of psoriasis and psoriatic arthritis, with 80% of patients achieving improvement or clearance of skin lesions [2]. Scientific evidence shows an increased amount of IL-17 and IL-17A, IL-17F mRNA in the intestinal mucosa in IBD patients [5]. However the literature describes a paradoxical immunological effect of IL-17 inhibitors that can lead to the IBD onset or flare [6]. The mechanism of this paradoxical effect is incompletely known. It seems to be related to the overexpression of type I interferon, as in the paradoxical occurrence of psoriasis in patients treated with anti-TNF agents [7]. Unlike IL-23 inhibitors, which are effective in the IBD treatment, IL-17 inhibitors affect the integrity of the intestinal mucosa and exacerbate IBD [8]. In Crohn's disease (CD) studies on patients that tried anti-IL-17 therapy did not reach the primary end point and even described cases of IBD worsening [9]. On the other hand, the prevalence of IBD in patients with psoriasis is higher compared with general population [10,11]. There is the hypothesis that anti-IL-17 only reveals a latent IBD, associated with other immune-mediated dermatologic or rheumatologic diseases [5,12].

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CASE REPORT

In this paper we present the case of a 42-year-old woman, smoker, who was diagnosed at the age of 31 years with cutaneous and nail psoriasis and at the age of 38 years with psoriatic arthropathy. She was first treated with Metotrexat 15mg/week and later with Adalimumab (Humira®). Due to recurrence of psoriatic lesions, Adalimumab was stopped and the first dose of Ixekizumab (Taltz®) (80 mg subcutaneous) was administered. The onset of digestive symptoms (abdominal pain, diarrhea (7-8 stools/day), rectal bleeding, fever) was one week after Ixekizumab administration. A rectosigmoidoscopy (without preparation) was performed, which revealed continuous congestive, friable rectal and colonic mucosa, spontaneously bleeding, deep

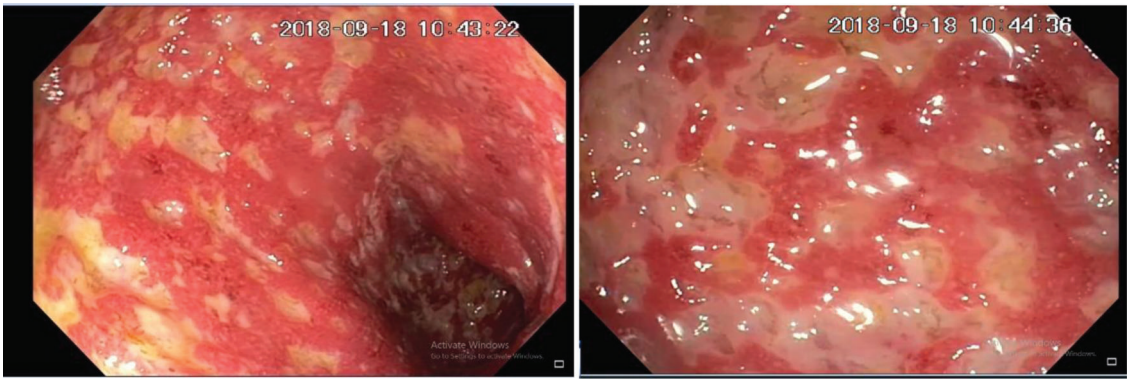

Fig. 1. Endoscopic appearance of colonic mucosa, with edema, congestion, large ulcerations.

and large ulcerations (Figure 1). The histopathological examination detected areas of degeneration and erosions of the surface epithelium, with neutrophilic inflammatory infiltrate disposed irregularly, edema and congestion, decrease of the crypts mucosecretion and crypt's abscesses. She was admitted to the Gastroenterology Clinic and laboratory examinations revealed the presence of anemia (Hb=10.9g/dL), increased white blood cells (12000/mm^3), severe electrolytes imbalances, significantly increased C reactive protein (28.41mg/dL) and hypoalbuminemia. *Clostridioides difficile* toxins A and B were negative. Patient was assessed urgently through computed tomography that highlighted the dilated large bowel more than 6 cm, with the characteristic aspect of toxic megacolon (Figure 2). The patient was initially treated with systemic antibiotics (Ciprofloxacin, Metronidazole), intravenous corticosteroids, anticoagulants, albumin; the correction of electrolytes was done and parenteral nutrition was administered. After 3 days without improvement, it was decided to initiate the second line therapy with Infliximab 5mg/kgc (300 mg). In the next day after Infliximab administration the patient accused a severe general condition with increased abdominal pain and elevation of inflammatory markers. The abdominal X-ray revealed the presence of pneumoperitoneum and hydro-aeric levels in the right iliac fossa. The patient was transferred to the surgery department where total colectomy with ileostoma and rectum preservation was performed. Patient was discharged after 7 days, without other complications. She was advised to quit smoking and no drugs were prescribed. On long-term an ileal pouch-anal anastomosis was planned. Definitive Ixekizumab cessation was recommended.

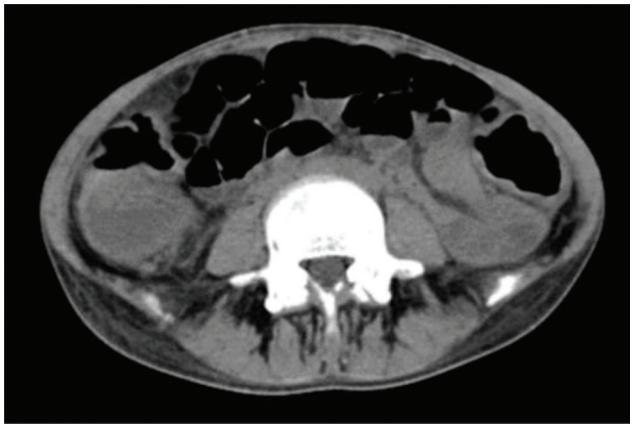

Fig. 2. Intravenous – contrast computed tomography: toxic megacolon

DISCUSSIONS

Our case describes a new onset severe ulcerative colitis (UC) after Ixekizumab treatment for psoriatic arthritis. There are multiple evidences showing that Ixekizumab - a useful drug in reducing inflammation in psoriasis and psoriatic arthritis - can induce/exacerbate IBD [7,13].

After the approval of Ixekizumab in the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis (2017), multiple cases of IBD-related therapy were reported [2]. Philipose et al. [14] reported a case of severe UC complicated with *Clostridioides difficile* colitis and Cytomegalovirus infection that responded to Infliximab. Also, similar to our case, another case of severe ulcerative colitis complicated with toxic megacolon requiring colectomy has been reported [15].

A lot of meta-analyses and systematic reviews regarding the association of IBD with anti-IL-17 drugs have been published in recent years. Yamada, in a meta-analysis published in 2019 regarding new IBD cases in patients treated with anti-IL-17, has analyzed 38 randomized trials, including 16690 patients [16]. The authors identified only 12 new IBD cases (4 related to Ixekizumab), with no significant increased risk compared to placebo [16]. Reich analyzed the adverse effects from 7 studies that included 4209 patients with psoriasis treated with Ixekizumab [17]. Cases of new-onset IBD were rare (<1%): 19 cases (7 CD, 12 UC), most during maintenance treatment compared to induction [17]. The same reduced frequency of new IBD cases was also identified by Burisch [18] in a meta-analysis of 66 studies, including 14,390 patients treated with anti-IL-17 drugs. The incidence of IBD cases related to Ixekizumab treatment (0.46 per 1,000 patient-years) was similar to that in the general population [18]. Analyzing 7 studies that included 4209 patients with psoriasis treated with Ixekizumab, IBD had a reduced frequency: 1 newly CD and 5 UC flares [19]. In a recently published paper that followed over 18,000 patient-years, 31 cases of IBD were identified (0.2 per 100 patients-year, 0.4%) in psoriatic patients treated with Ixekizumab [20]. There were 13 cases of CD and 18 UC, most of them being new IBD onset [20]. The reduced incidence of IBD

onset/flare in patients with anti-IL-17 treatment is also confirmed in the analysis of real-life data [21,22].

However, these data must be interpreted with caution. These meta-analyzes were done on inhomogeneous populations, with various diseases and many of the reported data overlaped. Follow-up periods were generally short, and the studied adverse event (IBD onset/flare) was defined in different modalities. For example, diarrhea, a commonly reported side effect, was not investigated for a possible IBD in many of the reviewed studies [16,18].

Even if there is no consensus, all patients starting treatment with anti-IL-17 drugs should be carefully screened in terms of digestive symptoms and IBD history. Some authors propose the dosage of fecal calprotectin before initiating anti-IL-17 treatment. A value greater than 250 μg/g indicates colonoscopy and/or magnetic resonance enterography; active IBD is a contraindication for initiating anti-IL-17 therapy [7,23]. Patients already known with IBD diagnosis should be carefully monitored in time of anti-IL-17 drugs treatment.

CONCLUSION

Our paper presented the particular case of a patient with no digestive history, diagnosed with severe acute colitis, refractory to drug therapy, complicated with toxic megacolon and perforation, which occurred one week after the first administration of Ixekizumab. Although the pathophysiological mechanisms are incompletely known, evidence from the literature supports the association between IL-17 inhibitors and IBD onset/flare. All patients under treatment with anti-IL-17 must be carefully evaluated and monitored from the point of view of intestinal symptoms or diseases.

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Authors' contributions

AMM, OG and MD collected the data and drafted the manuscript. IRM and AR searched the literature. CCP and CM reviewed the literature and the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Consent for publication of the patient's data and images in this case report was obtained.

Conflicts of interest

The authors declare no conflict of interest.

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