Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Intentional treatment with tofacitinib in a patient with severe refractory ulcerative colitis and concomitant Sars-CoV-2 infection

Dear Editor,

We have recently used Tofacitinib (TOFA) in a patient with severe ulcerative colitis (UC) refractory to intensive intravenous steroid treatment (IIVT) and with concomitant SARS-CoV-2 infection. Data addressing characteristics and outcomes of TOFA-treated UC patients with COVID-19 are limited and, to our knowledge, no cases of intentional TOFA therapy for steroid refractory UC in COVID-19 patients have been reported.

The patient was a 39 years-old woman who came to our first observation in January 2022 for a severe UC flare. She had a long history of left-sided UC followed in another tertiary center, without comorbidities in her past history. In September 2021 she experienced an acute severe attack requiring hospitalization, IIVT, and a rescue therapy with Infliximab (IFX) due to steroid refractoriness. She achieved complete clinical remission but a severe infusion reaction occurred during the first IFX maintenance dose. Shift to Adalimumab was then performed but a secondary loss of response progressively occurred finally leading to admission in the emergency room of our hospital with a severe acute flare: bloody diarrhea (8–10 movements per day), crampy abdominal pain, fever (37.6 °C), moderate anemia (Hb 9.8 g/dl), elevated C reactive protein (CRP 20 mg/dl - normal range <0.8 mg/dl), partial Mayo score 9. Body Mass Index was normal. No pathogens, ova or parasites could be detected in stools as well as Clostridium difficile toxin A and B. Abdomen x-ray findings were unremarkable. At admission, patient tested positive to a routine RT-PCR molecular swab for Sars-CoV-2 without respiratory symptoms and normal high-resolution CT scan, and was therefore admitted to COVID-19 ward. Of note, at the time of admission, the patient had not received any dose of COVID-19 vaccine before. Sigmoidoscopy showed deep ulcerations in the sigmoid colon and superficial ulcers in the rectum (no CMV inclusions were observed on rectal and colonic biopsies). Initial treatment consisted of intravenous and rectal steroids, anti-thrombotic prophylaxis, and supportive measures. An incomplete clinical response occurred within 5 days: despite a reduction of diarrhea, urgency and rectal bleeding, bowel movements were 5–6 per day and CRP values were 6.4 mg/dl. A shared decision-making approach was taken and different therapeutic options (conservative versus surgery) were discussed. Tofacitinib (TOFA) 10 mg twice daily was then started. A substantial clinical response occurred after few days and the patient entered remission within 10 days. The subsequent clinical course was uneventful, no respiratory symptoms occurred, and, at 10 days, nasopharyngeal swab turned negative and the patient was discharged. At the end of 8 weeks TOFA induction, the dose was tapered to 5 mg twice daily. At six months after starting TOFA, the patient was in steroid-free clinical remission, CRP was in the normal range, and fecal calprotectin was 109 mcg/kg. Colonoscopy showed near complete mucosa healing: patchy erythema, friability, and pseudopolyps in the sigmoid colon.

COVID-19 pandemic has renewed one of the most relevant clinical challenge in the management of Immune-mediated Inflammatory Diseases (IMIDs) that is the need to control inflammatory burden through Immunomodulators (IMs) versus the potential risk of developing severe and opportunistic infections. Available evidences suggest that the risk of SARS-CoV-2 infection in IBD patients is similar to that of general population and that the COVID-19 course does not appear to be influenced by IMs in IBD population [1, 2]. However, the best management strategy for the use of IMs in IBD patients during pandemic has yet to be established, and the current recommendations are mainly based on expert opinions [3]. Data exploring TOFA safety in the setting of active IBD and concomitant Sars-CoV-2 are limited mainly because of the recent introduction of the drug [4, 5]. In particular in the SECURE-IBD Registry 36 patients were receiving TOFA at the time of developing COVID-19 and, of these, only 12 had moderate/severe IBD [4]. TOFA belongs to the Janus kinase (JAK) inhibitors family that has been recently approved for the treatment of several IMIDs, including UC [6]. TOFA is a non-selective blocker of JAK-STAT pathways, mainly JAK 3 and JAK 1 and, to a lesser extent, JAK2 and tyrosine kinase 2 (TYK2) that regulate signaling for multiple immune mediators, including type I interferon, interferon-γ, and interleukins 2, 4, 6, 7, 9, 12, 15, 21, 23, and 27, involved in the pathogenesis of UC [7]. In particular, TOFA, modulating the action of interferons and interleukin-6, decreases the release of cytokines by type 1 and type 17 helper T cells, which are also implicated in the pathogenesis of the acute respiratory distress syndrome and in the progressive, inflammation-driven lung injury [8]. This provided the rationale leading to test a number of JAK-inhibitors as potential COVID-19 treatments and some RCTs have shown positive results in major clinical outcomes such as death, respiratory failure, and time to recovery in COVID- 19 hospitalized patients [9].

Our case describes a patient with severe UC with intolerance/failure to anti-TNF-alpha agents, steroid-refractoriness, and concomitant asymptomatic Sars-CoV-2 infection. Our challenge was the need to control inflammatory burden through IMs, possibly avoiding colectomy, versus the potential risk of developing COVID-19 disease. The choice of TOFA as third-line advanced therapy was supported either by retrospective studies of steroid-refractory severe UC patients [10] and by the available evidences favoring the efficacy and safety of JAK inhibitors in COVID-19 patients [9].

In conclusion, a shared-decision making and tight control monitoring approach appeared essential for the management of such a challenging case, that is, to our knowledge, the first case ever de-

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scribed of intentional treatment with TOFA in a patient with severe UC and concomitant Sars-CoV-2 infection. Treatment with TOFA represented an important therapeutic opportunity in the clinical management of our complex patient, and our experience may be clinically useful considering the still high number of Sars-CoV-2 infections in the general population as in IBD patients.

Declaration of Competing Interest

Stefano Festa: Advisory board for Janssen-Cilag. Consultancy fees and/or educational grants from Takeda, SoFar, Abbvie, Zambon, Pfizer.

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Fabiola De Biasio: consultancy fees from Janssen-Cilag.

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