Visceral Medicine

Case Report

Mild COVID-19 Symptoms in an Infliximab-Treated Ulcerative Colitis Patient: Can Ongoing Anti-TNF Therapy Protect against the Viral Hyperinflammatory Response and Avoid Aggravated Outcomes?

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Abstract

The ongoing coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, represents a potentially major challenge to patients with immune-mediated inflammatory diseases who are treated with immunomodulatory therapies. We report the case of an 18-year-old ulcerative colitis patient in sustained clinical remission who 4 days after application of her ongoing therapy with the anti-TNF antibody infliximab developed mild respiratory and abdominal symptoms. The patient was subsequently diagnosed with COVID-19 but did not need hospitalization. The clinical symptoms completely resolved within 1 week after onset and there was no change in ulcerative colitis activity. The recently applied anti-TNF therapy did not lead to exacerbation of the infectious symptoms. Current recommendations strongly favor continuation of effective maintenance anti-TNF therapy in inflammatory bowel disease patients, as there is no evidence for aggravated COVID-19 upon infection. It is unclear whether anti-TNF treatment might even have assisted in preventing worsening of COVID-19 and improving outcome. Further data in the group of immune-mediated inflammatory disease patients under anti-TNF therapy are urgently needed.

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Introduction

From December 2019 onwards, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for coronavirus disease 2019 (COVID-19) has caused a worldwide pandemic posing a critical challenge to health care systems [1, 2]. It is uncertain whether patients with immune-mediated inflammatory diseases, particularly with ongoing immunotherapy, have heightened susceptibility to COVID-19 infection. Furthermore, possible exacerbation of COVID-19 symptoms in patients under ongoing immunotherapy is investigated.

Anti-TNF agents are a mainstay in the therapeutic algorithm of inflammatory bowel disease (IBD) patients [3, 4], but may potentially weaken antiviral immunity, as evident by their ability to affect hepatitis B reactivation [5]. On the other side, TNF inhibition might also mitigate an exacerbated immune response during viral infection, resulting in a potentially protective effect [6].

The particular role of anti-TNF antibodies in the course of COVID-19 is unclear. We report the case of an ulcerative colitis patient who 4 days after administration of her ongoing therapy with the anti-TNF antibody infliximab developed mild respiratory and abdominal symptoms, leading to the subsequent diagnosis of COVID-19.

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Case Presentation

An 18-year-old ulcerative colitis patient presented to our outpatient department in March 2020 for continuation of her ongoing therapy with the anti-TNF antibody infliximab. The patient was first diagnosed with left-sided ulcerative colitis at the age of 15 and had no other comorbidities. Due to steroid-dependent disease, combination therapy with infliximab and low-dose azathioprine (50 mg/day) was initiated in August 2018. Concomitant medication consisted of oral mesalazine. Azathioprine was stopped in January 2020, as the patient achieved clinical and biochemical (fecal calprotectin and CRP levels within normal range) remission with adequate infliximab trough and absent antidrug antibody levels.

Upon admission to our department, the patient was still in clinical remission with 1–2 stools per day without occurrence of rectal blood and absent abdominal pain (partial Mayo score: 0). CRP levels were within the normal range. The patient reported occasional dry cough for the last 5 days, which had recurrently occurred since November 2019. Upon clinical investigation there were no other signs of a respiratory infection. The patient received 400 mg of infliximab, which was well tolerated. Four days after infliximab application, in addition to the dry cough symptoms, the patient also developed mild dyspnea, tachycardia, as well as moderate abdominal and back pain, but there was no measurable febrile temperature. In addition, there were intermittent headaches in the patient with known migraine. She was tested positive for SARS-CoV-2 RNA by polymerase chain reaction testing of oropharyngeal swabs taken 4 days later. As the symptoms were rather mild, inpatient monitoring was not required. Another 3 days later, the clinical symptoms completely resolved and there was no occurrence of fever. During that time and in the follow-up period of 3 weeks, there was no worsening of ulcerative colitis-related symptoms, and the patient remained in sustained clinical remission.

Discussion and Conclusion

The mechanism of viral infection in COVID-19 is based on binding of SARS-CoV-2 to the receptor angiotensin-converting enzyme 2 (ACE2), which is expressed on the host epithelial cells in the lung and intestine [7]. This enables fusion of the coronavirus envelope with the host cell membrane upon cleavage of the viral spike protein by the host transmembrane serine protease 2 (TMPRSS2) [8]. This leads to the activation of innate and adaptive immune cells in the infected host. Subsequently, accumulation of neutrophils, macrophages, and T lymphocytes takes place, which results in exuberant production of cytokines and chemokines. The effector cytokine-driven inflammatory response is characterized by heightened production of IL-6, IL-2R, IL-10, and TNF, but also of IL-2, IL-7, IL-8, IL-17, G-CSF, and GM-CSF. The number of CD4+ and CD8+ T cells was significantly decreased in severe COVID-19 [9]. IL-6, IL-2R, IL-10, and TNF levels were shown to be mildly elevated in moderate cases, but markedly heightened in more severe cases [9, 10]. These cytokines have been implicated to be part of the cytokine storm that perpetuates the hyperinflammatory state of the immune response, leading to deleterious outcomes like severe pneumonia, acute respiratory distress syndrome, and multiorgan failure [11] (Fig. 1). Accordingly, IL-6 concentrations have been identified as an indicator for the magnitude of the inflammatory response in COVID-19 [12]. First studies subsequently investigated the possible effectiveness of inhibiting the IL-6 pathway in COVID-19 [13]. Elevated systemic TNF levels in COVID-19 patients that were ICU-bound in comparison to non-ICU patients have also been reported [14]. It could be shown that IL-6 can effectively be downregulated by anti-TNF agents in Crohn's disease patients, independent of clinical response to therapy, indicative of a TNF-dependent IL-6 regulation [15].

There are accumulating data that concomitant therapy with anti-TNF antibodies is not associated with worse COVID-19 prognosis in IBD patients. The first published report described the case of a 30-year-old Crohn's disease patient in long-term clinical remission under adalimumab therapy who developed fever and chest pain, diagnosed as COVID-19. The patient only needed oxygen support upon hospitalization and the symptoms resolved within 24 h [16]. A recently published prospective case series of 86 immune-mediated inflammatory disease patients who were receiving immunomodulatory therapies indicated that the incidence of COVID-19 hospitalization was consistent with that of patients in the general population of New York City. Active disease, old age, as well as comorbidities were associated with worse outcomes, while baseline use of biologics did not impact COVID-19 severity. The study included 37 IBD patients, of whom 19 were under ongoing anti-TNF therapy. Two of the anti-TNF-treated patients needed hospitalization and were discharged within 48 h [17]. Another observational cohort study described the outcomes of COVID-19 in 79 IBD patients in Italy. Again, active disease, old age, and comorbidities were associated with a negative COVID-19 outcome. Twenty-nine of the analyzed IBD patients were under treatment with an anti-TNF agent, but this was again not associated with worse outcomes [18]. The SECURE-IBD database, which registers outcomes of IBD patients with COVID-19 worldwide, has similarly so far not indicated worse outcomes of patients under anti-TNF therapy [19]. In accordance, current recommendations by national and international organizations do not support preemptively stopping effective anti-TNF therapy, but rather recommend unchanged continuation if there are no signs of COVID-19 [20, 21]. In IBD patients with confirmed COVID-19, current recommendations advise to hold anti-TNF therapies during the viral illness [20]. On the other side, aforementioned data from case series and the SECURE-IBD database imply that direct exposure to anti-TNF agents does not have
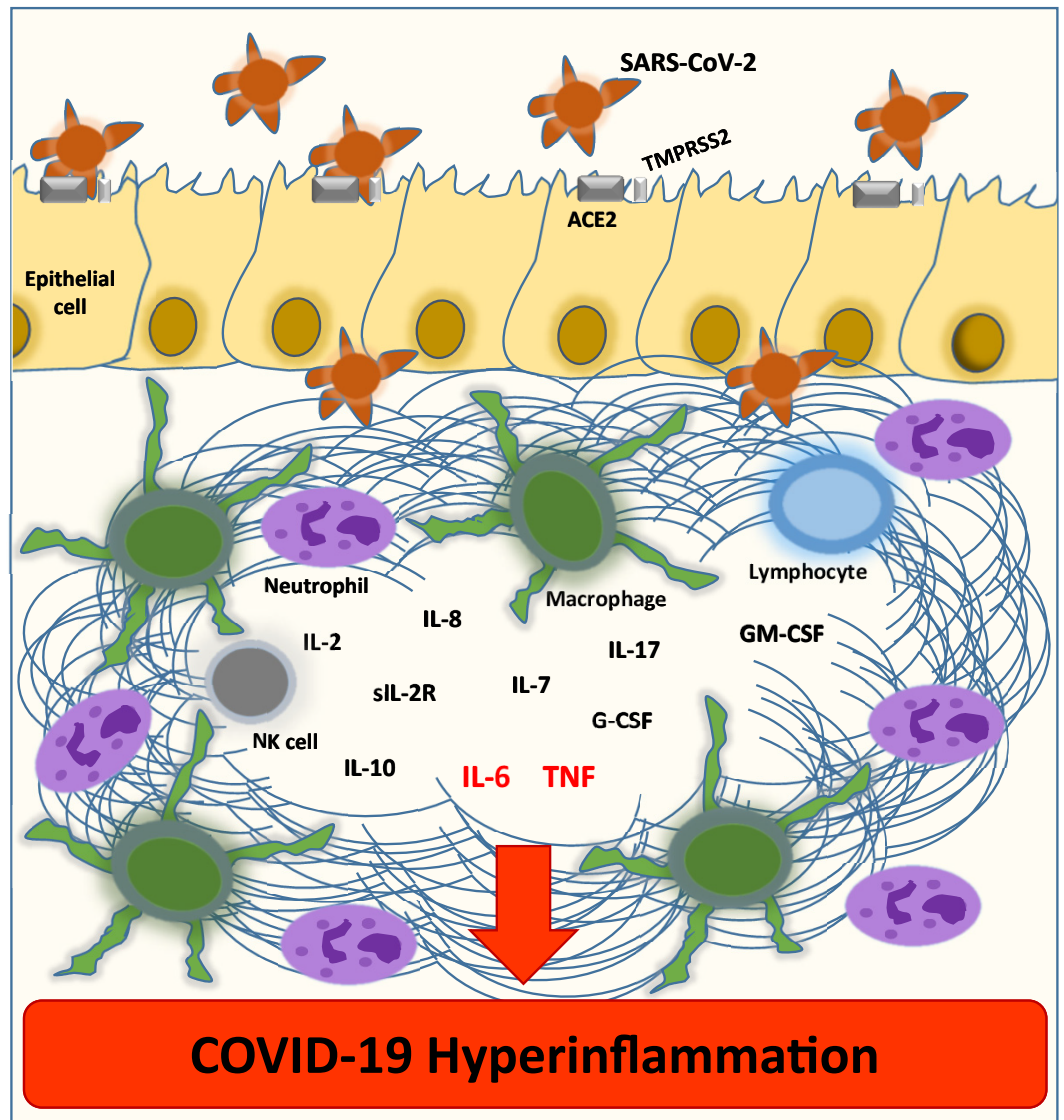
Fig. 1. Hyperinflammatory state in severe COVID-19. Binding of SARS-CoV-2 to the receptor ACE2 that is expressed on the host epithelial cell (lung/intestine) leads to the entrance of the virus upon cleavage of the viral spike protein by the host TMPRSS2. This leads to overwhelming immune cell activation and exaggerated production of cytokines and chemokines, led by IL-6 and TNF. This sort of cytokine storm perpetuates the hyperinflammatory state that leads to severe COVID-19. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

a negative impact on COVID-19 disease, as we can assume that most of the patients had detectable anti-TNF drug levels due to the long half-life of this substance class. We therefore propose that continuation of effective anti-TNF therapy in IBD patients with confirmed COVID-19 should be evaluated in cases of complicated disease, as this may be the best option to prevent recurrence of active disease that necessitates high-dose steroid therapy, which has been shown to be a risk factor for more severe COVID-19 disease. Data in this regard are needed. Similarly, in patients on immunosuppressant or tofacitinib therapy, lymphopenia is a common adverse event that

should be strictly avoided, as this has been described to be associated with heightened mortality in COVID-19 patients [22].

Our patient did not have any of the currently known risk factors for fatal COVID-19, as she was of young age, was a nonsmoker, and did not have any comorbidities. Furthermore, she benefited from being in sustained clinical remission and absence of active inflammation. It remains unclear in how far the patient might additionally even have benefited from ongoing anti-TNF treatment during COVID-19. There are so far only experimental data that indicate the possibility of actually improving

Table 1. Already recruiting or planned trials with immunosuppressants and biologicals in COVID-19 patients [adapted from 29]

Clinical trial ID	Treatment	Participants	Randomization	Blinded	Country of origin
NCT04288713 (ClinicalTrials.gov)	arm A: eculizumab	unspecified	unspecified	unspecified	USA
NCT04280588 (ClinicalTrials.gov)	arm A: fingolimod arm B: standard treatment	30	no	no	China
ChiCTR2000030703 (ICTPR)	arm A: ixekizumab + antiviral therapy arm B: antiviral therapy	40	yes	single	China
NCT04275245 (ClinicalTrials.gov)	arm A: meplazumab	20	no	no	China
NCT04315298 (ClinicalTrials.gov)	arm A: sarilumab high dose arm B: sarilumab low dose arm C: placebo	400	yes	quadruple	USA
ChiCTR2000030058 (ICTPR)	arm A: standard treatment + leflunomide arm B: standard treatment + placebo	200	yes	yes	China
ChiCTR2000030196 (ICTPR)	arm A: tocilizumab	60	no	no	China
ChiCTR2000029765 (ICTPR)	arm A: tocilizumab arm B: standard treatment	188	yes	unspecified	China
NCT04315480 (ClinicalTrials.gov)	arm A: tocilizumab	30	no	no	France
NCT04317092 (ClinicalTrials.gov)	arm A: tocilizumab	330	no	no	Italy
ChiCTR2000030442 (ICTPR)	arm A: tocilizumab + IVIG + CCRT	100	no	unspecified	China
ChiCTR2000030580 (ICTPR)	arm A: tozumab + adalimumab arm B: standard treatment	60	yes	unspecified	China
ChiCTR2000030089 (ICTPR)	arm A: conventional treatment + adalimumab arm B: conventional treatment	60	yes	no	China

outcomes of virus-induced immunopathology by TNF-inhibition [23, 24]. For SARS-CoV, it could be shown that viral entry into the host cell not only enhances TNF production, but also increases TNF-converting enzyme-dependent shedding of the ectodomain of ACE2, which facilitates viral entry [25]. Anti-TNF antibody treatment may also facilitate intestinal downregulation of ACE2 expression and shedding [26]. Nevertheless, one must of course be cautious that anti-TNF therapy can possibly not only inhibit a TNF-dependent cytokine cascade and thus prevent an excessive immunoreaction during COVID-19 [27], but might also increase the risk of viral replication, suppress adaptive immunity, and increase bacterial or fungal superinfections. Potential benefits of anti-TNF therapy are evaluated in a phase 4 randomized, open-label, controlled trial for the efficacy and safety of adalimumab in patients with severe COVID-19 and elevated TNF levels. The main outcome of the study is the time to clinical improvement [28, 29]. Another study combines tozumab (likely tocilizumab) with adalimumab in the treatment of critically ill patients with COVID-19 in a randomized, parallel controlled trial [29, 30]. Further studies might also investigate anti-TNF effectiveness in preventing disease worsening in specific cohorts of COVID-19 patients (older age, comorbidities) [27]. There are a number of planned or already recruiting clinical trials investigating the efficacy of immunosuppressants or biologicals for the treatment of COVID-19 patients (Table 1).

Altogether, current recommendations favor unchanged continuation of effective anti-TNF therapy in inflammatory immune-mediated disease. Available data are so far insufficient to make definite conclusions of possible better outcomes of anti-TNF-treated COVID-19 patients, but respective trials have been initiated. A better understanding of the implications of COVID-19 in IBD patients and the effects of anti-TNF therapy are urgently needed to ensure best available care of the patient by the treating physician.

Statement of Ethics

Written informed patient consent for publication of this case report was obtained.

Disclosure Statement

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Author Contributions

Conception, drafting, data acquisition, analysis, interpretation of data, critical revision of the article, and final approval of the article were done by all three authors.

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