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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Clinical and radiologic outcomes in two patients with multiple sclerosis treated with tocilizumab for COVID-19

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ABSTRACT

Background: Tocilizumab is an interleukin-6 receptor antagonist used to treat COVID-19. A previous case report described development of multiple sclerosis (MS) after treatment with tocilizumab for rheumatoid arthritis, leading to an FDA warning label. We sought to identify patients with multiple sclerosis (MS) who were treated with tocilizumab for coronavirus disease 2019 (COVID-19) and characterize clinical outcomes.
Methods: We electronically identified MS patients who received tocilizumab for COVID-19 from January 2019 to September 2021 and performed retrospective chart review.
Results: Two patients were identified. The patients were both treated with ocrelizumab and had an average disease duration of 10.5 years. Both patients were hospitalized with COVID-19 infection (with WHO COVID-19 severity scales of 5 and 6) and received tocilizumab as treatment for COVID-19. At post-discharge follow-up, EDSS showed no or a mild increase (stable in one patient, and 1 to 2 in the second patient). There was no increase in PDSS score. Follow-up MRI after discharge showed no new T2 lesions, enhancing lesions, or worsening atrophy.
Conclusions: In two MS patients who received tocilizumab for COVID-19, we did not observe significant clinical or radiologic worsening following treatment. Larger scale studies are needed to determine if use of tocilizumab for COVID-19 can provoke relapse or cause MS disease

Introduction

Tocilizumab is an interleukin-6 receptor antagonist used to treat many immunologic conditions including giant cell arteritis, rheumatoid arthritis, and cytokine release syndrome from chimeric antigen receptor-T cell therapy. More recently, tocilizumab has been studied for treatment of patients hospitalized with coronavirus disease 2019 (COVID-19) in multiple randomized clinical trials, some of which have demonstrated improved in-hospital outcomes and reduced mortality (Mariette et al., 2021).

While tocilizumab has also been studied as a treatment for some central nervous system (CNS) inflammatory disorders such as neuromyelitis optica (Zhang and Shi), a previous case report described development of multiple sclerosis (MS) after treatment with tocilizumab for rheumatoid arthritis. This raised concern for secondary CNS autoimmunity (Beauchemin and Carruthers, 2016) and led to a warning on the FDA label for tocilizumab. To our knowledge, only two additional case reports have been published on the effect of tocilizumab therapy in patients with known MS (Valencia-Sanchez and Wingerchuk, 2020; Sato et al., 2014).

Given the increase in use of tocilizumab for treatment of COVID-19, a better understanding of the relationship between tocilizumab treatment and development of MS or MS flares is imperative. Here we report additional data for two patients with MS hospitalized for COVID-19 who were treated with tocilizumab.

Methods

This study was approved by the BWH Institutional Review Board (Protocol #2021P002492). We electronically identified patients with MS who received tocilizumab within the Mass General Brigham hospital system from January 1, 2020 to September 2, 2021. Two patients were identified. We retrospectively reviewed demographic information, COVID-19 disease course, and clinical and radiologic outcomes.

Case description

Case 1

A 52 year old male with an 8 year history of relapse-remitting MS (RRMS) on ocrelizumab (since 2019) presented with fever, cough, and body aches and was positive for COVID-19 by nasopharyngeal PCR. His last ocrelizumab infusion was four months prior to admission. His baseline extended disability status scale (EDSS) was 2.5 and his patient determined disease step (PDSS) was 1. He had received the first dose of

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his mRNA COVID-19 vaccine 3 weeks prior to admission, but not the second dose. His maximum WHO COVID-19 severity scale during hospitalization was 5. He was treated with intravenous tocilizumab 800 mg 17 days after testing positive for COVID-19 which correlated with day 3 of hospitalization. He was discharged on hospital day 8. At last follow-up four months after discharge, his EDSS was stable at 2.5 and PDSS was stable at 1. MRI brain and spine performed six months after hospitalization was stable without evidence of new disease activity. Seven days after presenation his SARS-CoV-2 spike antibody was positive at 21.53 U/mL, and his nucleocapsid antibody was positive at 4.71 U/mL.

Case 2

A 39 year old female with a 13 year history of RRMS on ocrelizumab (since 2018) presented with fever, dyspnea, and hypoxia and tested positive for COVID-19 by nasopharyngeal PCR. Her last ocrelizumab infusion was six months prior to admission. She had not been vaccinated against COVID-19. Her baseline EDSS was 1 and her baseline PDSS was 1. Her maximum WHO COVID-19 severity scale was 6. She was treated with tocilizumab 800 mg 18 days after testing positive for COVID-19 and on hospital day 7. She was discharged on hospital day 26. At last follow-up four months after discharge, her EDSS was 2 and her PDSS was stable at 1. The increase in EDSS was attributable to worsening loss of vibratory sensation in the patient's lower extremities. MRI brain and spine with contrast performed at 3 month after hospitalization did not show evidence of disease progression with no new T2 FLAIR or contrast enhancing lesions. Her SARS-CoV-2 spike antibody was positive at 6.39 U/ml three weeks after admission.

Discussion

To date, over 43 million people have been diagnosed with COVID-19 in the United States. The prevalence of MS in the US has been estimated at approximately 309/100,000, (Wallin et al., 2019) and we therefore estimate that over 130,000 Americans with multiple sclerosis have been diagnosed with COVID-19, assuming that rates of infection are similar in those with or without MS. The COVID-19 hospitalization rate for patients with MS is 11%, (Sormani et al., 2021) which allows us to estimate that approximately 13,000 patients with multiple sclerosis have been hospitalized for COVID-19 symptoms and were potentially eligible for treatment with tocilizumab.

The potential of tocilizumab to provoke or exacerbate multiple sclerosis has been posited based on a single case report describing development of multiple sclerosis following treatment of rheumatoid arthritis with tocilizumab in 2016 (Beauchemin and Carruthers, Feb 2016). In personal experience, our center has received referrals to evaluate safety of tocilizumab initiation in patients with MS. However, the data on the effect of tocilizumab in MS patients remains very limited. Two subsequent case reports have not demonstrated adverse effects from tocilizumab treatment in patients with MS (Valencia-Sanchez and Wingerchuk, Jul 2020; Sato et al., 2014). In fact, another case report showed efficacy of tocilizumab in the treatment of fulminant multiple sclerosis in one patient (Hoshino et al., 2020). Based on these conflicting reports, additional clinical data is needed on the effect of tocilizumab treatment in patients with MS.

Il-6 is a cytokine hypothesized to be involved in pro-immune responses, and has been shown to play a role in differentiation of CD4+ T cells to TH17 T cells *in vitro* (Harbour et al., 2020). In animal studies of autoimmune encephalomyelitis (EAE), a murine model of MS, IL-6 blockade has been shown to inhibit the induction of Th17 T-cells in lymph nodes and inhibit the development of EAE. Based on this in vitro and animal data, some have hypothesized that IL-6 blockade with medications such as tocilizumab may actually be a potential therapeutic treatment for MS (Serada et al., 2008). Ancillary evidence supporting this hypothesis is the recently proven efficacy of tocilizumab in treating neuromyelitis optica, another CNS inflammatory disorder, though its pathogenesis differs from MS (Zhang and Shi).

Here we describe two patients with multiple sclerosis who were treated with tocilizumab. Neither patient demonstrated evidence of clinical or radiologic progression of their multiple sclerosis. One patient had a slight increase in EDSS due to worsening vibratory sensation in feet, though this exam finding is subject to inter-examiner variability and could also be related to critical illness. Based on these cases, and the demonstrated clinical benefit of tocilizumab treatment for severe COVID-19[1], we propose that a pre-existing diagnosis of multiple sclerosis should not prohibit treatment with IL-6 inhibitors including tocilizumab for COVID-19.

One notable feature of the patients described here is that they both were on treatment with ocrelizumab, a B-cell depleting DMT. As such, these cases cannot be compared directly to patients without a known diagnosis of MS or with MS but not on DMT who receive tocilizumab. Given that activated B-cells are involved in Il-6 secretion and signaling cascades, it is possible that treatment with ocrelizumab played a role in limiting potential autoimmunity secondary to tocilizumab. However, this conclusion cannot be drawn from two patients alone, and we acknowledge the limited generalizability of our findings to MS patients who may be on other DMTs or not on DMT. Our cases are also limited by their relatively short interval follow-up. Larger scale studies are needed to determine if use of tocilizumab for COVID-19 can lead to development of MS or provoke relapses in patients with known MS.

Declaration of Competing Interest

All authors report no relevant disclosures. S.B reports consulting fees from Teladoc Health and Alexion Pharmaceuticals; publishing honorarium from UpToDate and American Academy of Neurology; research support from Alexion Pharmaceuticals.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2022.100061.

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