Case report: Treatment of long COVID with a SARS-CoV-2 antiviral and IL-6 blockade in a patient with rheumatoid arthritis and SARS-CoV-2 antigen persistence

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Introduction: Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC) in ~30% of all infected individuals. Here, we present a case of PASC in a patient with rheumatoid arthritis characterized by viral persistence in the nasopharynx for 6 months after acute infection. We demonstrate transient disappearance of antigen persistence and decreased antiviral and autoimmune T cell responses after nirmatrelvir/ritonavir and tocilizumab treatment.

Case presentation: A 37-year-old female with a 7-year history of rheumatoid arthritis enrolled in a COVID-19 research study was found to continuously test SARS-CoV-2 antigen positive in the nasopharynx for 6 months after acute infection. She simultaneously presented with new-onset PASC symptoms including chronic occipital headache and periods of intense fatigue 8 weeks after acute infection. The patient was prescribed nirmatrelvir/ritonavir to treat SARS-CoV-2 persistence at 3.5 months post-acute infection and observed a reduction in PASC symptoms 3 weeks after completing antiviral treatment. After resurgence of PASC symptoms, she stopped treatment with tocilizumab for rheumatoid arthritis to attempt complete SARS-CoV-2 viral clearance. The severity of the patient’s PASC symptoms subsequently increased, and she developed new-onset brain fog in addition to previous symptoms, which resolved after resumption of tocilizumab treatment. Assessment of adaptive immune responses demonstrated that nirmatrelvir/ritonavir and tocilizumab treatment decreased antiviral and autoreactive T cell activation. After resuming tocilizumab treatment, the patient's PASC symptoms were significantly reduced, but nasopharyngeal antigen positivity remained.

Conclusion: These data suggest that nirmatrelvir/ritonavir should be considered in the treatment of PASC in patients who have SARS-CoV-2
Introduction

SARS-CoV-2 is a (+)-strand RNA β-coronavirus first identified in December, 2019 and is the causative agent of COVID-19. There have been more than 560 million cases and 6.3 million deaths globally attributable to the COVID-19 pandemic (1). Although highly effective vaccines are now used to prevent severe disease and death from SARS-CoV-2, long-term sequelae after infection have become an urgent medical concern (2, 3). The rapid emergence of variants with enhanced virulence profiles and increased ability to evade vaccine-elicited immunity make it crucial to find alternative treatment options for COVID-related sequelae (4).

Post-acute sequelae of SARS-CoV-2 infection (PASC), or “long COVID,” includes symptoms persisting for more than 4 weeks after acute infection and affects an estimated 30% of people infected with SARS-CoV-2 (5). Neuro-PASC is clinically defined as new neurologic or neurocognitive symptoms persisting for more than 4 weeks after disease onset and is often not concomitant with diagnosis of acute infection (6, 7). Currently, there are only symptomatic treatment options for Neuro-PASC (8), demonstrating the urgent need for new therapeutic approaches that address the underlying cause(s).

We describe a unique case of Neuro-PASC in a patient with a 7-year history of rheumatoid arthritis (RA). The patient tested continuously positive for SARS-CoV-2 by FlowFlex rapid antigen test for more than 6 months after acute infection. Treatment with nirmatrelvir/ritonavir and modifying treatment with tocilizumab decreased or eliminated PASC symptoms as well as antiviral and autoreactive T cell responses.

Case presentation

A 37-year-old South Asian woman on bi-weekly 162 mg/ml tocilizumab injections for RA was enrolled in a Neuro-PASC research study at Northwestern University in Chicago (demographics in Figure 1A; study design in Figure 1B). She was acutely symptomatic with new onset severe fatigue, occipital headache, and loss of appetite. She tested SARS-CoV-2+ by nasopharyngeal rapid antigen test in December, 2021. She experienced persistent headache and fatigue for >6 weeks after infection. The patient tested RT-PCR for SARS-CoV-2 at 14 days post-infection and multiple times thereafter but continued to test intermittently antigen+ for 14 weeks post-infection despite no overt exposure to SARS-CoV-2 infected individuals. The patient lived alone, did not leave her residence without a surgical-grade N95 mask, and never removed the mask in public. She was subsequently prescribed a 5-day course of nirmatrelvir/ritonavir 300/100 mg twice daily, a SARS-CoV-2-specific antiviral, on the basis of her continued positive antigen tests. Patient was in compliance with all prescribed treatment courses. Initially, all PASC symptoms resolved, and the patient tested antigen− 3 weeks after completion of nirmatrelvir/ritonavir, but PASC symptoms and antigen positivity subsequently reappeared at 4 weeks (Figures 1B,C). The patient halted tocilizumab therapy for RA upon her rheumatologist’s recommendation for 10 days in an attempt to fully clear the virus, during which time she developed more severe PASC symptoms and the appearance of new-onset cognitive impairment (brain fog). She resumed tocilizumab and within 3 weeks, her fatigue and brain fog had resolved while the occipital headache decreased in severity (Figure 1C).

Analysis of antiviral T cell responses by IFN-γ ELISPOT showed that Spike-specific T cell activation was induced by vaccination and infection, as expected after receiving Spike protein-based vaccines. However, the patient’s non-Spike responses (to Nucleocapsid) were enhanced as well after receiving the Moderna vaccine booster dose. Nirmatrelvir/ritonavir treatment resulted in the retention of Spike- but not Nucleocapsid-specific T cell responses, while halting tocilizumab correlated with elevated T cell responses against both proteins. Resumption of tocilizumab subsequently decreased T cell responses to both viral antigens (Figure 2A). Antibody titers against Spike receptor-binding domain (RBD) followed similar kinetics (Figure 2B, top), while the patient never mounted an antibody response against Nucleocapsid (Figure 2B, bottom).

Flow cytometric analysis of (antibodies used in Supplementary Table 1) CD4+ T follicular helper cells (Tfh; involved in T cell help for antibody production) showed that antiviral T cell activation was highest at V3 (post-infection, post-boost) and V5 (post-infection, -boost, -nirmatrelvir/ritonavir,
FIGURE 1
Post-acute sequelae of SARS-CoV-2 infection (PASC) patient exhibits persistent SARS-CoV-2 antigen positivity in nasopharynx. (A) Study visit timeline, including vaccination, infection, and intervention dates. (B) FlowFlex™ SARS-CoV-2 antigen test results over time. Time p.i., weeks post-infection. (C) PASC symptoms vs. rheumatoid arthritis symptoms.

FIGURE 2
IFN-γ T cell responses to SARS-CoV-2 vary over time. (A) IFN-γ production from SARS-CoV-2 Spike- and Nucleocapsid-specific T cells at each visit as determined by ELISPOT. (B) Spike receptor-binding domain (RBD)-specific IgG titers (top) and Nucleocapsid-specific IgG (bottom) at each visit. LoD, limit of detection. All ELISPOT data in panel (A) from duplicate wells. Data representative of 2 individual experiments, *p < 0.05 by Student’s t-test.
FIGURE 3

Virus-specific CD4+ and CD8+ T cell subset activation correlates with antiviral and tocilizumab treatment. (A) Flow cytometry showing elevated virus-specific CD4+ T helper cell (Tfh) cell activation after vaccine booster dose (V3, 2nd row) and stopping tocilizumab treatment (V5, 4th row). (B) Total CD4+ T cells (left), CD4+ T helper cells (Tfh, middle), and CD4+ memory T cells (TEM, right) have enhanced reactivity to SARS-CoV-2 structural (S, N) and non-structural (Orf1ab, Orf7) peptides after vaccine boost (V3) and stopping tocilizumab (V5), but low reactivity after nirmatrelvir/ritonavir treatment (V4) and resuming tocilizumab (V6). Total CD8+ T cells (right) and CD8+ memory T cell subsets (CD8+ TEMRA, TEM; middle, right) show increased activation after vaccine boost (V3) and stopping tocilizumab (V5), but low reactivity after nirmatrelvir/ritonavir treatment (V4) and resuming tocilizumab (V6). Data combined from 3 independent experiments.

and halting tocilizumab treatment). Tfh activation determined by the activation-induced marker assay (AIM) (9) was lowest 3 weeks after nirmatrelvir/ritonavir treatment and resumption of tocilizumab (Figure 3A). Similarly, total CD4+ and CD8+ T cells, CD4+ and CD8+ T effector memory (TEM) cells, and CD8+ TEM cells re-expressing CD45RA (CD8+ TEMRA; terminally differentiated and highly cytotoxic T cells) exhibited maximal SARS-CoV-2-specific activation to Spike, Nucleocapsid, Orf1ab, and Orf7 antigens at V3 and V5, with limited activation at V4 and V6 (Figure 3B).
Antiviral and autoreactive T cell responses demonstrated a parallel oscillation over time. Comparison of IFN-γ production from T cells in response to Spike and Orf1ab vs. the RA-associated cartilage antigen YKL-40 showed the highest activation at V3 and V5, and the lowest activation at V4 after nirmatrelvir/ritonavir and V6 after resuming tocilizumab treatment (Figure 4A). Flow cytometry revealed similar activation patterns in T cell memory and Tfh cell subsets (Figure 4B). No other clinical diagnostic testing was performed on the patient.

Discussion and conclusion

COVID-19 is increasingly being recognized as a multi-organ disease with long-term sequelae associated with neurological
dysfunction. PASC has been reported in up to 30% of those with mild disease who do not require hospitalization (10, 11). Long-term sequelae after coronavirus infections can persist for years (12); therefore, individual case reports can inform us on how PASC symptoms may be impacted by available treatment options.

This case study described a Neuro-PASC patient presenting with long-term nasopharyngeal viral shedding as determined by SARS-CoV-2 antigen tests. Persistent viral colonization has been described previously both in the nasopharynx and extra-respiratory sites (13, 14) and is associated with being immunocompromised (15), though it is unknown whether viral persistence is more common in PASC patients than in healthy COVID convalescents. In this case, the patient was on immunosuppressive therapy with tocilizumab for pre-existing RA when she contracted SARS-CoV-2, which may have contributed to viral persistence over 6 months. However, tocilizumab may also decrease the severity of acute SARS-CoV-2 infection in hospitalized patients (16). The patient's mild acute symptoms combined with an escalation in Neuro-PASC symptom severity after stopping tocilizumab, as well as their resolution after resuming treatment suggests that IL-6 blockade should be studied further as a potential therapeutic intervention for Neuro-PASC.

Nirmatrelvir/ritonavir (Paxlovid) treatment is indicated within the first 72 h of a confirmed SARS-CoV-2 infection diagnosis to limit disease progression and decrease symptom severity (17). Though not indicated for the treatment of PASC, the treating physician felt that her prolonged nasopharyngeal antigen positivity warranted the treatment. Indeed, the patient's PASC symptoms fully resolved 3 weeks after completing antiviral treatment, which was corroborated by testing antigen positive nasopharyngeal antigen tests (Figure 1C) and having decreased non-Spike adaptive immune responses (Figures 2, 3). Her symptoms and antigen positivity resolved 4 weeks post-nirmatrelvir/ritonavir treatment along with enhanced T cell and antibody responses to SARS-CoV-2 (Figures 2, 3), suggestive of viral reactivation after antiviral treatment. SARS-CoV-2 viral rebound has been reported after a 5-day course of nirmatrelvir-ritonavir. Additionally, we raise the possibility that tocilizumab should be further studied as a therapeutic intervention for Neuro-PASC. PASC impacts millions of people worldwide, and its incidence is only modestly diminished by vaccination (27, 28). Urgent research is needed to study the role of existing treatments to ameliorate the devastating impacts of PASC.

**Limitations**

The first author performed all experiments and analyses, and thus the study could not be blinded. We also note that this is one patient's experience and thus should not be used to generalize to larger patient populations without further clinical trials.

**Author disclosure**

The first author is the patient described in the study and gave full consent to use the data in this manuscript.
Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Northwestern University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. IRB study number STU00212583. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LV: conceptualization. LV and ZO: investigation and formal analysis. LV and IK: resources, data curation, supervision, project administration, and funding acquisition. LV: writing with feedback from all authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1003103/full#supplementary-material

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