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Letter to the Editor: New Observation

Axial Improvement after Casirivimab/Imdevimab Treatment for COVID-19 in Parkinson's Disease

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We report the case of a patient with advanced Parkinson's disease (PD) who developed significant improvement of freezing of gait (FOG) after receiving monoclonal antibodies cocktail casirivimab/Imdevimab (REGN-COV2, Regeneron-Roche) for the treatment of COVID-19 infection.

A 70-year-old PD patient started at the age of 47 with rigidity and bradykinesia in the left foot. At 63, his symptoms were not well controlled with severe motor fluctuations, peak-dose dyskinesia, and levodopa-responsive FOG, so he was treated with bilateral subthalamic deep brain stimulation. His motor conditions considerably improved after surgery with the disappearance of motor fluctuations and FOG and marked reduction of dyskinesia. However, after 5 years, he progressively complained severe FOG, also after levodopa intake, with instability and rare falls together with mild peak-dose dyskinesia.

In August 2021, he developed cough and myalgia and was diagnosed with mild COVID-19 infection after a positive nasopharyngeal swab for SARS-CoV-2. The patient was not vaccinated for COVID-19 before. In the very first days of infection, COVID-19 infection, PD symptoms did not worsen nor the patient required hospitalization. However, since the patient was considered to be at high risk of progressing to severe COVID-19 infection, he was immediately treated with a single intravenous infusion of REGN-COV2 (total dose: 2.4 g). No further drugs were administered except paracetamol. After REGN-COV2 infusion COVID-19 symptoms disappeared in few days. No changes were made to stimulation parameters or pharmacological daily treatment (levodopa/carbidopa 100/25 mg four tabs; rotigotine patch 6 mg; selegiline 5 mg). The day after REGN-COV2 infusion, he noticed a marked improvement of gait, particularly of FOG, and moderate improvement of speech. The benefits on walking remained unchanged for over 2 weeks (Video, segments 1, 2), then gradually reduced, and disappeared after about 40 days (Video, segment 3), as well as speech improvement.

REGN-COV2 is an antibody cocktail containing two neutralizing human IgG1 SARS-CoV-2-neutralizing antibodies, recently approved for non-hospitalized patients with COVID-19.[1] REGN-COV2 prevents viral entry into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor by targeting the receptor-binding domain of the SARS-CoV-2 spike protein.[1]

Different pathophysiological mechanisms underlie appendicular and axial motor symptoms in PD.[2,3] Axial symptoms, such as dysarthria, swallowing troubles, gait disorders, and postural instability, are considered mainly resulting from non-dopaminergic (i.e., cholinergic) lesions affecting brain areas.[3] In particular, nicotinic acetylcholine receptors subtypes such as the α4β2 (and potentially other subunits) may play a significant role in the pathophysiology of gait disorders in PD and there is emerging evidence that nicotinic receptors (nAChR) agonists targeting α4β2 subtype might improve gait and attention.[3] It has been reported that SARS-CoV-2 may disrupt the activity of central cholinergic system also considering that its spike protein has a sequence like neurotoxins, capable of binding nAChR.[4] Predictive models have showed that the viral spike protein peptide exhibits favorable binding affinity to nAChR.[5] In addition, the interaction of Y674-R685 region of the spike protein with the α4β2 receptors can force the loop C region of the receptor to adopt an open conformation, like other known nAChR antagonists.[5] Furthermore, emerging data underline the possible link between COVID-19 infection and parkinsonism particularly after the reported occurrence of parkinsonism after COVID-19 infections.[6,7] Several studies investigating the impact of COVID-19 on PD have suggested that PD patients are particularly susceptible to worsening symptoms,[6] especially bradykinesia, tremor, and gait disturbances[8]. ACE2 receptors, the target of the virus, are highly expressed in dopaminergic neurons, which are already compromised in PD and a SARS-CoV-2-induced downregulation of ACE2 expression might be at least theoretically associated with the worsening of symptoms.[9] The role of ACE inhibitors in PD has been previously investigated, with some controversies. Data from the PPMI study did not find any benefit associated with use of ACE inhibitors in newly diagnosed PD,[10] however, other studies reported some benefits of ACE inhibitors

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in PD patients with moderate–severe stages.[11,12] These authors speculate that ACE2 receptors are involved in advanced stages of PD and contribute to the onset of motor complications such as ON/OFF fluctuations and dyskinesias. This is potentially interesting for high-throughput drugs screening.

In our patient, the improvement on gait and speech started the day after the infusion, remained unchanged for over 2 weeks then gradually reduced, and disappeared after about 40 days. We may speculate that REGN-COV2 acted on other targets besides SARS-CoV-2 favorably modulating the activity of the cholinergic or less likely dopaminergic pathways. An alternative hypothesis is that the antibodies interaction with SARS-CoV-2 mediated the clinical improvement. This hypothesis appears less probable, particularly considering that in our patient the infection did not produce any worsening of PD symptoms. However, it should be kept in mind that he was immediately treated with REGN-COV2 infusion so we cannot exclude that without the antibody cocktail he could worsen during time. The patient was also treated with paracetamol, but he confirmed that he had taken this drug several times in his life at the same dosages without presenting any change in parkinsonian symptoms. Furthermore, the expected duration of effect of REGN-COV2 is similar with the duration of FOG improvement observed in our patient which remained unchanged for over 2 weeks then gradually reduced and disappeared after about 40 days. Indeed, the mean estimated half-life calculated during the elimination phase in animal models ranged from approximately 13 to 18 days across the various dose groups for REGN-COV2,[13] while a subsequent human study has confirmed that the mean estimated half-life for both casirivimab and imdevimab ranged from 25 to 37 days.[1,13] We cannot exclude that a possible placebo effect related to REGN-COV2 infusion played a role in our patient considering that placebo effect is common and lasting in PD. The prevailing effect on axial symptoms, without the worsening of dyskinesias, which would suggest a dopaminergic hyperactivity, supports the possible modulation of the cholinergic and/or glutamatergic pathways. These hypotheses need to be tested in future studies to better elucidate the possible effects of REGN-COV2 on parkinsonian symptoms, particularly considering the complex pathophysiology of FOG.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2022.269

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Conflicts of Interest. The authors declare that there are no conflicts of interest relevant to this work.

Ethics Statement. Written informed consent was obtained from the patient to be videoed for publication.

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