

CASE REPORT

Effectiveness of Aprepitant in post-acute COVID-19 syndrome

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Abstract

This is the first case of a patient taking Aprepitant for a post-acute COVID-19 syndrome. This case may encourage researchers to look for the evidence for the efficacy and safety of a neurokinin 1 receptor antagonist in this frequent syndrome.

KEYWORDS

aprepitant, post-acute, COVID-19, SARS-CoV-2

1 | INTRODUCTION

The post-acute COVID-19 syndrome (PACS) includes a plethora of non-specific symptoms with no approved therapy. We present a clinical case of a patient with PACS who reported considerable improvement with Aprepitant, a neurokinin 1 receptor (NK-1R) inhibitor. A 39-year-old woman, a nurse by profession, current smoker, diagnosed with asthma, and a depressive syndrome, was diagnosed with COVID-19 in May 2020, after a serological test carried out by ELISA assay. In mid-July 2020, she developed a severe PACS with significant physical limitation. She decided to self-medicate with Aprepitant at her own risk for 3 consecutive days at doses of 125 mg on day 1, and 80 mg on days 2 and 3, reporting improvement, with disappearance of most symptoms. This is the first case of a patient taking Aprepitant for a PACS, which may encourage researchers to look for the evidence for the efficacy and safety of NK-1R antagonists in PACS.

Despite the considerable impact on incidence and mortality of the current SARS-CoV-2 pandemic, many patients survive acute infection thanks to the therapeutic measures available. In recent months, some patients have been described whose symptoms persist despite having overcome the acute infection, which has given rise to the term post-acute COVID-19 syndrome (PACS).¹

The syndrome known as PACS includes the presence of persistent symptoms that could be related to three main spheres of the disease, namely the phenomena of persistent inflammation in the convalescent phase of the infection, damage to specific organs and the impact on pre-existing health conditions and in many cases prolonged mechanical ventilation after admission to intensive care.²⁻⁴

Unfortunately, due to the non-specificity of the symptoms and the multiple systems involved, to date there is no consensual and systematized diagnostic approach, nor any approved therapeutic option. The following is a clinical case of

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a patient with PACS who reported considerable improvement with aprepitant, a neurokinin 1 receptor (NK-1R) inhibitor which is indicated for the treatment of nausea and vomiting associated with chemotherapy, and which is currently being explored for use in acute COVID-19.

2 | CASE RECORD

The patient is a 39-year-old woman, a nurse by profession, current smoker. The medical history of interest included chronic bronchial asthma with treatment with formoterol/budesonide 4.5/160 two inhalations every 12 hours with an adequate control, and a depressive syndrome treated with venlafaxine retard 150 mg daily. During an occupational health check-up at her workplace in May 2020, a serological test for SARS-CoV-2 was carried out by ELISA assay, which produced a negative result for IgM and positive for IgG. With this information, the patient was diagnosed with an asymptomatic COVID-19 infection and, accordingly, no treatment for this infection was prescribed.

In mid-July 2020, she developed pain and edema in the lower limbs, together with asthenia. Over the following days, the symptoms increased progressively, including headaches, dizziness, blurred vision and photophobia, slight hearing loss, and sonophobia. This clinical deterioration progressed over the following months, with increased asthenia and muscle weakness, arthromyalgia and psychomotor slowness and significant physical limitation, and assistance in walking was required. In addition, from a neuropsychiatric point of view, increased lack of concentration, memory loss, and emotional lability were noted.

After several months with these symptoms, as a health-care worker, she carried out a search in PubMed and decided to self-medicate with aprepitant at her own risk. At the beginning of March 2021, she took aprepitant for 3 consecutive days at doses of 125 mg on day 1, and 80 mg on days 2 and 3. On day 4, the patient reported improvement, with disappearance of pain, asthenia, and psychomotor slowness, although with some variability over the 18 days, as she monitored her own symptoms using a diary of symptoms that she made herself. Today, two months later, the patient reports being in reasonably good health.

3 | DISCUSSION

The present article describes the subjective positive response to aprepitant of a patient with PACS. Although aprepitant and similar compounds are under exploration for acute COVID-19 (Clinicaltrials.gov NCT04326426 and NCT04468646) with a positive pre-print publication on the

effect of aprepitant combined with dexamethasone in severe to critical COVID-19 patients,⁵ this is the first report of a clinical experience in a PACS case.

PCAS is now considered part of the clinical expression of COVID-19. Case series have been reported with the incidence of persistent symptoms ranging from 40 to 90% of patients, identifying PACS as a very frequent clinical outcome.¹ However, the interpretation of the results is hampered by unsystematic and short-term evaluations, with a considerable number of confounding variables in relation to age, severity of infection, follow-up, and characteristics of the clinical evaluation. Accordingly, at the present time there are no universally accepted diagnostic criteria for this new clinical condition and the publications that describe this new syndrome are based on clinical descriptions referred by patients as in the case we present.^{6,7} Interestingly, neither these symptoms were not present before the acute infection nor the patient did suffer from any clinical condition that conditioned these symptoms before COVID.

Today, we know the infection caused by SARS-CoV-2 is a multisystemic disease that goes beyond the well-known respiratory symptoms. Among the systemic implications described is its ability to generate a state of neuroinflammation by entering the central nervous system either by retrograde neuronal dissemination through the olfactory nerves, through the autonomous nervous system, or via infected leukocytes that cross the blood-brain barrier allowing the virus to enter the brain and disrupt cells.⁸⁻¹⁰ Considering all the potential systemic symptoms associated with this, therapeutic options are currently needed.

Aprepitant is an antagonist of NK-1R and is a selective antagonist of the NK1 receptors of neurokinins, whose main natural ligand is substance P, which is capable by itself of inducing intense emesis. Its current indication is the prevention of nausea and vomiting associated with moderate and highly emetogenic cancer chemotherapy in adults and adolescents from 12 years of age. Substance P belongs to the tachykinin family,¹¹ is widely distributed, and is expressed in sensory nerve fibers that innervate the airways and lymphoid organs, in glial cells and cells of the immune system. It is involved in a large number of both physiological and pathological processes where there is inflammation, which makes it a possible target for certain inflammatory processes. When substance P interacts with its high-affinity receptor, NK-1R stimulates and modulates the release of cytokines. The main mechanisms by which substance P promotes inflammation, vasodilation and increased vascular permeability, facilitate the migration of leukocytes from the blood to the damaged tissue, and direct cell stimulation.^{12,13} It is currently known that aprepitant can cross the blood-brain barrier after oral administration.¹⁴ In this way, aprepitant would

block the storm of cytokines that maintain the state of neuro-inflammation activated by substance P.

The current case reports the subjective improvement of PACS after aprepitant intake. Although there was no objective physiological measurement of this improvement of the symptoms, the scientific rationale and the clinical impact of the role of NK-1R inhibitors both in PACS and in the acute phase would be worth exploring. Currently, aprepitant and similar compounds like Tradipitant are being studied in prospective clinical trials for acute COVID19, with patients now being recruited. Similarly, a pre-print publication has recently reported the beneficial effects of a combination of aprepitant plus dexamethasone in the treatment of acute COVID19.⁵ Therefore, its role as part of the therapeutic approach should be evaluated in prospective clinical trials.

One intriguing question remained related to the persistence of this effect on PACS over time. Our patient took only one cycle of three doses of aprepitant, and she monitored her symptoms during an 18-day period, and so the question of the persistence of the beneficial effect remains unclear. Apparently, the women continued to feel well and the biological rationale for a more prolonged impact of aprepitant after one single cycle should also be studied, if this therapeutic effect is maintained.

In summary, this is the first case of a patient taking aprepitant for a PACS. Considering the rationale, this clinical case may encourage researchers to look for the evidence for the efficacy and safety of NK-1R antagonist in PACS. If these findings are confirmed, we could be facing the first effective treatment against this frequent syndrome consequence of the current SARS-CoV-2 pandemic.

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CONFLICT OF INTEREST

JLLC has received honoraria for lecturing, scientific advice, participation in clinical studies or writing for publications for (alphabetical order): AstraZeneca, Bayer, Boehringer Ingelheim, Cantabria Pharma, Chiesi, CSL Behring, Esteve, Faes, Ferrer, Gebro, GlaxoSmithKline, Grifols, Menarini, MSD, Novartis, Pfizer, Rovi, Teva and Takeda. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

RRA, and JLLC summarized the clinical data over the time and wrote the drafts. JLLC and CLR provided her expertise on the studied syndrome and supervised the content. JAJR participated in the conception of the importance of the case and supervised and approved the content.

ETHICAL STATEMENT

Informed consent was obtained from the patient included in the case report.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this case are available within the article.

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REFERENCES

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615. <https://doi.org/10.1038/s41591-021-01283-z>
2. Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. 2021;11(3):e048391. <https://doi.org/10.1136/bmjopen-2020-048391>
3. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chronic Respir Dis*. 2021;18:14799731211002240. <https://doi.org/10.1177/14799731211002240>
4. Xiong Q, Xu M, Li J, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect*. 2021;27(1):89-95. <https://doi.org/10.1016/j.cmi.2020.09.023>
5. Mehboob R, Ahmad FJ, Qayyum A, et al. Aprepitant as a combinant with Dexamethasone reduces the inflammation via Neurokinin 1 Receptor Antagonism in severe to critical Covid-19 patients and potentiates respiratory recovery: A novel therapeutic approach. *medRxiv* 2020:2020.08.01.20166678. <https://doi.org/10.1101/2020.08.01.20166678>
6. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. <https://doi.org/10.1001/jama.2020.12603>
7. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8)
8. Jiao L, Yang Y, Yu W, et al. The olfactory route is a potential way for SARS-CoV-2 to invade the central nervous system of rhesus monkeys. *Signal Transduct Target Ther*. 2021;6(1):169. <https://doi.org/10.1038/s41392-021-00591-7>
9. Hewitt KC, Marra DE, Block C, et al. Central Nervous System Manifestations of COVID-19: A Critical Review and Proposed Research Agenda. *J Int Neuropsychol Soc*. 2021;1-15. <https://doi.org/10.1017/s1355617721000345>

10. Song WJ, Hui CKM, Hull JH, et al. Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses. *Lancet Respir Med*. 2021;9(5):533-544. [https://doi.org/10.1016/s2213-2600\(21\)00125-9](https://doi.org/10.1016/s2213-2600(21)00125-9)
11. Iftikhar K, Siddiq A, Baig SG, et al. Substance P: A neuropeptide involved in the psychopathology of anxiety disorders. *Neuropeptides*. 2020;79:101993. <https://doi.org/10.1016/j.npep.2019.101993>
12. O'Connor TM, O'Connell J, O'Brien DI, et al. The role of substance P in inflammatory disease. *J Cell Physiol*. 2004;201(2):167-180. <https://doi.org/10.1002/jcp.20061>
13. Endo T, Saijo T, Haneda E, et al. Quantification of Central Substance P receptor occupancy by aprepitant using small animal positron emission tomography. *Int J Neuropsychopharmacol*. 2015;18(2):pyu030. <https://doi.org/10.1093/ijnp/pyu030>
14. Bergström M, Hargreaves RJ, Burns HD, et al. Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry*. 2004;55(10):1007-1012. <https://doi.org/10.1016/j.biopsych.2004.02.007>

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