"Nirmatrelvir/ritonavir as a posible treatment for Long-COVID "

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Abstract

It is estimated that about 10% of patients who have been infected with SARS-CoV-2 worldwide suffer from Long-Covid, about 65 million people [1]. Although we are beginning to know its pathophysiology, there is still no evidence on its treatment. We present the case of a patient with persistent prolonged symptoms who had an optimal response to nirmatrelvir/ritonavir 2 years after acute infection.

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Dear Editor:

It is estimated that about 10% of patients who have been infected with SARS-CoV-2 worldwide suffer from Long-Covid, about 65 million people [1]. Although we are beginning to know its pathophysiology, there is still no evidence on its treatment. We present the case of a patient with persistent prolonged symptoms who had an optimal response to nirmatrelvir/ritonavir 2 years after acute infection.

A 38-year-old woman with a history of psoriasis (untreated and well controlled) who, after receiving the first dose of Pfizer-BioNTech® vaccine on January 13, 2021, presented with headache, fever of 38ºC and myalgias. Given the persistence of symptoms after 48 hours, RT-PCR against SARS-CoV-2 (ARGENE® SARS-COV-2 R-GENE®) was performed and was positive. Anosmia, ageusia and dry cough were added to the referred symptomatology. On February 8, serology was performed, detecting IgG against protein S of SARS-CoV-2 by chemiluminescence technique (CLIA) in automated equipment (Liaison ® SARS-CoV-2 S1/S2 IgG). Given the persistence of symptoms, including hyperthermia, corticotherapy was started at medium doses for 3 weeks. She presented better thermal and other symptom control, but persisted with afternoon febrile fever. He was referred to the Post-Covid-19 consultation of the Infectious Diseases Unit.

In a first contact, physical examination was normal and complementary tests were requested in which only elevated values of erythrocyte sedimentation rate [ESR: 20 mm/h (0-10)] and D-dimer [900 ng/mL (0-500)], with autoimmunity, hemogram, proteinogram, acute phase reactants, immunoglobulins, lymphocyte populations, liver enzymes, ions, hormone and vitamin studies were unremarkable. Serology was negative. A second course of corticosteroids was started, with no response, persisting with poorly tolerated afternoon febrile fever with headache, asthenia, myalgia and atypical chest pain. A complete computed axial tomography (CAT) scan was performed, showing adenopathies of non-significant size at the cervical, retroperitoneal and mesenteric levels. A positron emission tomography (PET) scan was requested, which only reported diffuse inflammatory gastric hypermetabolism, so gastroscopy was performed with biopsies that ruled out pathology including infection by *Tropheryma whipplei* . The initial analytical study was repeated 10 months after the onset of the clinical picture, adding tumor markers and extraction of blood cultures, and again the results were irrelevant.

One year after the onset of symptoms and due to the persistence of a poorly tolerated daily afternoon fever, treatment with colchicine was tried as an immunomodulator and a genetic study of autoinflammatory syndrome was requested, which was negative. After starting colchicine, the patient was afebrile and her general symptoms improved. The treatment was maintained for 5 months with good control and after its withdrawal she again presented febrile fever and worsening of the previous symptoms. Colchicine was reintroduced at the same dose and again she was asymptomatic.

A few weeks later, despite continuing with colchicine, the febrile fever reappeared and she presented a significant clinical deterioration that did not improve despite increasing the dose. Finally, two years after

the onset of symptoms and after the approval by a multidisciplinary committee, we withdrew colchicine and started antiviral treatment against SARS-CoV-2 (off-label) with nirmatrelvir/ritonavir for 5 days with immediate resolution of symptoms. After 6 weeks of treatment, she has not presented febrile fever or the symptoms previously mentioned.

Long-Covid has been more frequently associated with ages between 36-50 years, female sex and independently of the severity of the acute infection [2]. Multiple hypotheses have been proposed, including the persistence of viral activity from certain reservoirs [3, 4]. We suggest that, in the present case, viral persistence would have triggered a persistent inflammatory response, causing the symptomatology. Colchicine would have modulated the inflammatory response, thus explaining the good symptomatic control with its administration and the worsening with withdrawal.

After a literature review, we found only 4 case reports describing a clear improvement after the use of nirmatrelvir/ritonavir in patients with persistent symptoms after acute infection [5]. However, in most of them it was administered a few weeks later and after re-infection and none of them had such a prolonged and disabling evolution as in the referred patient. In addition, a recent preprint shows a decrease in the incidence of Long-Covid with the use of nirmatrelvir/ritonavir in the acute phase, supporting the practice [6].

In conclusion, the persistence of viral activity after acute infection could be a cause of Long-Covid and in this sense, the use of nirmatrelvir/ritonavir is a treatment option. However, the evidence is scarce and there are probably other influencing factors such as immune dysregulation, alteration of the microbiota or vascular microtombosis and endothelial dysfunction [4].

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