LETTERS TO THE EDITOR

Oral antiviral treatments for COVID-19 during severe connective tissue disease flares: report of two cases

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Antiviral therapies targeting SARS-CoV-2 replication change the course of COVID-19[1, 2]. The European Medicines Agency (EMA) has approved a nirmatrelvir/ritonavir combination[3] that inhibits the main protease of the virus[1]. Molnupiravir, an RNA polymerase misdirector[2], is proposed by EMA in selected cases[4], despite still without marketing authorisation. Both are for use in mild disease with a high risk of progression to severe COVID[3, 4], such as patients with inflammatory rheumatic diseases under immunosuppression[5]. Both antivirals were successfully used in these patients recently[6], although the baseline disease activity was not mentioned.

A 50-year-old woman with a previous clinical history of appendicectomy and a resolved primary syphilis, presented to the Rheumatology clinic due to a four-month history of generalised erythema, muscle weakness and dysphonia. Symmetrical proximal muscle weakness (MMT8 141/150), malar rash (not sparing the nasolabial fold), and V-neck, shawl, Gottron's and holster signs were noted. The patient was diagnosed with dermatomyositis and started on prednisolone 0.5 mg/kg/day. Anti-transcriptional intermediary factor-1γ (TIF1γ) antibodies were positive. Six weeks later, she was admitted due to worsening muscle weakness (MMT8 84/150) and ulcerative skin lesions. A breast mass identified in full-body computed tomography (CT) was biopsied and revealed an invasive breast carcinoma. Apart from axillary node infiltration, no other metastases were found. The patient was treated with prednisolone 1 mg/kg/day, intravenous immunoglobulin 2 g/kg, and hydroxychloroquine 400 mg/day. On the fifteenth day of hospitalisation, dysphonia suddenly worsened, and odynophagia ensued. After testing negative three days prior, the patient tested positive in an RT-PCR for SARS-CoV-2. Vaccination status was updated, with three previous innoculations of Comirnaty vaccine. Considering the mild symptoms, the initial phase of the infection and immunosuppression, oral antiviral therapy was recommended according to national recommendations[7]. Treatment with nirmatrelvir 300 mg/ritonavir 100 mg was given twice daily for five days. The symptoms promptly improved, and no dyspnoea or other severe disease manifestations ensued. No adverse events occurred.

A 43-year-old woman presented to the emergency department due to sudden onset precordial oppression, dyspnoea and asthenia with minimal effort. She had a previous history of systemic lupus erythematosus (SLE) with articular (Jaccoud's arthritis), haematological (anaemia, leukopenia, and lymphopenia), serosal (pleural and pericardial effusion) and vascular (Raynaud's phenomenon and digital ulcers) involvements. Other than that, she only suffered from primary arterial hypertension, controlled with nifedipine 30 mg and valsartan 160 mg, both twice daily. For her SLE condition, she was being treated with hydroxychloroquine 400 mg/day, mycophenolate mofetil 2g/day and deflazacort 30 mg/day until two months before admission, when she reduced the deflazacort dose to half and stopped taking mycophenolate after a skin burn. Arterial blood gas revealed severe hypoxemia, but blood workup, electrocardiogram, and chest CT angiography did not show signs of pulmonary embolism, peri/myocarditis, ischemia, or lung infection. An echocardiogram revealed a pulmonary artery estimated pressure of 79mmHg, with no evidence of left heart disease. The patient was transferred to our hospital, and a right heart catheterisation revealed a mean pulmonary artery pressure of 42mmHg, pulmonary artery wedge pressure of 4mmHg, and pulmonary vascular resistance of 8.3 Wood units, confirming pulmonary arterial hypertension. The patient was treated with oxygen, tadalafil 20 mg/day, ambrisentan 10 mg/day, three daily pulses of methylprednisolone 1g followed by prednisolone 1 mg/Kg/day, and cyclophosphamide 500 mg every two weeks. Seven days after admission, she was asymptomatic without oxygen, and NT-proBNP dropped from 10492 to 1090 pg/mL. Just after being discharged, she tested positive in an RT-PCR for SARS-CoV-2. The next day, rhinorrhea and nasal obstruction ensued. Vaccination status was also updated, with three previous innoculations of Comirnaty vaccine. Again, there was a

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formal indication to start an oral antiviral, but ritonavir was contraindicated due to drug interaction with tadalafil. She started molnupiravir 800 mg twice daily for five days. Symptoms resolved, and no severe disease manifestations ensued. No adverse events occurred.

In conclusion, we report two clinical cases in which nirmatrelvir/ritonavir and molnupiravir were used during severe flares of connective tissue diseases in immunosuppressed patients that developed mild COVID-19, with no adverse events noted and a favourable outcome. Although we cannot attribute and quantify the good outcome of our patients' infection to our therapeutic attitude, we believe that more positive data regarding usage of these new oral antivirals in severely ill rheumatic patients encourages its adeherence in clinical practice.

REFERENCES

1. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-408.
2. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalised Patients. N Engl J Med. 2022;386(6):509-20.
3. Agency EM. Paxlovid https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid: European public assessment reports: Paxlovid; 2022, January 28 [updated 2022, July 6.
4. Agency EM. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment of COVID-19 https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19: EMA_News; 2021, November 19 [
5. McKeigue PM, Porter D, Hollick RJ, Ralston SH, McAllister DA, Colhoun HM. Risk of severe COVID-19 in patients with inflammatory rheumatic diseases treated with immunosuppressive therapy in Scotland. Scand J Rheumatol. 2022:1-6.
6. Fragoulis GE, Koutsianas C, Fragiadaki K, Mariolis I, Panopoulos S, Tsalapaki C, et al. Oral antiviral treatment in patients with systemic rheumatic disease at risk for development of severe COVID-19: a case series. Annals of the Rheumatic Diseases. 2022;81(10):1477-9.
7. Direção Geral da Saúde (DGS). Terapêutica farmacológica para a Covid-19 https://www.dgs.pt/normas-orientacoes-e-informacoes/normas-e-circulares-normativas/norma-n--0052022-de-28052022-pdf.aspx2022, May 28