Severe COVID-19 caused by persistent SARS-CoV-2 infection successfully treated with dual direct acting antivirals.

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Abstract

We report the successful use of combination therapy with two direct acting antivirals for treatment of chronic COVID-19. An immunocompromised 60 year old male with persistent SARS-CoV-2 infection over 4 months had chronic, progressive COVID-19 requiring mechanical ventilation. After failing monotherapy with two antivirals and neutralising monoclonal antibodies, he was treated with a 10 day course of intravenous remdesivir and crushed nirmatrelvir/ritonavir (Paxlovid) administered through a nasogastric tube. Following treatment, SARS-CoV-2 RNA became undetectable, with resolution of supplemental oxygen requirement and acute inflammatory changes on computed tomography. This case demonstrates potential synergy between remdesivir and nirmatrelvir/ritonavir in treating persistent, symptomatic SARS-CoV-2 infection.

Introduction

Treatments for COVID-19 now include direct-acting antivirals (DAAs), neutralising monoclonal antibodies (nMAbs), steroids and other immunomodulation. Treatment strategies for most patients with acute infection can be broadly divided into two categories: pre-emptive anti-viral treatment of early non-severe disease to prevent deterioration, and immodulatory treatment of severe disease requiring hospitalisation [1]. Additionally, immunocompromised individuals can suffer from persistent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2], the treatment of which is poorly evidenced by only case reports and case series. For instance, viral clearance has been reported in several persistently infected patients treated with a combination of single agent DAA remdesivir and antibody therapy [3]. However, this situation has been complicated by the frequent emergence of SARS-CoV-2 variants such as Omicron with resistance to nMAbs [4].

There is limited data regarding combination treatment with dual DAAs. Preclinical data suggests that Paxlovid (nirmatrelvir/ritonavir) may show synergy with remdesivir *in vitro* [5]. In a Syrian hamster model, combined treatment with molnupiravir and favipiravir showed potentiation of antiviral efficacy [6]. Another study showed synergistic inhibition of viral replication by Paxlovid and molnupiravir *in vitro [7]*. Synergy was also seen with these two agents in a murine model of survival after infection with the SARS-CoV-2 Beta variant [8]. One other case report exists which corroborates our experience with dual DAAs [9].

Here we describe the successful treatment of chronic, severe COVID-19 with combined, dual DAAs: remdesivir and Paxlovid.

Case report

This report describes a 60 year old man who first developed COVID-19 symptoms on 25th April 2022 with a positive lateral flow test. After first testing positive for SARS-CoV-2 in April 2022, he was subsequently admitted on four occasions for COVID-19 symptoms. Figure 1 and Supplemental

Material contain cycle threshold (Ct values) of SARS-CoV-2 in respiratory samples, interval computed tomography (CT) imaging of the thorax, and treatment courses for COVID-19.

His past medical history included relapsed follicular lymphoma, receiving rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) (2017), followed by bendamustine and obinutuzumab (2019). He remained in remission, and was treated with regular, bimonthly obinutuzumab as monotherapy from August 2020. He had received four vaccinations against COVID-19 prior to testing positive with the last dose in February 2022, and had never had clinically suspected or laboratory confirmed SARS-CoV-2 infection prior to April 2022.

Admission one: day 20 - day 44

Patient was admitted with fever, cough and a minor oxygen requirement, and was SARS-CoV-2 PCR-positive. He had a CT chest which showed bilateral inflammatory changes. He received 10 days of remdesivir and 60mg prednisolone once daily. Whole genome sequencing confirmed infection with Omicron BA.2.3. He was discharged, without oxygen.

Admission two: day 49 - day 64

Within five days of discharge he had recrudescence of fever and cough, with a requirement for supplemental oxygen. High-resolution CT chest confirmed progression of the COVID pneumonitis. He was SARS-CoV-2 IgG negative. He received pulsed methylprednisolone (500mg for 3 days), sotrovimab (500mg) and a further 5 days of remdesivir. He was discharged continuing on prednisolone (40mg OD) and with ambulatory oxygen.

Admission three: day 68 - day 93

He was readmitted with fever and increasing breathlessness. CT thorax showed sub-segmental pulmonary embolism (PE) and increased ground-glass opacification, compatible with evolving COVID-19 pneumonitis. Lower respiratory tract sampling was negative by PCR for respiratory viruses, *Pneumocystis*, *Legionella pneumophila* and *Mycoplasma pneumoniae*. Microbiological culture of this

sample grew commensals. On day 75 he was transferred to intensive care unit (ICU) due to increasing hypoxia, and treated with high flow oxygen at an inspired concentration of 85%. He was treated with double dose sotrovimab (1000mg) and a five day course of Paxlovid, followed by 10 days of baricitinib 4mg OD. He also received pulsed methylprednisolone (1000mg) for 3 days, continuing on further daily doses of prednisolone 80mg. He remained in ICU for the next 10 days, before discharge to the ward on day 85 on low flow oxygen via nasal cannula. He was discharged 8 days later with ambulatory oxygen. Whole genome sequencing confirmed continuing infection with Omicron BA.2.3. At this time, the patient had undetectable B lymphocytes on peripheral immunophenotyping.

Admission four: day 96 - day 145

Fever recrudesced and shortness of breath worsened shortly after discharge, prompting readmission. CT of thorax showed resolution of the prior pulmonary embolus, with increase in the extent and density of ground-glass opacification tending towards an ARDS appearance. No overt fibrosis was reported. Lower respiratory tract sampling again did not identify any coinfection, but high SARS-CoV-2 viral loads. He was intubated and ventilated on day 103 until day 109. Overall clinical progression suggested a high likelihood of in-hospital mortality secondary to COVID-19 pneumonitis. Compassionate use of bebtelovimab and tixagevimab/cilgavimab (Evusheld) was declined by the manufacturers. After discussion at the COVID-19 treatment MDT, treatment with Paxlovid and remdesivir was started on day 109 for 10 days. Paxlovid was administered as crushed nirmatrelvir tablets and ritonavir sachets suspended in water via a nasogastric (NG) tube. The Ct values for SARS-CoV-2 RNA in nose and throat swabs increased during treatment (corresponding to falling viral load), PCR first becoming negative on day 119. The patient had two low-level positive results before becoming consistently negative. After day 119, the patient remained extubated and no longer required high flow oxygen. The patient was moved to the ward and over the next four weeks his oxygen requirement resolved. CT imaging on day 137, 19 days after treatment, showed significant improvement in comparison with previous imaging, with only mild ground-glass changes, and early fibrotic changes noted in the bases with evidence of traction bronchiectasis.

The patient has no oxygen requirement, and remains PCR negative 6 weeks after treatment on day 169. He still has undetectable B lymphocytes on peripheral immunophenotyping. The patient has shortness of breath on exertion attributed to post-COVID-19 lung fibrosis and deconditioning, but continues to show improvement in exercise tolerance - attending appointments by public transport and without supplemental oxygen.

Discussion

Important aspects of this case involve treatment with combination therapy of dual direct-acting antivirals, the use of an extended course of 10 days, and the crushing of nirmatrelvir to allow administration via a nasogastric tube. This case suggests the combination of Paxlovid and remdesivir may act synergistically as antivirals, as seen in pre-clinical studies.

During this illness hypoxia worsened requiring intubation, SARS-CoV-2 RNA cycle threshold values progressively decreased, and chest CT imaging progressively worsened prior to treatment with dual DAAs. Notably, disease progressed despite treatment with both agents as monotherapy and nMAbs. This suggests that during persistent infection a significant pathology is caused by ongoing viral replication. For this reason, antivirals may be needed to prevent direct pathology from viral replication during persistent infection. In this case, immunomodulation mediated by steroids likely offered additional benefit in reducing immunopathology caused by immune stimulation from the ongoing presence of viral antigen.

Experience from other viral pathogens suggests dual therapy may have benefit in reducing chance of emergent resistance, as recognised by expert opinion [10]. As the two antiviral agents have different targets, which are not present in humans, we believe co-administration poses little theoretical risk of additive or synergistic toxicity. Renal and hepatic function was monitored with regular biochemistry testing with no adverse effect identified.

Prolonged courses of antivirals in COVID-19 have previously been studied. Whilst Paxlovid is licensed in North America and Europe as a 5 day course [11], in a phase 2/3 study of Paxlovid as post-exposure prophylaxis, one arm received 10 days of Paxlovid [12] with no adverse safety signals after interim analysis [13]. The safety of remdesivir courses of 10 days is known from large randomised controlled trials [14].

The monograph for Paxlovid states tablets should be swallowed whole and not chewed, broken, or crushed [11]. Crushing tablets may alter the pharmacokinetics and therefore impact on drug absorption of either components, nirmatrelvir or ritonavir. This is seen with tablets containing related drug combination, lopinavir/ritonavir, with reduction in the bioavailability of ritonavir [15] Therefore, ritonavir tablets were substituted with ritonavir sachets for suspension, which is licensed for NG administration [16]. The use of crushed nirmatrelvir was supported by a previous publication documenting the pharmacokinetics of an oral suspension [17]. As noted by British Columbia COVID-19 Treatment Committee, crushed nirmatrelvir is unlikely to have any significant differences to those reported in the nirmatrelvir tablet monograph [18]. Indeed, nirmatrelvir tablets are film-coated for ease of swallowing and aesthetic purpose, rather than for pharmacokinetic reasons (Personal communication with Pfizer Medicines Information team, 09-Sep-22). The multidisciplinary team felt there was sufficient pharmacokinetic data to support crushing of nirmatrelvir and use of suspended ritonavir instead of Paxlovid tablets. TDM may be valuable for confirming differences in pharmacokinetics caused by crushing, but is not currently commercially available.

There is a theoretical concern around the safety of crushing nirmatrelvir tablets, due to evidence of teratogenicity from animal studies [11]. As such Paxlovid is not recommended in pregnancy [11]. Healthcare workers may be inadvertently exposed whilst crushing, and patients may have increased exposure from altered pharmacokinetics. However these animal studies were conducted at much higher doses, achieving plasma concentrations much higher than would be achieved in humans through accidental exposure during crushing [11]. Risk to staff was considered to be low, and further mitigated by use of personal protective equipment (gloves, gowns and FFP3 masks) during the care of SARS-CoV-2 positive patients.

This case report suggests dual DAA therapy may have utility in treating chronic COVID-19. In our experience, immunosuppressed patients with chronic COVID-19 often have poor outcomes, and clinical trials are urgently needed to confirm the efficacy, safety, optimum regimen and duration of treatments for persistent SARS-CoV-2 infection.

Ethics Treatment decisions outside of licence and/or commissioning policy were agreed by both the multidisciplinary team and local Drug & Therapeutics Committee. The multidisciplinary team was formed of virologists, infectious disease specialists and pharmacists. Informed, written consent was provided by the patient, including for use of images.

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Supplementary material: Online

Figure 1

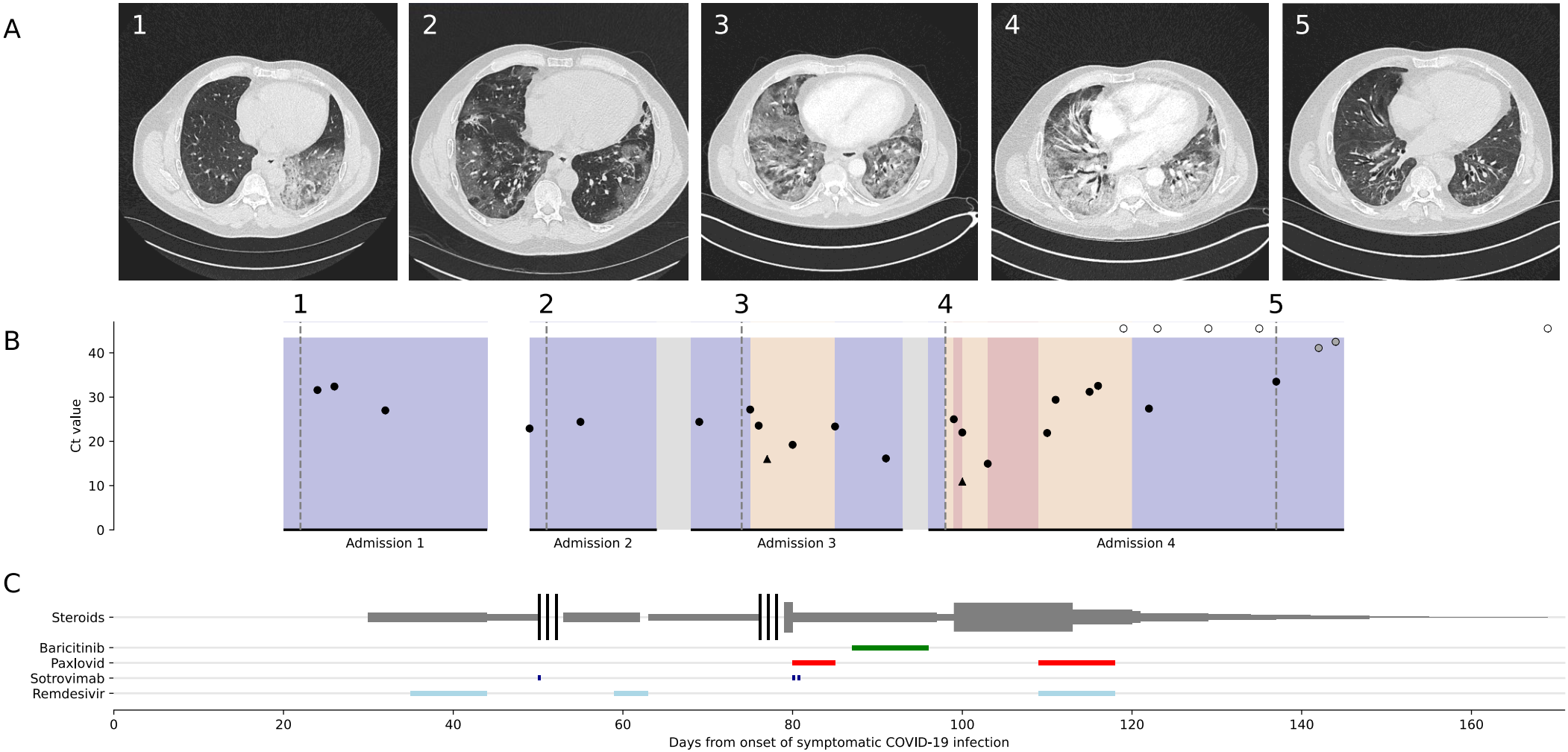
A
1
2
3
4
5
B
1
2
3
4
5
Ct value
0
10
20
30
40
Admission 1
Admission 2
Admission 3
Admission 4
C
Steroids
Baricitinib
Paxlovid
Sotrovimab
Remdesivir
0
20
40
60
80
100
120
140
160
Days from onset of symptomatic COVID-19 infection

Figure 1 Timeline of chronic COVID-19 illness, viral load and treatments.

Panel **A** shows serial CT imaging in chronological order. CT scans 1,2 and 5 are non-contrast scans, and CT scans 3 and 4 are CT Pulmonary Angiograms.

Panel **B** shows Ct values of SARS-CoV-2 PCR results, with a circle representing a Nose and Throat Swab and triangle representing a Broncho-alveolar lavage sample. Black points were positive on both PCR targets, grey points positive on one of two targets, and points with a white fill represent negative tests. The date of CT images 1 to 5 in panel **A** are marked by dotted lines in panel **B.** The background colour of panel B shows the patient's level of care: white = not admitted and not on oxygen, grey = not admitted and on ambulatory oxygen, blue = admitted to a ward, orange = admitted to ITU, red = intubated.

Panel **C** is a timeline of antiviral and immunomodulatory treatments. The thickness of the steroid bar corresponds to the steroid dose as prednisolone equivalent. Black lines mark the dates of pulsed methylprednisolone doses. Lines indicating sotrovimab treatment represent dosing of 500mg each.

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