aligning with prior publications.[8,9] Conversely, Manesh *et al.*[10] found that crushed posaconazole DR tablets given per feeding tube at a dose of 300 mg daily produced therapeutic levels after 2 weeks of therapy in 19 of 19 patients receiving treatment for rhino-orbito-cerebral mucormycosis.[10]

Many factors can impact drug levels of crushed posaconazole DR tablets, spanning from the obvious patient factors (i.e. absorption) to terminal tube placement (e.g. J-tube versus G-tube) or the more nuanced factors (preparation and administration technique). The literature supporting this practice is evolving, but still limited. It is currently unknown how different manufacturers' DR matrices may impact serum concentrations if crushed, or how crushed DR tablets would compare in a head-to-head comparison against the oral suspension. Our experience adds to the growing body of evidence suggesting that crushing and administering posaconazole DR tablets via enteral feeding tubes is safe and often results in therapeutic levels. Importantly, doses may likely need to be up- or down-titrated when switching to or from the formulation of crushed posaconazole DR tablets, respectively. Clinicians should consider this route of administration, when necessary, in conjunction with careful dose titration and frequent TDM.

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Successful use of nirmatrelvir/ritonavir in immunocompromised patients with persistent and/or relapsing COVID-19

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In immunocompromised hosts, coronavirus disease 2019 (COVID-19) can span from asymptomatic to severe life-threatening disease. Moreover, chronic infection with severe acute respiratory

syndrome coronavirus 2 (SARS-CoV-2) inducing prolonged viral shedding and persistent and/or relapsing symptoms has been reported in these patients.[1,2]

In chronic SARS-CoV-2 infection, off-label use of remdesivir, convalescent plasma and/or SARS-CoV-2-specific monoclonal antibodies (mAbs) has been anecdotally attempted to reduce disease severity and to achieve viral clearance, with variable results.[3,4]

Nirmatrelvir/ritonavir is an oral antiviral, which has been proven to reduce by 89% the risk of progression to severe COVID-19 among high-risk patients with early-stage, symptomatic COVID-19.[5] Early use of nirmatrelvir/ritonavir has also been shown to shorten time to viral clearance in patients who are immunocompromised and hospitalized with COVID-19.[6]

To date, there has been limited experience regarding nirmatrelvir/ritonavir efficacy in patients with prolonged and/or relapsing SARS-CoV-2 infection.[7] Here we describe three cases of relapsing COVID-19 at the Careggi University Hospital, Florence, Italy, in patients undergoing anti-CD20 immunosuppressant therapy, who showed a successful clinical, virological and radiological response to nirmatrelvir/ritonavir treatment.

Patient 1

A 62-year-old Caucasian male with non-Hodgkin lymphoma on anti-CD20 therapy with obinutuzumab developed mild SARS-CoV-2 infection in December 2021, reporting fever, cough and myalgia. He was treated with sotrovimab, with a rapid clinical improvement. Five months later he presented to the hospital with a 10 day history of fever and dyspnoea; antigenic testing of a nasopharyngeal swab (NPS) at admission was negative. A CT scan showed bilateral ground glass opacities (GGOs) and PCR detected SARS-CoV-2 RNA in a bronchoalveolar lavage (BAL). IgG antibodies against the SARS-CoV-2 spike protein (S) (LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin Inc., USA) were positive [154 binding antibody units (BAU)/mL], likely due to the previous infusion of mAbs. A central line-associated bloodstream infection was initially suspected but a complete microbiological work up did not identify infective foci. Despite multiple empirical antimicrobial regimens, including ceftriaxone, piperacillin/tazobactam, vancomycin and caspofungin, intermittent fever continued for 21 days, leading to discontinuation of antimicrobials and consideration of an off-label treatment with nirmatrelvir/ritonavir. Fever disappeared 24 h after the first nirmatrelvir/ritonavir dose, along with a rapid improvement of the respiratory parameters. The follow-up CT-scan 1 month later documented complete GGO resolution (Figure 1).

Patient 2

A 76-year-old Caucasian male on anti-CD20 treatment with rituximab due to non-Hodgkin lymphoma experienced moderate COVID-19 in February 2022 with fever, dyspnoea, cough and radiological evidence of interstitial pneumonia, requiring hospitalization and low-flow oxygen supplementation. While hospitalized he received a 5 day remdesivir course and off-label sotrovimab infusion, owing to his seronegative status for anti-S IgG. Within 10 days he was discharged home. Three months later he presented to the hospital with fever, dyspnoea and cough. Radiological CT study showed GGOs; PCR on NPS and BAL detected SARS-CoV-2, while anti-S IgG dosage was still negative. Nirmatrelvir/ritonavir treatment was started and fever disappeared 24 h after the first dose; NPS for SARS-CoV-2 yielded a negative result 5 days after antiviral treatment conclusion and a follow-up CT scan 1 month later showed significant GGO reduction (Figure 1).

Patient 3

A 59-year-old Caucasian male with ongoing mycophenolate and low-dose steroids with a previous 2 year course of rituximab for eosinophilic granulomatosis with polyangiitis suffered from severe COVID-19 on January 2022, requiring non-invasive ventilation. During the hospital stay he was treated with remdesivir and tocilizumab. After a 30 day hospitalization he was discharged with complete symptom resolution. Four months later, while SARS-CoV-2 RNA was still detectable on NPS, he complained of dyspnoea; a CT scan reported new GGO appearance. Anti-S IgG was still undetectable at that time. He received a complete course of nirmatrelvir/ritonavir and sotrovimab infusion; after 14 days from treatment conclusion, SARS-CoV-2 RNA on NPS yielded a negative result, while 1 month later a CT scan showed complete resolution of GGOs (Figure 1).

In all three cases, infections were caused by the Omicron variant (B.1.1.529 lineage). Further genomic characterization demonstrated that latter episodes were sustained by sublineage BA.1, which had almost disappeared in Italy (<1% prevalent) when they occurred (May to June 2022), thus suggesting that they were due to SARS-CoV-2 relapse rather than reinfection.[8] Complete demographics and clinical information about the three patients are reported in Table S1 (available as Supplementary data at *JAC* Online).

Although infections with the Omicron variant have been associated with reduced morbidity and mortality, immunocompromised patients remain at higher risk of severe COVID-19 outcomes, hospitalization and prolonged symptoms.[9,10] In these patients, the humoral and cellular immune response after vaccination is reduced, and protection against severe COVID-19 is lower than in the general population.[11] Antiviral agents proved their efficacy against COVID-19 when used in the first days after symptoms onset, during the viral replication phase.[5] However, viable SARS-CoV-2 can persist for several months in immunocompromised hosts,[1,2,12] thus warranting a late use of antiviral drugs in this population. Notably, in our cases, COVID-19 relapse occurred despite initial treatment with remdesivir and/or sotrovimab. At the time of writing, 5–6 months after nirmatrelvir/ritonavir administration, we have no evidence of further COVID-19 relapse in these patients.

Pending further studies on larger cohorts, the impressive response observed in the reported cases suggests that oral antiviral drugs may also have a role beyond the early stage of COVID-19, for the treatment of persistent and/or relapsing COVID-19 in immunocompromised hosts.

Ethics

The study was conducted in accordance with the Declaration of Helsinki. The patients provided signed informed consent for publication.

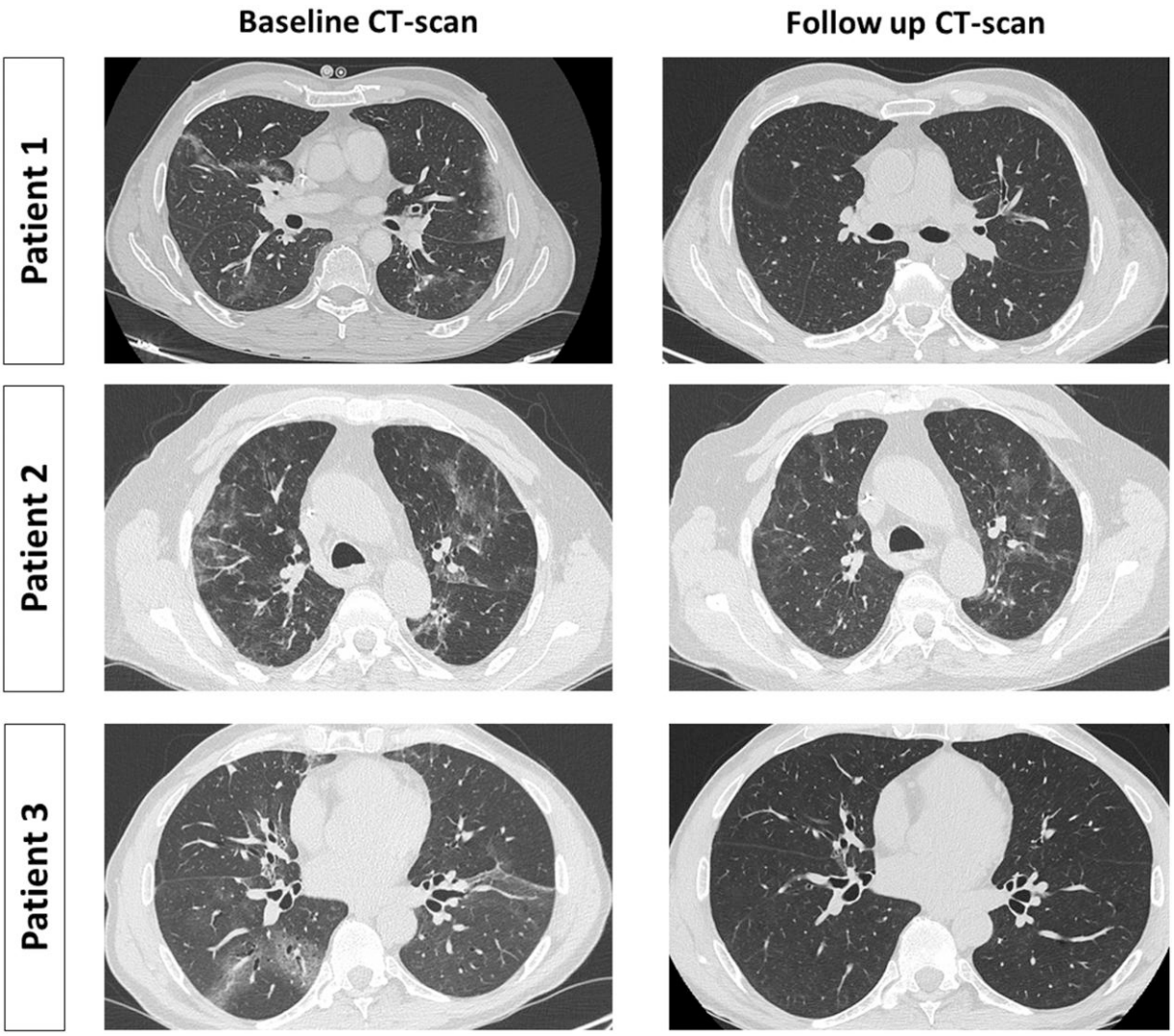

Figure 1. Comparison of CT scan findings pre- and post-treatment with nirmatrelvir/ritonavir. Follow up CT scan performed 1 month after treatment conclusion showed complete resolution of GGOs in Patient 1 and Patient 3, and significant improvement in Patient 2. Radiological findings were consistent with the successful clinical response to antiviral drugs in all three cases.

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Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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China's new national action plan to combat antimicrobial resistance (2022–25)

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Antimicrobial resistance (AMR) is a major challenge for global public health, and the wide spread of MDR organisms brings a heavy economic burden to infected patients, especially those in developing countries or low-resource countries or regions; this is a global problem of wide concern to governments and society.[1] The WHO has been calling on countries to pay attention to the threat of AMR for many years, and important international meetings such as the General Assembly of the United Nations, the World Health Assembly, and the G20 Summit have repeatedly studied and discussed AMR.[2,3] In 2016, in response to the global action plan on AMR issued by the WHO, 14 ministries and commissions of the Chinese government jointly issued a national action plan for combating AMR (2016–20), which adopted comprehensive management measures at the national level and strengthened regulation in all aspects of drug research and development, production, distribution, application and environmental protection.[4]

To further strengthen efforts to combat AMR and actively respond to international and domestic concerns, the Chinese government recently announced a new national action plan, the 'National Action Plan for Combating Antimicrobial Resistance (2022–2025)' in October 2022.[5] The action plan, led by the National Health Commission in conjunction with 12 ministries and commissions, focuses on the need to effectively control major pathogens of human and animal origin and gives new annual targets and more detailed indicators for combating AMR.

The prevalence of clinical MDR bacteria in China is still high.[6] According to the results in 2021 from the China Antimicrobial Surveillance Network (www.chinets.com; 71 hospitals from 29 provinces or cities), the resistance rates of meropenem-resistant *Klebsiella pneumoniae*, meropenem-resistant *Pseudomonas aeruginosa* and meropenem-resistant *Acinetobacter baumannii* were 24.4%, 18.9% and 72.3%, respectively. The rates of MRSA, ceftriaxone-resistant *Escherichia coli* and ceftriaxone-resistant *K. pneumoniae* were 30%, 52.4% and 41.5%, respectively. Carbapenem-resistant Gram-negative bacilli are the priority organisms that WHO and CDC jointly believe the world should take urgent measures to address, including infection prevention and control and the development of new antimicrobial agents.[1,7] In China, few antimicrobial agents are available for treating infections caused by a carbapenem-resistant organism, including ceftazidime/avibactam, polymyxins and tigecycline, while other new β-lactam/β-lactamase inhibitor combinations including meropenem/vaborbactam, imipenem/relebactam, and cefiderocol are not yet available.[8]

Therefore, with the current limited resources, there is a need for multisectoral and multidisciplinary cooperation, communication and education to improve the rational use of antimicrobial agents to combat AMR in China. Based on this, China has carried out various targeted efforts. For example, since 2015, the National Institute of Hospital Administration has organized the 'Peiyuan project',[9] the 'Peiying project',[10] the 'Peiwei project'[11]