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CASE SERIES

Antiviral Treatment in Older Chinese Patient with SARS-CoV-2 and Influenza A Virus Co-Infection: A Case Series

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Abstract: Coronavirus disease 2019 (COVID-19) emergence in late 2019, and wide spread quickly in the world. In China, the COVID-19 epidemic situation entered a low level now. With the arrival of flu season, the number of patients with respiratory symptoms is increasing. We reported three cases of patients who co-infected with SARS-CoV-2 and influenza A virus (IAV), and they were all treated with nirmatrelvir-ritonavir (NMV/r) and baloxavir marboxil. Due to the overlapping clinical features between the two diseases, it is important to identified them and gave the antiviral therapy timely.

Keywords: COVID-19, influenza, co-infection, baloxavir marboxil, nirmatrelvir-ritonavir

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in late 2019 and has spread rapidly across the globe. In China, COVID-19 emerged as a large-scale epidemic in February 2020 and entered a normalization stage for prevention and control in May 2020.[1,2] Most nonpharmaceutical interventions (NPIs) were canceled in 2022, except for indoor mask-wearing.[3] After three years of anti-epidemic efforts, COVID-19 public health control measures were downgraded in China in January 2023, and the epidemic situation reached a low level.[4] However, studies have speculated that the number of individuals susceptible to influenza infection increased after the easing of NPIs, which could lead to a large epidemic in many countries, including China. Additionally, the coexistence of COVID-19 and influenza in the upcoming season could pose a significant threat to the population, potentially altering the transmission patterns of the diseases and exacerbating the disease burden.[5,6] Recently, a study quantified the rebound of influenza activity in southern and northern China during the 2023–2024 and 2024–2025 epidemiological years and found that the epidemic would increase by 3.8 times and 3.0 times, respectively, in southern China and northern China when the NPIs were completely relaxed in the 2022–2023 period, and which would be more pronounced in southern China, partly due to the relatively low rebound of influenza activity in the 2021–2022 period.[7]

Study illustrated that co-infection with influenza A virus (IAV) can enhance the infectivity of SARS-CoV-2.[8] As a result, physicians should be vigilant about the possibility of co-infection cases with particularly in vulnerable patients such as the elderly and immunosuppressed individuals, and prioritize early diagnosis and combined antiviral treatment. However, distinguishing between SARS-CoV-2 and IAV poses a challenge due to their similar clinical symptoms and mode of transmission.[9] Fever and cough are the most common clinical signs shared by both SARS-CoV-2 and IAV. However, runny nose is a prominent clinical finding in IAV cases but less common in COVID-19 patients. Moreover, COVID-19 patients tend to exhibit more abnormalities of the lower respiratory system on chest imaging compared to IAV cases.[10] Compared to IAV, COVID-19 patients commonly experience fatigue, headache, myalgia, and digestive tract

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symptoms as early signs of the disease. Furthermore, elevated C-reactive protein levels are more frequently observed in COVID-19 patients, and these patients tend to have higher levels of creatine kinase.[11]

Currently, reverse transcription polymerase chain reaction (RT-PCR) remains the gold standard diagnostic method for detecting SARS-CoV-2 and IAV.[12] However, a recent study proposed using a multiplex quantitative RT-qPCR method to quickly diagnose co-infection in suspected patients. This method offers faster results and is more cost-effective than the conventional monoplex quantitative RT-qPCR-based method.[13] Furthermore, vaccination continues to play a crucial role in controlling the resurgence of the influenza epidemic. A study suggested that influenza vaccination rates should be increased to 53.8% in southern China and 33.8% in northern China to control the influenza epidemic and return it to pre-pandemic levels.[7] Therefore, promoting influenza vaccination is necessary to prevent the potential reemergence of the influenza epidemic in the coming years. Enhancing preparation efforts to decrease the overall burden of influenza and SARS-CoV-2 infections is important. Additionally, it is essential to be adequately prepared to handle the co-occurrence of seasonal influenza and COVID-19 during the flu season.[14]

So far, several studies have reported cases of SARS-CoV-2 and IAV co-infection.[15–17] However, there have been limited reports on using antiviral treatments, specifically nirmatrelvir-ritonavir (NMV/r) and baloxavir marboxil (hereafter referred to as baloxavir), for co-infection patients in mainland China. In this report, we present three cases of Chinese patients with SARS-CoV-2 and IAV co-infection.

Case Reports

Case 1

An 80-year-old man weighing 60kg was diagnosed with Alzheimer's disease and had a medical history of organic mental disorders, hypertension, and sleep disorders. The patient was admitted to our hospital on November 30, 2022. The patient was taking the following medications: quetiapine (325 mg QN), memantine (10 mg QN), sacubitril-valsartan (1 tablet QD), zolpidem (5 mg QN), finasteride (5 mg QN), tamsulosin hydrochloride (0.2 mg QD) and divalproex sodium (450 mg BID).

On the 119th day of hospitalization, the patient was diagnosed with co-infection of SARS-CoV-2 and IAV. The cycle threshold (Ct) values for the SARS-CoV-2 genotype (Orf gene and N gene) were both 36. The patient had a fever with a body temperature of 39.3°C, and subsequently, an indomethacin suppository was used subsequently. NMV/r (300mg/100mg q12h for 5 days) (eGFR 68 mL/min) and baloxavir (40 mg, a single dose) were also administered for treatment. The dose of quetiapine was reduced to 50mg once nightly. On the following day, the patient's body temperature was returned to normal. However, on the 121st day of hospitalization, the SARS-CoV-2 nucleic acids and IAV were all were still detected, indicating persistent infection with both viruses. The Ct values of the Orf gene and N gene for SARS-CoV-2 increased to 38 and 37, respectively. Additionally, the patient's estimated glomerular filtration rate (eGFR) decreased significantly from 68 mL/min to 50mL/min. As a result, the dose of NMV/r was adjusted to 150mg/100mg q12h. On the 124th day of hospitalization, the patient developed a slight cough with no phlegm. On the 125th day of hospitalization, the SARS-CoV-2 nucleic acids and IAV detection tests returned negative results. On the 127th day of hospitalization, the patient's eGFR improved to 88mL/min. On the 133rd day of hospitalization, the patient started experiencing phlegm production, and as a result, budesonide suspension, ambroxol, and acetylcysteine were prescribed. The patient's symptoms improved, and he was eventually discharged from the hospital on the 141st day of hospitalization.

Case 2

An 86-year-old man weighing 70 kg was diagnosed with organic mental disorders. He had a past medical history of coronary heart disease, myocardial infarction and cerebral infarction. The patient was admitted to our hospital on March 5, 2023. The patient's medication regimen included: aspirin (100 mg QD), atorvastatin (20 mg QN), ticagrelor (60 mg BID), digoxin (0.125 mg QD), olanzapine (5 mg QN), quetiapine (62.5 mg QN), estazolam (1 mg QN), divalproex sodium (250mg BID) and aripiprazole (5 mg QN).

On the 25th day of hospitalization, the patient was diagnosed with COVID-19. The Ct values for the Orf gene and N gene of SARS-CoV-2 were 22 and 20, respectively. The patient had a fever with a body temperature of 39°C, and was

treated with a single dose of ibuprofen (300 mg) that day. The following day, azvudine (2 mg once daily) was prescribed. On the 28th day of hospitalization, quetiapine was discontinued due to concerns about potential drug-drug interactions (DDIs). Unfortunately, the next day, the patient was diagnosed with IAV virus infection, and baloxavir (40 mg, a single dose) was prescribed. Additionally, the patient experienced sudden chest tightness, shortness of breath, and obvious phlegm sound, leading to the administration of methylprednisolone (40mg, once). On the 30th day of hospitalization, the patient still had a fever with a body temperature of 38.2°C. Furthermore, the patient developed a cough and had phlegm production, resulting in the prescription of budesonide suspension and ambroxol. The Ct values for the Orf gene and N gene of SARS-CoV-2 decreased to 18 and 15, respectively. Additionally, the patient's eGFR was declined from 68 mL/min to 51 mL/min. As a result, azvudine was replaced by NMV/r (150mg/100mg once daily for 5 days). Furthermore, digoxin, clopidogrel and estazolam were discontinued. On the 36th day of hospitalization, the IAV test returned negative, but the SARS-CoV-2 nucleic acid detection test (Orf gene: Ct 30, N gene: Ct 29) remained positive. Finally, on the 40th day of hospitalization, the SARS-CoV-2 nucleic acid detection test returned negative. The patient's symptoms improved, and the antipsychotic treatment was continued at the hospital.

Case 3

An 85-year-old woman weighing 52 kg diagnosed with Alzheimer's disease was admitted to our hospital on November 30, 2022 and had a past medical history of hypertension, coronary heart disease, type 2 diabetes, and Stage 3 chronic kidney disease. The patient's current medication regimen consisted of digoxin (0.125mg QOD), sacubitril-valsartan (1 tablet BID), donepezil (5mg QN), quetiapine (25 mg QN), atorvastatin calcium (20 mg QN), acarbose (0.05g TID), amlodipine (5mg TID), clonidine (75ug TID).

On the 118th day of hospitalization, the patient was diagnosed with co-infection of SARS-CoV-2 and IAV. The Ct values for the Orf gene and N gene of SARS-CoV-2 were 32 and 33, respectively. The patient had a fever with a body temperature of 38.3°C and was prescribed Tylenol (1 tablet once). On the 119th day of hospitalization, the patient still had a low-grade fever, and as a result, baloxavir (40 mg, a single dose) and NMV/r (150mg/100mg twice daily for 5 days) were prescribed. It's worth noting that the patient's eGFR was 49 mL/min. On the 121st day of hospitalization, the patient's body temperature returned to normal. The IAV test returned negative on the 125th day of hospitalization, but SARS-CoV-2 nucleic acid detection still showed positivity with Ct values of 36 for the Orf gene and 33 for the N gene. Finally, on the 133rd day of hospitalization, the SARS-CoV-2 nucleic acid detection test turned negative. Currently, the patient's dementia treatment in our hospital.

Discussion

In the present study, we report on the efficacy of the combination treatment of NMV/r and baloxavir in Chinese patients with co-infection of SARS-CoV-2 and IAV. To the best of our knowledge, this is the first study to explore this treatment approach in such patients.

NMV/r, a newly authorized drug, received conditional approval from the National Medical Products Administration (NMPA) in China in February 2022.[18] It is indicated for patients with mild to moderate COVID-19 infection with risk factors for severe illness and a high risk of disease progression.[19] NMV/r, a combination of two medications, have different mechanisms action. In the first component, nirmatrelvir is a potent SARS-CoV-2 main protease (Mpro) inhibitor, it can inhibit Mpro and prevents the virus from processing the polyprotein precursors which is required for viral replication. In the second component, ritonavir, a human immunodeficiency virus-1 (HIV-1) protease inhibitor, acts as a pharmacological enhancer. Ritonavir is an inhibitor of the enzymes of cytochrome P-450 (CYP450) pathway, mainly CYP3A4, which can decrease the CYP3A-mediated metabolism of nirmatrelvir and lead to pharmacokinetic enhancing of nirmatrelvir. It's required for patients to coadministration of nirmatrelvir and ritonavir, and the plasma concentration of nirmatrelvir can enough to achieve the targeted therapeutic range.[20,21] Study have shown that NMV/r effectively reduces severe outcomes in unvaccinated COVID-19 patients.[22] Furthermore, a network meta-analysis has demonstrated that compared to other antiviral drugs like molnupiravir and remdesivir, NMV/r has a lower risk of hospital admission.[23] With the approaching flu season, there is an increasing demand for effective anti-influenza drugs. Currently, two main classes of viral protein-targeting drugs are approved for influenza treatment and post-exposure prophylaxis: neuraminidase inhibitors and polymerase inhibitors.[24] Baloxavir, an oral anti-influenza drug that is

administered as a single dose. It is metabolized into its active form, baloxavir acid, which inhibits the cap-dependent endonuclease and prevents viral transcription, thereby impeding the spread of the influenza virus.[25–28]

SARS-CoV-2 and IAV co-infection cases have been reported, but most studies have focused on diagnostics rather than treatment.[15,17,29] A review of co-infection cases found that 64.3% of patients were treated with oseltamivir.[29] However, there is a lack of studies specifically investigating the combined antiviral treatment of baloxavir and NMV/r in patients with SARS-CoV-2 and IAV co-infection. Research has shown baloxavir treatment for influenza leads to a shorter fever duration than oseltamivir.[30] It has also been found that baloxavir reduces the incidence of influenza in China during seasonal flu epidemics compared to oseltamivir.[31] Considering that the patients in the present study had multiple risk factors, such as older age, male gender (cases 1 and 2), and many comorbidities, baloxavir was chosen for anti-influenza treatment. In the first two cases, the patients' body temperature returned to normal within 24 hours of taking baloxavir. It took approximately 7 days for the influenza virus test to become negative, consistent with previous findings.[26] All of the patients in present study were moderate COVID-19 cases, and in case 1, the SARS-CoV-2 nucleic acid detection became negative after about 6 days of taking NMV/r. However, in cases 2 and 3, it took about 15 days for SARS-CoV-2 nucleic acid to become negative, probably attributed to the delayed measurement of which was SARS-CoV-2 nucleic acids. Additionally, the eGFR of the first two cases declined after antiviral treatment.

A study mentioned that COVID-19 patients hospitalized during the fall/winter of 2022–2023 had an increased risk of death compared to patients with seasonal influenza.[32] It was also highlighted that co-infections with respiratory viruses are more likely to occur in future winter seasons, emphasizing the importance for vaccination against SARS-CoV-2 and influenza viruses and the need for influenza viruses testing in patients with COVID-19.[33] Furthermore, age, sex, and comorbidities were identified as the main risk factors in COVID-19 patients with other diseases, such as cancer.[34] A real-world study specifically examined cancer patients and found that those with hematologic malignancies were at a higher risk of developing breakthrough infections and experiencing severe outcomes. However, the risk significantly decreased in vaccinated patients.[35] Therefore, vaccination is crucial for individuals with cancer, especially those with hematologic malignancies.

It is well known that ritonavir is a CYP 3A4 inhibitor, DDIs can occur when it is combined with other medications that are also dependent on CYP3A4 metabolism.[36] A study reviewed the potentiation of DDIs with NMV/r, including antipsychotics, antidepressants, benzodiazepines, and other related drugs. Ritonavir is expected to increase the area under the curve (AUC) of quetiapine by eightfold, thereby increasing the risk of QT interval prolongation.[37] Additionally, study recommended NMV/r contraindicated with quetiapine due to quetiapine AUC is increased by a factor 6.5 when combined with NMV/r.[38] However, the study showed that it is overly restrictive to contraindicate the coadministration of quetiapine and protease inhibitors, because the quetiapine dose can be titrated over a wide range. Instead, the study recommended using a 6-fold lower quetiapine dose when combined with strong CYP3A inhibitors.[39]

In the present study, the doses of quetiapine were adjusted based on individual cases. For case 1, the dose was reduced to 50mg when combined with NMV/r, whereas, for case 2, quetiapine was discontinued. In case 3 quetiapine was continued at a dose of 25mg while using NMV/r. It should be noted that none of the patients experienced sedation or coma. However, the serum concentration of quetiapine was not monitored during the combination therapy with NMV/r. Our findings suggest that baloxavir and NMV/r can be used simultaneously in patients with SARS-CoV-2 and IAV co-infection. Nonetheless, it is crucial to monitor hepatic and renal function during the treatment.

However, there were several limitations in our study. Firstly, the number of patients included was small, which may affect the generalizability of the findings. Secondly, the serum concentration of quetiapine was not monitored when combined with NMV/r, and therefore, the exact quetiapine AUC in low-dose combination with NMV/r is unknown. Study reported that increased quetiapine AUC by a factor 6.5 when combined with NMV/r, which is at normal dose or high doses of quetiapine. Consequently, it is worth exploring quetiapine AUC when low-dose quetiapine combined with NMV/r. Thirdly, SARS-CoV-2 nucleic acid measurements were not taken in a timely manner for cases 2 and 3 after using NMV/r. Further studies are necessary to evaluate the efficacy and safety of NMV/r combined with baloxavir in patients with SARS-CoV-2 and IAV co-infection.

Conclusion

The co-infection of SARS-CoV-2 and IAV observed in our cases highlights the presence of overlapping infections. Since seasonal influenza and COVID-19 share some respiratory symptoms, it is important to simultaneously monitor both IAV

and COVID-19 during the flu season. Additionally, it is very important to prescribe antiviral agents against IAV and SARS-CoV-2 timely in SARS-CoV-2 and IAV co-infection patients, especially vulnerable patients.

Statement of Ethics

Our study was approved by the Ethics Committee of Tongde Hospital of ZheJiang Province (Ethical approval number is 2023-062-JY). The written and informed consent for publication of three cases and any details were obtained from the legal guardian of the patients because the patients were unable to communicate properly. We strictly abided by data protection legislation and ethical standards, patient`s personal information such as name, hospitalization number won`t be appeared in our report.

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Disclosure

The authors report no conflicts of interest in this work.

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