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Safety, Efficacy and Relapse of Nirmatrelvir-Ritonavir in Kidney Transplant Recipients Infected with SARS-CoV-2

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Safety, Efficacy and Relapse of Nirmatrelvir-Ritonavir in Kidney Transplant Recipients Infected with SARS-CoV-2

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Abstract

Introduction: Nirmatrelvir-ritonavir (NR) has demonstrated its efficacy to decrease the risk of progression to severe COVID-19 in high-risk patients. However, evidence in infected kidney transplant recipients (KTRs) is lacking. Moreover, NR has significant and potentially harmful interactions with calcineurin inhibitors (CNIs).

Methods: In this single-center retrospective study, we included all KTRs treated with NR from April 28th to June 3th, 2022. A standard management strategy of CNIs dose adaptation (discontinuation of tacrolimus 12 hours before the start of NR and administration of 20% the cyclosporine dose) and laboratory follow-up was applied.

Results: Fourteen patients were included. Compared to day-0 (day before NR initiation), day-7 plasma creatinine concentrations and SARS-CoV-2 viral loads were similar (p = 0.866) and decreased (p=0.002), respectively. CNIs trough concentrations at the end of the treatment were satisfactory, with nevertheless high individual variability. After a median follow-up time of 34 days, no death nor viral pneumonia were observed. However, 2 patients experienced early SARS-CoV-2 infection relapses (at day-10 and day-21) associated with an increase in SARS-CoV-2 viral loads.

Conclusions: NR can be used in KTRs but requires a strict protocol of drug adaptation. We observed two cases of early relapse after NR treatment that need further investigations.

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Main Body Text

Introduction

Emerging new SARS-CoV-2 variants constantly modify therapeutic strategies for kidney transplant recipients (KTRs) with COVID-19. Recently, *in-vitro* data have suggested that most monoclonal antibodies - widely used with previous variants - had lost their neutralizing ability against the BA2 variant.[1] This led the Federal Drug Administration (FDA) to recommend the use of alternative treatments in areas where BA2 variant is endemic[2], despite low clinical evidence. Among alternatives, nirmatrelvir-ritonavir (Paxlovid®, Pfizer, USA) has demonstrated its safety and efficacy to decrease the risk of progression to severe disease in high-risk patients.[3] Consequently, nirmatrelvir-ritonavir recently became one of the promising treatments for KTRs infected with SARS-CoV-2.[4] However, several uncertainties remain. First, strong evidence regarding the efficacy of nirmatrelvir-ritonavir in reducing the risk of progression to severe disease in large cohorts of infected KTRs is lacking, as those patients were not represented in clinical trials.[3] Secondly, due to the inhibitory effect of ritonavir on cytochrome P450-3A (CYP-3A) and P-glycoprotein nirmatrelvir-ritonavir has significant and potentially harmful interactions with many medications including calcineurin inhibitors (CNIs), due to the inhibitory effect of ritonavir on cytochrome P450-3A (CYP-3A) and P-glycoprotein .[4]

The aim of the present study is to provide data regarding the management, safety, and efficacy of nirmatrelvir-ritonavir treatment of SARS-CoV-2 infection in a cohort of KTRs.

Materials and methods

Patient selection

Nirmatrelvir-ritonavir has been available in Belgium since April 15, 2022. Since then, this treatment was applied for KTRs followed in our center, with the following inclusion criteria : (1) confirmed SARS-CoV-2 infection with positive polymerase-chain reaction (PCR) on naso-pharyngeal swab, (2) symptoms evolving < 5 days, (3) baseline estimated glomerular filtration rate (eGFR, by CKD-EPI) > 30 mL/min/1.73 m^2, (4) no dyspnea and oxygen saturation> 95% at room air, and (5) no pregnancy or breast feeding.

This study retrospectively includes all KTRs followed in our KT center who actually received the treatment between April 28 and June 3, 2022. Patients were followed until June 16 2022 (data cutoff) for a median time of 34 days (ranging from 14 to 51 days). This work received the approval from the Ethic Committee of Cliniques universitaires Saint-Luc, Brussels, Belgium (2022/25MAI/220).

Local standard protocol.

Before the first use of nirmatrelvir/ritonavir, we have implemented a standardized management protocol for all KTRs with suspicion of SARS-CoV-2 infection (symptoms and/or positive antigenic test and/or high-risk contact)- still ongoing. The patient is first examined in our SARS-CoV-2 outpatient clinic and a polymerase chain reaction (PCR) on a naso-pharyngeal swab is performed. If eligible to treatment with nirmatrelvir/ritonavir, all patient's concurrent medications (immunosuppressive drugs and others) are carefully reviewed and are adapted by the nephrologist together with the clinical pharmacologist according to recommendations recently published by the French Society of Pharmacology and Therapeutics (SFPT).[5] Detailed

management of both CNIs and mechanistic target of rapamycine inhibitors (mTORi)-following nirmatrelvir-ritonavir prescription- is described in Figure 1.

According to our local protocol, the antimetabolite drug is interrupted for 7 days and steroid dose remains unchanged. Written recommendations are provided to the patient with treatment adaptation. Nirmatrelvir-ritonavir is then prescribed (100 mg of ritonavir combined with 150 mg [if baseline eGFR 30-60 mL/min/1.73 m^2] or 300 mg [if eGFR> 60 mL/min/1.73 m^2] of nirmatrelvir, bid, for 5 days).

During and after nirmatrelvir-ritonavir treatment, standard biological monitoring is performed, including serum creatinine and CNIs or mTORi trough levels at several time points (day [D] 0 [D1= first day of treatment], D2, D5, D7 and D9), assessment of anti-SARS-CoV2 serology at D0 and SARS-CoV-2 viral load (D0, D7). Finally, patients are clinically re-evaluated at D9 at the outpatient clinic. Patients are advised to reach the nephrologist if they experienced any side effect at anytime.

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Microbiology

The vaccine-induced humoral response was measured using an immunoassay detecting Ab against the spike protein receptor-binding domain (RBD) (Elecsys anti-SARS-CoV-2, Roche Diagnostics GmbH, Mannheim, Germany - positive threshold >0.8 BAU/mL).

The detection of SARS-CoV-2 on nasopharyngeal swab was performed using the Alinity m SARS-CoV-2 assay (Abbott Molecular Inc., Des Plaines, IL, USA). This real-time reverse transcription polymerase reaction test is a dual target assay for the RdRp and N genes.

Positive samples presenting Ct values < 25 were then sequenced starting from the same Nasopharyngeal swabs. The technique of sequencing is detailed in the Supplementary Material.

Statistics

Paired samples T-test and Wilcoxon test were applied for comparison of serum creatinine and viral loads between the different time points, respectively. All tests were two-sided and p-values ≤.05 were considered significant. Statistical analysis was performed using SPSS v27 (IBM) and Prism v9 (GrapPad)

Results

Baseline characteristics

Fourteen patients were eligible for treatment with nirmatrelvir-ritonavir during the study period. Baseline characteristics of the cohort are detailed in Table 1. Briefly, the median age was 60 (ranges 33-79) years, 9 (64%) were male, and 3 (24%) diabetic. Immunosuppressive therapy mainly consisted on a combination of tacrolimus (86%), mycophenolate mofetil (79%) and steroids (100%). None of the patients had a history of prior Sars-CoV-2 infection. All but one received anti SARS-CoV-2 vaccine (4 doses [last dose a median time of 69 days before] and 3 doses [last dose a median time of 210 days before], in 10 and 3 KTRs, respectively) before infection. Eight patients mounted a robust humoral response (anti-RBD antibody titers >250 BAU/mL), 2 patients had a moderate humoral response (0-250 BAU /mL), and 4 had no humoral response after vaccination. Sequencing (available for 13 patients) revealed that all were infected by Omicron variants at D0. Several sublineages were identified: 8 patients with a BA.2 (Nextstrain clade 21L), 1 patient with a BA.2.3 (Nextstrain clade 21L), 2 patients with a BA.2.9 (Nextstrain clade 21L), 1 patient with a BA.2.36 (Nextstrain clade 21L) and 1 patient with a BA.2.12.1 (Nextstrain clade 22C) (Table 2).

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Evolution of laboratory parameters during and after treatment with nirmatrelvir-ritonavir.

D0 and D7 mean (± standard deviation) plasma creatinine concentrations were comparable (1.43 ± 0.39) mg/dL vs 1.45 (± 0.50) mg/dL, p= 0.866) (Figure 2).

Two patients experienced acute kidney injury respectively at D0 (patient 7) and D9 (patient 3) due to urinary infection requiring hospitalization and acute diarrhea, respectively. In both cases, plasma creatinine rapidly returned to baseline values after hydration and resolution of clinical symptoms.

Compared to D0, median SARS-CoV-2 viral load assessed at D7 dramatically dropped (23,137,656 (interquartile ranges [IQR]: 15,574,853-44,408,247) copies/mL vs 1707 (IQR: 100-5372) copies/mL, p= 0.001) (Figure 3).

Therapeutic drug monitoring (TDM) data were analyzable for the first 12 patients (Figure 4 and Figure 5). CNIs trough concentrations at the end of the treatment (day-5/7) were satisfactory. However there was a large variability in tacrolimus half-life during antiviral treatment (range from 173h to 619h). Four patients (#2, 3, 6 and 9) presented CNI accumulation from D9 with trough concentrations increasing above 10 ng/mL for tacrolimus and 300 ng/mL for cyclosporine.

Clinical outcome

Nirmatrelvir-ritonavir was well tolerated with no treatment discontinuation. No clinical biopsy-proven acute rejection was diagnosed during the study period. Two patients required hospitalization, respectively on D11 (patient 4) and D2 (patient 7) for acute pyelonephritis of the graft rapidly resolving with antibiotics (iv ceftriaxone and then oral cirpofloxacine). No

patient died during the study period and none presented with viral pneumonia. However, early relapses of COVID-19 symptoms occurred in two patients (patient 1 and 4, Figure 6) together with an increase in viral load.

Patient 1 was a 47-year-old male transplanted 10 years ago. His immunosuppressive regimen consisted in a combination of tacrolimus, mycophenolate mofetil and steroids. After 5 days of symptoms (runny nose, sore throat, cough, chills and muscle pain), he was treated with 150 mg of nirmatrelvir and 100 mg of ritonavir bid for 5 days. Symptoms rapidly resolved. SARS-CoV-2 viral loads at D0 and D7 were measured at 18,941,591 and <1000 copies/mL respectively. At D21, the patient experienced a new onset of symptoms (runny nose, fatigue, headaches) and a repeated PCR (D22) showed a viral load relapse at 3,148,427 copies/mL.

Patient 4 was a 68-year-old female transplanted 1 year earlier. Her immunosuppressive regimen consisted in a combination of tacrolimus, mycophenolate mofetil and steroids. After 5 days of symptoms (runny nose and cough), she was treated with 150 mg of nirmatrelvir and 100 mg of ritonavir bid for 5 days. Symptoms rapidly resolved, though a mild cough persisted. SARS-CoV-2 viral loads at D0 and D7 were measured at 131,344,593 and 1,189 copies/mL respectively. At D10, the patient presented new symptoms (malaise, fatigue and nausea) and a repeated PCR (D11) showed a relapse in the viral load at 1,616,064 copies/mL.

Both patients had rapid resolution of symptoms within few days without further intervention and a negative PCR test was subsequently obtained at D26 (patient 1) and D35 (patient 4), respectively.

For patient 1, although the viral strains sequenced at D0 and at relapse are Omicron variants with the same sublineage assignment BA.2.3 (or Nextstrain clade: 21L) (Table 2), the strain present at the time of relapse (D22) shows additional variations: one amino acid substitution in the Spike protein compared to the starting strain S:R408S as well as the deletions

ORF1a:G82-, ORF1a:G83-, ORF1a:G84-, ORF1a:G85-, ORF1a:G86- and S:Y144-. For patient 4, the viral strains sequenced at D0 and at relapse (D11) are Omicron variants with the same sublineage assignment BA.2.9 (or Nextstrain clade: 21L) (Table 2). In this second case, no differences could be demonstrated between the strains present at the beginning of the infection and at the time of relapse.

To assess whether patient 1 was infected by another SARS-CoV-2 strain, a phylogenic analysis was performed (Supplementary Material, Figure S1) showing that both strains (the one of the initial infection compared to the one during relapse) were very close making the hypothesis of an infection by a new strain unlikely.

Discussion

Rapidly emerging new VOCs of SARS-CoV-2 represent a constant challenge requiring frequent adaptations in therapeutic strategies for KTRs infected with SARS-CoV-2. To date, three treatments are indicated to treat SARS-CoV-2 infection in areas where BA.2 variant is prevalent: remdesivir (only intra-venous administration), molnupiravir (oral administration, not currently available in our country outside medical need programs), and nirmatrelvir-ritonavir (oral administration).[4] However, evidence regarding safety and efficacy of all these treatments in KTRs is very low, because of the exclusion –or the very low rate of inclusion- of transplanted patients in clinical trials. Consequently, there is an urgent need to collect available data on this subject. That is even more relevant for nirmatrelvir-ritonavir use because of the high risk of potentially harmful drug interactions associated with its use. We here report the largest case series of KTRs treated with nirmatrelvir-ritonavir.

Treatment with nirmatrelvir-ritonavir was effective in our patients to prevent severe COVID-19. Indeed, none of them required hospitalization for viral pneumonia and none of them died.

In addition, viral load massively decreased at day 7 in all patients. Noteworthy two patients were hospitalized for urinary sepsis, but the causal relationship with the treatment is unlikely as not reported in the phase 3 trial.[3] This is in line with previous case-series on the use of nirmatrelvir-ritonavir in transplanted patients.[6-8] Salerno et al reported that amongst 25 solid organ transplant (including 5 KTRs) patients, 4 patients required hospitalization (one for diarrhea and 3 for COVID-19 symptoms), and none died, within 30 days.

The strategy of CNI adaptation during nirmatrelvir-ritonavir treatment we applied was based on the strategy proposed by the French Society of Pharmacology and Therapeutics (SFPT) (Figure 1).[5] Ritonavir is well known to significantly increase CNI concentrations, which could lead to drug toxicity.[9] Lange et al proposed another -yet rather similar- strategy consisting on immediate holding of tacrolimus or 80% dose reduction of cyclosporine upon initiation of nirmatrelvir/ritonavir, until the end of the 5-day course treatment.[10] Measuring the CNI level on Day 3 and Days 6–7 after nirmatrelvir/ritonavir initiation was also recommended to assist with timing of CNI resumption. This strategy was tested in 4 KTRs by Wang et al.[8] The authors found high variability in tacrolimus concentrations evolution between patients but they anticipated that tacrolimus might be reintroduced partially or in full dose between days 8 and 10. Salerno et al further evaluated the strategy on their larger cohort (25 SOT) and obtained similar tacrolimus concentrations before and after treatment.[6] However, 4 patients experienced a supra-therapeutic tacrolimus concentration after restarting tacrolimus. In our study, TDM data were available for 12 patients. Using the proposed recommendations[5] of discontinuation 12h before the start of nirmatrelvir-ritonavir for tacrolimus and administering 20% of the usual daily dosage for cyclosporine, CNIs trough concentrations at the end of the treatment were mostly satisfactory. However, we also observed important individual variability. These data suggest that CNI clearance might present a large inter-individual

variability in transplant recipients and that some patients may display a longer cytochrome (CYP) 3A4 and/or P-glycoprotein inhibition leading to increased exposure upon restarting immunosuppressive treatment. TDM is thus particularly recommended in this population of patients. The day-7 to 10 period appears particularly at-risk and should be closely monitored. While the number of patients included is limited, no risk factor (CYP3A5 or CYP3A4 genotype, concentration over dose ratio) for higher or lower CNI clearance during nirmatrelvir-ritonavir treatment or for longer CNI metabolism and/or transport inhibition have been found. The identification of such factors would be particularly relevant to identify at-risk patients of rapid CNI elimination and therefore at-risk for rejection or in opposite at-risk patients for CNI accumulation and toxicity. Importantly, kidney function remained remarkably stable during the study period (at the exception of both patients with concomittant affection-sepsis and diarrhea), suggesting that this rather simple strategy seems safe regarding the graft function. In our experience, the management of nirmatrelvir-ritonavir was much more demanding than the management with previous treatments, such as sotrovimab.[11] Indeed, it requires manpower, important logistics to control tacrolimus concentrations,… Moreover and most importantly, it requires an active participation of the patient because of the modifications made to the immunosuppressive treatment as well as the temporary discontinuation of some other drugs. We think that providers should be very selective in prescribing nirmatrelvir-ritonavir only to patients who can understand and strictly adhere to drug modifications, and also in centers having the logistics to manage the treatment.

Emerging data have demonstrated that nirmatrelvir-Ritonavir can be associated with early relapse.[12-14] A recent US retrospective study that included 11,270 people treated with nirmatrelvir-ritonavir showed 7-day and 30-day relapse rates of 3.53% and 5.40% for COVID-19 infection, 2.31% and 5.87% for COVID-19 symptoms, and 0.44% and 0.77% for

hospitalizations.[14] In our study, we observed 2 cases (14% of the cohort) who experienced early relapse of COVID-19 symptoms associated with proven increase in SARS-CoV-2 viral load. The two patients did not differentiate in baseline characteristics compared to those who did not experience early relapse. Both patients reported no deviation in the prescribed posology of nirmatrelvir-ritonavir making the hypothesis of low adherence unlikely. For one patient (patient 4), SARS-CoV-2 strains present at the beginning of the infection and at the time of relapse were similar. However, we detected additional variations in the strain at the time of relapse-compared to the initial strain- in the Spike protein and in the ORF-1 gene in the other patient (patient 1). Phylogenic analysis revealed that these variations were most likely acquired during or after nirmatrelvir-ritonavir treatment. However, the clinical relevance of this finding in explaining the COVID-19 relapse experienced by the patient is uncertain and remains to be demonstrated.[15-18] Lower blood concentrations of nirmatrelvir (not routinely available) or other-here undetected- acquired genetic mutations are other hypothesis to explore on larger cohorts.

Our study has limitations. It is a small cohort with a retrospective design making it subject to bias, and a short follow-up. It also lacks a control group that could help determine the drug's true efficacy in a predominantly vaccinated population. Nevertheless, we administered the currently recommended treatment to our vulnerable population and were able to closely monitor and follow-up our patients.

In conclusion, nirmatrelvir-ritonavir can be used in kidney transplant recipients infected with SARS-CoV-2. It seems effective in preventing the occurrence of severe COVID-19. Drug adaptation is mandatory to avoid calcineurin inhibitors toxicity but feasible. We observed two cases of early relapse after nirmatrelvir-ritonavir treatment that need urgent further investigations.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary information is available at KI Report's website.

Supplementary Material (PDF).

1. **Supplementary Material and Methods (PDF)**

SARS-CoV-2 variants sequencing

2. **Supplementary Figure (PDF)**

Figure S1: Phylogeny of the 14 patients at day 0 and of the 2 patients (patient 1 and 4) at relapse.

3. **Supplementary references (PDF)**

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Table 1. Baseline characteristics at SARS-CoV-2 infection of the cohort.

Variable	Population N=14
Age, years, median (ranges)	60 (33-79)
Male, n (%)	9 (64)
Time since transplantation, months (ranges)	116 (10-332)
Treated hypertension, n (%)	10 (71)
Treated diabetes, n (%)	3 (21)
Overweight-obesity, n (%)	8 (57)
Treated dyslipidemia, n (%)	11 (79)
Prior anti-SARS-CoV-2 vaccine	
4 doses, n (%)	10 (71)
3 doses, n (%)	3 (21)
0 dose, n (%)	1 (8)
Anti-RBD antibody level prior infection	
>250 BAU/mL, n (%)	8 (57)
0-250 BAU/mL, n (%)	2 (14)
0, n (%)	4 (29)
Prior COVID-19 infection, n	0
CYP3A5 genotype	
3*/3*, n (%)	8 (57)
1*/3*, n (%)	2 (14)
CYP3A4 genotype	
1*/1*, n (%)	7 (50)
Immunosuppression at admission	
Immediate release tacrolimus, n(%)	1 (7)
Slow release tacrolimus, n (%)	11 (79)
Mycophenolate mofetil, n (%)	11 (79)
Cyclosporine, n (%)	2 (14)
Azathioprine, n (%)	1 (7)
Steroids, n (%)	14 (100)
Nirmatrelvir-ritonavir dose	
300/100 mg, n (%)	5 (36)
150/100, n (%)	9 (64)

Abbreviation : CYP : cytochrome P450

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Table 2: Baseline and relapse Nextstrain Clade, Pangolin Sublineage assignment and GISAID submission references.

	Day 0			Relapse		
	Nextclade	**Pangolin**	**GISAID**	**Nextclade**	**Pangolin**	**GISAID**
Patient 1	21L	BA.2.3	EPI_ISL_12587374	21L	BA.2.3	EPI_ISL_13017215
Patient 2	21L	BA.2	EPI_ISL_12587390			
Patient 3	21L	BA.2	EPI_ISL_12660432			
Patient 4	21L	BA.2.9	EPI_ISL_13017301	21L	BA.2.9	EPI_ISL_13017221
Patient 5	21L	BA.2	EPI_ISL_13017302			
Patient 6	21L	BA.2	EPI_ISL_13017212			
Patient 7	21L	BA.2.9	EPI_ISL_13017210			
Patient 8	NA	NA	NA			
Patient 9	21L	BA.2.36	EPI_ISL_13204423			
Patient 10	21L	BA.2	EPI_ISL_13204424			
Patient 11	21L	BA.2	EPI_ISL_13204422			
Patient 12	21L	BA.2	EPI_ISL_13424237			
Patient 13	21L	BA.2	EPI_ISL_13424225			
Patient 14	22C	BA.2.12.1	EPI_ISL_13424238			

Abbreviations : GISAID, Global Initiative on Sharing Avian Influenza Data ; NA, not available

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Figure legends

Figure 1: Protocol of calcineurin inhibitors and mechanistic target of rapamycine inhibitors dose adpatation during nirmatrelvir-ritonavir treatment.

Figure 2: Comparison of plasma creatinine concentrations before (day 0) and 7 days after (day 7) nirmatrelvir-ritonavir initation. Day 0 and Day 7 plasma creatinine concentrations were comparable (1.43 (1-2.23) mg/dL vs 1.45 (0.9-2.81) mg/dL, p= 0.866, Paired-samples T-test). Means ± standard deviations of plasma creatinine values are represented.

Figure 3: Evolution of SARS-CoV-2 viral load values. Comparison before (day 0) and 7 days after (day 7) nirmatrelvir-ritonavir initation. Compared to day 0, median SARS-CoV-2 viral load assessed at day 7 dramatically dropped (23,137,655 copies/mL vs 1746 copies/mL, Wilcoxon Signed rank test; p= 0.002). Medians and interquartile ranges of SARS-CoV-2 viral loads are represented.

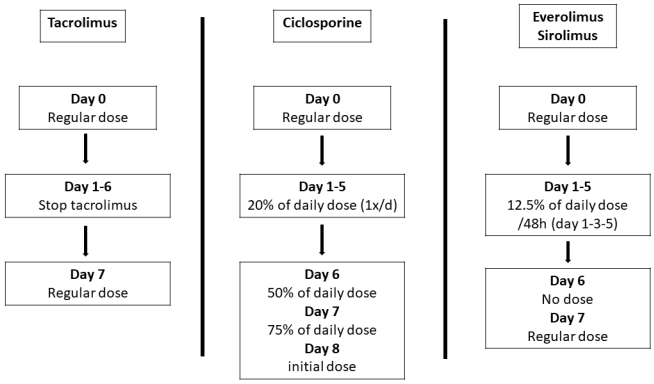
Figure 4: Evolution of tacrolimus trough concentrations (C_{trough}) during and after nirmatrelvir-ritonavir administration. Ten patients received nirmatrelvir-ritonavir 12h after the last dose of tacrolimus for a period of 5 days (day 1 to day 5). Tacrolimus was restarted at the initial dose on day 7. Tacrolimus C_{trough} increased above 10 ng/mL for 3 patients (#2, 3 and 6), so the dosage was adjusted after D9 for these patients.

Figure 5: Evolution of cyclosporine trough concentrations (C_{trough}) during and after nirmatrelvir-ritonavir administration. Cyclosporine was administered to 2 patients at 20% of the usual daily dosage during nirmatrelvir-ritonavir treatment (day 1 to day 5) and then

gradually increased from day 6 to day 8 (day 6 : 50%, day 7 : 75%, day 8 : 100% of the initial dose). Cyclosporine C_{trough} remained stable during nirmatrelvir-ritonavir administration. On day 7, the patient 9's cyclosporine trough level rose above 350 ng/mL, warranting a subsequent dose reduction.

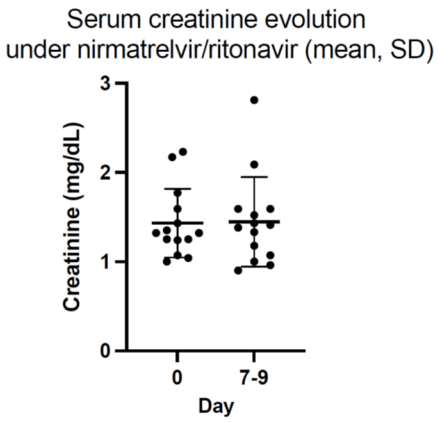
Figure 6: Individual evolution overtime of SARS-CoV-2 viral loads. Early relapses of COVID-19 symptoms occurred in two patients (patient 1 and 4) together with a relapse in viral load. SARS-CoV-2 viral load data were not available for one patient (patient 8).

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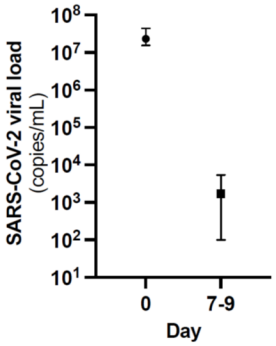
Day 1: first day of nirmatrelvir-ritonavir treatment

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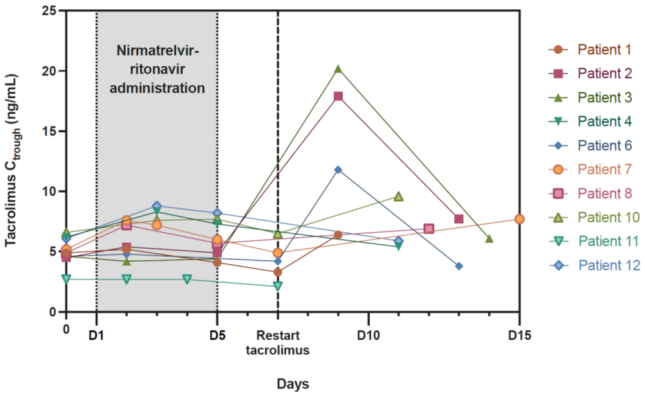


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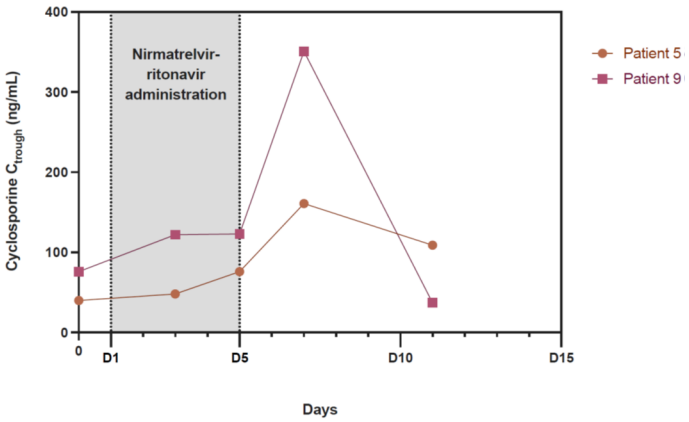
SARS-CoV-2 viral load evolution
under nirmatrelvir/ritonavir (median, IQR)



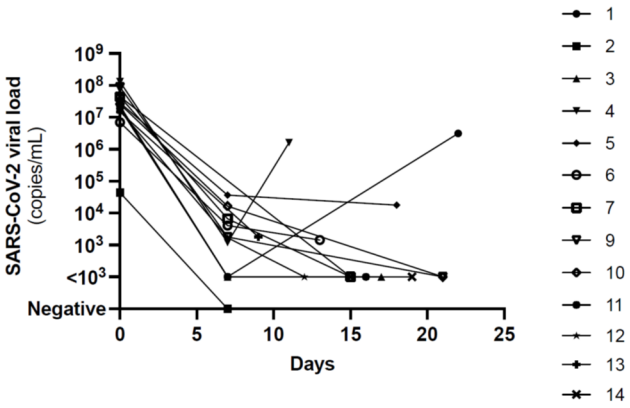
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