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LETTER TO THE EDITOR

Effect of nirmatrelvir/ritonavir on calcineurin inhibitor levels: Early experience in four SARS-CoV-2 infected kidney transplant recipients

To the Editor:

We read with great interest the recent letter by Lange and colleagues describing a proposed strategy of calcineurin inhibitors (CNI) management in COVID-19 positive solid organ transplant recipients (SOTR) treated with nirmatrelvir/ritonavir.[1] As ritonavir is a potent, irreversible CYP3A4 inhibitor, their strategy proposed immediate holding of tacrolimus or empiric dose reduction of cyclosporine upon initiation of nirmatrelvir/ritonavir, through to completion of the 5-day course. Measuring the CNI level on Day 3 and Days 6–7 from nirmatrelvir/ritonavir initiation was also recommended to assist with timing of CNI resumption. However, experience with this strategy in a real-world setting is limited.

We retrospectively reviewed our first four kidney transplant recipients on tacrolimus-based immunosuppressive therapy who received nirmatrelvir/ritonavir utilizing the strategy proposed by Lange et al. Two patients were on tacrolimus immediate release (IR) and two on tacrolimus extended release (ER). In all patients we held tacrolimus on the day of nirmatrelvir/ritonavir initiation. Except for one patient on atorvastatin, the remaining three were not on other medications with potential drug interactions with nirmatrelvir/ritonavir.[2] Patient characteristics and laboratory data are summarized in Table 1. All patients were >1-year post-transplant with estimated glomerular filtration rate (eGFR) > 30 ml/min. All patients had a baseline creatinine (Cr) and tacrolimus level within 3 months of nirmatrelvir/ritonavir initiation. Follow up blood work were obtained at a laboratory facility capable of phlebotomy from COVID-positive patients.

Tacrolimus levels were near prior baseline in all patients on Day 2–3 of nirmatrelvir/ritonavir therapy (Figure 1). Levels began to downtrend and then became low/undetectable on Day 8–9 (in Patients 3 and 4). Of note, Patients 1 and 2 had a slower decline in tacrolimus levels, which may have resulted from decreased hepatic clearance due to mild transaminitis. Patient 1 was also diagnosed with acute kidney injury on Day 2 of therapy, thought due to dehydration and hyperglycemic hyperosmolar state from self-discontinuing insulin. Patient 1 was on atorvastatin, which was held on day of nirmatrelvir/ritonavir initiation. There were no noticeable differences in trend of tacrolimus levels in patients who were on tacrolimus IR versus ER. All recovered from COVID-19 at time of last follow-up with no hospitalizations.

Based on our observations we agree with holding tacrolimus for SOTR treated with nirmatrelvir/ritonavir, along with close CNI monitoring. However, ascertaining the optimal timing and dose of tacrolimus re-introduction proved more challenging. During the 5-day course of nirmatrelvir/ritonavir while holding tacrolimus, levels only very gradually declined, but became sub-therapeutic several days after completion of the course. Based on these data, we anticipate tacrolimus can be reintroduced at partial or full dose between Days 8 and 10, ideally guided by drug levels. Given mild transaminitis observed it might also be prudent to discontinue statins on the day of nirmatrelvir/ritonavir initiation. While nirmatrelvir/ritonavir appears to possess potent antiviral activity against SARS-CoV-2, providers caring for SOTR on CNI should be very selective in its use, particularly in situations where access to phlebotomy for COVID-positive patients is limited, turnaround time for CNI levels is prolonged, or immunologic risk is high.

KEYWORDS

clinical research/practice, drug interaction, immunosuppressant - calcineurin inhibitor (CNI), infection and infectious agents—viral: SARS-CoV-2/COVID-19, infectious disease, pharmacology, solid organ transplantation

TABLE 1 Patient characteristics and laboratory data

Pt #	Age (nearest decade)	Sex	Race	Years post-Tx	IS regimen (Tac dose in mg)	Sx onset from initiation[a] (days)	BL Cr	BL FK	Lab 1 Cr	Lab 1 AST/ ALT	Lab 1 FK	Lab 2 Cr	Lab 2 FK	Lab 3 Cr	Lab 3 AST/ ALT	Lab 3 FK	Tac restart day[b] (dose in mg)	Lab 4 Cr	Lab 4 AST/ ALT	Lab 4 FK
1	60	M	Hispanic	9	MMF/ Tac IR (1/0.5)	3	1.43	6.4	2.50 (Day 2)	59/50	4.5	2.50 (Day 4)	4.5	2.06 (Day 10)	78/113	3.4	Day 13 (0.5/0.5)	1.45 (Day 17)	28/40	3.2
2	70	M	Caucasian	4	MMF/ Tac ER (1.5 daily)	7	1.17	6.6	1.33 (Day 3)	72/52	8.6	1.23 (Day 6)	6.8	1.03 (Day 9)	44/56	5.6	Day 9 (1.5 daily)	1.04 (Day 14)	36/42	7.8
3	50	F	Asian	6	MMF/ Tac ER (5 daily)/ Pred	7	0.80	10.5	0.80 (Day 2)	24/18	10.5	0.79 (Day 4)	9.1	0.80 (Day 9)	21/20	<2.0	Day 9 (5 daily)	0.82 (Day 17)	13/14	7.2
4	40	F	Asian	2	MMF/ Tac IR (1/2)	6	0.98	5.0	0.95 (Day 2)	26/29	7.6	1.27 (Day 6)	4.4	1.00 (Day 8)	16/18	2.6	Day 9 (1/2)	1.08 (Day 16)	17/20	4.5

Cr/AST/ALT/FK were all obtained at the same time during each lab interval.

Abbreviations: ALT, alanine transaminase (U/L); AST, aspartate aminotransferase (U/L); BL, baseline; Cr, creatinine (mg/dL); ER, extended release (Envarsus®); FK, tacrolimus level (mcg/L); IR, immediate release; IS, immunosuppression; MMF, mycophenolic acid; Pred, prednisone; Pt, patient; Sx, symptom; Tac, tacrolimus; Tx, transplant.

[a]Initiation day of nirmetralvir/ritonavir by each patient was defined as Day 1. Tacrolimus for all patients were stopped on Day 1 of nirmetralvir/ritonavir initiation.

[b]Tacrolimus was restarted after levels (from Lab 3) resulted.

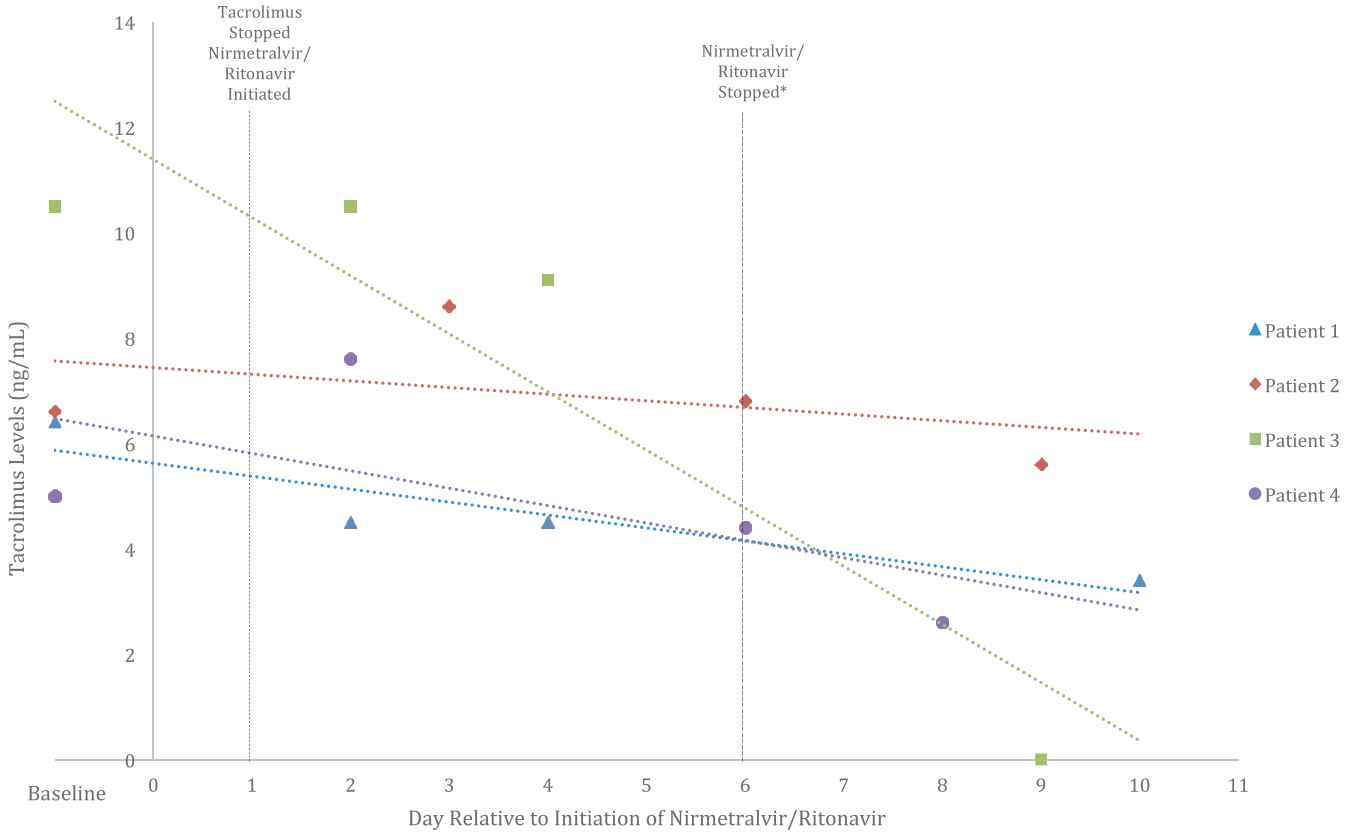

FIGURE 1 Trend of tacrolimus levels on days relative to initiation of nirmatrelvir/ritonavir

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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