Evaluation of a Protocol for Managing Cyclosporine and Nirmatrelvir/Ritonavir Drug-Drug Interaction

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BACKGROUND

- Morbidity and mortality of COVID-19 is higher in immunocompromised people including kidney transplant recipients (KTRs).[1,2]
- Nirmatrelvir/ritonavir (NRMr) interacts with many medications, particularly calcineurin inhibitors such as cyclosporine (CsA).[3,4]
- There is evidence supporting an 80% CsA dose reduction at the start of NRMr therapy, but guidance is lacking with respect to CsA dosing post-NRMr.[4,5,6,7,8,9]
- This Quality Improvement initiative developed and implemented a protocol for managing CsA dosing post-NRMr.

OBJECTIVES

This study aims to:

1. Describe the application of, and adherence to, the protocol;
2. Evaluate the impact of the protocol on cyclosporine levels;
3. Describe safety outcomes with respect to serum creatinine (SCr) levels, kidney dysfunction, hospitalizations, and death.

METHODS

- Inclusion of consecutive KTRs being followed at The Ottawa Hospital renal transplant clinic who were on CsA and required NRMr therapy between May 2022 and November 2023.
- CsA levels, acute kidney injury (AKI) defined as a 30% increase in serum creatinine, hospitalization, and death were collected through 30-days post-NRMr therapy.

Figure 1. Dosing Protocol for CsA Dosing Post-NRMr Therapy.

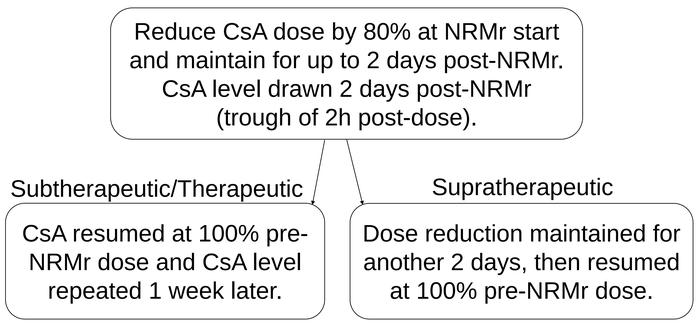


Table 1. Baseline Characteristics of KTRs Included for Analysis.

Age, mean (SD), years	65.3 (10.3)
Sex, n (%), Female	14 (40%)
Number of vaccines, n (%)	
Not reported	10 (29%)
3	3 (9%)
4	17 (49%)
5	3 (9%)
6	2 (6%)
Time since transplant, mean (SD), years	19.6 (10.9)
Duration of NRMr, 5-day course, n (%)	35 (100%)
Monitoring parameter, n (%)	
Peak	14 (40%)
Trough	21 (60%)
Dose of CsA prior to NRMr, mean (SD), mg	147 (39)
CsA level prior to NRMr, mean (SD), µg/L	258 (234)
SCr level prior to NRMr, mean (SD), µmol/L	146 (62)
Stable CsA dosing* prior to NRMr, n (%)**	24 (69%)

*Stable defined as no CsA dose changes in the past 12 months.
** n=34, one patient did not have documented CsA doses prior to baseline.

Table 2. Evaluation of Dosing Protocol on CsA Levels From Baseline to 3rd Follow-up.

	Baseline n=35 (%)	1st FU n=35 (%)	2nd FU n=35 (%)	3rd FU n=16 (%)
Median time [IQR], days	Reference	2 [1,2]	9 [8,12]	18 [12,23]
Serum CsA level change, Median [IQR], µg/L	Reference	26 [-43,96]	5 [-19, 39]	-4 [-21,77]
Subtherapeutic, n (%)	3 (9%)	7 (20%)	5 (14%)	2 (13%)
Therapeutic, n (%)	29 (83%)	17 (49%)	25 (71%)	11 (69%)
Supratherapeutic, n (%)	3 (9%)	11 (31%)	5 (14%)	3 (19%)

RESULTS

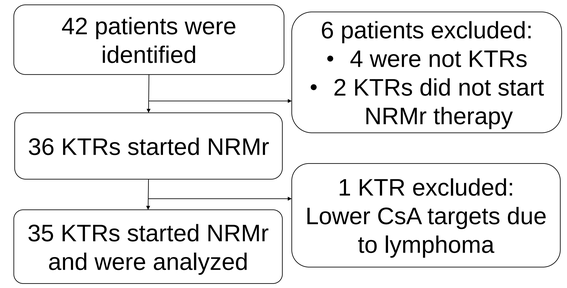
Application and Adherence to the Protocol

- Median dose reduction at initiation of NRMr was 80% [IQR 75-83].
- At the 1st follow-up (FU) 2 days post-NRMr, the mean CsA level was higher by 23 µg/L from 258 µg/L at baseline (P=0.51).
- Nonadherence to the protocol was observed in 9/38 (24%).
- Out of the 18 levels outside therapeutic range at 1st FU, 5 (28%) were non-adherent to the protocol.

Safety Outcomes

- At the 1st FU 2 days post-NRMr, the average SCr level was 1.15 µmol/L higher than baseline (p=0.769).
- Two (6%) AKI for unrelated reasons to COVID-19 treatment (unstable atrial flutter, gastroenteritis) and one that resolved with increased fluid intake were reported.
- There were 4 hospitalizations, but none were attributed to NRMr therapy.
- There were no reports of graft rejection or death 30 days.

Figure 2. Diagram of Included and Excluded Patients.



DISCUSSION

- KTRs with CsA levels outside of therapeutic range at 1st FU could be the result of:
  - being unstable at baseline;
  - not being in therapeutic range at baseline; and/or
  - patient nonadherence to therapy or to the protocol.
- The changes in CsA level were transient. The majority returned to their baseline values 9 days after the end of NRMr.
- No hospitalizations, graft rejections or death were attributed to the CsA serum changes.

LIMITATIONS

- Patients may have been missed as KTRs needed to self-report COVID-19 infection to the clinic.
- CsA and SCr were taken during FU visits but do not reflect fluctuations happening between FUs.
- Patient adherence was determined through Wellness Check-In notes which were not always completed.

CONCLUSIONS

Although CsA levels outside therapeutic range were common immediately post-NRMr treatment, levels were restored to therapeutic range rapidly and there were no clinically relevant safety events within the 30-day FU period. Adherence to the protocol is imperative from the clinical and patient perspective to ensure CsA is safely managed post-NRMr therapy.

RESOURCES

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