Tacrolimus toxicity in a kidney transplant recipient due to Nirmatrelvir/Ritonavir interaction managed with Rifampicin

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Objective

To report on using Rifampicin (RIF) to treat Nirmatrelvir / Ritonavir (NIR/RIT) induced Tacrolimus toxicity in a 73 year old female kidney transplant recipient with COVID-19.

Timeline of case (days)

Before COVID (−2) — 23 Mar 2023
Patient well
Tac level 6.3mcg/L
Cr 66mmol/L

Tested COVID +ve (0) — 25 Mar 2023
Prescribed NIR/RIT by GP. Tacrolimus dose unchanged (1mg twice daily)

Clinic review (6) — 30 Mar 2023
Reported lethargy, vomiting, watery diarrhoea.
Tacrolimus withheld

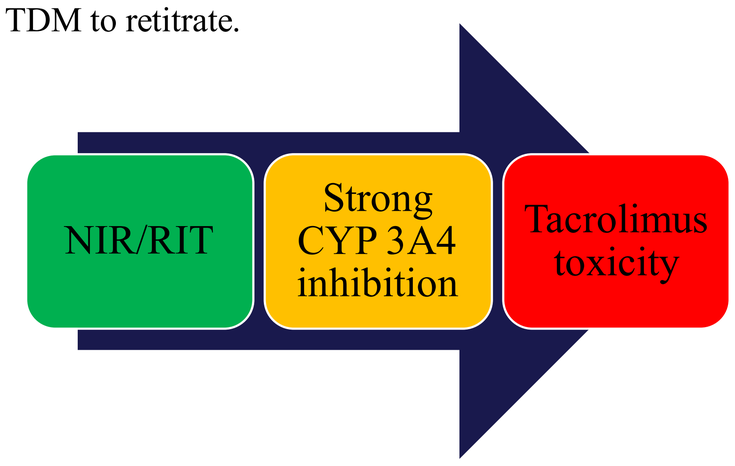
Hospital admission (7) — 31 Mar 2023
Tac level **46.9**mcg/L
Cr **168**mmol/L
Rifampicin started – 300mg bd for 4 doses

Discharged home (9) — 2 Apr 2023
Clinically improved
Tac level 20.1mcg/L
Cr 88mmol/L

Tac & Cr normalised (13) — 12 Apr 2023
Tac level 6.1mcg/L
Dose 1mg twice daily
Cr 62mmol/L

Drug Interaction Review

Ritonavir is potent CYP3A4 & P-gp inhibitor & CYP3A4 substrate.
Tacrolimus is metabolized by CYP3A4 and is a substrate of P-gp.
Coadministration of Ritonavir and Tacrolimus has been reported to profoundly reduce Tacrolimus metabolism due to CYP3A4 & P-gp inhibition.
This rapidly increases Tacrolimus concentrations to toxic levels and can cause seizures, encephalopathy, optic neuropathy and nephrotoxicity.
Usual practice at Royal Melbourne Hospital is to withhold Tacrolimus during NIR/RIT course and use TDM to retitrate.



Case Progress and Outcomes

Figure 1: Tacrolimus level and serum Creatinine during and after NIR/RIT course and RIF rescue

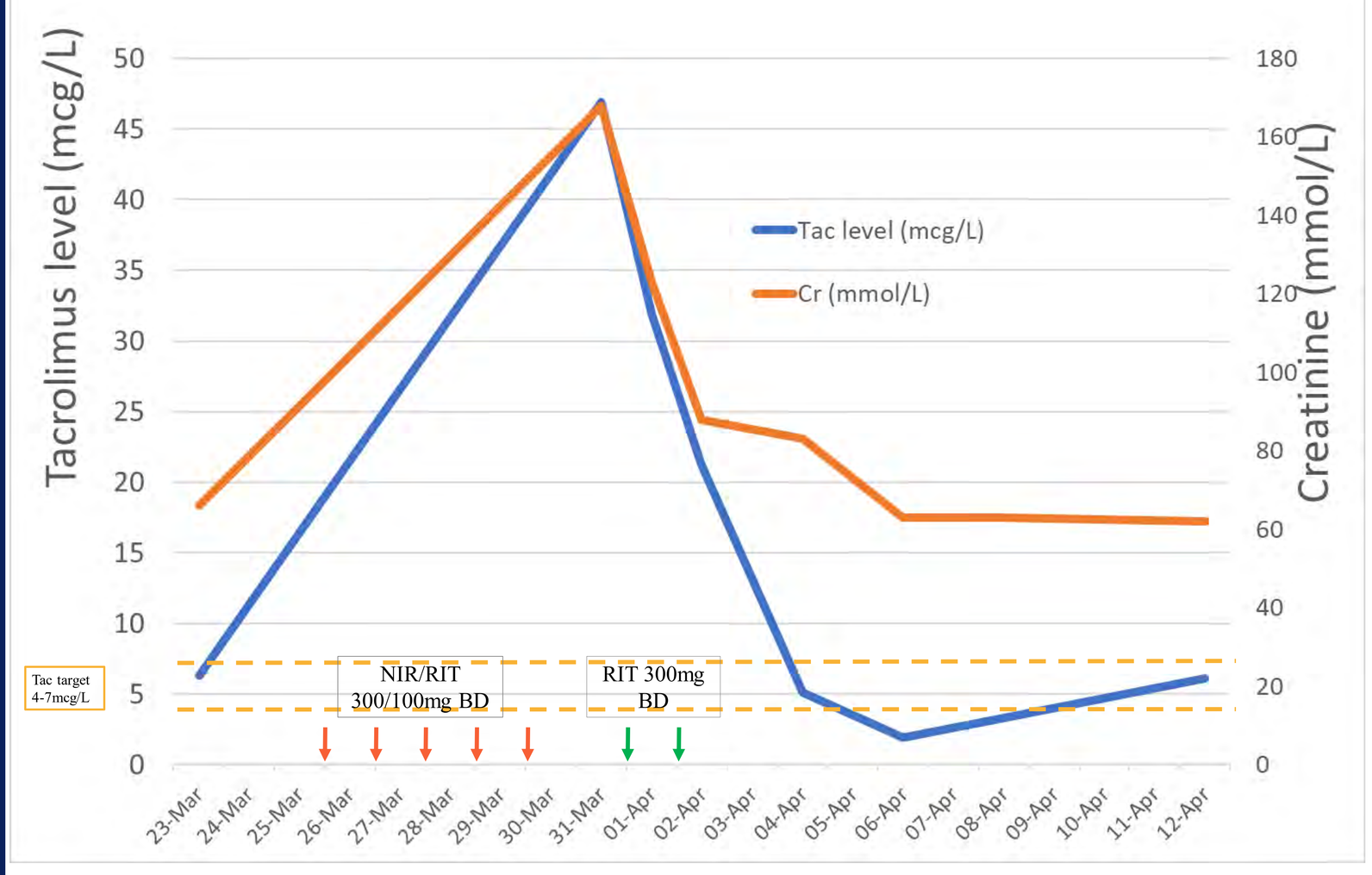


Table 1: Tacrolimus level, serum Creatinine and Tacrolimus dose during NIR/RIT course and RIF rescue

Date	Baseline	31-Mar	1-Apr	2-Apr	4-Apr	6-Apr	8-Apr	12-Apr
Tac level (mcg/L)	6.3	46.9	31.9	21.2	5.1	1.9	3.3	6.1
Cr (mmol/L)	66	168	123	88	83	63	63	62
Tac dose (mg/day)	2	1	0	0	1	2	2.5	2

Pharmacist Literature Review

- **Avoid use of NIR/RIT unless close monitoring of Tacrolimus serum concentrations is feasible.**[1]
- Case reports and case series using short courses of potent CYP3A4 inducers Rifampicin[2] or Phenytoin[3] to treat Tacrolimus toxicity due to NIR/RIT coadministration.
- Without rescue Tacrolimus levels can take >7 days[4] to return to a safe, therapeutic level (<7mcg/L)

CYP 3A4 inducer	Rifampicin	Phenytoin
PROS	-Potent CYP3A4 inducer -Short half-life (3-5 hours) -Minimal S/E: red/orange colouration of bodily fluids	-Potent CYP3A4 inducer -Seizure prophylaxis
CONS	-Transaminitis (rare)	-Long half-life (7-42 hours) -non-linear PK -CNS S/E: sedation, ataxia

Discussion

By using a limited course of Rifampicin, we were able to increase the clearance of both Ritonavir and Tacrolimus and achieve a resolution of the patient's symptoms and AKI within 2 days.
The Tacrolimus level dropped below target for 2-3 days due to excess metabolism. This fits with the delay in seeing the full effect of CYP3A4 enzyme induction by even a short course of Rifampicin. The pharmacist and doctors were not experienced with how long the inducing effect of Rifampicin would last and how soon and at what dosage to re-introduce Tacrolimus.
This case has given the team a better understanding of how to manage Tacrolimus toxicity rescue and Tacrolimus re-titration to a target range if this situation occurs again in the future.

References

1. University of Liverpool. COVID-19 Interaction Checker website (covid19-druginteractions.org)
2. Rose et al. Open Forum Infectious Diseases, Volume 9, Issue 7, July 2022
3. Sindelar et al. Journal of Medical Toxicology (2023) 19:45–48
4. Prikis et al. Transplantation Proceedings, 54, 1557–1560 (2022)