ANALYSIS OF TACROLIMUS TRENDS AND TROUGH LEVELS < 5 UG/L PRECEDING DEVELOPMENT OF BIOPSY PROVEN ACUTE REJECTION IN RENAL TRANSPLANT PATIENTS

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INTRODUCTION

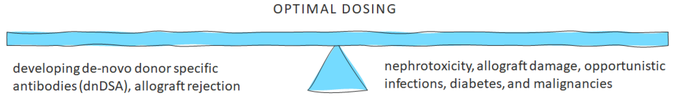
CONTEXT

British Columbia Transplant (BCT) modified the tacrolimus (TAC) target guideline for kidney transplant patients beyond 6 months post-transplant from 4-6 µg/L to 5-7 µg/L in 2021.

Although TAC is the mainstay medication used in the prevention of allograft rejection in kidney transplants, optimal target concentration is still being actively researched and guidelines differ locally.

IMPORTANCE OF TACROLIMUS (TAC) DOSING

- Insufficient TAC dosing risks higher probability of developing de-novo donor specific antibodies (dnDSA) which is the hallmark of allograft rejection
- Overdosing of TAC could result in nephrotoxicity, allograft damage, opportunistic infections, diabetes, and malignancies
- The complex balance for optimal dosing depends on a variety of factors such as the degree of HLA mismatch, concomitant drugs, patient genetics, adherence, immune function, and others alike



PURPOSE

This retrospective case series as a part of a QI project aims to evaluate BCT's decision to increase TAC target levels to 5-7 µg/L by investigating the mean TAC and TAC level trends of those adult patients who experienced biopsy proven acute rejection (BPAR) at Fraser Health in the past 3 years.

METHODOLOGY

STUDY DESIGN

A retrospective patient chart review was conducted on 6 adult patients treated in the Fraser Health Post Transplant Clinic in Surrey, BC, Canada, as a quality improvement project. This project was approved by the BCT Research Committee, and QI acknowledgement was issued by the Fraser Health Research Ethics Board.

Enrolled patients followed the defined inclusion criteria:

1. Experienced biopsy-proven acute rejection of the kidneys (Diagnosis of BPAR was determined adhering to the Banff classification system) in the last 3 years (2019-2021) at Fraser Health Post Transplant Clinic
2. Used TAC as a part of their antirejection regimen following BCT guidelines

DATA COLLECTION

- Patient demographics, laboratory values, medical and medication history were collected from electronic medical records on PROMIS® and paper-based charts
- TAC trough levels within 1 year leading up to kidney graft rejection were gathered along with the regimens of other coadministered immunosuppressant drugs

RESULTS

PATIENT DEMOGRAPHICS

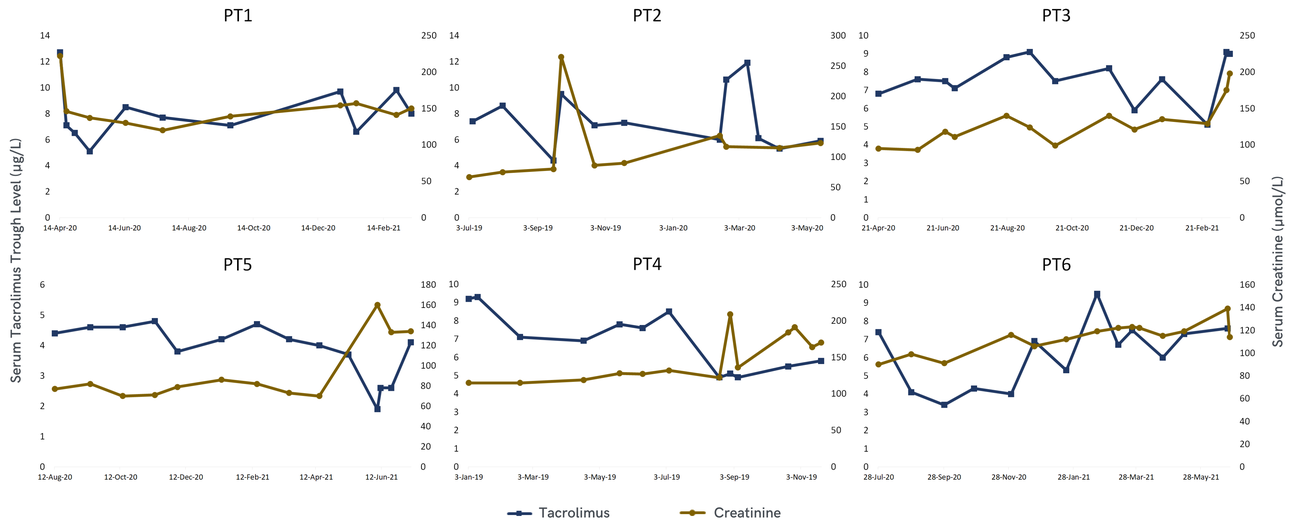
Six adult female patients

Mean age (SD): 61.5 (13.0)

Mean cPRA% (SD): 55.97 (45.14)

3 (50%) On steroid regimen

1 (16.7%) Living donor kidney



Finding #1: One out of six BPAR patients had average TAC <5 µg/L

Patient	Mean trough TAC (µg/L)	95% CI	P value
PT1	8.1	6.7–9.5	0.99
PT2	7.5	6.1–8.9	0.99
PT3	7.6	6.9–8.4	>0.99
PT4	6.8	5.3–8.2	0.98
PT5	3.9	3.4–4.4	0.0002
PT6	6.2	5.1–7.2	0.98

Finding #2: Four out of six BPAR patients had TAC measurement < 5 µg/L on at least one occasion

- The other subjects experienced rejection despite their average TAC level exceeding the new target minimum
- Two patients (PT1, 3) experienced rejection without any instance of TAC falling below 5 µg/L in the previous year
- This is a strong indicator that extraneous factors outside of the patient's TAC levels were responsible for BPAR

Finding #3: Declines in TAC are consistently followed by a sharp or baseline-altering increase in serum creatinine indicating a potential decline in graft function

- Fluctuations and especially the drops < 5 µg/L may play a role in BPAR even though the average trough levels were above minimum
- Existing literature studies showed an increased risk of rejections in patients with higher TAC variability

Finding #4: Only in PT5, graft stability was maintained even when TAC concentrations were persistently between 4-5 µg/L

- Suggests that the target minimum of 4 µg/L in the past was an effective regimen in this particular patient, and not others

CONCLUSION

1. Many factors, not just TAC targets are determinants for BPAR

2. Fluctuations and especially the drops below 5 µg/L played a role in BPAR even while the mean TAC levels are maintained above new guideline minimum (5 µg/L)

3. Target minimum of 4 µg/L in the previous guideline may have been an effective regimen in some patients but was not sufficient in others

In result, targeting > 5 µg/L may be beneficial to a wider range of patients when used as a general guideline.

FUTURE DIRECTIONS

1. To determine optimal TAC dosing on an individual basis with regards to recognizing specific BPAR risks
2. To account for the risks (i.e., potential for CNI toxicity) involved from the higher target range
3. To investigate outcomes from varying TAC levels in steroid-free regimens as these are becoming increasingly prescribed

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