Switching From Ciclosporin To Tacrolimus As De Novo Calcineurin Inhibitor In Lung Transplantation: First Results of a Multidisciplinary Quality Assurance Project

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Purpose of the Study

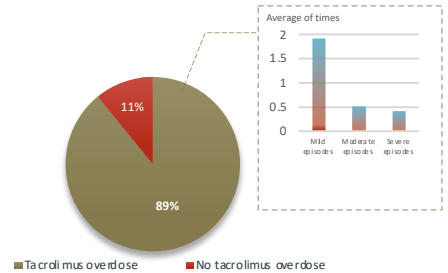
For three decades, the first choice calcineurin inhibitor (CNI) in our transplant center has been Ciclosporin. Most transplant centers worldwide use Tacrolimus (Tac) as the first choice CNI and favorable results from the ScanCLAD study (Dellgren 2024 Lancet Resp Med) support this practice. Starting January 2023 we changed our first choice CNI to Tac and made a special effort to address all issues arising in the first months after this change by a multidisciplinary team approach. Our audit aims to assess the incidence of tacrolimus overdose episodes and their impact on renal function and other medical complications in lung transplant recipients with a further goal to analyze our experience with Tac and document the implications on our daily management of lung transplant recipients by including the insights in our standard operating procedure documents (SOPs).

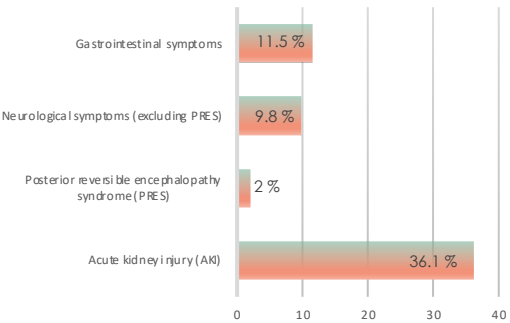
Methods

- retrospective analysis of lung transplant recipients at a medium volume lung transplant center. Time frame01/2022 – 12/2023 (2 yrs)
- Reviewed patient data included renal function parameters such as creatinine levels and estimated glomerular filtration rate (eGFR), assessing the occurrence of acute kidney injury (AKI) and chronic kidney disease (CKD), as well as potassium and C-reactive protein (CRP) levels. All recently transplanted inpatients are discussed weekly by a multidisciplinary team including a pharmacologist and ID specialist.
- Additionally, symptoms indicative of tacrolimus toxicity, including neurological and gastrointestinal manifestations and medication were documented. The frequency of infections and allograft dysfunctions including acute rejections are still being evaluated. Bronchoscopic evaluations included transbronchial biopsies and cryobiopsies
- Measured drug levels of >15 µmol/L were considered to be caused by tacrolimus overdosing, drug levels >25 µmol/L were considered as intoxications. Levels >2 µmol/L above target values were also considered to be overdosed. Our immunosuppressive strategy has been published previously (Schuurmans 2023 Medicina).

Results

- 61 lung transplant recipients, more males (39; 63.9%) than females (22), mean age 58 years (22-73)
- Tacrolimus overdose occurred in 55 out of 61 patients (89%) at a mean of 81 days post-transplantation (1-459) with a peak mean level of 22 ng/ml (10-39) and an average of 11 days to normalization/reaching target levels (0-87).
- Mild overdose episodes occurred on average 1.9 times (0-6), moderate episodes occurred on average 0.5 times (0-2) and severe 0.4 times (0-4).
- AKI was diagnosed in 22 (36.1%) patients.
  - mean creatinine level: 102 µmol/L (47-417)
  - mean eGFR at maximal tacrolimus levels: 72 ml/min/1.73m² (29-126)
- CKD was observed in 3 (4.9%) of patients.
  - 1 patient classified as stage KDIGO G3, 2 as stage KDIGO G4, none in stage KDIGO G5
- At the time of overdose potassium levels had a mean of 4.4 mmol/L (3.1-5.6) and mean CRP levels of 39 mg/L (0.6-209).
- Posterior reversible encephalopathy syndrome (PRES) was observed in 1 patient (2%), while neurological symptoms (excluding PRES) were observed in 9.8% and gastrointestinal symptoms in 11.5% of patients.
- Comedications included itraconazole and proton pump inhibitors were prescribed to 98.4% of patients, whereas macrolide maintenance therapy to 11.5% of patients.
- Two SOPs were created to improve drug dosing and co-medication choice and timing





Conclusion

Approximately 9/10 of lung transplant recipients experienced some extent of tacrolimus overdosing in the study period. The findings underscore the importance of vigilant monitoring and timely intervention in managing tacrolimus therapy post-transplantation and the need to improve the choice and timing of co-medication and have a good starting dose and dose correction strategy. This is part of an ongoing improvement process to avoid adverse outcomes related to tacrolimus overdosing resulting in two new SOPs for the treatment team.