# Clinical Challenges of Tacrolimus for Maintenance Immunosuppression Post–Lung Transplantation

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## ABSTRACT

Lung transplantation (LTx) is a successful treatment option for end-stage lung disease, and immunosuppressant regimens, utilized to prevent rejection of the transplanted graft, are paramount to maintaining long-term graft survival. Immunosuppression can be classified as induction, maintenance, and antirejection therapy. This article focuses on maintenance immunosuppression that includes a combination of a calcineurin inhibitor (CNI), cell cycle inhibitor, and corticosteroid. CNIs remain the cornerstone of immunosuppression following LTx, and tacrolimus is now the preferred CNI, based on a better adverse effect profile and some limited evidence for enhanced efficacy. Tacrolimus is associated with a number of unique challenges post-LTx, with erratic and highly variable absorption making it difficult to achieve and maintain therapeutic levels. Current methods of therapeutic drug monitoring are extrapolated from models in liver and kidney transplants and are not validated in the LTx population. Alternative methods of delivering tacrolimus can address some of the issues associated with their use and can be utilized in particular clinical scenarios. Long-term toxicities attributed to tacrolimus, such as nephrotoxicity and neurotoxicity, can limit the long-term success of tacrolimus in preventing allograft rejection. This article emphasizes the current clinical challenges faced when managing LTx recipients with tacrolimus, offers strategies to manage these issues, and highlights the areas that need further research.

LUNG transplantation (LTx) is now an established and successful lifesaving treatment option for patients with end-stage lung disease. Significant improvements in survival can be attributed to the evolution of immunosuppressant regimens to help prevent acute and chronic rejection and subsequent loss of the lung allograft. Protocols for immunosuppression can be divided into 3 categories: induction, maintenance, and antirejection therapy. Induction therapy aims to induce T-cell inhibition perioperatively to reduce the risk of acute rejection or delay the introduction of maintenance immunosuppression. Maintenance immunosuppression, the focus of this review, is given lifelong and aims to protect the graft while balancing against long-term toxicities associated with immunosuppression. Rejection can be classified as acute cellular rejection (AR), antibody-mediated rejection (AMR), or chronic lung allograft dysfunction (CLAD), and additional immunosuppression is given for shorter periods at greater intensity with the intent of arresting rejection episodes.

A typical maintenance immunosuppressive regimen consists of a triple combination of a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine, a cell cycle inhibitor, such as mycophenolate mofetil or azathioprine, and a corticosteroid. The aim of the triple regimen is to target multiple immune pathways, allowing protection against rejection as well as utilizing lower doses of each agent to minimize side effects.

CNIs remain the cornerstone of maintenance immunosuppression following LTx, and tacrolimus is now the preferred CNI, based on a better adverse effect profile and some limited evidence for enhanced efficacy [1]. Despite advances in the long-term survival of LTx recipients, median

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**Table 1. Suggested TDM Recommendations for Tacrolimus Post-LTx [9,45]**

| | Month | | |
|---|---|---|---|
| | 0–6 | 6–12 | >12 |
| Tacrolimus trough level | 10–12 | 8–10 | 4–8 |
| Low dose TAC+ mTOR inhibitor | Not recommended unless anastomotic healing confirmed | 4–6 | 4–6 |

Abbreviations: mTOR, mammalian target of rapamycin; TAC, tacrolimus.

survival continues to lag behind other solid organ transplants (SOTs) with long-term graft and patient survival limited by CLAD.

LTx recipients require higher maintenance immunosuppression due to the apparent higher immunogenicity of lung tissue. There is also greater diversity among LTx recipients, with the more common indications for LTx such as cystic fibrosis (CF) or chronic obstructive pulmonary disease having highly variable pharmacokinetic properties and high variations in age. Given the small number of randomized controlled trials in LTx, practice is often guided by retrospective case series, expert consensus, or extrapolating the abundance of evidence from other SOTs to the LTx setting. Considering survival outcomes continue to lag behind other SOTs, this strategy may be not be addressing the unique challenges of immunosuppression in LTx.

The aim of this article is to highlight the current clinical challenges faced when managing LTx recipients with tacrolimus, offers strategies to manage these issues, and highlights areas that require further research.

## EVIDENCE TO GUIDE THERAPEUTIC DRUG MONITORING

Tacrolimus has a narrow therapeutic index, and therapeutic drug monitoring (TDM) is imperative post-LTx for treatment individualization. There are some challenges in clinical practice to determine the most appropriate approach to TDM in LTx, because there is no specific practice guideline that recommends how to monitor tacrolimus in this population.

LTx recipients with CF have the greatest need for improvement of TDM methods. TDM does not take into account the delayed absorption or increased clearance unique to this cohort. Although literature exists examining the difference between CF and non-CF populations, no specific recommendations have been published discussing how to monitor tacrolimus in this population.

### Tacrolimus

Pharmacokinetic studies investigating tacrolimus TDM are limited. Current TDM methods for tacrolimus are based on $C_0$ levels extrapolated from models in kidney and liver transplantation [2,3]. Currently, there is limited prospective evidence to guide practice and inform the direct relationship between trough concentrations ($C_0$) and efficacy and toxicity [4].

Studies investigating the correlation between tacrolimus $C_0$ and area-under-the-concentration-over-time curve ($AUC_{0-12}$) have yielded a wide range of results with single-concentration monitoring at 3 or 4 hours postdose ($C_3$ or $C_4$) suggested as the best marker of $AUC_{0-12}$ [3]. Despite these proposals, $C_0$ monitoring continues to be the mainstay of estimating tacrolimus exposure in clinical practice [3]. A recent study demonstrated that the relationship between $AUC_{0-12}$ and trough concentration ($C_{24}$) was similar for once-daily tacrolimus and twice-daily tacrolimus, supporting the use of the same TDM methods for both formulations [5].

Monitoring of blood concentration (BC) tacrolimus levels, with recommendations from our institution suggested in Table 1, depends on a number of factors including time post-LTx, concomitant immunosuppression, and clinical markers such as infection or episodes of AR. Measured levels should not be the only variable considered when adjusting doses—trend of levels, clinical status, renal function, and side effects, such as headaches or tremor, should all be taken into account. Sampling errors or variations in assays may be possible reasons for anomalies, and repeating levels should be the preferred approach, rather than withholding or excessively adjusting doses, potentially exacerbating the fluctuating level.

## FACTORS INFLUENCING TACROLIMUS CONCENTRATION VARIABILITY

The pharmacokinetics of the tacrolimus can be associated with unacceptable variability in BC, increasing the risk of

**Table 2. Suggested Summary of Doses and Dose Conversions [9,45]**

| | | |
|---|---|---|
| Oral tacrolimus | Starting dose | <50 kg: 3 mg twice daily<br>>50 kg: 5 mg twice daily |
| | When to use | Maintenance dosing<br>No GI abnormalities |
| Sublingual tacrolimus | Starting dose | <50 kg: 1 mg twice daily<br>>50 kg: 1.5 mg twice daily |
| | Dose conversion | PO = 2× sublingual dose<br>1 mg PO twice daily = 0.5 mg sublingual twice daily |
| | When to use | Variable GI absorption with oral intake<br>No IV access |
| Intravenous tacrolimus | Starting dose | <50 kg: 0.3 mg twice daily<br>>50 kg: 0.5 mg twice daily |
| | Dose conversion | PO = 10× IV dose<br>1 mg PO twice daily = 0.1 mg IV twice daily over 4 h |
| | When to use | Short-term use<br>Early post-transplant<br>GI absorption unavailable |

Abbreviations: GI, gastrointestinal; IV, intravenous; PO, per oral.