Application for Scandiatransplant Research Grant 2025:

Personalising Immunosuppression after Lung Transplantation: Insights from a Nordic randomised controlled multicentre Study

Applicant: Are Holm, Dept. of Respiratory Medicine, Oslo University Hospital, Norway

Summary

For some, the immunosuppressive medication necessary after organ transplant has insufficient effect, with ensuing chronic rejection and organ failure. For others, these drugs lead to serious and sometimes lethal side effects. This project aims to improve the drug monitoring and dosing of immunosuppressive drugs after lung transplantation by analysing available data from the ScanCLAD-study, a large, multicentre, randomized controlled trial (RCT) recently performed in a collaboration between five lung transplant centres within Scandiatransplant (Gothenburg, Lund, Copenhagen, Helsinki, and Oslo).[1] By utilising the data registered in this study, data on drug dosage and measured plasma concentrations will be related to the registered outcomes. By using regression models, receiver operating characteristic (ROC), and other analyses, the optimal target concentrations will be determined. The study is approved for all countries by national ethics committees.[1] The study will be a collaboration between all participants in the original ScanCLAD study group, thus including all Scandiatransplant lung transplant centres except Tartu. The study will be lead by drs. Holm and Leuckfeld in Oslo and dr. Magnusson in Gothenburg. The grant will be used as salary to a pharmacist in Oslo (part time employment over two years). The results are likely to improve individualised immunosuppression in lung transplanted patients and will be published in international peer reviewed journals.

Background

The most important life-limiting factor after lung transplantation is chronic lung allograft dysfunction (CLAD), which is understood to be a form of irreversible chronic rejection. It is estimated that about 30-50% of the patients develop CLAD.[2] To prevent allograft rejection and CLAD, life-long immunosuppression is necessary. To this end, a combination of three drug types is employed. The calcineurin inhibitors (CNIs) Cyclosporin A (CyA) and tacrolimus (Tac) both have a narrow therapeutic window, and frequent side effects include kidney failure, increased risk of opportunistic infections, and increased risk of malignancies. Tac may additionally increase the risk of developing diabetes mellitus. Common side-effects of MMF are leukopenia and gastrointestinal symptoms, in addition to increased risk of opportunistic infections. A number of side effects are associated with long-term use of prednisolone, including osteopenia/osteoporosis, weight gain, dyslipidemia, hypertension, new-onset diabetes and infections.[3,4] Importantly, to minimize the risk of adverse events related to under- and overdosing, the CNI are monitored by frequent analyses of blood concentration. To this end, blood samples are frequently taken immediately before intake of the drug to determine the lowest levels, also called the 0-concentration (C0), or trough concentration. Unfortunately, the trough concentrations do not perfectly mirror the total drug exposure, and other

modes of monitoring are conceivable, such as measuring levels two hours after drug intake (C2), or at several time points after intake to calculate the area under the curve (AUC). For LTx, no alternative method has so far been demonstrated to be superior to the measurement of the trough concentrations.[5,6]

Specific ranges for target levels are defined for specific intervals after LTx, with highest levels in the early weeks after LTx. For instance, at Oslo University Hospital the target trough level for Tac is 10-14 ng/mL in the first 12 weeks, 3-6 ng/mL in the following 12 weeks, then 6-12 ng/mL the following six months, then 6-8 ng/mL for all subsequent years. Internationally, however, the target levels vary between centres, and there is scarce evidence to guide what should be the recommended target levels.[7,8][9] Similarly, despite the severity of the common side-effects, no strong evidence exists to guide the dosage of MMF or prednisolone. There are only a few small studies suggesting an association between low exposure to mycophenolate and unfavourable outcome after LTx.[10] Adding to this complexity, the immunosuppressive drugs are typically administered with the highest doses (or target levels) in the first 12 weeks after transplant, then reduced at 6 months post-transplant, and again reduced at 1 year after transplant, and no clear evidence exists to guide the timing or degree of these dose adjustments.

The ScanCLAD study

In the ScanCLAD-study, all patients listed for LTx at any of the Scandiatransplant LTx centres (except Tartu, Estonia) in the period from October 2016 to July 2019 were screened for inclusion. A total of 249 patients were transplanted and included and had been followed for 3 years at the time of publication (long-term follow up still ongoing). All administered medications, and all blood sample results, including concentrations of CNI and MMF in blood, were thoroughly monitored and registered and are available for further analysis in a study repository. About 90% had at least one serious adverse event.[1] Prior to this study, CyA was the primary CNI of choice in all Scandiatransplant LTx centres. Due to the convincing observations in the study, showing significantly greater risk of CLAD in the CyA group, all centres have now switched to a regimen including Tac as the primary CNI.[1]

Hypothesis and aims

In the ScanCLAD study not only the adverse events but also all administered drugs and all measured plasma concentrations of immunosuppressive drugs was registered. The hypothesis of this study is that by analysing the unique set of data available in the data repository of the ScanCLAD study, we will be able to determine the optimal target levels for therapeutic drug monitoring of the CNIs and MMF. The ultimate aim is to improve individualised drug dosage in lung transplant recipients.

Materials and methods

Data for all 249 lung transplanted patients included in the ScanCLAD study with follow up data for five years will be analyzed. *Multivariate regression models*: The probability of achieving the desired effect will be modeled as a function of the serum concentration using appropriate multivariate regression models, depending on the nature of the outcome (binary, quantitative etc.). Similarly, the

probability of experiencing specific undesired side effects will be modeled as a function of the blood concentration. *Receiver Operating Characteristic (ROC) Analyses.* After fitting logistic regression models, ROC curves will be calculated to evaluate the sensitivity and specificity of different blood concentrations in predicting the desired effect and side effects. A threshold concentration will be determined that maximizes the sensitivity for the desired effect while minimizing the probability of side effects.[11-14] Following this, the stratified analyses by major risk groups will be done. Furthermore, the analyses will be done for each of the different time periods after LTx separately (first 12 weeks, next 12 weeks, next 6 months, then for the remaining time observed).

Ethics considerations and approvals

This study is approved by regional ethics committees in all countries as a substudy of the ScanCLAD study.[1] The study was also approved by the ScanCLAD study group at a meeting on Marstrand, Sweden, 18.-19. September 2024. Importantly, if this study is not done, the data may remain undescribed.

Project collaborators

Principal investigator: Professor Are Holm MD PhD, Oslo University Hospital, Oslo, Norway Collaborators/co-supervisors: Dr. Inga Leuckfeld MD PhD, Oslo University Hospital, Dr. Jesper Magnusson MD PhD, Sahlgrenska University Hospital, Gothenburg, Sweden, Associate professor Nils Thore Vethe MSc PhD, Dept. of Pharmacology, Oslo University Hospital, Celine Cunen, MSc PhD, Statistician, Oslo Centre for Biostatistics and Epidemiology (OCBE), Asbjørn Lunnan MSc, pharmacists, Oslo University Hospital. Support has been pledged by all members of the ScanCLAD study group.

Timeline and dissemination

Spring 2025: Data extraction from the ScanCLAD database, inventory and quality check. Analyse ScanCLAD data for immunosuppression, acute and chronic rejection (CLAD), and adverse events related to medication . Identify predictors of undesired effects of immunosuppression for later stratification.

Fall 2025, Spring 2026: ***Subproject 1: Optimal serum levels of cyclosporine A and of tacrolimus after lung transplantation***. Statistical methods as described above will first be used to analyse the CNIs. The report will first descriptively summarize number of serum samples drawn, number of dosage changes and similar data describing clinical practice. Then, the observed risk factors in the ScanCLAD population, the occurrence of undesired effects, and the determined optimal serum concentration ranges for both CNIs will be summarized. The tentative title of paper 1 is "*Optimal serum levels of cyclosporine A and of tacrolimus after lung transplantation*".

Fall 2026: ***Subproject 2. Optimal therapeutic drug monitoring of mycophenolate after lung transplantation.*** Similarly as in subproject 1, the plasma MMF trough levels will be analysed and optimal MMF trough levels will be determined. The analyses will be stratified according to the risk groups identified for undesired effects of MMF. A parallel analysis using the AUC levels will be done,

and the two (trough levels and AUC) will be compared to determine which one has the superior predictive capacity. The results will be related to the findings in subproject 1. The observed risk factors in the ScanCLAD population, the occurrence of undesired effects and the determined optimal plasma concentration ranges for MMF will be summarized in paper nr. 2, with the tentative title "*Optimal therapeutic drug monitoring of mycophenolate after lung transplantation*". As in paper 1 the report will also summarize descriptive data associated with MMF administration.

Budget

We apply for a Scandiatransplant Research Grant of totally 400,000 DKK.

The funding will be used as salary for Cand.Pharm. Asbjørn Lunnan to conduct the study in a part time (40%) position. His current full time salary (including overhead cost) is about 600.ooo DKK. The amount of 400.ooo DKK will suffice for a 40% position for a total of 18 months. We will also apply for additional funding internally at Oslo University Hospital. If granted, this funding will be used to extend the employment time. No other funding is currently available.

References

1. Dellgren G, Lund TK, Raivio P, et al.: **Effect of once-per-day tacrolimus versus twice-per-day ciclosporin on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD): a multicentre randomised controlled trial**. *Lancet Respir Med* 2024, **12**:34-44.
2. Verleden GM, Glanville AR, Lease ED, et al.: **Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT**. *J Heart Lung Transplant* 2019, **38**:493-503.
3. Fardet L, Feve B: **Systemic glucocorticoid therapy: a review of its metabolic and cardiovascular adverse events**. *Drugs* 2014, **74**:1731-1745.
4. Oray M, Abu Samra K, Ebrahimiadib N, et al.: **Long-term side effects of glucocorticoids**. *Expert Opin Drug Saf* 2016, **15**:457-465.
5. Braithwaite HE, Darley DR, Brett J, et al.: **Identifying the association between tacrolimus exposure and toxicity in heart and lung transplant recipients: A systematic review**. *Transplant Rev (Orlando)* 2021, **35**:100610.
6. de Wall C, Fuehner T, Wehmeier P, et al.: **Therapeutic drug monitoring of mycophenolic Acid after lung transplantation-is it clinically relevant?** *Transplantation* 2011, **91**:e33-34.
7. Garrity ER, Jr., Hertz MI, Trulock EP, et al.: **Suggested guidelines for the use of tacrolimus in lung-transplant recipients**. *J Heart Lung Transplant* 1999, **18**:175-176.
8. Brunet M, van Gelder T, Asberg A, et al.: **Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report**. *Ther Drug Monit* 2019, **41**:261-307.
9. Nelson J, Alvey N, Bowman L, et al.: **Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation**. *Pharmacotherapy* 2022, **42**:599-633.
10. Bergan S, Brunet M, Hesselink DA, et al.: **Personalized Therapy for Mycophenolate: Consensus Report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology**. *Ther Drug Monit* 2021, **43**:150-200.
11. Clements JD, Perez Ruixo JJ, Gibbs JP, et al.: **Receiver Operating Characteristic Analysis and Clinical Trial Simulation to Inform Dose Titration Decisions**. *CPT Pharmacometrics Syst Pharmacol* 2018, **7**:771-779.
12. Minto C, Schnider T: **Expanding clinical applications of population pharmacodynamic modelling**. *Br J Clin Pharmacol* 1998, **46**:321-333.
13. Hirayama H, Morita Y, Imai T, et al.: **Ustekinumab trough levels predicting laboratory and endoscopic remission in patients with Crohn's disease**. *BMC Gastroenterol* 2022, **22**:195.
14. Northwood K, Pearson E, Arnautovska U, et al.: **Optimising plasma clozapine levels to improve treatment response: an individual patient data meta-analysis and receiver operating characteristic curve analysis**. *Br J Psychiatry* 2023, **222**:241-245.