HALFWAY REVIEW REPORT

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The intricate balance between under- and over-immunosuppression after heart transplantation – clinical experiences from Skåne University Hospital in Lund 1988-2010 with special emphasis on acute cellular rejection, chronic kidney disease and the conversion to generic immunosuppressants

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Background and purpose

Heart transplantation (HT) remains the ultimate treatment choice for many patients with end-stage heart failure who remain symptomatic and worsen despite optimal medical and surgical therapy [1]. The first HT ever was performed in 1967 [2] and, since then, survival has steadily increased. According to a recent report [3] from the International Society for Heart and Lung Transplantation (ISHLT) based on data from 394 HT centres and 104 000 HT patients worldwide, the median survival increased from 8.5 years 1982-1992 to 10.9 years 1993-2003, and is predicted to continue to improve. Unfortunately, issues related to under- and over-immunosuppression after HT remain common and continue to constitute the most important limiting factors for successful long-term outcome. This is clearly reflected by the same report from the ISHLT, which concludes that most of the improvement in survival is due to mortality reduction in the first year following transplantation and that mortality beyond the first year has remained relatively constant over the past 20 years [3].

Whereas the long-term use of the immunosuppressive therapy is associated with increased risks of serious medical problems such as infections [4, 5], osteoporosis [4, 6], malignancies [4, 7] and chronic kidney disease (CKD) [4, 8], insufficient immunosuppressive exposure may lead to rejection – a potentially deadly process which can be either chronic, such as in “cardiac allograft vasculopathy” (CAV), or acute, as in “acute cellular rejection” (ACR) or “antibody-mediated rejection” (AMR) [9]. For clinicians treating HT patients this is a difficult dilemma between “too much” and “too little” which likely will remain complex as long as human HT, and thereby the consequent need of life-long immunosuppression, continue to be the golden standard therapy for patients in need of a new heart. Recent years´ of research, however, has led to advancements that may aid in this intricate balance – notably the standardized nomenclatures for CAV and AMR [10, 11], novel immunosuppressants such as mammalian target of rapamycin inhibitors (m-TORS), and different strategies aimed at minimizing the use of calcineurin inhibitors (CNIs) [12-14] and corticosteroids (CSs) [15].

Skåne University Hospital in Lund (SUS-Lund) have performed HTs since 1988 and is currently
one of two referral centres for HTs in Sweden, the other being Sahlgrenska University Hospital [16]. Since the beginning of the HT-program at SUS-Lund a systematic follow up, with frequent check-ups, has been conducted in order to optimize outcome of the patients that have undergone HT. In order to evaluate more than 20 years of clinical experience of HT at SUS-Lund and to gain further knowledge on factors influencing both morbidity and mortality after receiving a transplanted heart, the Lund Heart Transplantation Research Register (LHTRR) was established by Göran Rådegran in 2014, on the basis of data collection initiated 2010. The purpose of the present PhD project is to contribute to this database with data on patients transplanted 1988-2010 in order to study consequences related to the intricate balance between under- and over-immunosuppression following HT.

The introductory part of the present PhD thesis will be based on a review article that we published in July 2015 [17], focusing on relevant aspects of transplant immunology, rejection, issues related to the immunosuppressive treatment, and different types of immunosuppressive drugs and therapies. The final thesis will include four papers. Three of these will focus on two of the most clinically relevant aspects related to the intricate balance regarding immunosuppression – i.e. ACR and CKD. The papers will be based on follow-up data from patients that were transplanted at SUS-Lund 1988-2010, with the main purpose of studying the incidence, predictors, and outcome of ACR and CKD after HT. The fourth paper will cover another aspect of immunosuppressive treatment after HT, namely the somewhat controversial question of converting from branded to generic immunosuppressive drugs. Such a conversion was made at SUS-Lund 2012-2013 in order to reduce drug costs. The purpose of the fourth article is to evaluate the safety and efficacy of such a switch.

- **Paper I: ACR early after HT (published)**

- **Methods:** A retrospective analysis of the incidence, predictors, and outcome of ACR during the first year after HT, based on 2635 routine and 355 additionally clinically indicated (ACI) endomyocardial biopsies (EMBs) from 215 HT patients transplanted at SUS-Lund 1988-2010.

- **Results:** The frequency and severity of first-year ACRs was low, with 6.5% of routine EMBs and 14.1% of ACI EMBs showing ACR ≥ grade 2. Proportionally more (p<0.05) first-year ACRs ≥ grade 2 were found among EMBs in HTs performed during 1988-1999 (9.6%) than 2000-2010 (5.5%), EMBs performed during 16-52 weeks (8.8%) than 1-12 weeks (6.3%) after HT, EMBs in HTs with pediatric (11.3%) than adult (7.1%) donors, and EMBs in sex-mismatched (10.4%) than sex-matched (6.3%) HTs. Five- and ten-year survival was furthermore lower (p<0.05) among HTs with ≥ 1 compared with 0 first-year ACRs ≥ grade 3A/3B (82% vs 92% and 69% vs. 82%, respectively). Ten-year survival at SUS-Lund was 74% compared with 53% in the ISHLT registry.

- **Conclusions:** The results indicate that first-year ACRs ≥ grade 3A/3B affect long-term survival. The study suggests that frequent first-year EMBs may allow early ACR detection and continuous immunosuppressive adjustments, preventing low-grade ACRs from progressing to ACRs ≥ grade 3A/3B, thereby improving survival.

- **Paper II: ACR late after HT (in progress)**

  Söderlund C, Higgins T, Rådegran G. Acute cellular rejection later than one year after heart transplantation: a single-centre retrospective study at Skåne University Hospital in Lund 1988-2010.

  - **Methods:** A retrospective analysis of the incidence, predictors, and outcome of ACR later than the first year after HT, based on 399 routine and 440 additionally clinically indicated (ACI) endomyocardial biopsies (EMBs) from 215 HT patients transplanted at SUS-Lund 1988-2010.

  - **Data analysis is expected to be finalized at the end of 2015. The manuscript should be ready for submission during the spring of 2016.**
• Paper III: CKD following HT (Submitted to Transplant International)


- Methods: Retrospective analysis of the incidence, predictors, and outcome of CKD following HT. Data based on annual follow-ups of HT-patients that underwent HT at SUS-Lund 1988-2010, including evaluation of glomerular filtration rate (GFR) using iohexol clearance measurements and the CKD-EPI or Schwartz formulae - the currently recommended GFR estimating equations for adults and children, respectively.

- Results: Median GFR (Q1-Q3)(mL/min/1.73m²) declined from 67.0 (50.0–82.0) during transplant assessment (TA), to 56.0 (45.0-69.0) at year 1, 53.0 (41.0-68.0) year 5 and 44.5 (25.0-57.3) year 10. The cumulative incidence of CKD ≥ stage 4 was 25% at 5 years and 41% at 10 years post-transplant. Proteinuria the first year post-HT was the only predictor related (p<0.05) to a higher rate of GFR decline (HR 5.15, 95% CI 1.23-21.55). GFR ≥60 as compared to <60 before HT, or a first year GFR decline <30% as compared to >30%, was moreover associated (p<0.05) with a lower risk of death (HR 0.30, 95% CI 0.12-0.76 and HR 0.35, 95% CI 0.13-0.90, respectively). Notably, the CKD-EPI and Schwartz formulae overestimated GFR by 28±29% and 26±33%, respectively.

- Conclusions: CKD in HT patients is common and associated with worse outcome. To avoid diagnostic delay, GFR estimating equation’s validity in HT patients needs further study.

• Paper IV: Conversion to generic immunosuppressants in HT patients (published)


- Methods: Evaluation of the safety and efficacy of the switch to generic mycophenolate mofetil (from CellCept® to Myfenax Teva® [MT]) and tacrolimus (from Prograf® to Tacrolimus Sandoz [TS])
through an acute monitoring and a retrospective follow-up. ACRs on EMBs four weeks after the MT switch were specifically compared to a matched retrospective control group.

- **Results:** Tacrolimus trough levels (TS switch) as well as hemoglobin, leukocytes, and thrombocytes (MT switch) did not change (p=NS) during the three weeks after each respective switch (8.7±2.9 vs. 8.4±1.9 µg/L, 129.1±12.6 vs. 130.1±12.8 g/L, 6.3 vs. 6.2 x10⁹/L, and 217.4±56.6 vs. 219.3±61.8 x10⁹/L). 0% of the EMBs in the MT switch vs. 3% of the EMBs in the control group showed ACR > grade 1R (p=NS). After six months, survival was 96% (MT switch) and 100% (TS switch), and the frequency of severe ACR was low. Safety parameters measured at the next annual follow-up were also stable following each switch.

- **Conclusions:** Switching to MT and/or TS several years after HT appeared safe as evaluated in the short-term perspective, showing no detectable changes in tacrolimus trough levels, safety or efficacy, during an average follow-up of six months.

- **Summary**

Following HT there is an intricate balance between under- and over-immunosuppression. The aim of the present PhD project is to contribute to the LHTRR with data on patients transplanted at SUS-Lund 1988-2010 in order to study consequences related to this balance. The papers so far included in the PhD thesis contribute with important data on ACR and CKD, as well as on the safety and efficacy of the switch to generic immunosuppressants. To be finalized remains a paper focusing on ACR beyond the first year after HT. The results of this paper will be of particular interest as many HT centres nowadays only perform EMBs on a routine basis during the first postoperative year.

- **References**


http://www.socialstyrelsen.se/rikssjukvard/Documents/Tillst%C3%A5nd%20hj%C3%A4rta%20Region%20Sk%C3%A4ne.pdf