Balancing immunogenicity and histocompatibility in kidney transplantation
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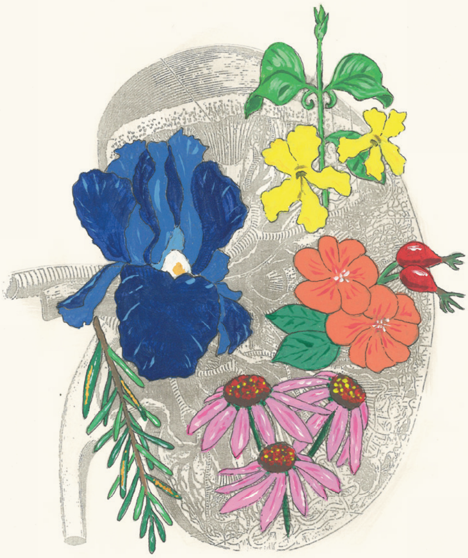

CHAPTER 8

SUMMARY AND GENERAL DISCUSSION

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End-stage kidney disease (ESKD) has a devastating impact on quality of life and life expectancy. There also is an economic impact with a significant rise in the annual cost of chronic kidney disease (CKD) management upon progression towards CKD stage-5.[1, 2]

Among therapeutic options, dialysis is immediately life-saving and crucial as maintenance treatment for many patients. Dialysis, however, is a very time-consuming and costly therapy carrying a high physical and mental burden with profound impact on quality of life. Therefore, kidney transplantation is the preferred treatment option for most patients. Beside improvement of quality of life after kidney transplantation, there is a well-documented improvement in survival rates as compared to remaining on the transplant waiting list. Adequate outcome parameters have been documented across all age categories, including patients over the age of 70 years.[3, 4] Despite superior survival after kidney transplantations, there still is considerable room for improvement both in kidney graft and patient survival. In this thesis we discuss several strategies to ultimately improve survival after kidney transplantation with a focus on the elderly, since they represent the fastest growing ESKD population with almost 50% of new patients entering renal replacement programs being 65 years of age or older.[5]

In **chapter 2** and **chapter 3** we reviewed the specific characteristics of older kidney transplant candidates, aged 65 years and older. Overall, the risk of an acute rejection episode is lower in older recipients. The increased immunogenicity of a kidney graft from older or marginal donors, however, apparently overrides the effect of reduced immune reactivity in elderly. In addition, in case of acute rejection, older kidney transplant recipients are more vulnerable for infectious complications due to immunosenescence and additional immunosuppressive treatments. Since the balance between infection and rejection is an important aspect when transplanting elderly, several immunosuppressive protocols with diminished immunosuppressive drug levels were reviewed in **chapter 3**.

Access to renal replacement therapy is also different for elderly as compared to younger counterparts with end-stage kidney failure. We should bear in mind that older patients are being waitlisted less frequently as compared to younger patients and that a timely transplant is even more important with increasing age. In **chapter 2** we compared different allocation methods which both contain strategies to reduce waiting time for the elderly, the Eurotransplant Senior Program (ESP) and the US allocation system. The former preferentially allocates kidneys from donors aged 65 years and older to recipients of 65 years and older within the same region in order to reduce cold ischemia time and thus the likelihood of delayed graft function. The current ESP allocation strategy, however, does not take HLA matching into account. Alternatively, the US allocation system is based on a score of the donor (Kidney Donor Profile Index (KDPI)) and a score of the recipient (Estimated Post-Transplant Survival (EPTS)) in order to match the anticipated survival of the kidney allograft and the recipient.

To overcome the challenge of a timely transplant and immunogenicity in the elderly we reviewed the relevance and potential of prospective HLA matching within the ESP in **chapter 3**.

In **chapter 4** we showed the results of a prospective allocation cohort study performed within the Eurotransplant Senior Program (ESP). In this study a paired allocation was performed, in which the first kidney was allocated with the current ESP allocation strategy and the second kidney was allocated with prospective HLA-DR matching within the ESP. Here we showed the benefit of prospective matching for HLA-DR antigens, which was associated with a significantly lower five-year risk of mortality and significantly lower risk for kidney graft failure and return to dialysis at one year and five years post-transplant. We also observed that shifting the current ESP allocation strategy towards a zero HLA-DR mismatch strategy resulted in a significantly shorter median dialysis vintage.

In **chapter 5** we looked more into detail into the importance of HLA matching in the formation of anti-HLA donor specific antibodies (DSA). The formation of DSA was examined in different groups of renal transplant recipients with a standard to low immunological risk profile, who all participated in randomized trials with standardized therapeutic regimens and defined standard clinical follow-up. In these patients, risk factors for the formation of DSA were assessed. HLA matching was analyzed at the amino acid level by determining the solvent accessible amino acid mismatches using the software program HLA-EMMA.[6] We found that the number of solvent accessible amino acid mismatches was an independent risk factor for the development of anti HLA-DQ DSA. A second independent risk factor was a having a kidney donor after circulatory death procedure.

In **chapter 6** a new therapeutic regimen was investigated in a phase 1b trial. In this trial, the Neptune study, ten renal transplant recipients were treated with HLA-selected allogeneic mesenchymal stromal cells (MSC). We used HLA selected MSC to prevent repeated HLA mismatches and herewith minimize the risk of inducing an anti-donor immune response. This study showed that the infusion of HLA-selected allogeneic MSC after kidney transplantation was safe and that it could potentially allow a reduction in immunosuppressive drug levels, in particular tacrolimus.

Although the effects of MSC have been documented in several clinical studies, the working mechanism is still not fully elucidated. Whether the working mechanism is more local or direct interaction or distant by for example involving endocrine factors is important for their future use and therapy. The life span of MSC in vitro is relatively short, but in vivo after infusion this was not yet known. To investigate the life span in vivo, we measured the cell free DNA from the MSC at different time points after infusion in **chapter 7.** This is the first study where three genomes were separated and the first to investigate MSC derived cell free DNA in vivo. In line with preclinical studies, we found a steep rise of cell free DNA up to four hours after MSC infusion. One week after infusion, however, no more MSC derived cell free DNA was detectable. This information adds an important piece to the puzzle of the mechanism of action of MSC therapy in vivo.

FUTURE PERSPECTIVE

This thesis elaborates on the challenges regarding immunogenicity and histocompatibility in kidney transplantation and strategies for innovation to improve survival rates, with special attention for elderly patients. The first goal should be a timely kidney transplant for all patients with ESRD but the reason why is different in different age categories. Younger patients should receive a timely transplant, since dialysis vintage is an important factor when it comes to patient survival also after a successful kidney transplant. Older patients should receive a timely transplant since their life span is limited and the time they have to enjoy the benefits of a transplantation shorter. Therefore, expansion of the kidney donor pool remains the key challenge for the future. In the Netherlands, a new law was introduced in 2020 in which every Dutch citizen aged 18 years or older is registered as an organ donor, unless they actively withdraw their consent beforehand. In 2023 the number of organ donors reached a record of 292 in the Netherlands, the highest annual number ever. Whether this is due to the new law from 2020 or others factors such as innovations which make more organs suitable for transplantation, will be evaluated after 2024 and further. On the other hand, this increase is limited and still far from sufficient, since in 2023 in the Netherlands more patients were placed on the waiting list (n=1616) than removed from the list (due to transplantation, death or other causes). Expansion from the donor pool could also be accomplished by encouraging patients to find a living kidney donor. Several hospitals have set up projects to better inform patients and their family members about their kidney disease and therapeutic options to increase the awareness and knowledge about kidney donation.

Timing in kidney transplantation is not only important for the patient, to reduce dialysis vintage, since this is associated with worse outcome. The kidney graft itself should also be transplanted as soon as possible to reduce cold ischemic time, also associated with outcome. Introduction of the ESP program with local or regional kidney allocation increased the chance for elderly transplant candidates to receive a kidney offer while also limiting the cold ischemic time. In addition, allocation with a zero mismatch for HLA antigens in the study described in **chapter 4**, significantly reduced the mean dialysis vintage. Expansion of the donor pool to maintain or even increase HLA diversity is pivotal for this aspect.

This thesis sets the stage for a more important role or re-activation of HLA matching in kidney transplantation in total. As shown in **chapter 4**, especially in elderly kidney transplant recipients receiving kidneys from an older donor, allocation based on zero HLA-DR mismatch should be considered as the standard (minimal) matching strategy. HLA-DR matching offers a lower risk of rejection and less need for (additional) high dose treatment of acute rejection or more intense maintenance immunosuppression. Especially in elderly, with already a higher risk of infectious complications, reduced immunosuppression could offer an important benefit. However, as shown in

chapter 5, not only the elderly but a variety of renal recipients may develop DSA and have a higher risk of premature transplant failure. Currently matching in kidney transplantation has focused on HLA--A, -B and -DR on the serological antigen level (broad for HLA-A and -B and at the split level for HLA-DR). As shown in **chapter 5**, patients with de novo DSA formation against HLA-DQ have the highest risk of transplant failure. Since HLA-DR and HLA-DQ loci are located close to each other resulting in strong linkage disequilibrium this suggests that matching for HLA-DR would result in compatibility for HLA-DQ in the majority of cases. However, in only 22.4% a linkage disequilibrium between HLA-DR and -DQ was found.[7, 8] Recently, the 'sensitization in transplantation: assessment of risks' 2022 working group published a clinical guideline of post-transplant DSA assessment summarizing the current clinical problems and recommendations.[9] Using epitope or amino acid mismatches rather than the currently defined HLA allele mismatches, will improve the knowledge on which patients are at an increased risk for de novo DSA formation and inferior outcome parameters. Matching on amino acid level may ultimately result in a better matched or compatible organ with more possibilities to subsequently lower the current standard immunosuppressive regimens and improve long-term graft and patient survival.

In addition, novel therapeutic modalities could help to improve kidney graft outcome. In this thesis a clinical study with allogeneic MSC, which were selected to have no repeated HLA mismatches with the donor kidney to diminish the risk of DSA formation, was described. This safety study sets the stage for further research with allogeneic cell therapies. In kidney transplantation there could be a place for MSC therapy as induction or maintenance therapy or as a treatment option for an acute rejection episode. Especially for the latter indication, allogeneic therapy would be most useful since this product could be used in the acute setting or 'off-the-shelve'. With these newer therapeutic options, the regular immunosuppressive drugs could potentially be tapered, ultimately leading to less side effects as infections and nephrotoxicity, especially from the long-term use of CNI. Since these are important causes of chronic allograft injury, this could to lead to improvement of graft survival.[10]

Not only novel (cell-based) therapies are desirable, but also patient-specific or tailor-made therapeutic regimens hold promise for the future. A number of patient-specific and kidney donor related characteristics, for example age and cardiovascular comorbidities, concomitantly influence the delicate balance between immunogenicity and histocompatibility. Timing of the kidney transplantation and taking into account histocompatibility and age factors, creates options to maintain optimal function of the kidney transplant and improve life expectancy and quality of life of patients with ESKD.

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