Hypertension after kidney transplantation: still a SECRET?

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With kidney transplantation coming of age, our major focus today is directed towards improving long-term graft survival and cardiovascular outcome. Despite the high incidence of hypertension in transplanted patients and the well-known deleterious effects on end organs, it is still a major question which blood pressure-lowering drugs are optimal to achieve improved outcome. Since many years, blockade of the renin–angiotensin system (RAS) is used in kidney transplant patients for blood pressure lowering, although concerns of safety have been raised in respect to the risk of hyperkalaemia, anaemia and acute kidney injury due to undetected renal artery stenosis.

In this regard, the ‘Study on the Evaluation of Candesartan cilexetil after Renal Transplantation (SECRET)’ by Philipp et al. [1] in this issue of Nephrology Dialysis Transplantation has addressed the questions in a prospective way. The endpoint, a composite of all-cause mortality, cardiovascular mortality and all-cause graft failure, was relevant. Power calculation was done on the basis of data available at the time of study design assuming a 13% event rate per year in the placebo group. After applying inclusion and exclusion criteria, it turned out to be far too high with 5.2% during interim analysis at 20 months. Interestingly, the ‘Assessment of LEscol in Renal Transplantation (ALERTE) Study’ [2] assumed a 5% placebo event rate after 1 year of follow-up, but later on revised its assumption to a more realistic 4.5% by adding additional patients to maintain original power. Unfortunately, this was not possible in the SECRET study.

Even if the study was terminated prematurely due to low numbers of events, several important conclusions on safety and efficacy can be drawn: First, treatment with a RAS blocker allows better blood pressure control with less antihypertensive co-medication than the usual antihypertensive medication. The distinct effect is also seen in the analysis of proteinuria and albuminuria showing a reduction of both parameters only in candesartan-treated patients. Second, angiotensin II-receptor blockade (ARB) treatment is accompanied by acceptable benefit/risk ratio: even if creatinine clearance decreased in about 10% of candesartan patients, six grafts on placebo and one on candesartan ultimately failed. Third, if one uses strict screening criteria, for example an enalapril test as in SECRET, hyperkalaemia and anaemia were not major concerns.

The early termination of the trial can also be seen in a positive way: of the 210 primary events predicted to occur over 3 years, only 26 took place in 20 months of follow-up which could be the success of tight blood pressure control and improved long-term management of transplanted patients under study conditions. The results of this randomized controlled trial (RCT) may serve for evidence gathering, guideline development in the planning of future studies in this field. It is the merit of the SECRET authors to bring the results finally to the attention of the scientific community and to set up a reference for long-term post-transplant care.

What do we know already?

The Collaborative Transplant Study (CTS) group taught us already in 1988, in quite a number of patients [3], that the levels of systolic as well as diastolic blood pressure were associated with functional graft survival over at least 7 years. Mange and coworkers from the University of Pennsylvania obtained similar results in their monocentric analysis of 277 patients [4]: each 10-mmHg increase in systolic as well as diastolic blood pressure increased the risk of graft loss by about a quarter, independently of kidney function, acute rejection episodes, diabetes mellitus and ethnicity. A few years later, Kasiske and colleagues, utilizing the United States Renal Data System [5], demonstrated dramatically increased risks for graft failure and all-cause mortality upon increases in arterial blood pressure. We also learned from this study that the number of antihypertensive agents prescribed increased from the 1980s to the 1990s, arguing for a greater interest of physicians in blood pressure issues as a major cardiovascular risk factor. Subsequently, the severity of hypertension did not, however, improve significantly and the incidence of hypertension in the transplant population remained high over time. Another CTS analysis published a few years later emphasized that the struggle of controlling blood pressure seems to be worth the effort [6]: the longer the systolic blood pressure could be adjusted below 140 mmHg, the better the outcome (graft survival and cardiovascular mortality) was after 10 years.

Uniformly, all retrospective analysis points toward the same direction: control of blood pressure is important to prevent graft loss and death. Waiting for further results from RCTs to prove the benefit, especially in transplant patients, appears to be rather inappropriate in this situation.
What do we not know?

Recently published KDIGO guidelines [7] suggest the use of blood pressure targets for high-risk populations (130/80 mmHg) and remind us of the classical guidelines for the general population or other kidney patients. Admittedly, the level of evidence was low (evidence level 2C; 1 = recommendation, 2 = suggestion, quality of evidence A, B, C = low, D). Overall, the suggestions of the KDIGO workgroup are threefold: (i) the use of office and ambulatory blood pressure measurements together with automated 24-h blood pressure monitoring, (ii) exclusion of secondary causes of hypertension such as renal artery stenosis of native or transplanted kidneys and (iii) inclusion of concomitant diseases in the choice of antihypertensive treatment options. All antihypertensive measures and agents may be used, some perhaps being preferable over others.

In a short-term trial, a very-low-sodium diet (9 mmol/day) was compared to regular sodium intake in a crossover design in 15 cyclosporine-treated patients. A remarkable decrease of 11 mmHg systolic blood pressure was demonstrated during the 4-day treatment period and, unfortunately, the trial was not further extended [8].

Patients treated with calcineurin inhibitors may be treated with calcium channel blockers due to the direct vasodilating properties of this class [9], always taking into account the potential interactions with calcineurin inhibitors as well as mTOR inhibitors. Two different European randomized studies showed promising results of lacidipine compared to placebo [10] and extended-release nifedipine compared to lisinopril [11] over a period of 2 years each. In both trials, blood pressure was comparable in each arm and the administration of calcium channel blockers respectively led to significant increases in graft function without relevant side effects.

Prospective data in humans considering antihypertensive treatment with non-RAS-inhibiting agents have unfortunately not been done so far making extrapolation from treatments of non-transplanted patients the preferred method.

What do we want to know?

The rationale behind the use of RAS blockers is based on the accepted principles of treating progressive kidney diseases and the impact on plasma cytokines as surrogates for progressive fibrosis in transplanted kidneys. In several studies, losartan was administered to decrease the expression of TGF-β and PAI-1 and to inhibit interstitial fibrosis [12–14] without investigating graft survival or long-term graft functioning. Patient numbers have always been small. Hirnemath et al., in 2007, reviewed the evidence available from further clinical RCTs [15]. Unfortunately, only surrogate parameters could be analysed in this meta-analysis. It was concluded that RAS blockade leads to a significant decrease in proteinuria by about 0.5 g/day (in two studies lasting longer than 12 months) despite comparable blood pressure levels, a slightly lower GFR and slightly higher serum potassium levels. Registry data do not really take the evidence further: whereas the group from Vienna [16] demonstrated a perspicuously better graft and patient survival over 10 years, the CTS could not confirm these findings [17]. Overall, we conclude that, under certain conditions, it should be imperative for the transplant community to randomize this special patient population and show in a convincing trial the benefits or harms of RAS blockade.

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References


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