Commentary

Belatacept in renal transplantation—quo vadis?

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Whereas short-term outcomes after renal transplantation have substantially improved in the past decades, long-term outcomes have not changed in the sammer manner with regard to both graft survival and mortality. The main reason for the lacking improvement in patient survival are cardiovascular events. Kidney transplantation ameliorates the risk compared to patients on the waiting list, but cardiovascular morbidity and mortality remain largely increased compared to the general population (1). Cardiovascular events are the leading cause of death and constitute one of the leading reasons of graft failure (2,3). In this context, the deleterious effects of calcineurin inhibitors (CNI) are a hot topic in the transplant community. Due to their undoubted potency in preventing rejections they revolutionized transplant medicine since the approval of cyclosporine A (CsA) in 1983 and still constitute the standard immunosuppression in most transplant centers worldwide. CNI are both potent vasoconstrictors and promoters of intravascular fibrosis leading to obliterative arteriolopathy. They thereby lead to acute and chronic CNI nephrotoxicity and accelerate systemic arteriosclerosis. Thus, "*one kidney for life will remain largely unrealized with CNI-dependent therapy*" (4).

The search for alternative drugs with comparable immunosuppressive potency but a more favorable side effect profile led to the development of belatacept, a costimulation inhibitor. In 2010, the BENEFIT and BENEFIT-EXT studies demonstrated a preservation of glomerular filtration rate (GFR) compared to a CsA based immunosuppressive regimen in the first 12 months after kidney transplantation (5,6). Moreover, belatacept was associated with less hypertension, hyperlipidemia, and new-onset diabetes (NODAT, pooled analysis of BENEFIT and BENEFIT-EXT) (7). Hence, several dreams of the transplant community appeared to have come true. But what happened since the approval of this new star on the transplant sky in 2011? The proportion of transplant recipients receiving belatacept is still low in both America and Europe. Besides potential economic reasons, the lack of long-term experiences and the fear for early acute rejections and posttransplant lymphoproliferative disorders (PTLD) may have contributed to the reluctance in prescribing this new drug.

Recently, Vincenti *et al*. published the 7-year long-term results of the BENEFIT study. Following 447 of the initial 666 study participants for the full period, a 43% reduction in the risk of death or graft loss were observed (8). GFR increased over this period in the belatacept groups but declined in the CsA group. Development of donor specific antibodies was significantly lower with belatacept. These findings are noteworthy for three reasons: first, Vincenti's study is one of the longest term follow-up trials in transplantation so far. Second, it shows that an immunosuppressive regimen can indeed be superior to another in terms of mortality. Third, the difference in GFR is substantial achieving an 50% improvement compared to CsA. A closer look on the course of renal function helps to understand the underlying mechanisms. There is already a difference in GFR of >10 mL/min in the first month after transplantation (5). At this early timepoint, structural CNI-induced nephrotoxicity is absent or minimal. This early effect can only be explained by a hemodynamic mechanism,

namely the lack of CNI-induced vasoconstriction. The diverging slopes of the two groups, in contrast, may indeed mirror the lack of chronic CNI-toxicity in the allograft in the belatacept groups. The synergy of these two effects explains the large difference in GFR after 7 years. But, by the way, how can GFR continuously increase over years? Even in the healthy non-transplant population there is a mean annual decrease of 0.5–1 mL/min beyond the age of 40 years (9). Is the allograft under belatacept better than an orthotopic healthy kidney? Surely not. This phenomenon can only be explained by hyperfiltration, comparable to the change of the remaining kidney after renal donation. Proteinuria may be a clinically relevant consequence of hyperfiltration. Therefore, it is regrettable that quantitative data on proteinuria are lacking in both the initial publication and the 84 months data.

A limitation of the study is the choice of CsA instead of tacrolimus as control drug. Tacrolimus has a higher potency in preventing rejections (10) and was therefore declared as firstline immunosuppression after renal transplantation in the 2009 KDIGO guidelines (11). Moreover, CsA reduces the exposure to mycophenolic acid through an inhibition of the enterohepatic recirculation (12). Hence, the difference in mycophenolic acid exposure might have been lower, if belatacept would have been compared to tacrolimus. However, the BENEFIT study was designed prior to the KDIGO guidelines. At that time CsA was the only CNI-mycophenolate mofetil (MMF) regimen approved by the Food and Drug Administration (13). A second difference to the most widespread immunosuppressive regimens are the CsA target levels of 150–300 ng/mL in the first month and 100–250 ng/mL from month 2–12 in the core study (5). The majority of transplant centers—at least in Europe—prefer lower target levels for maintenance immunosuppression. Thus, the GFR advantage might be more pronounced in BENEFIT than in daily clinical practice.

The traditional end point in the majority of transplant studies is acute rejection in the first year after transplantation. Only a minority of trials have long-term extensions of >3 years beyond the core study. Potential benefits or harms of a drug in terms of blood pressure, lipids, glucose tolerance or promotion of arteriosclerosis determine cardiovascular risk. The net effect of all these drug-related parameters on mortality, however, remains speculative. Therefore, the translation of a drug's cardiovascular profile to cardiovascular end points is usually discussed with many “coulds” and “shoulds”. Assessment of cardiovascular risk is extraordinarily complex after renal transplantation. Traditional risk factors like hypertension, diabetes, smoking, and hyperlipidemia mix with non-traditional, transplant-related factors like time on dialysis prior to transplantation, graft function, and the immunosuppressive regimen. Therefore, the presentation of data on mortality—the straightest of all end points—should be welcomed. Of note, the combined end point graft loss and mortality reached significance after 7 years, mortality alone tended to be substantially lower as well (hazard ratio for death 0.55 for approved dosing scheme) but did not reach statistical significance (P=0.06). Maybe it is time to rethink the definition of end points in renal transplant trials. Acute cellular rejections are usually treatable and have limited effects on long-term outcomes. Antibody-mediated rejection, GFR and the development of DSA might be more relevant clinical end points (13).

One of the most frequently expressed concerns about belatacept is PTLD. One of the lessons that the BENEFIT study taught us was that this drug should not be administered to EBV-naive subjects. Consecutively, the drug was approved only for subjects with a positive EBV-IgG status. The 7-year analysis reveals that all but one case of PTLD occurred in the first 24 months after transplantation (8). In the meantime, a registry, called “ENLiST”, has been established that intends to define how often PTLD occurs in patients taking belatacept in a real-life setting.

So, belatacept, quo vadis after these final results of the BENEFIT study? There is a drug that outperforms a CNI based immunosuppressive regimen with regard to graft survival and mortality but it is administered to only a small minority of renal transplant recipients. Are we too conservative? It is regrettable that only two large scale studies are available. We need more data to define who is the ideal candidate for belatacept. So far, we can only state that it is an immunological low-risk person with positive EBV status. Additionally, conversion from CNI to belatacept may be a very attractive strategy for the future. In the first months after transplantation there are more acute rejections with belatacept than with CsA. Afterwards, there is no significant difference anymore and the lower occurrence of donor specific antibodies is promising with regard to chronic antibody-mediated rejection. A successful proof of principle study has already been performed by Grinyo and colleagues (14), a manufacturer sponsored larger study is in progress and successful first real-life data have been published recently (15). The more data, the more we trust.

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