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ORIGINAL ARTICLE

Long-term outcome of belatacept therapy in de novo kidney transplant recipients – a case-match analysis

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Summary

While belatacept has shown favorable short- and midterm results in kidney transplant recipients, only projections exist regarding its potential impact on long-term outcome. Therefore, we performed a retrospective case-match analysis of the 14 belatacept patients originally enrolled in the phase II multicenter trial at our center. Fifty six cyclosporine (CyA)-treated patients were matched according to age at transplantation, first/retransplant, and donor type. Ten years after kidney transplantation, kidney function remained superior in belatacept-treated patients compared with the CyA control group. Moreover, none of the belatacept-treated patients had donor-specific antibodies ≥10 years post-transplantation compared with 38.5% of tested CyA-treated subject (0/10 vs. 5/13; $P = 0.045$). Notably, however, patient and graft survival was virtually identical in both groups (71.4% vs. 71.3%; $P = 0.976$). In the present single-center study population, patients treated with belatacept demonstrated a patient and graft survival at 10 years post-transplant which was comparable to that of similarly selected CNI-treated patients. Larger studies with sufficient statistical power are necessary to definitively determine long-term graft survival with belatacept.

Introduction

Belatacept is a costimulation blocker recently approved by the FDA and EMA for immunosuppressive prophylaxis in EBV-positive kidney transplant recipients. By selective binding of B7.1 and B7.2 on antigen-presenting cells, belatacept has a specific mechanism of action without any known off-target adverse effects such as those commonly seen with calcineurin inhibitors (CNI) [1]. In large randomized controlled trials, belatacept consistently showed a significantly better preserved kidney function over time compared with patients on CNI treatment. However, while short- and midterm outcomes have been reported in detail [2–7], results from the long run are still being awaited.

Based on the estimated glomerular filtration rate (eGFR) at 1 year after transplantation (TX), which is a predictor

for long-term graft survival [8], it has been projected that the superior kidney function observed in belatacept-treated patients would lead to a graft survival benefit of 5 to 7.1% at 9 years after transplantation compared with cyclosporine (CyA)-treated patients [9]. However, the use of eGFR to predict long-term outcome remains controversial [10,11]. So far, no study has analyzed the outcome of belatacept-treated patients for more than 5 years post-transplant compared with an adequate control group [12].

Herein, we report the 10-year outcome of the 14 belatacept patients originally enrolled in the phase II multicenter trial at our center. These patients were compared with 56 case-matched patients treated with CyA.

Materials and methods

Study design

This retrospective, controlled, case-matched analysis was conducted at the Vienna General Hospital. The 14 patients originally included in the phase II belatacept trial in our center were case-matched in a 1:4 ratio with 56 CyA-treated patients followed at our center. Donor type (living versus deceased), age at transplantation, and first/re-TX were used as match criteria. Patients were selected from 660 patients receiving a transplant at our center between 1999 and 2002. The ex- and inclusion criteria of the phase II study were applied for patient selection [2]. Belatacept patients were enrolled in 2001 and 2002. All but one patient had a complete follow-up for the whole study period. At 10 years post-transplant, 9 (64.3%) patients in the study group and 33 (58.9%) patients in the control group were still on therapy.

The study was powered to detect a 20 ml/min difference in eGFR at 120 months post-transplantation. This value was based on the difference in GFR seen at 36 months in the multicenter phase III trial [3]. All analyses were performed on the intent-to-treat (ITT) population (defined as all patients who received a transplant) unless stated otherwise. In case of death or graft loss, the eGFR was imputed with 0 [3]. In the on-treatment analysis, all the patients were analyzed who were still on their assigned treatment arm. Herein, no data imputation was conducted. Data were collected from a prospective transplant database, laboratory records, and patients' charts. Patient information was anonymized and de-identified prior to analysis.

The study protocol was reviewed and approved by the institutional review board of the Medical University of Vienna (EK nb.1211/2011).

Immunosuppression

The immunosuppressive regimen for patients in the study group is described in detail elsewhere [2]. Briefly, belatacept (Nulojix®, Bristol-Myers Squibb, Princeton, New Jersey, USA) was combined with mycophenolate mofetil (MMF; CellCept®, Roche Pharmaceutical, Basel, Switzerland), steroids and induction therapy with basiliximab (Simulect®, Novartis Pharma AG, Basel, Switzerland). The study group comprised patients with a 4- and an 8-week dosing regimen, respectively (nine and five patients, respectively). For the control group, CyA (Sandimmun® or Neoral®, Novartis Pharma AG) was combined with corticosteroids and MMF according to our center's practice. Most patients of the CyA cohort did not receive basiliximab therapy (85.7%), as induction therapy was not part of the standard immunosuppressive regimen at our center at that time (1999–2002). In the control group, a switch from CyA to tacrolimus was not regarded as an exclusion criterion from the on-treatment analysis [13].

Endpoints

Primary endpoint was kidney function 10 years after transplantation. GFR was calculated with the abbreviated MDRD formula [14]: eGFR [ml/min/1.73 m^2] = 186* (serum creatinine [ml/dl])$^{-1.154}$ * (age [years])$^{-0.203}$* (0.742 if female) * (1.21 if patient is African American).

Secondary endpoints included overall patient and graft survival and biopsy-proven rejection ≥ Banff I. Furthermore, the incidence of malignancies was analyzed descriptively. In a *post hoc* analysis, the combined endpoint death, graft-loss, or an eGFR less than 30 ml was assessed. Additionally, kidney function at the study endpoint was described *post hoc* according to the chronic kidney disease stages classification. A graft was considered to be lost when a patient returned to dialysis.

DSA results were available for twenty-three consenting patients of the study cohort who were screened between October 2013 and November 2014 as part of a randomized controlled trial to assess the efficacy of bortezomib in the treatment of late antibody-mediated rejection (recruitment ongoing) [15]. Applying standard bead array assays (One Lambda, Canoga Park, CA, USA), heat-inactivated sera (elimination of the prozone effect) containing detectable HLA reactivity were subjected to HLA class I and/or II single antigen testing [test threshold: 1000 mean fluorescence intensity (MFI)]. To assess the presence or absence of DSA, individual reactivity patterns were analyzed in the context of donor/recipient HLA A, B, C, DR, and DQ typing results.

Lipid profiles were analyzed at 120 months post-transplant. Hypertension was defined as the need for antihypertensive therapy. The incidence of post-transplantation diabetes mellitus (PTDM) was defined as the need for antihyperglycaemia therapy at 10 years post-transplant [16].

Statistical analysis

Statistical analysis was performed using GraphPad Prism, version 5 (GraphPad Prism Software®, La Jolla, CA). Data were expressed as mean ± standard deviation (SD) or as median with interquartile range (1st quartile; 3rd quartile). Differences between the groups were compared by a *t*-test or the Mann–Whitney *U*-test, as indicated. Categorical values were compared with Fisher's exact test or chi-square test. Survival was calculated using a Kaplan–Meier analysis, and comparison was performed using a log-rank test. A *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics were broadly comparable between the two groups except for glomerulonephritis which was more often the cause for ESRD in the belatacept group (Table 1). Notably, all belatacept-treated patients received basiliximab induction therapy (100%), compared with only 14.3% of the control group ($P < 0.0001$). All patients had at least 10 years of post-transplant follow-up at the time of analysis. Belatacept was discontinued in five patients (35.7%), in one due to PTLD, in one due to withdrawal of consent, in two due to infection, and in one due to lack of efficacy (ATG-resistant Banff IIb rejection).

Renal function

In the ITT analysis, kidney function measured as eGFR was higher in the belatacept group at all but one measured time points, although the difference did not reach statistical significance (Fig. 1a). Renal function declined from month 12 to month 120 from 55 (±14.7) to 42.2 ml (±28.6) in the belatacept group and from 48.3 (±19.9) to 35.3 ml (±27.5) in the CyA control group (Table 2) (difference at 12 months: 6.7 ml; $P = 0.146$; difference at 120 months: 6.9 ml; $P = 0.248$). Notably, for this analysis 0 imputation was performed for missing values due to death or graft loss. A similar trend was observed in the on-treatment analysis with patients on belatacept having a numerically higher eGFR compared with the control group (Table 2; Fig. 1b). The mean difference between the two study groups at the study endpoint (120 months) was 7.8 ml ($P = 0.211$). GFR was well preserved in on-treatment patients in both the belatacept group and the CyA group. In a *post hoc* analysis evaluating the chronic kidney disease stages at 120 months post-transplant, 28.6% in the belatacept group had an eGFR ≥ 60 ml (stage 1 or 2) compared with 18.2% in the CyA control group ($P = 0.460$) (Fig. 1c).

Table 1. Recipient and donor characteristics.

Patient characteristics	Belatacept *n* = 14	CyA *n* = 56	*P*
Sex [female], *n* (%)	4 (28.6)	18 (32.1)	1.000
Age, median (1st and 3rd quartile)*	45.9 (39.2–54)	45.8 (38.7–54.6)	0.930
Deceased donor, *n* (%)*	10 (71.4)	40 (71.4)	1.000
Living donor, *n* (%)*	4 (28.6)	16 (28.6)	1.000
Reported cause of ESRD			
Glomerulonephritis, *n* (%)	5 (35.7)	6 (10.7)	0.036
Diabetes, *n* (%)	0	6 (10.7)	0.337
PCKD, *n* (%)	4 (28.6)	7 (12.5)	0.212
Hypertensive nephrosclerosis, *n* (%)	0	4 (7.1)	0.577
Others, *n* (%)	4 (28.6)	16 (28.6)	1.000
Unknown, *n* (%)	1 (7.1)	17 (30.4)	0.096
TX history*			
First TX, *n* (%)	13 (92.9)	52 (92.9)	1.000
Re-TX, *n* (%)	1 (7.1)	4 (7.1)	1.000
Time on dialysis prior to TX, median (1st and 3rd quartile)	13.5 (5–36)	25.5 (8–46)	0.259
MM, median (1st and 3rd quartile)	3 (2–4)	3 (2–3.5)	0.363
PRAh, median (1st and 3rd quartile)	10 (7–16)	8 (2–18)	0.360
PRAl, median (1st and 3rd quartile)	4 (0–6)	0 (0–4)	0.053
CMV status			
Rec/Don +/+, *n* (%)	7 (50)	19 (35.8)	0.369
Rec/Don −/−, *n* (%)	2 (14.3)	7 (13.2)	1.000
Rec/Don −/+, *n* (%)	2 (14.3)	13 (24.5)	0.719
Rec/Don +/−, *n* (%)	3 (21.4)	14 (26.4)	1.000
Donor age, median (1st and 3rd quartile)	45.5 (43–51)	45.5 (36–53.5)	0.815
CIT, median (1st and 3rd quartile)	7.7 (3.6–15)	9.2 (3.9–14.6)	0.837
Detailed immunosuppression			
Patient on MPA, *n* (%)			
1 year	14 (100)	45 (88.2)	0.327
5 year	10 (100)	33 (89.2)	0.564
10 year	10 (100)	30 (90.1)	1.000
MPA dose [g/day], median (1st and 3rd quartile)			
1 year	2 (2)	2 (2)	0.564
5 year	2 (2)	1.25 (1.25–1.88)	0.049
10 year	2 (2)	1 (1–1.5)	0.136
Patients on steroids, *n* (%)			
1 year	14 (100)	50 (98)	1.000
5 year	10 (100)	25 (67.6)	0.046
10 year	10 (100)	21 (63.6)	0.040
Steroid dose [mg/day], median (1st and 3rd quartile)			
1 year	5 (5)	5 (5)	0.401
5 year	5 (5)	5 (5)	0.574
10 year	5 (5)	5 (5)	0.785
CyA dose [mg/day], median (1st and 3rd quartile)			
1 year	–	175	
5 year	200†	175	
10 year		100	
CyA levels, median			
1 year	–	122.5	
5 year	52†	81	
10 year	–	75	

*Matching criteria.

†One patient was switched to CyA (ITT analysis).

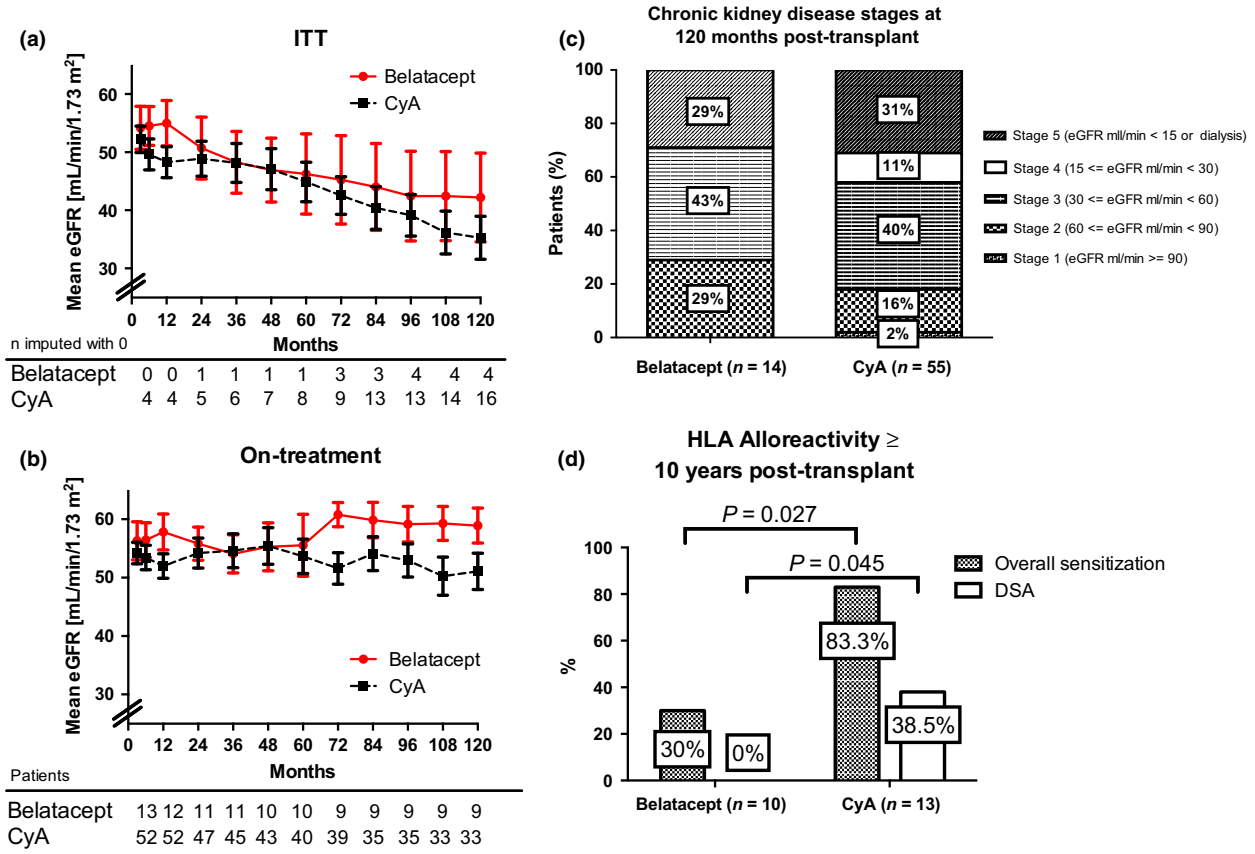

Figure 1 Kidney function. Kidney function over time was expressed as mean eGFR (MDRD) ± SEM. In case of death or graft loss, the eGFR was imputed with 0 in the ITT analysis. The eGFR difference was 6.9 ml in the ITT (P = 0.248, Mann–Whitney U-test) (a) and 7.8 ml in the on-treatment analysis (P = 0.211, t-test) (b) at 120 months post-transplant. (c) In an analysis evaluating kidney function at the study endpoint according to chronic kidney disease stages, a numerically higher proportion of patients with an eGFR ≥60 ml (stage 1 or 2) were observed in the belatacept group (28.6% vs. 18.2%; P = 0.460, Fisher's exact test). (d) More than 10 years post-transplant, there were a higher proportion of HLA class I and/or II antibody-positive patients among CyA-treated subjects (30% vs. 83.3%; P = 0.027, Fisher's exact test). Further specification of reactivity patterns revealed no DSA in the belatacept group, whereas five patients in the control group were found to have one or more DSA (0% vs. 38.5%; P = 0.045, Fisher's exact test).

Patient and graft survival

Ten-year patient and graft survival was high in both cohorts (71.4% and 71.3% in the belatacept and the CyA group, respectively (P = 0.976)) (Fig. 2a). Overall, four patients in the belatacept group (28.6%) and 14 patients in the CyA control group (25%) died before the end of follow-up. In two of the four patients who died in the belatacept group, death was temporally close to belatacept therapy (one due to post-transplant lymphoproliferative disorder (PTLD), one due to sepsis). The other two died long after discontinuation of belatacept, one due to a cerebrovascular accident (CVA, 78 months after the last belatacept dose) and the other one due to myocardial infarction (84 months after the last belatacept dose).

Similar to overall patient and graft survival, there was also no statistical difference in death-censored graft survival (83.9% vs. 88.4%, P = 0.740) (Fig. 2b). The main reason for graft loss was chronic allograft failure (belatacept: n = 2 (14.3%) vs. CyA: n = 4 (7.1%), P = 0.592) followed by primary nonfunction [0 (0%) vs. 2 (3.6%), P = 1.000].

In a more sensitive analysis evaluating the impact of either regimen on overall outcome in a combined endpoint model (including death, graft loss, or an eGFR < 30 ml), comparable results were observed again between both groups (P = 0.359) (Fig. 2c).

Biopsy-proven rejections

Biopsy-proven acute rejection (Banff ≥ I) within 6 months post-transplant occurred in two belatacept (14.3%) and 18 CyA patients (32.1%) (Table 2). One patient in the belatacept group was switched to CNI therapy due to an ATG-resistant Banff IIb rejection; one patient regained graft

Table 2. Transplant outcome.

Outcome	Belatacept $n = 14$	CyA $n = 56$	P
BPAR ≤ 6 months, *n* (%)	2 (14.3)	18 (32.1)	0.321
Banff I, *n* (%)	0	8 (14.3)	0.343
Banff II, *n* (%)	2 (14.3)	10 (17.9)	1.000
Banff III, *n* (%)	0	0	
BPAR > 6 months, *n* (%)	2 (14.3)	1 (1.8)	0.100
Banff I, *n* (%)	2 (14.3)	1 (1.8)	0.100
Banff II, *n* (%)	0	0	
Banff III, *n* (%)	0	0	
ITT			
eGFR at 3 months, mean (SD)	54.2 (13.9)	52.2 (16.7)	0.779
eGFR at 12 months, mean (SD)	55 (14.7)	48.3 (19.9)	0.146
eGFR at 120 months, mean (SD)	42.2 (28.6)	35.3 (27.5)	0.248
OT			
eGFR at 3 months, mean (SD)	56.3 (11.8)	54.2 (13.3)	0.604
eGFR at 12 months, mean (SD)	57.8 (10.7)	52 (15.2)	0.213
eGFR at 120 months, mean (SD)	58.9 (9)	51.1 (17.8)	0.211
Death			
Cardiovascular, *n* (%)	1 (7.1)	3 (5.4)	1.000
Cancer, *n* (%)	1 (7.1)	0	0.200
Sepsis, *n* (%)	1 (7.1)	2 (3.6)	0.494
CVA, *n* (%)	1 (7.1)	2 (3.6)	0.494
Unknown, *n* (%)	0	7 (12.5)	0.331
Post-transplantation diabetes mellitus, *n* (%)	0	5 (12.5)	0.569
PTLD, *n* (%)	1 (7.1)	0	0.200
Serum lipids at 120 months			
Cholesterol, mean (SD)	210.3 (89)	209 (56.5)	0.946
HDL cholesterol, mean (SD)	48.1 (16.9)	52.6 (14.4)	0.326
LDL cholesterol, mean (SD)	125.9 (65.8)	123.6 (43.4)	0.875
Triglyceride, mean (SD)	181.2 (80.7)	155.8 (86.5)	0.324
Patients on lipid-lowering therapy, *n* (%)	3 (30)	12 (34.3)	1.000
Arterial hypertension treated, *n* (%)	8 (80)	33 (94.3)	0.209
Systolic blood pressure, mean (SD)	121.1 (6.1)	127.9 (11.1)	0.138
Diastolic blood pressure, mean (SD)	76.9 (5.3)	79.3 (7.1)	0.402

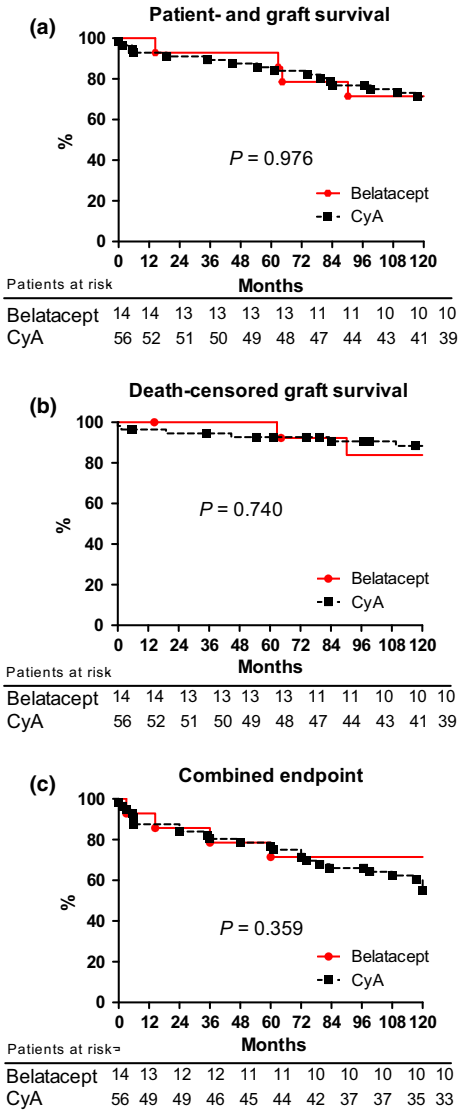

Figure 2 Patient and graft survival. (a) Ten-year patient and graft survival was 71.4% and 71.3% in the belatacept and CyA group, respectively ($P = 0.976$). Similar results were observed in death-censored graft survival (b) and in a combined endpoint analysis including death, graft loss, and an eGFR less than 30 ml (c). (a) and (b) depict Kaplan–Meier survival estimates, and (c) depicts freedom from reaching combined endpoint. The indicated *P*-values were calculated using a log-rank test.

function after a Banff IIa rejection upon treatment with ATG therapy. Late rejection episodes (BPAR > 6 months, <120 months) were observed in two patients in the belatacept group (14.3%) and in one patient in the CyA control group (1.8%) ($P = 0.100$).

DSA screening ≥10 years post-transplantation was performed in all 10 belatacept-treated patients with a functioning graft in 2014 (71.4%) and in 13 CyA-treated patients (23.2%). Applying prescreening assays, we noted a higher proportion of HLA class I and/or II antibody-positive patients among CyA-treated subjects (30% vs. 83.3%; $P = 0.027$). Further specification of reactivity patterns revealed no DSA in the belatacept group, whereas five patients in the control group were found to have one or more DSAs (0% vs. 38.5%; $P = 0.045$) (Fig. 1D). In four of the DSA-positive patients, kidney biopsy was performed. One of these patients was diagnosed for C4d-negative antibody-mediated rejection.

Metabolic and cardiovascular profiles

Serum lipids were measured at 120 months post-transplantation. We observed similar serum levels in cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in belatacept- and CyA-treated patients, respectively. Furthermore, the number of patients on lipid-lowering therapy was comparable in both groups (30 vs. 34.3, $P = 1.000$) (Table 2). Mean blood pressure was 121.1 (6.1)/76.9 (5.3) in the belatacept group and 127.9 (11.1)/79.3 (7.1) in the CyA group, with most patients being on antihypertensive therapy in both groups (80% vs. 94.3%, $P = 0.138$).

Safety

Overall, two patients in the belatacept group (14.3%) and seven patients in the control group (12.5%) developed malignancy within 10 years after transplantation. Notably, PTLD was diagnosed in one EBV-negative patient of the belatacept group 9 months post-transplant. The patient was switched to sirolimus and died 5 months after onset of disease.

No infusion-related side effects were noted at our transplant center, and intravenous therapy was generally well accepted.

Discussion

New immunosuppressive strategies have the potential for further improving long-term outcome after kidney transplantation. Belatacept is a recently approved immunosuppressant offering a CNI-free treatment alternative for kidney transplant recipients [17]. A benefit to kidney function was demonstrated for belatacept in several multicenter trials up to 60 months, but it remains to be determined whether this translates into a benefit in graft survival. In the present single-center analysis, we describe the long-term outcome of 14 belatacept-treated patients compared with a carefully matched control group.

In the ITT as well as in the on-treatment analysis, patients treated with belatacept displayed superior GFR 120 months post-transplant, although the difference was not statistically significant. These findings are in line with previous reports, observing better renal function at 6, 12, 24, and 36 months post-transplant in belatacept-treated patients [18]. Moreover, more patients of the belatacept group were in chronic kidney disease stage 1 or 2 compared with the CyA control group. Thus, these results are suggestive that belatacept's favorable impact on graft function is maintained over time.

Importantly, patient- and death-censored graft survival was high and comparable in both groups. In an elegant analysis, Schnitzler *et al.* [9] computed a model of survival prediction from early kidney function in a large registry cohort. From this analysis, they predicted that belatacept would lead to an increase in graft survival of 5 to 7.1% at 9 years after transplantation. As the present study was not powered to detect such a small survival difference between the two cohorts, our findings need to be interpreted with caution and cannot rule out a survival benefit. However, the graft survival of 71% at 10 years that was observed with both belatacept and CyA was remarkably high and points to the fact that patients enrolled in the phase II trial were highly selected and are not representative of the standard case mix treated in most transplant centers. Similar graft survival with belatacept was also described in a recent single-center report [19]. Thus, we think that projections regarding graft survival that are based on graft function observed in such selective cohorts need to be interpreted with extra caution when extrapolated to the "average" transplant recipient.

We observed substantially more BPAR within 6 months in patients treated primarily with CyA compared with the study group, which is probably related to the fact that induction therapy was not standard of practice at our center at that time [20,21]. The rejection rate in the belatacept group was lower than the range observed in the BENEFIT trial (17–22%), but higher than the ones seen in the phase II trial (6–7%). Current standard regimens used at our and many other centers rely on tacrolimus and basiliximab induction, leading to substantially lower rejection rates than the one observed in the historical CyA cohort. Whether such a regimen would indeed lead to different survival rates in similarly selected patients remains speculative at the present time. We noted a significantly lower proportion of DSA-positive patients at the end of the follow-up in patients in the belatacept group. These findings are in line with previous clinical and experimental observations underlining a potential protective role of costimulation blockade on alloantibody formation [3,4,22]. However, use of MMF after 5 years and of steroids after 5 and 10 years was significantly lower in the CyA group and may also have contributed to the higher percentage of DSA+ patients when compared to the belatacept group.

The incidence of malignancies was low and similar in both groups. However, regarding the retrospective nature of this analysis, underreporting may occur. One case of PTLD occurred with belatacept in an EBV-negative patient. PTLD is a major concern with belatacept especially in EBV-negative patients. Thus, belatacept was approved for EBV-positive patients only [23]. The intravenous administration was well tolerated and well accepted throughout the 10 years.

This study has several limitations, including its retrospective nature. Careful case matching was applied to mini-

mize problems inherent in retrospective analyses. Besides, the sample size of only 14 belatacept patients limits the study's statistical power. Despite these limitations, we think that the results from this case-matched study are of relevance as they suggest that the favorable impact of belatacept on kidney function is maintained in the long run and that they re-emphasize the need for actual data regarding long-term graft survival to definitively assess the drug's potential. As the number of patients needed to detect a 5% difference in graft survival with sufficient statistical power is prohibitive for the design of a randomized controlled trial, such data can only come from the retrospective analysis of adequate numbers of belatacept-treated patients, which is urgently needed.

To sum up, in the present study population, patients treated with belatacept demonstrated a patient/graft survival at 10 years post-transplant which was comparable to that of similarly selected CNI-treated patients. Larger studies with sufficient statistical power are necessary to definitively determine long-term graft survival with belatacept.

Authorship

CS: designed and performed the study, analyzed data, and wrote the paper. SM: designed and performed the study and analyzed data. GAB, RS, TS, BW, GB, FE and FM: collected data. FK: performed the statistical analysis. TW: designed the study, analyzed data, and wrote the paper.

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