Conversion From Calcineurin Inhibitors to Belatacept in HLA-sensitized Kidney Transplant Recipients With Low-level Donor-specific Antibodies

Camilo E. Ulloa, MD,[1,2,3] Dany Anglicheau, MD, PhD,[3] Renaud Snanoudj, MD, PhD,[3] Anne Scemla, MD,[3] Frank Martinez, MD,[3] Marc-Olivier Timsit, MD, PhD,[4] Christophe Legendre, MD, PhD,[3] and Rebecca Sberro-Soussan, MD[3]

Background. Belatacept could be the treatment of choice in renal-transplant recipients with renal dysfunction attributed to calcineurin inhibitor (CNI) nephrotoxicity. Few studies have described its use in patients with donor-specific antibody (DSA). **Methods.** We retrospectively evaluated conversion from CNIs to belatacept in 29 human leukocyte antigen-immunized renal-transplant recipients. Data about acute rejection, DSA, and renal function were collected. These patients were compared with 42 nonimmunized patients treated with belatacept. **Results.** Patients were converted from CNIs to belatacept a median of 444 days (interquartile range, 85-1200) after transplantation and were followed up after belatacept conversion, for a median of 308 days (interquartile range, 125-511). At conversion, 16 patients had DSA. Nineteen DSA were observed in these 16 patients, of which 11/19 were <1000 mean fluorescence intensity (MFI), 7/19 were between 1000 and 3000 MFI, and one was >3000 MFI. At last follow-up, preexisting DSA had decreased or stabilized. Seven patients still had DSA with a mean MFI of 1298 ± 930 at the last follow-up. No patient developed a de novo DSA in the DSA-positive group. In the nonimmunized group, one patient developed de novo DSA (A24-MFI 970; biopsy for cause did not show biopsy-proven acute rejection or microinflammation score). After belatacept conversion, one antibody-mediated rejection was diagnosed. The mean estimated glomerular filtration rate improved from 31.7 ± 14.2 mL/min/1.73 m^2 to 40.7 ± 12.3 mL/min/1.73 m^2 (P < 0.0001) at 12 months after conversion. We did not find any significant difference between groups in terms of renal function, proteinuria, or biopsy-proven acute rejection. **Conclusions.** We report on a safe conversion to belatacept in human leukocyte antigen-immunized patients with low DSA levels.

(*Transplantation* 2019;103: 2150–2156)

INTRODUCTION

Since Nankivell's groundbreaking report[1-3] showing that chronic allograft nephropathy was linked to calcineurin inhibitor (CNI) toxicity,[4] several strategies to limit this problem have been proposed, including CNI minimization or conversion to mTOR inhibitors or belatacept. About the early conversion to mTOR inhibitors, several studies have reported an increased risk of acute rejection and apparition of de novo donor-specific antibody (dnDSA).[5–10] About conversion to belatacept, the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXtended (BENEFIT-EX)[11–14]

Received 1 May 2018. Revision received 31 October 2018.

Accepted 2 November 2018.

[1] Nephrology Department, Clínica Alemana de Santiago – UDD, Santiago de Chile, Chile.

[2] Nephrology Service, Hospital Barros Luco de Santiago de Chile, Santiago de Chile, Chile.

[3] Service de Néphrologie – Transplantation rénale Adulte, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes Sorbonne Paris Cité, Paris, France.

[4] Service d'Urologie, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes Sorbonne Paris Cité, Paris, France.

The Renal Transplant Unit at Necker Hospital belongs to the Fondation Centaure and the Transplantex group, which supports a French research network on transplantation.

The authors declare no conflicts of interest.

C.E.U. participated in the acquisition, concept and design of the project, analysis and interpretation, and writing and final approval of the version to be published. R.S.-S. participated in the concept and design of the project, analysis and interpretation of the study, and final approval of the version to be published. D.A., R.S., A.S., F.M., and M.-O.T. participated in revising the study. C.L. participated in the concept, final approval of the version to be published, and revising the study.

Correspondence: Rebecca Sberro-Soussan, MD, Service de Néphrologie – Transplantation Adulte, Hôpital Necker Enfants-Malades, 149 Rue de Sèvres, 75015 Paris, France. (rebecca.sberro@aphp.fr).

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

ISSN: 0041-1337/18/10-2150

DOI: 10.1097/TP.0000000000002592

<zdoi;10.1097/TP.0000000000002592>

showed excellent results for graft function during long-term follow-up but a higher incidence of early acute rejection in the first year after transplantation. Recently, the last follow-up of the BENEFIT trials showed a 43% reduction in the risk of death or graft loss and a lower incidence of DSA between de cyclosporine-based group and the belatacept group.[15] In a conversion trial[16] from a CNI-based regimen to belatacept, Grinyó et al[16] showed a significantly better estimated glomerular filtration rate (eGFR) at both 1- and 2-year follow-ups without a significant incidence of acute rejection compared with a CNI-based regimen.

To the best of our knowledge, there are limited data on the conversion to belatacept in human leukocyte antigen (HLA)-sensitized patients with DSA at time of transplantation. A recent report[18] of 6 DSA kidney recipients who were converted to belatacept showed acceptable outcomes after one year.

We report our experience in 29 DSA-positive renal-transplant recipient (RTR), who were switched from a CNI-based regimen to belatacept. We studied the incidence of acute rejection, the course of apparition of dnDSA, and patients' renal function. We then compared this cohort to 42 non-HLA sensitized patients who were converted to belatacept during the same period.

MATERIALS AND METHODS

Study Population

This is a retrospective, single-center, controlled study performed at Necker Hospital in Paris, France. We included 29 RTR who were converted from a CNI to a belatacept-based therapy between February 2011 and March 2015. All patients signed their agreement to anonymous clinical recollection data in DIVAT (Données Informatisées et VAlidées en Transplantation) before transplant surgery. The conversion was always performed after a renal allograft biopsy. In both groups, the conversion to belatacept was based on biopsy findings of suspected CNI toxicity and moderate to severe chronic vascular lesions (Banff cv score > 2 and Banff ah score > 2) or moderate to severe interstitial fibrosis/tubular atrophy (IF/TA > 2) with allograft dysfunction (evolution <3 months) without other proven cause. In the DSA (+) group, all patients were known to bear anti-HLA DSA (mean fluorescence intensity [MFI] > 500) measured by single antigen bed assay (Luminex), in a pretransplant serum sample and at transplantation's day and at the day of belatacept convertion.

A control group included 42 DSA-negative patients (with panel reactive antibodies [PRA] < 10%) from the transplantant day to the belatacept conversion. These patients were converted to belatacept during the same period of time and were consecutively matched to the renal-transplant patients by sex and age. All patients were followed up for at least 6 months. DSA, renal function, and acute rejection occurrence data were collected at 3 months after the switch, each year thereafter, and at the last follow-up.

End Points

The primary end points of the study were the occurrence of biopsy-proven acute rejection (BPAR). Acute rejection was defined according to the International Banff classification.[20]

The secondary end points included renal allograft function (serum creatinine and eGFR by the Modification of Diet in Renal Disease formula), proteinuria, patient and graft survival at the last follow-up, and the development of DSA during the first 12 months after belatacept conversion.

Immunosuppressive Treatment Protocol and Conversion to Belatacept

All patients received an initial standard posttransplant CNI-based triple-drug immunosuppression therapy, including tacrolimus (through levels between 8 and 10 ng/mL before 3 months and 6 and 8 ng/mL thereafter) or cyclosporine (through levels between 150 and 200 ng/mL before 3 months and 100 and 150 ng/mL after 3 months); mycophenolate mofetil (mycophenolic acid [MPA]; 1 to 2 g/day); prednisone (tapered to 5 to 10 mg/day by 3-month posttransplant); and an induction with either ATG (Thymoglobulin, Lyon, France; 1.5 mg/kg/day by central venous catheter for 5 days) or Basiliximab (Simulect, Novartis, Switzerland; intravenous dose, 20 mg at day 0 and 4). Any patient had received desensitization therapy before or after kidney transplantation. All patients were confirmed to be Epstein-Barr virus seropositive. Belatacept was administered based on published protocols.[11–14] If the conversion was performed before 4-month posttransplantation, the dose of belatacept was 10 mg/kg every 2 week for 10 weeks and then 5 mg/kg every month. For late belatacept conversion, the patient received 5 mg/kg on days 1, 15, 29, 42, and 57 and every 28 days thereafter. Given the presumed high risk of rejection, the MPA was maximized if possible to 2 g/day. The CNI-tapering protocol was performed as follows: 50% at day 1, 25% at day 16, and stopped at day 30. Adverse events, such as infections and drug withdrawal, after conversion to belatacept were recorded until the last follow-up.

Biopsy Assessment

Biopsies were performed after conversion for acute allograft dysfunction or persistent proteinuria (>0.6 g/g).

Detection of Donor-specific Antibodies

Routine HLA-antibody monitoring was performed before transplantation, at day 0, at the day of belatacept conversion, at 3 months and annually after conversion, and at time of indication biopsy. The presence of circulating DSA was analyzed using single antigen flow bead assays (One Lambda, Canoga Park, CA; on the Luminex platform) in one central laboratory (Saint-Louis Hospital, Paris, France). The HLA typing of transplant recipients was performed using routine molecular biology techniques (Innolipa HLA typing kit, Innogenetics, Belgium). The identification of anti-class I (96 beads) and anti-class II (76 beads) HLA antibodies was performed by Luminex SA as recommended by the manufacturer (Luminex LABScreen Single Antigen; One-Lambda Inc, CA). The fluorescence of each bead was detected with a LABscan, and the mean intensity of fluorescence (MFI) was recorded. The histocompatibility laboratory, consider positive, all beads showing a normalized MFI of >500. All these patients had negative complement-dependent cytotoxicity crossmatch on the transplant day. As the histocompatibility French program propose, only the living donor kidney transplant were tested with flow-crossmatch. No patient received desensitization protocols.

Statistical Analysis

Continuous variables were expressed as means and SD (normally distributed continuous variables) or medians

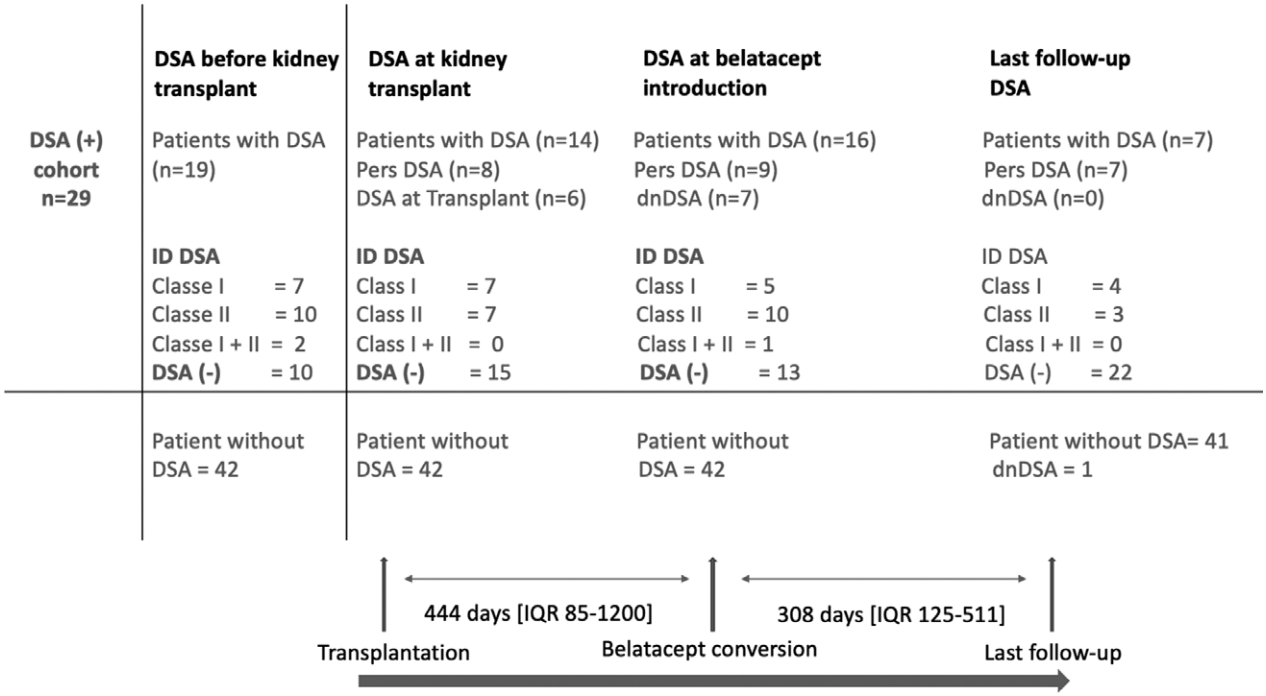

FIGURE 1. Immunological characteristics. Donor-specific antibody (DSA) presence at transplantation, belatacept conversion, and at last follow-up. Anti-HLA DSA-positive patients (upper quadrant) and anti-HLA–negative patients. dnDSA, de novo DSA; ID DSA, immunodominant DSA; IQR, interquartile range; PersDSA, patients with persistent DSA.

and interquartile ranges (not normally distributed continuous variables). The nominal variables were expressed by count and percentages. Statistical analyses were performed using Prism v.5, GraphPad Software, Inc. A paired *t* test or *t* test was used for parametric variables, and the Mann-Whitney test was used for nonparametric variables. For nominal variables, Fisher exact test was used. A P value < 0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

We included 29 DSA-positive RTRs, who had positive anti-HLA DSA before belatacept introduction. Because of the fluctuant nature of the HLA antibodies, the titer of DSA was not the same during the observation period. Before kidney transplant, 19 patients had a DSA. In this group of 19 patients, we observed 26 DSA, of which 21/26 had a MFI < 1000, 3/26 were between 1000 and 3000 MFI, and 2/26 were > 3000 MFI. In 7 of 19 patients, the immunodominant DSA was class I, 10/19 class II, and 2/19 class I and II. At transplantation, 17 DSA were observed in 14 patients. Nine DSA had a MFI < 1000, 7/17 were between 1000 and 3000 MFI, and one was > 3000 MFI. At transplantation, 8/14 patients had a persistent DSA. We observed 4 new patients, with DSA at day 0 and 2 patients who had DSA before transplantation but acquired a different one at day 0. In 7 of 14 patients, the immunodominant DSA was class I. At belatacept introduction, 16 patients had a DSA, of which 9/16 were persistent DSA from transplantation's day or before. Seven patients had a dnDSA before belatacept was indicated. Nineteen DSA were observed in these 16 patients of which 11/19 DSA were <1000 MFI, 7/19 were between 1000 and 3000 MFI, and 1/19 was >3000 MFI. In 5 of 16 patients, the immunodominant DSA was class I, 10/16 class II, and 1/16 class I and II. The immunological characteristics of the observation period of the patients are summarized in **Figure 1** and (**Table S1, SDC**, http://links.lww.com/TP/B668).

The demographics characteristics of the patients are summarized in **Table 1**. In DSA (+) group, the median patient age was 58.5 ± 13.7 years, and the patients were predominantly men (n = 20). Four patients received a second transplant (13.8%). The mean calculated panel reactive antibodies (cPRA) was 22.5 ± 37.9%. Before belatacept initiation, 24 patients (82.8%) received tacrolimus, 3 patients (10.3%) received cyclosporin, and 2 patients (6.9%) received everolimus-based therapy. Patients were converted to belatacept at a median of 444 days (interquartile range, 85 to 1200) after transplantation and were followed up after belatacept conversion, for a median of 308 days (interquartile range, 125 to 511). The patients were compared with a control group of 42 DSA-negative patients (mean cPRA was 3.1 ± 15.1%). There were no significant differences between the groups except for the IF/TA grade on biopsy before the conversion to belatacept.

Primary Outcome: BPAR and Immunologic Outcomes of DSA-positive Patients Converted to Belatacept

One patient (3.4%) in the DSA-positive group presented a mix antibody-mediated rejection (AMR) at 120 days after the conversion (the Banff score was g_1 ptc_2 t_1 ti_2 v_0), but with no DSA identified (patient *5*, **Table S1, SDC**, http://links.lww.com/TP/B668). He was treated with methylprednisolone boluses, 5 sessions of plasmapheresis, 4 monthly intravenous immunoglobulin perfusions, and converted back to a tacrolimus-based immunosuppressive therapy. We did not observe any T cell-mediated rejection (TCMR) in this group.

In the DSA (–) group, we observed 2 BPAR (1 AMR and 1 TCMR). One severe DSA-negative mix AMR (Banff

TABLE 1.

Basal characteristics of HLA—sensitized DSA (+) and DSA (–) patients

Basal characteristics	Total cohort (n = 71)	DSA (+) (n = 29)	DSA (–) (n = 42)	*P*
Age, y, mean (±SD)	57.7 ± 13.7	58.5 ± 13.7	57.2 ± 13.9	0.7
Gender, M (%)	50 (70.4)	20 (69)	30 (71.4)	1.0
Pretransplant dialysis duration, y, mean (±SD)	3.1 ± 2.6	3.2 ± 2.7	3.0 ± 2.6	0.78
Transplantation rank = 1, n (%)	61 (85.9)	25 (86.2)	36 (85.7)	1.0
Deceased donor, n (%)	60 (84.5)	25 (86.2)	35 (83.3)	1.0
Donor age, y, mean (±SD)	64.4 ± 13	62.9 ± 14.2	65.4 ± 12.3	0.43
Cold ischemia time, min, mean (±SD)	1186 ± 616	1277 ± 599.1	1123 ± 1050	0.3
Delayed graft function, n (%)	25 (35.2)	13 (44.8)	12 (28.6)	0.21
cPRA, %, mean (±SD)	11 ± 28.3	22.5 ± 38	3.1 ± 15.1	0.001
Time for belatacept conversion, days, median (IQR)	396 (87-1260)	444 (85-1200)	321 (84-1295)	0.93
Follow-up after belatacept, days, median (IQR)	364 (165-701)	308 (125-511)	442 (209-707)	0.14
ah > 2, n (%)	58 (81.7)	24 (82.8)	34 (81)	0.87
cv > 2, n (%)	47 (66.2)	20 (69)	27 (64.3)	0.15
IF/TA > 2, n (%)	36 (50.7)	10 (34.5)	26 (61.9)	0.03
Immunosuppression before belatacept, n (%)				
Tacrolimus (Prograf)	58 (81.7)	24 (82.8)	34 (81)	0.85
Cyclosporin (Neoral)	9 (12.7)	3 (10.3)	6 (14.3)	0.62
Everolimus (Certican)	4 (5.6)	2 (6.9)	2 (4.7)	1.0

Basal characteristics of HLA—sensitized DSA (+) and DSA (–) patients and total cohort. Delayed graft function was defined by need for dialysis up to 1 wk after transplantation. Time for belatacept conversion was the period in days between the transplant day and the first administration of belatacept. Banff scores on the biopsy performed before the switch to belatacept. AH, arteriolar hyalinosis; cPRA, calculated panel reactive antibodies; CV, chronic vascular changes (arteriosclerosis); DSA, donor-specific antibody; IF/TA, interstitial fibrosis/tubular atrophy.

score g_1 ptc_3 v_3 t_3 i_3) was observed in a young woman who missed belatacept infusion during 2 months. She returned to a tacrolimus-based immunosuppressive therapy after AMR treatment. Two years after, in the last control, she had a serum creatininemia (Scr) 176 mmol/L, a proteinuria index of 1.2 g/g and no DSA was detected.

We observed a clinical relevant TCMR (Banff score g_0 ptc_0 t_3 i_2), in a 55 years old woman who presented a severe delayed graft function, after a postbiopsy hemorrhagic shock complicated with septic shock. A minimization of the immunosuppression was prescribed before the belatacept conversion. At the 3-month posttransplant protocol biopsy, we observed an acute graft dysfunction (Scr at biopsy of 96 mmol/L from a baseline Scr of 56 mmol/L). She was treated with methylprednisolone boluses and prednisone tapering thereafter with good results. The DSA remained negative at last follow-up.

At time of belatacept conversion, 16/29 patients still had circulating DSAs with a mean MFI of 1037 ± 694. At last follow-up, 7/29 patients had persistent and stable circulating DSAs, with a mean MFI of 1298 ± 930. Among them, 6 DSA had MFI < 1000, 3 had MFI between 1000 and 3000, and 1 patient had MFI > 3000. In the DSA (+) group, no patient developed dnDSA after belatacept conversion (**Figure 1**). One patient (2.4%) in the DSA-negative group developed an anti-class I dnDSA with a low MFI of 970 at the last follow-up.

Secondary Outcomes: Patient and Graft Survival, Renal Function, Proteinuria, in DSA-positive Patients Converted to Belatacept

On the entire cohort 2 patients (2/71; 2.8%) died, one for suddenly of cardiovascular cause and one of suicide. We did not observe any significant differences between groups in terms of death (1 death in each group).

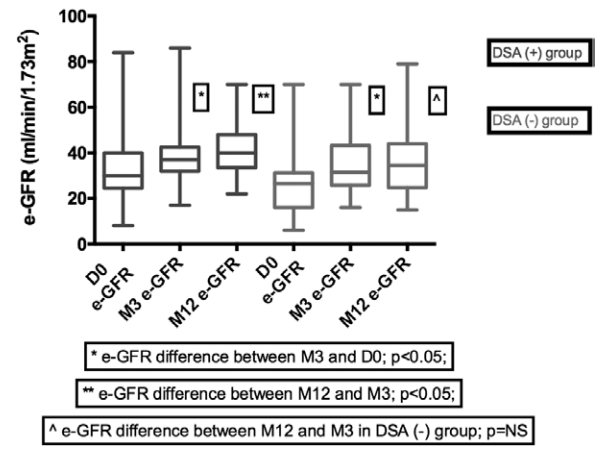

FIGURE 2. eGFR before and after belatacept (at M3 and M12). DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; NS, not significant.

One year after the belatacept conversion, no graft loss was observed. The mean Scr improved from 212 ± 120.2 mmol/L to 168.9 ± 59.2 mmol/L and 161.2 ± 59.3 mmol/L at 3 and 12 months, respectively. The mean eGFR improved from 31.7 ± 14.2 mL/min/1.73 m^2 to 40.7 ± 12.3 mL/min/1.73 m^2 ($P < 0.0001$) at 12 months. The greatest improvement occurred during the first 3 months (Figure 2). The mean proteinuria remained stable over time with a median value g/g at time of belatacept conversion, 0.2 g/g ($P = 0.51$) at 3 months after conversion and 0.3 g/g at 1 year ($P = 0.44$). There was no difference in renal function or proteinuria between the DSA-positive and DSA-negative groups at 3 or 12 months. The comparison between the 2 groups is summarized in Table 2.

TABLE 2.

Comparison of clinical outcomes between HLA—sensitized DSA (+) and DSA (–) patients

Results	Total cohort, n = 71	DSA (+) patients, n = 29	DSA (–) patients, n = 42	*P*
Day 0 Scr, mmol/L, mean ± SD	241.1 ± 140	212.1 ± 120.2	271.2 ± 161.3	0.09
M3 Scr, mmol/L, mean ± SD	176.9 ± 65.3	168.9 ± 59.2	182.4 ± 69.4	0.34
M3 proteinuria index, g/g, median (IQR)	0.46 ± 0.6	0.2 (0.1-0.55)	0.25 (0.165-0.35)	0.51
M12 Scr, mmol/L, mean ± SD	170.8 ± 69	161.2 ± 59.3	177.1 ± 75.2	0.35
M12 proteinuria index, g/g, median (IQR)	0.39 ± 0.65	0.3 (0.1-0.37)	0.25 (0.1-0.33)	0.44
de novo DSA after conversión, n (%)	1 (1.4)	0	1 (2.4)	1.0
Death, n (%)	2 (2.8)	1 (3.4)	1 (2.4)	1.0
Graft loss, n (%)	4 (5.6)	0	4 (9.5)	0.14
Belatacept withdrawal, n (%)	10 (14.1)	3 (10.3)	7 (16.7)	0.51

Comparison of clinical outcomes between HLA—sensitized DSA (+) and DSA (–) patients, at day 0 of belatacept, at M3 and M12 postbelatacept. Mean Scr (mmol/L) and proteinuria index (g/g). DSA, donor-specific antibody; IQR, interquartile range; Scr, serum creatininemia.

Complications and Belatacept Withdrawal

In the DSA-positive group, no patient developed severe infection (bacterial, fungicidal, or viral cause). Three patients discontinued belatacept: 1 for AMR, 1 for personal reasons, and 1 for a cutaneous Kaposi sarcoma. Seven patients discontinued belatacept in the DSA-negative group: 4 graft function loss, 1 Kaposi disease, 1 cytomegalovirus (CMV) chorioretinitis, and 1 nephrotic syndrome due to segmental focal glomerular sclerosis. The median delay of belatacept withdrawal was 282 days (Q_{25-75}, 173.5 to 597.5). In several cases, the belatacept indication was chosen as a "rescue therapy" to improve or to keep a baseline poor graft function. Among the 4 patients who lost their graft, 2 were converted to belatacept as a rescue therapy. They had a primary graft dysfunction, with a baseline Scr of 597 and 543 mmol/L, respectively. Their Banff graft biopsy prebelatacept showed, no microinflammation lesions, but moderate or severe chronic vascular and tubule-interstitial lesions, IF/TA_2 cv_2 ah_2 c4d (–) and IF/TA_0 cv_3 ah_2. Belatacept was introduced at 2 months after transplantation in both cases. Unfortunately, these patients did not improve their clinical condition and returned to dialysis 1 year and 9 months after belatacept, respectively.

The other graft loss was a women that were not compliant to belatacept treatment (the case was described in the primary outcome section). This patient had a baseline Scr of 255 mmol/L and was reconverted to classical therapy (tacrolimus, MPA, and steroids). At last follow-up, the Scr was 176 (35 mL/min/1.73 m^2) mmol/L with a proteinuria of 1.2 g/g.

The last patient, who lost his graft, had severe vascular and tubulointerstitial lesion without AMR or CAMR signs, who was converted to belatacept as a intent to improve his clinical condition without any result. His baseline Scr was 238 µmol/L. At one year after belatacept switch, the SCr was 268 µmol/L. For these reason, belatacept was stopped (**Table S1, SDC**, http://links.lww.com/TP/B668).

DISCUSSION

Our data suggest that conversion from a CNI-based therapy to belatacept is safe in patients with low-level DSAs. Only 1 out of 29 patients experienced an AMR. At last follow-up, all preexisting DSA had disappeared or remained stable. One patient in the DSA-negative group developed low level, dnDSA after belatacept conversion. These results are consistent with the incidence noted about dnDSA in the literature. In a recent meta-analysis published by Masson et al,[22] no difference was observed in dnDSA (relative risk [RR], 0.41; 95% confidence interval [CI], 0.01-1.31) between RTRs receiving belatacept or CNI. In the latest long-term results of the BENEFIT study,[15] the cumulative event rate for the development of DSA at 7 years was <20%. In our study, we observed 5 BPAR (7%) after conversion in the whole cohort. Our results are concordant with a previous conversion trial[16] from CNI-based therapy that found a 5% BPAR incidence in the belatacept group. As well as in the study of Gupta et al[18] that shows a low frequency of BPAR. In the study of Elhamahmi[32] in a low immunological risk population (the study excluded patients with preformed DSA with MFI > 1000), the conversion to belatacept in patients with low renal function was correlated with similar incidence of BPAR.

Belatacept is a selective inhibitor of the CD28-CD80/86 pathway.[23-25] The preventive effect on acute rejection may theoretically be explained by its actions on regulatory T cells and the interruption of the Tfh (IL-21$^+$CXCR5$^+$follicular T-helper)—B-cell interaction.

Both interleukin (IL)-2 and CD28-CD80/CD86 signaling pathways are critical for CD4$^+$CD25$^+$FOXP3$^+$ regulatory T cells survival in mice, as showed Bluestone et al,[26] in an ancillary study of the BENEFIT trial. In this study, belatacept-treated patients had a significantly greater number of FOXP3$^+$ T cells in graft biopsies during acute rejection compared with CNI-treated patients. This effect on the local alloimmune milieu could explain the lower acute rejection rate.

In animal transplant models, belatacept or abatacept (CTLA4 immunoglobulin), inhibited germinal center formation, clonal B-cell expansion, IL-21 production, and the development of DSA.[27] However, in a recent published article when belatacept was compared with tacrolimus, donor antigen-driven Tfh-B-cell crosstalk was similar in patients who were treated with belatacept or tacrolimus.[28]

Conversion to belatacept is a new alternative to mTOR-inhibitors conversion in sensitized patients with CNI toxicity. In these patients, the conversion to an mTOR-based therapy may be unsafe because of the immunologic risk (preformed DSA, preexistent acute rejection episodes, a significant propensity to new acute rejection, and a low GFR or significant proteinuria). In the present study, we tried to show "the real life use" of belatacept in a group

of patients with allograft dysfunction or in many "rescue" cases. We explain this mediocre allograft function by principally moderate/severe vascular lesions and interstitial fibrosis/tubular atrophy in the prebelatacept allograft biopsy. For these reasons, the dropout rate was 14.1% (10/71 patients of the entire cohort). Nevertheless, in the literature, the mTOR inhibitors had a described range of dropout rate of 30% to 40%.[29,30]

Renal function improved in both groups. This significative observation can be explained by the absence of the acute nephrotoxic effect of the CNI.[31] Tacrolimus and cyclosporin blood levels are fluctuants and have a moderate correlation with nephrotoxic effect (many patient can have "normal level" but present tremor or allograft dysfunction) or with the patient compliance. The complexity to evaluate a representative CNI blood level (eg, isolated? Mean of 2, 3, more month?) would invalidate the data itself. We believe the eventual effect of permanent high levels of CNI, may be not relevant to the study purpose, because these patients are frequently controlled and protocol-adjusted blood levels.

The DSA-positive patients had an improvement in renal function and a low frequency of BPAR. Despite the small cohort of patients and the retrospective nature of the analysis, the selection bias possibility, the absence of power calculation and the type-2 risk error, the data presented here may provide new insights about the characteristics of patients who can be converted to belatacept. We think that our experience is relevant—despite the relatively low immunological risk profile of our cohort—and strengthens the BENEFIT trial that was attempted in nonsensitized cohort and compared against cyclosporine. This study is concordant with others that reported similar longitudinal allograft failure compared with tacrolimus-based regimens.[23-34] However, we must be aware of glucocorticoid-resistant cytotoxic memory T cells–mediated rejection in belatacept-treated patients.[35]

Gupta et al[18] reported the safe belatacept conversion in 6 DSA-positive RTRs. In a recent published article, Dürr et al[18] showed in 70 kidney transplant patients no AMR and only 1 patient who developed dnDSA. All patients in our cohort had a DSA of <3000 MFI. In patients with high levels of DSA, the conversion has to be evaluated carefully, and additional studies are required.

In conclusion, we report a safe conversion to belatacept in transplant recipients with low-MFI DSA. We do not observe significant differences in BPAR occurrence, renal function, or DSA apparition compared with a low-risk group. Because the above-noted limitations, future prospective studies with larger cohorts and longer follow-up periods are of course needed to further validate these observations.

REFERENCES

1. Nankivell BJ, Borrows RJ, Fung C, et al. The natural history of chronic allograft nephropathy. *N Engl J Med*. 2003;349:2326–2333.
2. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. *Am J Transplant*. 2009;9:527–535.
3. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12:388–399.
4. English J, Evan A, Houghton DC, et al. Cyclosporine-induced acute renal dysfunction in the rat. Evidence of arteriolar vasoconstriction with preservation of tubular function. *Transplantation*. 1987;44:135–141.
5. Lim WH, Eris J, Kanellis J, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant*. 2014;14:2106–2119.
6. Bemelman FJ, De Maar EF, Press RR, et al. Minimization of maintenance immunosuppression early after renal transplantation: an interim analysis. *Transplantation*. 2009;88:421–428.
7. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. *Am J Transplant*. 2011;11:1633–1644.
8. Sharif A, Shabir S, Chand S, et al. Meta-analysis if CNI sparing regimens in kidney transplantation. *J Am Soc Nephrol*. 2011;22:2107–2188.
9. Liefeldt L, Brakemeier S, Glander P, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. *Am J Transplant*. 2012;12:1192–1198.
10. Rostaing L, Hertig A, Albano L, et al. Fibrosis progression according to epithelial-mesenchymal transition profile: a randomized trial of everolimus versus CsA. *Am J Transplant*. 2015;15:1303–1312.
11. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant*. 2010;10:535–546.
12. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant*. 2010;10:547–557.
13. Rostaing L, Vincenti F, Grinyó J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. *Am J Transplant*. 2010;13:2875–2883.
14. Charpentier B, Medina Pestana JO, del C. Rial M, et al. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. *Am J Transplant*. 2013;13:2884–2891.
15. Vincenti F, Rostaing L, Grinyó J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374:333–343.
16. Grinyó J, Alberu J, Contieri F, et al. Improvement in renal function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study. *Transplant Int*. 2012;25:1059–1064.
17. Deleted in proof.
18. Gupta G, Regmi A, Kumar D, et al. Safe conversion from tacrolimus to belatacept in high immunologic risk kidney transplant recipients with allograft dysfunction. *Am J Transplant*. 2015;15:2726–2731.
19. Deleted in proof.
20. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*. 2014;14:272–283.
21. Deleted in proof.
22. Masson P, Henderson L, Chapman JR, et al. Belatacept for kidney transplant recipients, review. *Cochrane Database Syst Rev*. 2014;11:CD010699.
23. Malvezzi P, Jouve T, Rostaing L. Costimulation blockade in kidney transplantation: an update. *Transplantation*. 2016;100:2315–2323.
24. Shiao SL, McNiff JM, Masunaga T, et al. Immunomodulatory properties of FK734, a humanized anti-CD28 monoclonal antibody with agonistic and antagonistic activities. *Transplantation*. 2007;83:304–313.
25. Dengler TJ, Szabo G, Sido B, et al. Prolonged allograft survival but no tolerance induction by modulating CD28 antibody JJ319 after high-responder rat heart transplantation. *Transplantation*. 1999;67:392–398.
26. Bluestone JA, Liu W, Yabu JM, et al. The effect of costimulatory and interleukin 2 receptor blockade on regulatory T cells in renal transplantation. *Am J Transplant*. 2008;8:2086–2096.
27. Larsen CP, Pearson TC, Adams AB, et al. Rational development of LEA29Y (belatacept), a high-affinity variant of CTLA4-Ig with potent immunosuppressive properties. *Am J Transplant*. 2005;5:443–453.
28. de Graav RN, Hesselink DA, Dieterich M, et al. Belatacept does not inhibit follicular T cell-dependent B-cell differentiation in kidney transplantation. *Front Immunol*. 2017;8:641.
29. Stallone G, Infante B, Grandaliano G, et al. Management of side effects of sirolimus therapy. *Transplantation*. 2009;87(Suppl 8):S23–S26.
30. Heilman RL, Younan K, Wadei HM, et al. Results of a prospective randomized trial of sirolimus conversion in kidney transplant recipients on early corticosteroid withdrawal. *Transplantation*. 2011;2011:19.
31. Guba M, Pratschke J, Hugo C, et al. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal

transplant patients: one-year analysis of a randomized multicenter trial. *Transplantation*. 2010;90:175–183.
32. Abdelwahab Elhamahmi D, Heilman RL, Smith B, et al. Early conversion to belatacept in kidney transplant recipient with low glomerular filtration rate. *Transplantation*. 2018;102:478–483.
33. Cohen JB, Eddinger KC, Forde KA, et al. Belatacept compared with tacrolimus for kidney transplantation: a propensity score matched cohort study. *Transplantation*. 2017;101:2582–2589.
34. Darres A, Ulloa C, Brakemeier S, et al. Conversion to belatacept in maintenance kidney transplant patients: a retrospective multicenter European study. *Transplantation*. 2018;102:1545–1552.
35. de Graav GN, Hesselink DA, Dieterich M, et al. An acute cellular rejection with detrimental outcome occurring under belatacept-based immunosuppressive therapy: an immunological analysis. *Transplantation*. 2016;100:1111–1119.