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BRIEF COMMUNICATION**Belatacept in renal transplant recipient with mild immunologic risk factor: A pilot prospective study (BELACOR)**

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The benefit of belatacept on antibody-mediated rejection (ABMR) incidence after kidney transplant with preformed donor-specific antibodies (DSAs) has never been assessed. Between 2014 and 2016, we conducted a multicenter prospective clinical trial with 49 patients to determine kidney allograft outcome in recipients with preformed DSAs (maximal mean fluorescence intensity 500 to 3000) treated with belatacept (BELACOR trial). Immunosuppressive strategy included antithymocyte globulin, belatacept, mycophenolate mofetil, and steroids. An ancillary control group was designed retrospectively, including patients fulfilling the same inclusion criteria treated with calcineurin inhibitors. In BELACOR group, no patient exhibited acute ABMR, patient and allograft survival at 1 year was 100% and 95.4%, respectively, and the estimated glomerular filtration rate was 53.2 mL/min/1.73 m². However, the 12-month incidence of acute T cell-mediated rejection was 25.4% (14.5% to 42.4%). Comparison with the control group showed significantly higher T cell-mediated rejection incidence only in the BELACOR group ($P = .003$). Considering the DSAs, the

Abbreviations: ABMR, antibody-mediated rejection; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; dnDSA, de novo donor-specific antibody; DSA, donor-specific antibody; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; MFI, mean fluorescence intensity; MMF, mycophenolate mofetil; SAE, serious adverse event; TCMR, T cell-mediated rejection.

Claire Leibler and Marie Matignon contributed equally to the manuscript.

outcome was similar in the 2 groups except a significantly higher number of patients displayed a complete disappearance of class II DSAs in the BELACOR group ($P = .001$). Belatacept was not associated with an acute ABMR increased risk and may be considered as immunosuppressive strategy in transplant recipients with preformed DSAs (maximal mean fluorescence intensity 500 to 3000). Prospective randomized trials are needed to confirm these results.

KEYWORDS

antibody-mediated (ABMR), belatacept, clinical research/practice, clinical trial, immunosuppressant - fusion proteins and monoclonal antibodies, immunosuppression/immune modulation, kidney transplantation/nephrology, panel reactive antibody (PRA), rejection

1 | INTRODUCTION

One of the main goals after kidney transplant is avoidance of antibody-mediated rejection (ABMR), the leading cause of allograft loss.¹ ABMR is likely to occur in sensitized kidney allograft recipients with anti-HLA donor-specific antibodies (DSAs) before and after (de novo DSA [dnDSA]) transplant.² The growing number of sensitized patients before transplant has become a major challenge. Currently, the incidence is up to 30%-40% of the transplant candidates.³

Numerous strategies to improve access to kidney transplant of sensitized recipients with preformed anti-HLA DSAs have been developed, including specific graft allocation policies⁴ and immunosuppressive protocols that attempt to remove antibodies.⁵ Those protocols involved antibody clearance using apheresis (immunoadsorption or plasmapheresis),⁵ B cell-modulating therapies (high dose of intravenous immunoglobulin or rituximab)⁵ or plasma cell depletion (bortezomib),⁵ complement inhibition (eculizumab)⁵ and, more recently, IgG-inactivating agents.⁶ The principal limitation of those strategies is the high prevalence of acute and chronic ABMR (up to 30%) early after transplant associated with poor allograft survival.^{5,6} In kidney allograft recipients with preformed DSAs, induction therapy with antithymocyte globulin is strongly recommended.⁷ However, no prospective randomized clinical trial aiming to define the best maintenance immunosuppressive therapy in this immunological context is available.

Belatacept (cytotoxic T-lymphocyte-associated antigen 4 [CTLA4]-Ig) is a costimulation blocker approved by the US Food and Drug Administration in June 2011 to prevent acute rejection in kidney transplant recipients displaying a low immunological risk (BENEFIT trials).⁸ In the 7-year follow-up, recipient and kidney allograft survivals after transplant were significantly better in the belatacept group compared with the calcineurin inhibitors (CNIs) group, and the incidence of dnDSAs within 7 years was significantly lower in belatacept-treated recipients.⁹ This clinical result is in accordance with former experimental data showing that belatacept inhibits T cell-dependent antibody production.¹⁰ The combined blockade of CD28:B7 and CD40:40L pathways can suppress DSA formation

in kidney-transplanted macaques.¹¹ Belatacept or anti-CD40 murine antibody with lymphodepletion could also suppress the humoral immune response and prevent ABMR.¹² Delayed introduction of CTLA4-Ig in animal allograft models collapsed the allospecific germinal center B and inhibited alloantibody production.¹³ Moreover, CTLA4-Ig was able to constrain B cell responses and heart rejection in sensitized mice.¹⁴ Taken together, these clinical and experimental results suggest that belatacept may be widely responsible for lower immune humoral responses in kidney transplant recipients.

So far, the potential benefit of belatacept on the incidence of ABMR after kidney transplantation in sensitized recipients with preformed DSAs has never been assessed. We present here the results of the first multicenter open clinical trial aiming to determine the impact of belatacept-based maintenance immunosuppressive therapy in kidney transplant recipients with preformed DSAs on the acute ABMR 12-month incidence. Results were compared with results observed in an ancillary control group that included patients fulfilling the same inclusion criteria and treated with CNIs.

2 | PATIENTS AND METHODS

2.1 | Study design

We conducted a single-arm, multicenter (CHU Henri Mondor, CHU Kremlin Bicêtre, CHU Tenon, and Assistance-Publique-Hôpitaux de Paris, France) clinical trial (the BELACOR trial) between September 2014 and September 2017. The inclusion period was 24 months from September 2014, and all patients were followed for 12 ± 3 months after transplant. All kidney transplant recipients >18 years old with preformed DSAs and maximal mean fluorescence intensity (MFI_{max}) between 500 and 3000 within 1 year of a previous transplant were included.

Exclusion criteria were as follows: idiopathic focal segmental glomerulosclerosis, cold ischemia time >30 hours, belatacept contraindication (negative recipient Epstein-Barr virus [EBV] serology), thymoglobulin, steroids, mycophenolate mofetil (MMF) or high-dose intravenous Ig contraindications or allergy, no active contraception

for women, pregnancy or breastfeeding, acute infections (bacterial or viral), and uncontrolled psychosis.

All patients gave personally signed and dated written informed consent before completing any study-related procedure. The study protocol was approved by the French National Drug Security Authority (Agence Nationale de Sécurité du Médicament) and the institutional review board of Bicêtre Hospital (CPP Ile-de-France VII). The study was an investigator-initiated trial (Ph. Grimbert, MD, principal investigator) and was designed, conducted, and evaluated solely by the investigators after approval by Bristol-Myers-Squibb.

An ancillary control group was built retrospectively. Control patients had the same inclusion and exclusion criteria as the patients in the BELACOR trial except for EBV serology. All kidney allograft recipients engrafted between January 2013 and March 2017 with pretransplant DSAs who fulfilled the inclusion criteria were included in the study. A signed consent for participation was obtained from all patients included in the control group (IRB No. 00003835).

2.2 | Study endpoints

The primary endpoint was the response rate defined by no acute ABMR according to BANFF 2011 criteria within 12 months after transplant.¹⁵ Secondary endpoints were (1) subclinical ABMR incidence on protocol biopsies performed at months 3 and 12, (2) patient and allograft survival at 12 months, (3) estimated glomerular filtration rate (eGFR)¹⁶ and proteinuria:creatinine ratio (mg/mmol) at months 3 and 12, (4) clinical and subclinical T cell-mediated rejection (TCMR) frequency at months 3 and 12, and (5) preformed DSA outcome and dnDSA frequency at 12 months.

2.3 | Immunosuppressive therapy

All patients assigned to be treated with belatacept-based (Nulojix; Bristol-Myers Squibb Company, New York, NY) immunosuppression received doses as follows: 10 mg/kg at days 1 and 5 and at weeks 2, 4, 8, and 12 and then 5 mg/kg every 4 weeks. Induction therapy was thymoglobulin (Genzyme, Cambridge, MA) given as 3 mg/kg total dose over 4 days and steroids (methylprednisolone 500, 250, and 100 mg days 0-3). Maintenance therapy included MMF (2 g/d) and steroids (prednisone from day 4 at 20 mg/d tapered by 5 mg weekly to a final maintenance dose of 5 mg/d). MMF could be modified at physician discretion. Control group treatment was the same except for belatacept. CNIs could be cyclosporine or tacrolimus, and both could be modified at physician discretion.

2.4 | Procedures

Patients were included in the study at the time of transplant. At day 0, inclusion and exclusion criteria were assessed for each patient. Follow-up visits were scheduled at 3 months (M3) and 12 months (M12) after transplant. At M3 and M12, clinical data (eGFR and proteinuria), histological characteristics (kidney allograft biopsy), and DSA data were recorded in a standardized electronic case report

form (CleanWeb, Telemedicine Technologies [https://www.tentel-emed.com/]). Control group visits were similar, and all data were recorded retrospectively in our own database.

2.5 | Anti-HLA antibody screening

All sera before and after transplant (M3 and M12) were examined for the presence of circulating preformed DSAs and dnDSAs directed against donor HLA-A, HLA-B, HLA-Cw, HLA-DR, or HLA-DQ antigens by using high-resolution Luminex SAB assay technology (One Lambda, Inc., Canoga Park, CA) on a Luminex platform. All beads showing a normalized MFI >500 were considered positive.

2.6 | Histologic analysis

Protocol kidney allograft biopsies were performed 3 and 12 months after transplant, and specimens were analyzed as recommended according to Banff 2011 updated classification.¹⁵ Treatment of acute rejection episodes was decided by the physician. Acute ABMR episodes should be confirmed centrally by a trained pathologist (A.M.).

2.7 | Infectious prophylaxis

Participants with positive cytomegalovirus (CMV) serology before transplant or positive donors were treated with valganciclovir within 6 months after transplant. *Pneumocystis jiroveci* and *Toxoplasma gondii* prophylaxis included sulfamethoxazole/trimethoprim or pentamidine isetionate aerosol within the study.

2.8 | Statistical analysis

Sample size calculation was based on the single-arm trial design according to a Fleming 1-step plan. Response rate (no acute ABMR within 12 months) $\leq 80\%$ did not warrant further drug investigation, while response rate $\geq 90\%$ did warrant further investigation. With an α risk of .05 and β of .1, 83 patients were needed. Ancillary control group was based on an exhaustive retrospective recruitment of patients with pretransplant DSAs fulfilling inclusion criteria during the same period as the BELACOR group.

Analysis was performed according to the intent-to-treat principle. Categorical data are given as number (%), and continuous data are given as mean (SD) or median (quartile 1-quartile 3) as appropriate. Main and secondary endpoint analyses were based on modified intent-to-treat analysis including all patients except for early allograft loss (<7 days). Incidences of acute ABMR, TCMR, death, and allograft loss were expressed by using survival rate and 95% confidence interval (CI) according Kaplan-Meier methods. Survival rates and curves were compared according to group by using the log-rank test. Preformed DSA outcome, dnDSA frequency, histological data, and serious adverse events (SAEs) were expressed by using binomial proportions and 95% CI. Evolution analysis of preformed DSAs within the first year after transplant (before transplant, M3, and M12) used linear or logistic mixed models including repeated data.

Incidence and evolution of dnDSAs and histological data within the first year after transplant (M3 and M12) were analyzed by using the same methodology. Baseline characteristics, binary secondary endpoints (new-onset diabetes, CMV viremia, BK viremia) or continuous secondary endpoints (eGFR, proteinuria, and SAEs) were compared between groups. No interim analysis was planned.

The means and the proportion were compared by using Student *t* test or the Mann-Whitney *U* test and the χ^2 test or Fisher exact test. Paired means and proportions were compared by using the Wilcoxon signed-rank test and McNemar test. Values of $P < .05$ were considered statistically significant, and all tests were 2-sided. All analyses were performed using STATA version 15.0 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Patient characteristics

Fifty-one patients fulfilling the inclusion criteria were included in the BELACOR trial between September 2014 and September 2016, and 76 patients were included in the control group between

January 2013 and March 2017. The final sample size was finally reduced because the prespecified sample size of the belatacept group was not reached at the end of the scheduled inclusion period. The observed ABMR rate was lower than expected (0%; 95% CI 0%-7.25%). Therefore, despite the lower sample size than expected, the a posteriori power was satisfactory (90%). A flowchart of the patients included in the study is presented in Figure 1. In both groups, 2 patients were excluded before 1 week posttransplant because of allograft nephrectomy (vascular thrombosis), leading to 49 and 74 patients for the main modified intent-to-treat analysis in the BELACOR group and the control group, respectively. In the control group, 5 patients died within the first year after transplant, leading to 72 patients at the M3 follow-up point and 69 patients at the M12 follow-up point. Demographic and transplant characteristics in both groups are depicted in Table 1. Recipients and donors characteristics at the time of transplant were similar except for significantly more isolated class II anti-HLA DSA antibodies in the control group ($P = .02$) and more association of class I and class II in the control group ($P = .002$). Median class I and class II MFI_{max} values of preformed DSAs detected within 1 year before transplant were 957 (740-1911) and 1140 (753-1419), respectively, in the BELACOR

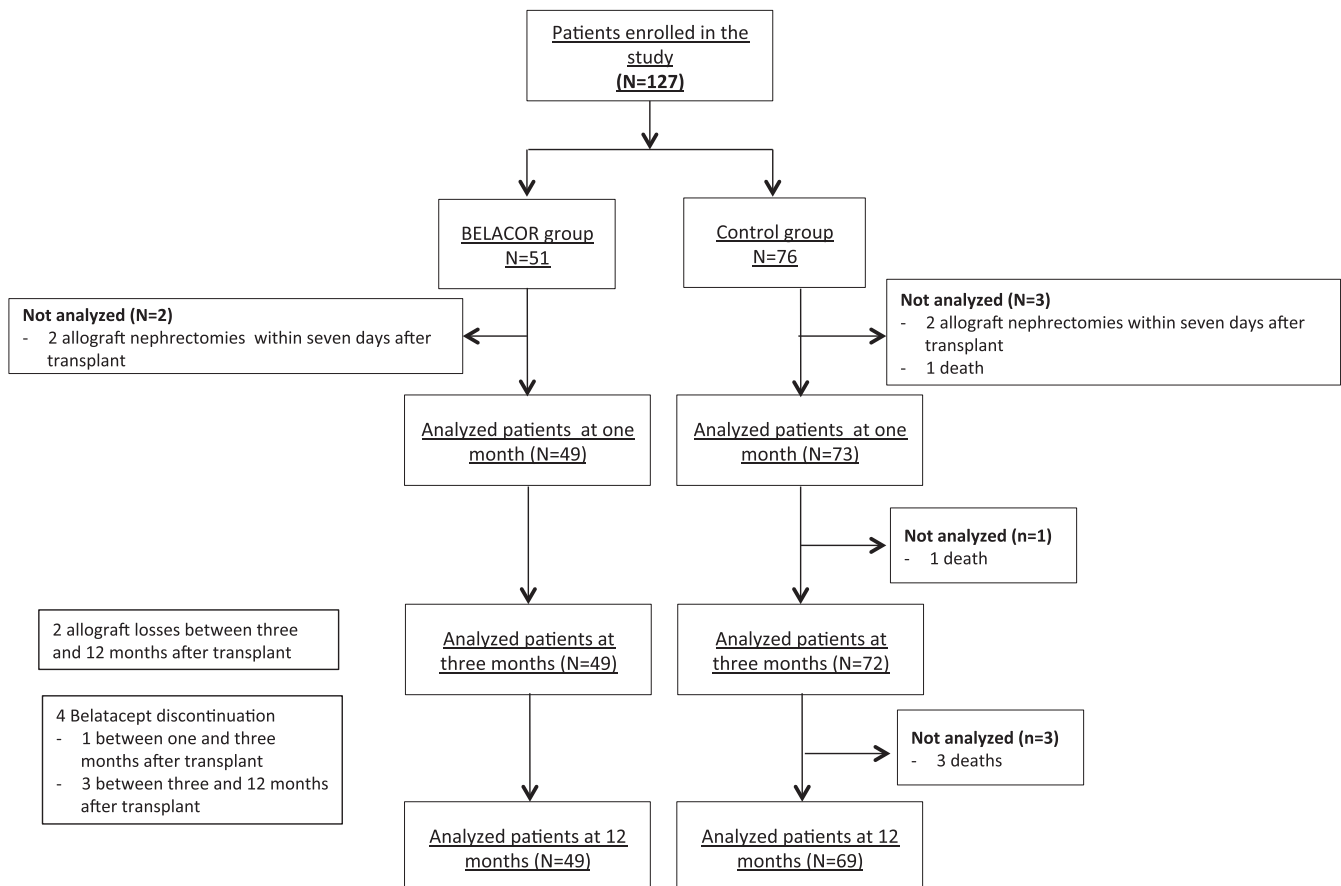


FIGURE 1 Flowchart of the patients included in the study. Fifty-one patients fulfilling inclusion criteria were included in the BELACOR trial between September 2014 and September 2016 and 76 patients were included in the control group between January 2013 and March 2017. In both groups, 2 patients were excluded before 1 week after transplant because of allograft nephrectomy (vascular thrombosis) leading to 49 patients and 74 patients for the main modified intent-to-treat analysis in the BELACOR group and the control group, respectively

TABLE 1 Patient and recipient characteristics

Variables	BELACOR group	Control group	P value ^a
Recipients, n	49	74	
Age, y, mean ± SD	51 ± 15	53 ± 14	.47
Sex, female, n (%)	15 (31)	28 (38)	.41
Dialysis, n (%)	41 (82)	65 (88)	.51
Dialysis duration, y, median [IQR]	3.6 [2.2-6.1]	4 [2.4-6.3]	.60
Initial nephropathy			
Immunological disease ^b , n (%)	9 (19)	18 (24)	
Nonimmunological disease ^c , n (%)	29 (59)	41 (56)	.74
Undetermined, n (%)	11 (22)	15 (20)	
HIV positive	4 (8)	3 (4)	.44
HCV negative	1 (2)	1 (1)	1.00
Donor			
Age, years, mean ± SD	57 ± 16	57 ± 14	.94
Living donor, n (%)	3 (6)	12 (16)	.09
Deceased donor, n (%)	46 (94)	62 (84)	
Sensitization			
Blood transfusions, n (%)	11 (22)	37 (50)	.002
Pregnancy, n (%)	10 (20)	24 (32)	.14
cPRA ^d %, median [IQR]	46 [27-72]	53 [12-79]	.74
>1 transplant, n (%)	4 (8)	12 (16)	.19
Anti-HLA donor-specific antibodies, n (%)			
Class I, n (%)	21 (43)	31 (42)	.92
Class II, n (%)	15 (31)	38 (51)	.02
Class I and class II, n (%)	13 (26)	5 (7)	.002
Crossmatch			
Flow cytometry, n	3	—	
B-crossmatch	1 (20)	—	
T-crossmatch	0 (0)	—	
Lymphocytotoxicity, n	48	—	
B-crossmatch	2 (4)	—	
T-crossmatch	0 (0)	—	
Kidney transplant			
Cold ischemia time, hours, median [IQR]	18 [14-20]	17 [15-24]	.52

HCV, hepatitis C virus.

^aComparison of secondary endpoints between the BELACOR group and control group χ^2 test or Fisher exact test for categorical variables and the Student t-test or Mann-Whitney U test for quantitative variables.

^bImmunological disease includes IgA nephropathy, Wegener granulomatosis, membranous nephropathy, focal and segmental glomerular sclerosis, HIV associated nephropathy, and systemic lupus.

^cNonimmunological disease includes uropathy, nephroangiosclerosis, autosomal dominant polycystic kidney disease, diabetic glomerulopathy, sickle cell disease, and tubulointerstitial kidney disease.

^dCalculated PRAs.

group (Table 2). Among those, 19 (37%) patients presented with MFImax >1000 and 32 (63%) presented with MFImax <1000. Distribution of DSAs in the BELACOR group was 34 for class I (69%) and 28 for class II (57%), and for class II–positive DSAs, 5 (17%) patients have DP antibodies. In the control group, class I and class II MFImax values of preformed DSAs were similar to the values of the BELACOR group ($P = .12$ and $P = .72$, respectively; Table 2).

3.2 | Primary and secondary endpoints

Follow-up characteristics in both groups are presented in Table 3. In the BELACOR group, no patients exhibited clinical or subclinical acute ABMR in either for-cause or protocol kidney allograft biopsies performed at M3 and M12; the rate of clinical or subclinical acute ABMR was 0% (95% CI 0%-7.25%). In the control group, 4 patients

TABLE 2 Preformed and de novo anti-HLA donor-specific antibodies (DSAs) evolution within the first year after transplant

Variables	Peak serum within 1 year before transplant			Month 3			Month 12		
	BELACOR group	Control group	P value ^a	BELACOR group	Control group	P value ^b	BELACOR group	Control group	P value ^c
Patients, n	49	74	—	49	72	—	49	69	—
Available, n (%)	49 (100)	74 (100)	—	49 (100)	71 (99)	—	49 (100)	68 (99)	—
Preformed DSAs, patients, n (%)	49 (100)	74 (100)	—	21 (43)	27 (38)	—	20 (41)	24 (35)	—
Class I, n (%)	34 (69)	36 (49)	.03	16 (76)	7 (26)	.26	11 (55)	4 (17)	.35
Number									
1, n (%)	24 (71)	27 (75)		9 (56)	6 (85)		7 (64)	4 (100)	
2, n (%)	8 (23)	7 (19)		2 (13)	0 (0)		3 (27)	0 (0)	
3, n (%)	2 (6)	1 (3)	.97	1 (6)	1 (14)	.03	1 (9)	0 (0)	.33
4, n (%)	0 (0)	0 (0)		4 (25)	0 (0)		0 (0)	0 (0)	
5, n (%)	0 (0)	1 (3)		0 (0)	0 (0)		0 (0)	0 (0)	
Median [IQR]	1 [1-2]	1 [1-1.5]	.97	1 [1-3.5]	1 [1-1]	.03	1 [1-2]	1 [1-1]	.33
Mean fluorescence intensity (MFI) max, median [IQR]	957 [740-1911]	967 [708-1350]	.12	1118 [620-2497]	887 [677-940]	.12	1243 [837-1859]	785 [721-1837]	.88
Class II, n (%)	28 (57)	43 (62)	.46	14 (67)	21 (78)	.45	14 (70)	22 (92)	.56
Number									
1, n (%)	19 (68)	33 (77)		10 (71)	20 (95)		9 (64)	18 (82)	
2, n (%)	6 (21)	10 (23)		0 (0)	1 (5)		4 (29)	3 (14)	
3, n (%)	3 (11)	0 (0)	.15	2 (14)	0 (0)	.06	1 (7)	1 (5)	.77
4, n (%)	0 (0)	0 (0)		1 (7)	0 (0)		0 (0)	0 (0)	
5, n (%)	0 (0)	0 (0)		1 (7)	0 (0)		0 (0)	0 (0)	
Median [IQR]	1 [1-2]	1 [1-1]	.15	1 [1-3]	1 [1-1]	.06	1 [1-2]	1 [1-1]	.77
MFI max, median [IQR]	1140 [753-1419]	795 [623-1111]	.72	1288 [776-2300]	1081 [754-1506]	.90	1716 [1235-2735]	903 [723-1439]	.46
De novo DSAs, patients, n (%)	—	—		7 (14)	15 (20)	.45	7 (14)	19 (28)	.50
Class I, n (%)	—	—		6 (86)	6 (40)	.07	2 (29)	6 (32)	.62
Number									
1, n (%)	—	—		1 (17)	5 (83)		2 (100)	4 (67)	
2, n (%)	—	—		3 (50)	1 (17)		0 (0)	2 (33)	
3, n (%)	—	—		2 (33)	0 (0)		0 (0)	0 (0)	

(Continues)

TABLE 2 (Continued)

Variables	Peak serum within 1 year before transplant			Month 3			Month 12		
	BELACOR group	Control group	P value ^a	BELACOR group	Control group	P value ^b	BELACOR group	Control group	P value ^c
Median [IQR]	—	—	—	2 [2-3]	1 [1-1]	.001	1 [1-1]	1 [1-2]	.007
MFImax, median [IQR]	—	—	—	1700 [1516-1890]	803 [603-1056]	<.001	942 [643-1240]	729 [652-851]	.009
Class II, n (%)	—	—	—	6 (86)	14 (93)	.86	6 (86)	17 (90)	.12
Number									
1, n (%)	—	—	—	3 (50)	10 (72)		5 (83)	14 (82)	
2, n (%)	—	—	—	1 (17)	3 (21)		1 (17)	3 (18)	
3, n (%)	—	—	—	1 (17)	0 (0)		0 (0)	0 (0)	
4, n (%)	—	—	—	0 (0)	1 (7)		0 (0)	0 (0)	
5, n (%)	—	—	—	1 (16)	0 (0)		0 (0)	0 (0)	
Median [IQR]	—	—	—	1.5 [1-3]	1 [1-2]	.08	1 [1-1]	1 [1-1]	.33
MFImax, median [IQR]	—	—	—	1066 [595-2796]	784 [563-1417]	.05	1586 [685-2735]	973 [659-1864]	<.001

^aComparison of preformed DSAs between the BELACOR and the control group at month 0 (mixed linear or logistic model).

^bComparison of preformed DSA and dnDSA evolution between day 0 and M3 in the BELACOR group vs the control group (mixed linear or logistic model).

^cComparison of preformed DSA evolution and dnDSA between M3 and M12 in the BELACOR group vs the control group (mixed linear or logistic model).

TABLE 3 Follow-up characteristics

	BELACOR group	Control group	P value ^a
3-month follow-up			
Patients, n	49	72	—
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m ² , median [IQR]	56 [43-67]	52 [40-67]	.48
Proteinuria:creatinine ratio, mg/mmol, median [IQR]	21 [13-40]	14 [10-28]	.03
12-month follow-up			
Patients, n	49	69	—
New-onset diabetes, n (%)	4 (8)	6 (8)	1.00
Cytomegalovirus viremia, n (%)	7 (14)	3 (4)	.09
BK viremia, n (%)	12 (24)	7 (10)	.03
eGFR, mL/min/1.73 m ² , median [IQR]	53 [39-67]	49 [37-66]	.67
Proteinuria:creatinine ratio, mg/mmol, median [IQR]	21 [15-47]	12 [5-24]	<.001

^aComparison of secondary endpoints between the BELACOR group and the control group χ^2 test or Fisher exact test for categorical variables and the Student t-test or Mann-Whitney U test for quantitative variables.

presented with clinical and subclinical ABMR; the rate was 5.81% (2.22%-14.77%). No difference has been observed between the 2 groups ($P = .12$) (Figure 2A).

After 12 months, in the BELACOR group, no patient died (death rate 0% [0%-7.25%]) and 2 allograft losses were reported (allograft loss rate 5.6% [1.4%-21.4%]). Patient and allograft survival rates in the BELACOR group at 1 year were 100% and 95.4%, respectively.

Causes of allograft loss were 1 thrombotic microangiopathy recurrence 3 months after transplant and 1 plasma cell-rich acute rejection 4 months after transplant. In the control group, 5 patients died (death rate 6.78% [2.88%-15.52%]) and none had lost their allograft (allograft loss rate 0% [0%-4.86%]). Causes of deaths were hemorrhagic shock in 3 patients, acute respiratory distress syndrome in 1 patient, and unknown in 1 patient. The incidence rates for death

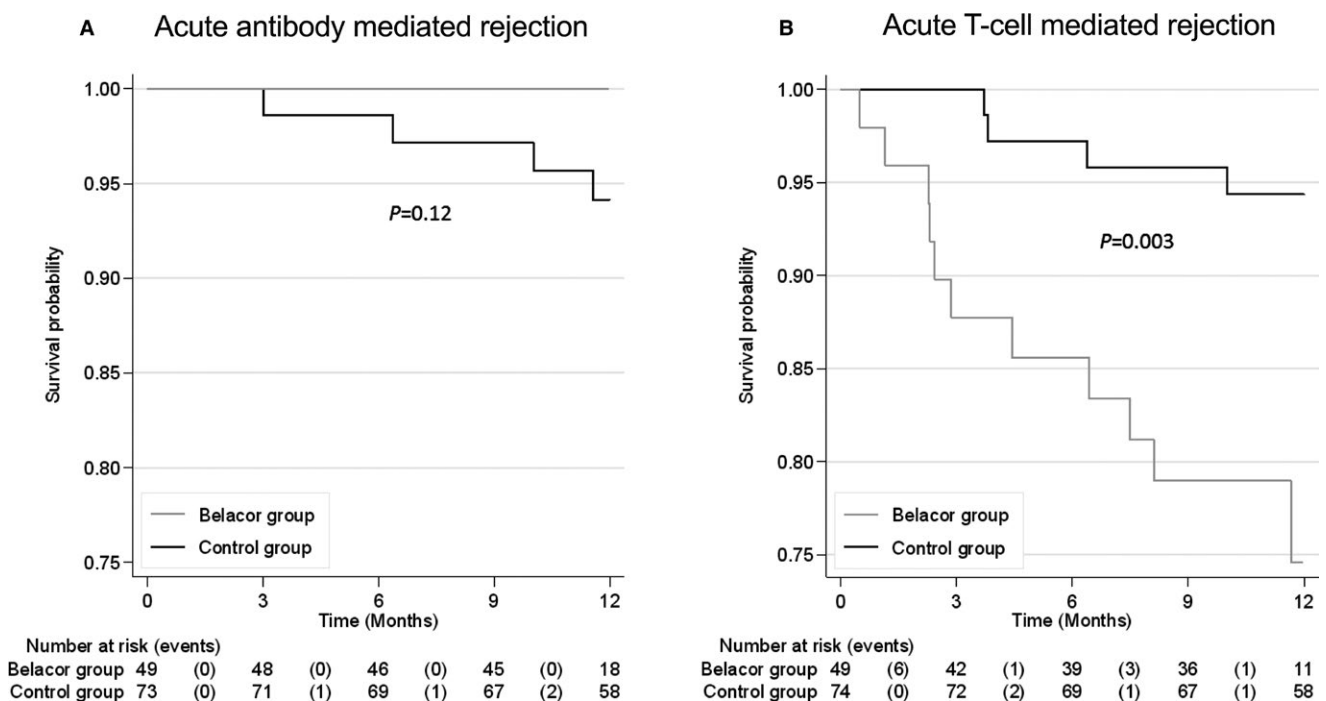


FIGURE 2 A, Preformed class I and class II donor-specific antibody (DSA) outcomes (maximum mean fluorescence intensity [MFI_{max}]) in the BELACOR group; B, preformed class I and class II DSA outcomes (MFI_{max}) in the control group. In the BELACOR group (2.A), class I and class II MFI_{max} decreased significantly between 1 year before transplant peak and 12 months after transplant (−822 [−1595 to −595], $P < .001$, and −647 [−836 to 0], $P = .002$, respectively). In the control group (2.B), class I and class II MFI_{max} decreased significantly between 1 year prior transplant peak and 12 months after transplant (−888 [−1233 to −638], $P < .001$, and −508 [−786 to 83], $P = .009$, respectively)

and allograft loss were similar for the 2 groups ($P = .07$ and $P = .05$, respectively) (Figure 3).

After 3 and 12 months, eGFR was similar in the 2 groups ($P = .48$ and $P = .67$, respectively), while proteinuria:creatinine ratio was significantly lower in the control group ($P = .03$ and $P < .001$, respectively). However, those values remained clinically insignificant.

In the BELACOR group, at 12 months, 12 episodes of clinical and subclinical acute TCMR including borderline were reported in 11 patients. Acute TCMR were grade IA in 6 patients, grade IB in 1 patient, grade IIA in 1 patient, and borderline changes in 3 patients. One patient presented with 2 episodes of acute TCMR within 12 months after transplant. Median delay of acute TCMR was 0.35 (0.19-0.62) years after transplant. Incidence was 25.4% (14.5%-42.4%). All patients were treated with high-dose steroids. Thymoglobulin was used in 5 (42%) patients. In the control group, 4 episodes of clinical and subclinical TCMR were reported in 4 patients. Acute TCMR were grade IIA in 1 patient, and borderline changes occurred in 3 patients. Median delay of acute TCMR was 0.42 (0.31-0.68) year after transplant. Incidence of acute TCMR was significantly lower in the control group: 5.64% (2.15%-14.33%); $P = .003$. All patients were treated with high-dose steroids.

Histological analysis on protocol biopsies performed at M3 and M12 are depicted in Table 4. At 3 months, in the BELACOR group, 2 patients presented with acute TCMR grade IA, and in the control group, 2 patients presented with acute borderline changes. At 12 months, microvascular inflammation including isolated glomerulitis grade 1 and isolated peritubular capillaritis grade 1 were found in 1 patient and 3 patients, respectively, in the BELACOR group. In the control group, microvascular

inflammation was depicted in 4 patients. No transplant glomerulopathy was observed in any groups. No significant difference in kidney allograft biopsies data was observed between the 2 groups at any time.

The number of patients displaying disappearance of class I preformed DSAs was similar in the 2 groups (27/34 [74%] and 23/28 [82%]; $P = .91$ in the BELACOR and control groups, respectively), while significantly more patients displaying a complete disappearance of class II DSAs were observed in the BELACOR group (29/36 [81%] and 18/43 [42%]; $P = .001$ in the BELACOR and control groups, respectively). Class I and class II MFImax between 1 year prior transplant peak and 12 months after transplant decreased significantly in both groups: -822 (-1595 to -595 , $P < .001$) and -647 (-836 to 0 , $P = .002$), respectively, in the BELACOR group and -888 (-1233 to -638 , $P < .001$) and -508 (-786 to 83 , $P = .009$), respectively, in the control group (Figure 4). The dip MFImax was similar in both groups either in class I ($P = .86$) or in class II ($P = .31$). Preformed DSA evolution within the first year after transplant (number, MFImax) was similar for the 2 groups (Table 2). The dnDSA incidence was higher within 12 months after transplant in the control group with 7 (14%) patients in the BELACOR group and 19 (28%) in the control group ($P = .08$). Evolution of dnDSAs between M3 and M12 is presented in Table 2. Class I dnDSA number rose significantly more in the control group than in the BELACOR group ($P = .007$). Class I dnDSA MFImax decreased significantly more in the BELACOR group between M3 and M12 ($P = .009$), while class II MFImax decreased significantly more in the control group ($P < .001$); however, those values remained in the same clinical ranges.

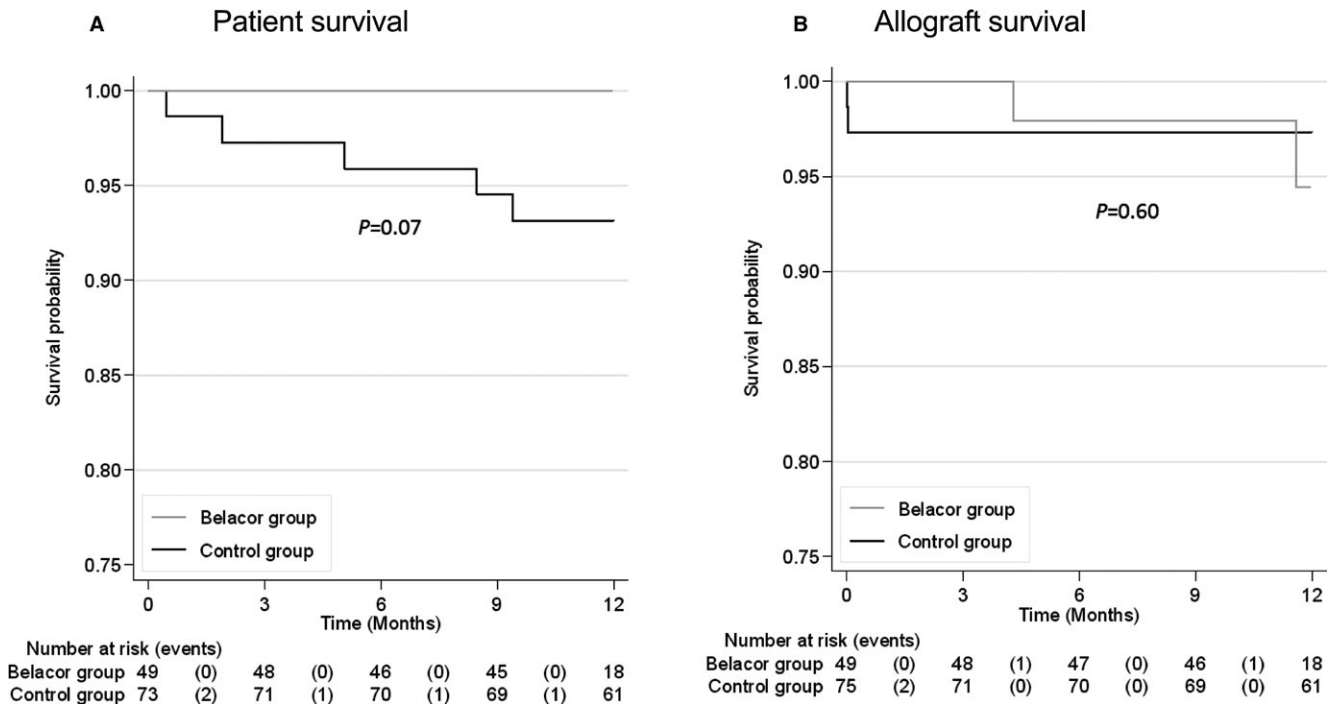


FIGURE 3 A, Clinical and subclinical antibody-mediated rejection (ABMR) within 12 months after transplant in both groups (Kaplan-Meier analysis); B, clinical and subclinical acute T cell-mediated rejection (TCMR) within 12 months after transplant in both groups (Kaplan-Meier analysis). Rate of clinical or subclinical acute ABMR was similar in both groups (3.A) (0% [0%-7.25%] in the BELACOR group and 5.81% [2.22%-14.77%] in the control group; $P = .12$). Rate of clinical and subclinical acute TCMR was significantly higher in the BELACOR group (3.B) (25.4% [14.5%-42.4%] vs 5.64% [2.15%-14.33%] in the control group; $P = .003$)

TABLE 4 Kidney allograft biopsy data (month 3 and month 12)

Variables	Month 3			Month 12		
	BELACOR group	Control group	P value ^a	BELACOR group	Control group	P value ^b
Patients, n	49	72		49	69	
Biopsy specimens available, n (%)	47 (96)	64 (89)	.12	44 (90)	50 (72)	.60
Cause of biopsies						
Systematic biopsy	41 (87)	—		42 (95)	—	
For-cause biopsy	6 (13)	—		2 (5)	—	
Acute rejection						
Antibody-mediated rejection	0 (0)	2 (3)	.85	0 (0)	3 (5)	.97
T cell-mediated rejection	2 (4)	2 (3)	—	0 (0)	1 (2)	—
Grade IA	2 (100)	—		0 (0)	—	
Grade IB	0 (0)	—		0 (0)	—	
Grade IIA	0 (0)	—		0 (0)	—	
Grade IIB	0 (0)	—		0 (0)	—	
Grade III	0 (0)	—		0 (0)	—	
Acute primary lesions						
Glomerulitis, n (%)	2 (4)	2 (3)	—	1 (2)	2 (4)	—
Grade, 1/2/3	2/0/0	1/1/0		1/0/0	1/0/1	
Peritubular capillaritis, n (%)	2 (4)	1 (2)	—	3 (7)	2 (4)	—
Grade, 1/2/3	2/0/0	1/0/0		3/0/0	0/1/1	
Interstitial inflammation, n (%)	6 (14)	1 (2)	.04	2 (5)	1 (2)	.37
Grade, 1/2/3	3/2/1	1/0/0		2/0/0	1/0/0	
Tubulitis, n (%)	8 (17)	4 (6)	.10	3 (7)	6 (12)	.08
Grade, 1/2/3	6/2/0	4/0/0		1/2/0	5/1/0	
Vasculitis, n (%)	1 (2)	1 (2)	—	0 (0)	0 (0)	—
Grade, 1/2/3	0/1/0	1/0/0		0/0/0	0/0/0	
Thrombotic microangiopathy	2 (5)	—	—	1 (2)	—	—
Chronic primary lesions						
Chronic glomerulopathy, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Interstitial fibrosis, n (%)	13 (30)	32 (50)	.04	19 (43)	32 (65)	.87
Grade, 1/2/3	12/1/0	29/2/1		14/4/1	22/8/2	
Tubular atrophy, n (%)	8 (17)	18 (28)	.16	21 (48)	27 (55)	.51
Grade, 1/2/3	8/0/0	16/1/1		17/3/1	22/5/0	
Vascular						
cv, n (%)	16 (34)	22 (34)	.97	21 (48)	16 (33)	.27
Grade, 1/2/3	13/1/2	18/3/1		8/10/3	11/4/1	
ah, n (%)	21 (45)	28 (44)	.84	16 (36)	19 (39)	.59
Grade, 1/2/3	16/5/0	26/2/0		15/1/0	13/5/1	
C4d positive, n (%)	2 (4)	0 (0)	—	1 (2)	2 (4)	—
Grade, 1/2/3	2/0/0	0/0/0		0/0/1	1/1/0	

^aComparison of kidney allograft biopsies data in the BELACOR group vs control group at M3 (mixed linear or logistic model).

^bComparison of evolution of kidney allograft biopsies data between M3 and M12 in the BELACOR group vs control group (mixed linear or logistic model).

3.3 | Safety and tolerability

In the BELACOR group, 82 SAEs were reported in 31 (63%) patients. In the control group, 172 SAEs were reported in 48 patients

(Table 5). Median delay after transplant was significantly lower in the control group (0.25 [0-0.5] year) than in the BELACOR group (0.31 [0.16-0.66] year) ($P = .003$). Investigators considered 20 (24%) episodes as treatment (belatacept) related. Patients in the control

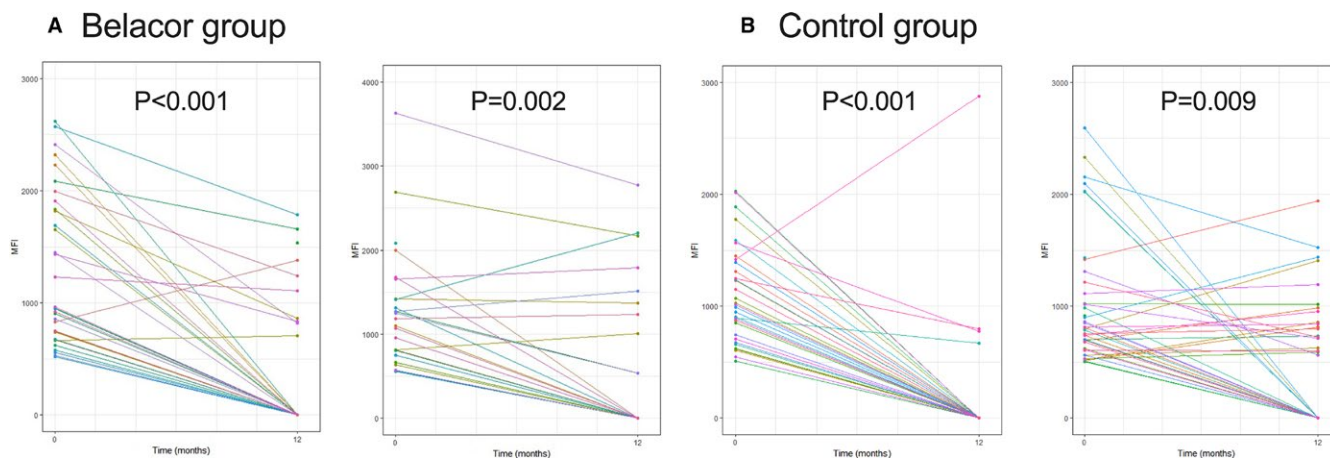


FIGURE 4 Patient (A) and kidney allograft (B) survival within 12 months in both groups (Kaplan-Meier analysis). Patient survival within 12 months after transplant (A) was similar in both groups: death rate in BELACOR group was 0% [0%-7.25%] and in the control group 6.78% [2.88%-15.52%] ($P = .07$). Allograft survival within 12 months after transplant (B) was also similar in both groups with an allograft loss rate in the BELACOR group of 5.6% [1.4%-21.4%] and in the control group 0% [0%-4.86%] ($P = .05$) [Color figure can be viewed at wileyonlinelibrary.com]

group presented with significantly more infections ($P = .008$) and cardiovascular disorder ($P = .003$), while patients in the BELACOR group presented with significantly more BK viremia and blood and pulmonary disorders ($P = .03$, $P = .01$, and 0.005 , respectively) (Tables 3 and 5). One localized B cell posttransplant lymphoproliferative disorder occurred 12 months after transplant in 1 EBV-positive recipient in the BELACOR group. Evolution with specific treatment was favorable.

4 | DISCUSSION

We have provided here results of the first single-arm clinical trial with an ancillary control group built retrospectively aiming to determine the impact of a belatacept-based immunosuppressive strategy on 12M kidney transplant outcome in recipients with preformed DSA MFI_{max} 500-3000 within 1 year before transplant.

Our primary objective was to assess the response rate defined by no acute ABMR within 12 months and we did not observe any episode of acute ABMR within 12 months after transplant in patients treated with belatacept. It has been established that acute ABMR incidence directly correlates with DSA MFI_{max} before transplant and rises significantly from 0.9% in MFI_{max} <465 to 18.7% in those with MFI_{max} 466-3000.¹⁷ We provide evidence that belatacept could significantly reduce such incidence in patients exhibiting peak preformed DSAs within the same range without any episodes of clinical or subclinical acute ABMR in both for-cause or protocol biopsies performed 3 and 12 months after transplant. Incidence of ABMR in the control group was lower than expected and comparable to the that in the BELACOR group. The absence of difference between the BELACOR and the control group may indicate whether there was an absence of difference regarding ABMR or a lack of power for detecting a small difference in the direction of higher ABMR in the control group. Indeed, the observed sample size of the 2 groups

($n = 49$ vs $n = 76$) could be considered as sufficient (ie, with a power of at least 80%) to detect a statistical difference between groups of at least 15% in ABMR occurrence. However, there is a deep lack of available data to confirm the study cited above and to address the question specifically for patients exhibiting DSAs with MFI between the detection threshold and 1000. Risk of acute ABMR in those patients remains hard to judge. As half of patients have low-titer DSAs, we could not exclude false-positives. However, DSAs with low MFI without any sensitized event have been detected in 63% of a large cohort of male blood donors without risk of immunization and are called "natural" alloantibodies of unknown etiology.¹⁸ Causes of antibodies could include cross-reactivity to epitopes of several bacterial, fungal, or viral antigens and autoreactivity against HLA antigens. Pathogenicity of those antibodies is now well recognized with a significant higher rate of acute ABMR within 1 year after transplant.¹⁹

We observed in both groups a significant decrease in class I and class II DSA MFI_{max} within 12 months after transplant. Surprisingly, a significantly higher number of patients displaying a complete disappearance of class II DSAs was observed in the BELACOR group compared with the control group. We previously reported in kidney transplant recipients from the BENEFIT trials an increasing proportion and absolute number of CD19⁺CD24^{hi}CD38^{hi} B cells, known to be associated with operational tolerance.²⁰ Moreover, we recently showed that belatacept may uniquely control B cell responses by modulating both their antigen-presenting capacities leading to the impairment of T follicular helper-B cell crosstalk and the production of antibodies by effector B cells.²¹ These in vivo data were obtained in kidney transplant recipients without pretransplant DSAs treated with belatacept.²¹ Whether the results observed in the BELACOR trial are related to the ability of belatacept to modulate memory B cell response remains to be established. In both groups, dnDSA incidence was higher than previously described,¹² although the incidence was higher in the control group compared with the BELACOR group. However, patients included in former studies exhibited a

TABLE 5 Serious adverse events

SAEs, patients	BELACOR group, n = 49	Control group, n = 74	P value
Patients, n (%)	31 (63)	48 (65)	.86
Number, n (%)	82 (100)	172 (100)	
Number per patient, median [IQR]	2 [1-3]	2.5 [1-4.5]	.09
Delay from transplant, year, median [IQR]	0.31 [0.16-0.66]	0.25 [0-0.5]	.003
Treatment related, n (%)	20 (24)	—	
SAE type			
Kidney allograft pyelonephritis, n (%)	24 (29)	44 (26)	.54
Acute T cell-mediated rejection, n (%)	12 (15)	4 (5)	.003
Infections, other, n (%)	4 (5)	29 (17)	.008
Pulmonary infection, n (%)	1 (1)	8 (5)	.28
New-onset diabetes after transplant, n (%)	3 (4)	17 (10)	.09
Acute kidney injury, n (%)	14 (17)	21 (12)	.29
Blood disorder, n (%)	4 (5)	0 (0)	.01
Cardiovascular disorder, n (%)	2 (2)	25 (14)	.003
Pulmonary disorder, n (%)	6 (7)	1 (1)	.005
Other, n (%)	12 (15)	27 (16)	.83
B cell posttransplant lymphoproliferative disorder	1 (1)	—	
Mediterranean Kaposi	1 (2)	—	

SAE, serious adverse event.

low immunological risk profile defined by no pretransplant DSAs and a low PRA. In low-immunological risk kidney allograft recipients, dnDSA incidence is up to 15% within 5 years.²² The patients included in both groups were all engrafted with pretransplant DSAs and are likely to exhibit a B cell memory response that could favor the occurrence of posttransplant dnDSAs.

We also observed a significantly higher incidence of acute TCMR with a higher number of steroid-resistant rejection leading to allograft loss in 1 case in the BELACOR group compared with the control group. Phase 3 clinical trials have already reported significantly

higher incidence and severity of acute TCMR in belatacept-treated patients with significantly better kidney allograft function compared with CNI-based therapy at the end of follow-up.⁹ However, <10% of acute rejections were steroid resistant.⁸ This higher acute TCMR incidence may be explained by susceptibility differences of immune cells to belatacept-inhibiting effects. Cytotoxic T memory lymphocytes do not express CD28 and are not dependent on this molecule for activation. Thus, it was recently shown that glucocorticoid-resistant cellular rejection occurring under belatacept was predominantly mediated by cytotoxic (CD8) memory T cells less susceptible to costimulatory blockade.²³ Alloreactive Th17 T cells have also been incriminated in this process, as they seemed resistant to belatacept inhibition *in vitro* and *in vivo*²⁴ or resulted from incomplete CD80/86 blockade at the tissue level.²⁵ The high incidence of acute TCMR observed in our cohort of pretransplant sensitized recipients is therefore not surprising because the proportion of cytotoxic memory T cells is likely to be higher in sensitized recipients.²⁶ This result highlights the potential interest already published of an immunosuppressive strategy combining CNIs and belatacept early after transplant (9 months), the high-risk period of acute TCMR, or switching CNIs to belatacept 6 months to 1 year after transplant in order to limit the incidence of T cell-mediated immune events in sensitized recipients and the development of dnDSAs.²⁷

The next remarkable finding was related to the different SAE profile observed in the 2 groups. Patients from the BELACOR group exhibited significantly less infection excluding kidney allograft pyelonephritis and less cardiovascular disorder. In contrast, we observed a higher proportion of patients with BK viremia compared with the control group. Surprisingly, a high incidence of BK viremia (72%) has also been reported in a retrospective cohort of kidney transplant recipients that combined belatacept and thymoglobulin induction.²⁸ This result is likely to be related to the association of belatacept and depletive induction strategy because the incidence of BK viremia in transplant recipients receiving belatacept and nondepletive induction strategy (basiliximab) was not significantly different than the incidence observed in different control groups treated with CNIs.²⁷ Such a hypothesis remains to be confirmed by a prospective analysis aiming to compare belatacept and CNIs with polyclonal induction therapy.

Our study has some limitations. Indeed, the prespecified sample size was not reached, but the low threshold of the 95% CI of the main endpoint (response rate) was higher than the prespecified threshold indicating a positive result. Second, the control group was retrospectively built. But patients included in the control group fulfilled the same inclusion criteria, were engrafted during almost the same period, and were followed in the same way as patients in the BELACOR group.

In conclusion, belatacept was not associated with an increased risk of acute ABMR and may be considered as immunosuppressive strategy in kidney allograft recipients with preformed DSAs exhibiting a mild MFI_{max} (500-3000). However, the incidence of acute TCMR was significantly higher with a significant proportion of steroid-resistant rejections, suggesting the potential benefit of CNIs in the early posttransplant period. Contrasting with previous results from phase 3 clinical trials, belatacept did not significantly prevent

the occurrence of dnDSAs within the first year after transplant in recipients with preformed DSA MFI_{max} (500-3000). Further prospective randomized studies are mandatory to confirm these encouraging preliminary results.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

REFERENCES

- Smith RN, Colvin RB. Chronic alloantibody mediated rejection. *Semin Immunol*. 2012;24(2):115-121.
- Aubert O, Loupy A, Hidalgo L, et al. Antibody-mediated rejection due to preexisting versus. *J Am Soc Nephrol*. 2017;28(6):1912-1923.
- Süsal C, Fichtner A, Tönshoff B, Mehrabi A, Zeier M, Morath C. Clinical relevance of HLA antibodies in kidney transplantation: recent data from the Heidelberg transplant center and the collaborative transplant study. *J Immunol Res*. 2017;2017:5619402.
- Stewart DE, Kucheryavaya AY, Klassen DK, Turgeon NA, Formica RN, Aeder MI. Changes in deceased donor kidney transplantation one year after KAS implementation. *Am J Transplant*. 2016;16(6):1834-1847.
- Sethi S, Choi J, Toyoda M, Vo A, Peng A, Jordan SC. Desensitization: overcoming the immunologic barriers to transplantation. *J Immunol Res*. 2017;2017:6804678.
- Jordan SC, Lorant T, Choi J, et al. IgG endopeptidase in highly sensitized patients undergoing transplantation. *N Engl J Med*. 2017;377(5):442-453.
- Noël C, Abramowicz D, Durand D, et al. Daclizumab versus antithymocyte globulin in high-immunological-risk renal transplant recipients. *J Am Soc Nephrol*. 2009;20(6):1385-1392.
- Larsen CP, Grinyó J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation*. 2010;90(12):1528-1535.
- Vincenti F. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;374(26):2600-2601.
- 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(3):443-453.
- Pearson TC, Trambley J, Odom K, et al. Anti-CD40 therapy extends renal allograft survival in rhesus macaques. *Transplantation*. 2002;74(7):933-940.
- Kim EJ, Kwun J, Gibby AC, et al. Costimulation blockade alters germinal center responses and prevents antibody-mediated rejection. *Am J Transplant*. 2014;14(1):59-69.
- Young JS, Chen J, Miller ML, et al. Delayed cytotoxic T lymphocyte-associated protein 4-immunoglobulin treatment reverses ongoing alloantibody responses and rescues allografts from acute rejection. *Am J Transplant*. 2016;16(8):2312-2323.
- Chen J, Yin H, Xu J, et al. Reversing endogenous alloreactive B cell GC responses with anti-CD154 or CTLA-4Ig. *Am J Transplant*. 2013;13(9):2280-2292.
- Loupy A, Haas M, Solez K, et al. The Banff 2015 kidney meeting report: current challenges in rejection classification and prospects for adopting molecular pathology. *Am J Transplant*. 2017;17(1):28-41.
- Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766-772.
- Lefaucheur C, Loupy A, Hill GS, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *J Am Soc Nephrol*. 2010;21(8):1398-1406.
- Morales-Buenrostro LE, Terasaki PI, Marino-Vázquez LA, Lee JH, El-Awar N, Alberú J. "Natural" human leukocyte antigen antibodies found in nonalloimmunized healthy males. *Transplantation*. 2008;86(8):1111-1115.
- Sicard A, Amrouche L, Suberbielle C, et al. Outcome of kidney transplantations performed with preformed donor-specific antibodies of unknown etiology. *Am J Transplant*. 2014;14(1):193-201.
- Leibler C, Matignon M, Pilon C, et al. Kidney transplant recipients treated with belatacept exhibit increased naïve and transitional B cells. *Am J Transplant*. 2014;14(5):1173-1182.
- Leibler C, Thiola A, Hénique C, et al. Control of humoral response in renal transplantation by belatacept depends on a direct effect on B cells and impaired T follicular helper-B cell crosstalk. *J Am Soc Nephrol*. 2018;29(3):1049-1062.
- Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant*. 2012;12(5):1157-1167.
- Kitchens WH, Haridas D, Wagener ME, et al. Integrin antagonists prevent costimulatory blockade-resistant transplant rejection by CD8(+) memory T cells. *Am J Transplant*. 2012;12(1):69-80.
- Krummey SM, Cheeseman JA, Conger JA, et al. High CTLA-4 expression on Th17 cells results in increased sensitivity to CTLA-4 coinhibition and resistance to belatacept. *Am J Transplant*. 2014;14(3):607-614.
- de Graav GN, Bergan S, Baan CC, Weimar W, van Gelder T, Hesselink DA. Therapeutic drug monitoring of belatacept in kidney transplantation. *Ther Drug Monit*. 2015;37(5):560-567.
- Poggio ED, Augustine JJ, Clemente M, et al. Pretransplant cellular alloimmunity as assessed by a panel of reactive T cells assay correlates with acute renal graft rejection. *Transplantation*. 2007;83(7):847-852.
- Adams AB, Goldstein J, Garrett C, et al. Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. *Am J Transplant*. 2017;17(11):2922-2936.
- Wojciechowski D, Chandran S, Yang JYC, Sarwal MM, Vincenti F. Retrospective evaluation of the efficacy and safety of belatacept with thymoglobulin induction and maintenance everolimus: a single-center clinical experience. *Clin Transplant*. 2017;31(9). <https://doi.org/10.1111/ctr.13042>

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