

# Conversion From Belatacept to Another Immunosuppressive Regimen in Maintenance Kidney-Transplantation Patients



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**Introduction:** During the coronavirus disease 2019 (Covid-19) pandemic, several physicians have questioned pursuing belatacept in kidney-transplant patients in order to reduce the risk of nosocomial transmission during the monthly infusion. The effect of the conversion from belatacept to another immunosuppressive regimen is underreported. The aim of the present retrospective study was to assess the effect on kidney function and the clinical outcome of the conversion from belatacept to another regimen.

**Methods:** We have identified 44 maintenance kidney transplantation patients from five French kidney transplantation centers who were converted from belatacept to another regimen either because of a complication ( $n = 28$ ) or another reason (patients' request or belatacept shortage,  $n = 13$ ). The follow-up after the conversion from belatacept was  $27.5 \pm 25.3$  months.

**Results:** Overall, mean estimated glomerular filtration rate (eGFR) decreased from  $44.2 \pm 16$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $35.7 \pm 18.4$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.0002$ ). eGFR significantly decreased in patients who had been given belatacept at transplantation as well as in those who had been converted to belatacept earlier. The decrease was less significant in patients who had stopped belatacept without having experienced any complications. Finally, eGFR decreased more severely in patients who were converted to calcineurin inhibitors (CNIs), compared to those who received mammalian target of rapamycin inhibitor (mTORi). Few patients also developed diabetes and hypertension.

**Conclusions:** Thus, transplantation physicians should avoid stopping belatacept when not clinically required.

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KEYWORDS: belatacept; calcineurin inhibitor; conversion; donor-specific antibody; kidney function; safety

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## See Commentary on Page 2123

Although CNI-based immunosuppression has dramatically improved the outcome of kidney transplantation, its use is responsible for nephrotoxicity and increased risk for tumoral proliferation. This has prompted transplantation physicians to try using CNI-free regimens. An mTORi CNI-free regimen was

used in *de novo* and maintenance kidney transplantation patients.<sup>1–3</sup> It was associated with significantly improved kidney function in patients who tolerated this therapy compared to those who remained on CNI-based therapy.<sup>1–3</sup> However, mTOR inhibitor CNI-free regimens were associated with an increased risk of occurrence of acute rejection and *de novo* donor-specific anti-human leukocyte antibodies (DSAs).<sup>4–6</sup> Thus, they are now rarely used. Conversely, CNI-avoiding regimens based on the use of belatacept were confirmed to be effective in preventing acute rejection and safe after kidney transplantation.<sup>7,8</sup> In *de novo* kidney transplantation patients, long-term

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**Table 1.** Patients' characteristics<sup>a</sup>

Variables	Numbers
Characteristics at transplantation	N = 44
Recipients' sex: male	27 (61.4)
Deceased donor	36 (81.8)
Rank of transplantation (first/second)	41/3
Initial kidney disease	
Glomerulopathy	18 (40.9)
Interstitial nephropathy	7 (15.9)
Diabetes mellitus and/or nephroangiosclerosis	4 (9.1)
Genetic disease	7 (15.9)
Other	8 (18.2)
EBV serostatus	
Donor positive/recipient positive	42 (95.4)
Donor negative/recipient positive	1 (2.3)
Donor positive/recipient negative	1 (2.3)
Immunologic recipient status	
Anti-HLA antibodies at kidney transplantation	8 (18.2)
Donor-specific antibodies at kidney transplantation	5 (11.4)
Donor-specific antibodies at conversion to belatacept	4 (9.3)
Start of belatacept	
Age upon starting belatacept (years)	54.8 ± 13
De novo belatacept/conversion to belatacept	14 (13.6)/30 (68.2)
Time from transplantation to conversion to belatacept (months)	7.2 (0.6 to 223)
Induction therapy at transplantation	
Anti-interleukin 2 receptor blocker	34 (77.3)
Polyclonal antibodies	6 (13.6)
None	4 (9.1)
Calcineurin inhibitors before conversion to belatacept	n = 30
Cyclosporine A	3 (10)
Tacrolimus	27 (90)
mTORi-based therapy before conversion to belatacept	5 (16.7)
MPA before conversion to belatacept	27 (90)
Steroids before conversion to steroids	30 (100)

EBV, Epstein-Barr virus; HLA, human leukocyte antibody; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

<sup>a</sup>Values shown are n (%) unless otherwise stated.

use of belatacept was associated with better kidney function and an increase in patient and graft survivals compared to patients who were given cyclosporin A-based immunosuppression.<sup>9</sup> In maintenance kidney transplantation patients, several studies, including a phase II trial and a large retrospective real-life study, have shown that the conversion from CNI to belatacept leads to an improvement in kidney function.<sup>10,11</sup>

To our knowledge, the effect on kidney function and the clinical outcome of the conversion from belatacept to another regimen has not been assessed. Thus, this was the aim of the present retrospective study.

## PATIENTS AND METHODS

We have identified 44 maintenance kidney transplantation patients from five French kidney transplantation centers who were converted from belatacept: Besançon University Hospital (n = 10), Necker University Hospital (Paris, France) (n = 15), Rouen University Hospital (n = 1), and Toulouse University Hospital (France) (n = 18). Conversion was conducted between

December 2006 and June 2018. The 44 patients had been given belatacept + mycophenolic acid (MPA) + steroids (S) (n = 37), belatacept + MPA (n = 2), or belatacept + mTORi S (n = 5) for 14 (2–137) months. Fourteen patients (31.8%) had been given *de novo* belatacept at transplantation, and 30 patients had been converted at 7.2 (0.6 to 223) months from CNI to belatacept for impaired kidney function and/or histology (n = 29) or post-transplantation diabetes mellitus (n = 1). All 14 *de novo* kidney transplantation patients were given belatacept + MPA + S. For the 30 patients who were converted to belatacept, initial immunosuppression was based on CNI + MPA + S (n = 11), CNI + MPA + mTORi + S (n = 2), or CNI + mTORi + S (n = 3). The patients' characteristics at and before conversion from belatacept to other immunosuppressive regimens are presented in Table 1. No specific antimicrobial prophylaxis was given after conversion from belatacept.

Kidney parameters were assessed at conversion to belatacept (in the 30 patients who were converted to belatacept) 6 and 3 months before the conversion from belatacept, at conversion from belatacept, and at 3, 6, and 12 months after conversion, as well as at the last follow-up. eGFR was estimated using the abbreviated Modification of the Diet in Renal Disease formula. In all centers, DSAs were assessed yearly or in case of impaired kidney function and/or increased proteinuria. Efficacy and safety parameters were assessed after the conversion from belatacept until last follow-up (i.e., 27.5 ± 25.3 months [median 20 (6–138) months]).

According to French law (Loi Jardé), anonymous retrospective studies do not require Institutional Review Board approval. In each center, patients were identified and data were obtained from the local database, and then electronic medical records were shared by all institutions.

## Statistical Analyses

Reported values represent either means (±SD) or medians (ranges). Proportions were compared by the chi square test or Fisher exact test. The nonparametric Friedman test for serial measurements was used to compare quantitative variables. The Student *t* test was used to compare quantitative variables. A *P* < 0.05 was considered statistically significant.

## RESULTS

### Conversion From Belatacept

Belatacept was stopped in 44 patients. The descriptions of baseline characteristics for all patients as well as their outcomes are presented in Supplementary Table S1. They had been given belatacept for 14 (2–137) months. Their mean age at conversion from belatacept was 57 ± 12.6 months. The reasons for stopping

**Table 2.** Reasons for conversion from belatacept

Reasoning	N = 44
Conversion for a complication	n = 28
Infections <sup>a</sup>	15
CMV	13
Human herpes virus 8	1
BK virus	1
Acute rejection	7
T-cell-mediated rejection	5
Antibody-mediated rejection	1
Mixed T-cell and antibody-mediated rejection	1
T-cell-mediated rejection and CMV infection	1
Colon cancer	2
T-lymphoma and human papilloma virus infection	1
No improvement in kidney function and recurrent CMV infection	1
No improvement in kidney function and BK virus infection	1
Conversion without a complication	n = 13
Belatacept shortage	5
Patients' request	7
Improvement in kidney function	1
No improvement in kidney function after conversion to belatacept	n = 3

CMV, cytomegalovirus.

<sup>a</sup>Among patients who were converted from belatacept because of a complication, CMV replication persisted in patients having resistant CMV infection (n = 3) whereas no CMV replication recurrence occurred in the nine remaining patients. All other viruses were cleared after conversion from belatacept.

belatacept are detailed in [Table 2](#) and [Supplementary Table S1](#). In 28 patients (63.6%), it was stopped because of a complication; in 13 patients, it was ceased without patients having experienced any complications; and in the last 3 patients, belatacept was interrupted because no improvement in kidney function was observed. In 34 patients, belatacept was replaced by a CNI-based regimen, and 10 patients were given an mTORi-CNI-free-based regimen. Post-conversion from belatacept immunosuppression was as follows: CNI + MPA ± S (n = 21, 47.7%), CNI + mTORi ± S (n = 7, 15.9%), CNI + azathioprine ± S (n = 3, 6.8%), CNI + S (n = 3, 6.8%), mTORi + MPA ± S (n = 8, 18.2%), and mTORi + azathioprine ± S (n = 2, 4.6%). Tacrolimus was the most commonly used CNI after belatacept cessation (94%). Its median trough level was 6 (4 to 8) ng/ml. Everolimus was the most commonly used mTORi after belatacept cessation. Its median trough level was 3 (2 to 6) ng/ml when associated with CNI and 5 (4 to 8) ng/ml when given without CNI.

### Kidney Function Outcome

Overall, in the whole population (N = 44), eGFR decreased after belatacept cessation ( $P = 0.0002$ ). Mean eGFR decreased from  $44.2 \pm 16$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $39.3 \pm 18.5$  ml/min per  $1.73 \text{ m}^2$  at 12 months post-conversion ( $P = 0.01$ ), and  $35.7 \pm 18.4$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.0002$ ) ([Figure 1a](#)). eGFR decreased in 29 patients (66%), remained stable in 8 patients (18%), and

improved in 7 patients (16%). Proteinuria remained unchanged (i.e.,  $0.09 [0 \text{ to } 2.1]$  g/d at conversion from belatacept vs.  $0.13 [0 \text{ to } 1.7]$  g/d at last follow-up;  $P = 0.27$ ).

Because some patients were given belatacept at transplantation (*de novo* patients) whereas others were converted to belatacept mainly because of impaired kidney function and/or histology, and because in some patients belatacept was ceased due to complications that can negatively impact kidney function, we have analyzed the outcome of different subgroups of patients separately.

### De novo Kidney-Transplantation Patients Who Were Given Belatacept

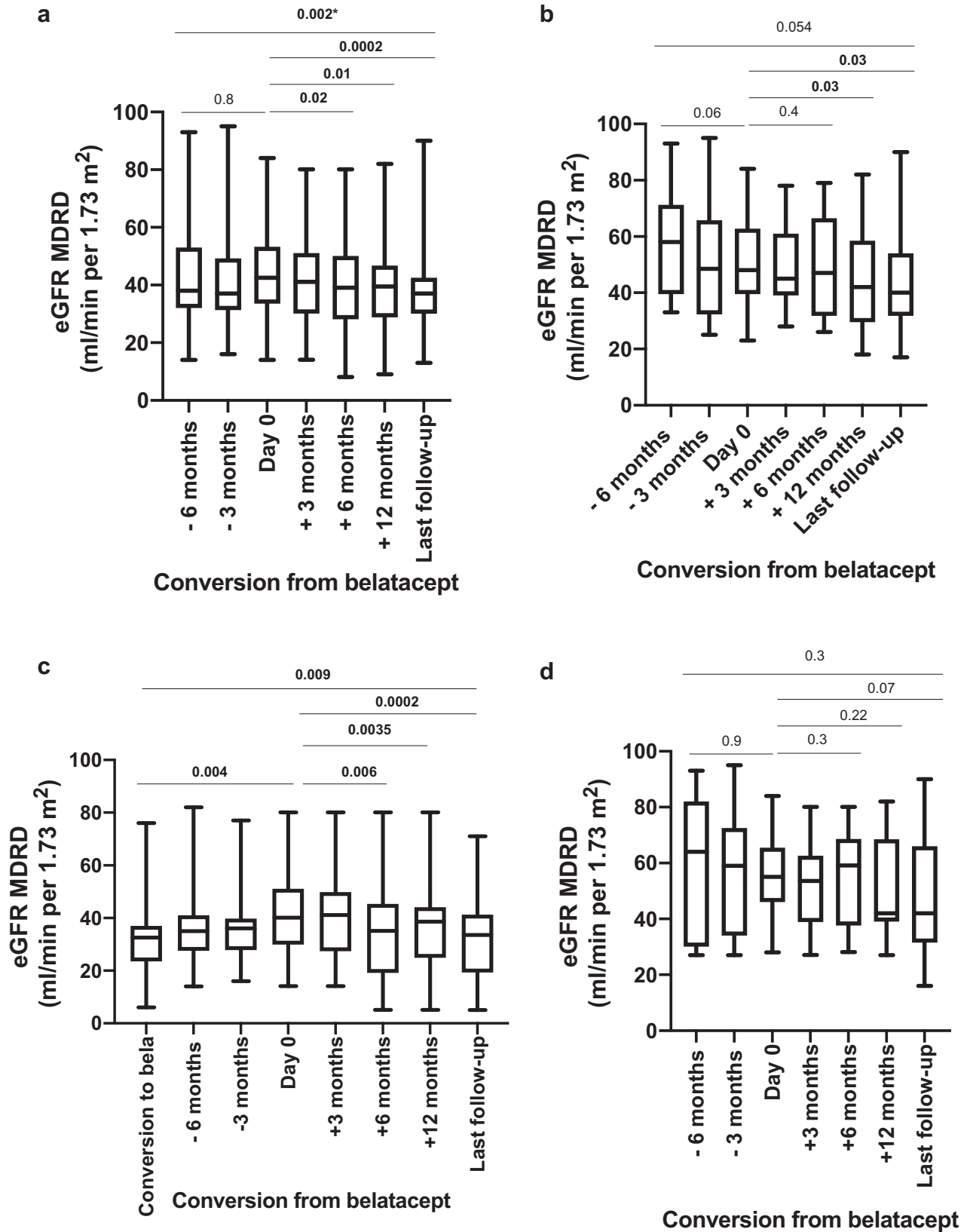
Fourteen patients who were given belatacept immediately after transplantation stopped it 12.5 (3 to 137) months later. The mean follow-up after conversion from belatacept was  $41.5 \pm 38.4$  months. eGFR decreased after belatacept cessation ( $P = 0.054$ ). Mean eGFR decreased from  $51.4 \pm 16.6$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $44.5 \pm 18.6$  ml/min per  $1.73 \text{ m}^2$  at 12 months post-conversion ( $P = 0.03$ ), and  $43.3 \pm 19.4$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.03$ ) ([Figure 1b](#)).

### Maintenance Kidney Transplantation Patients Who Were Converted to Belatacept

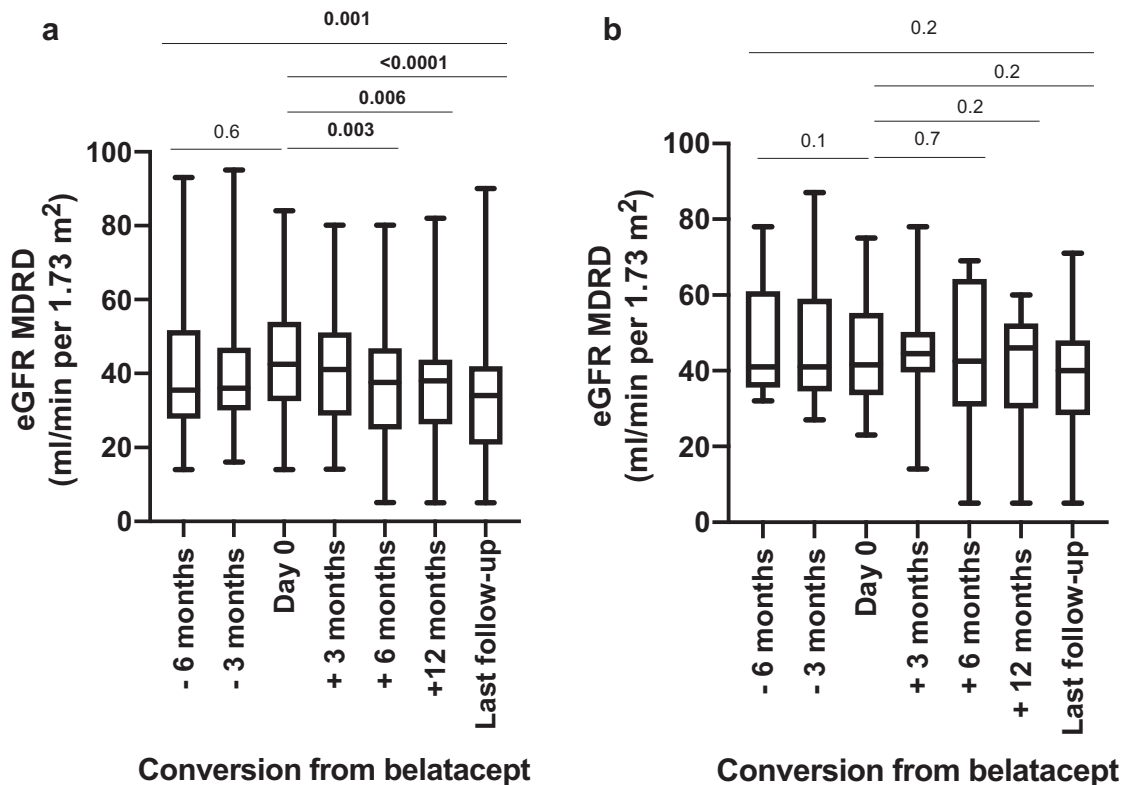
Thirty patients were converted to belatacept at 7.2 (0.6 to 223) months. The mean follow-up after conversion from belatacept was  $21 \pm 13.1$  months. eGFR decreased after belatacept was stopped ( $P = 0.0009$ ). Mean eGFR initially improved from  $32.4 \pm 13.6$  ml/min per  $1.73 \text{ m}^2$  at conversion to belatacept to  $40.8 \pm 14$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept ( $P = 0.004$ ). Thereafter, it decreased to  $36.9 \pm 18.7$  ml/min per  $1.73 \text{ m}^2$  at 12 months post-conversion from belatacept ( $P = 0.035$ ) and  $32.1 \pm 17.4$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.0002$ ) ([Figure 1c](#)).

### Patients Who Stopped Belatacept Without Experiencing a Complication

Thirteen patients stopped belatacept because of the shortage of belatacept that occurred 3 years ago (n = 5), upon their request (n = 7), or because kidney function had improved after the initiation of belatacept given because of prolonged delayed graft function (n = 1). The mean follow-up after conversion from belatacept was  $27.9 \pm 21.9$  months. Overall, no significant change was observed in eGFR ( $P = 0.3$ ). Mean eGFR decreased from  $56.4 \pm 15.6$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $47.7 \pm 20$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.07$ ) ([Figure 1d](#)).



**Figure 1.** Outcome of kidney function before and after conversion from belatacept. (a) In the whole population (n = 44). (b) In *de novo* kidney transplantation patients who were given belatacept (n = 14). (c) In maintenance kidney transplantation patients who were converted to belatacept earlier (n = 30). (d) In patients who stopped belatacept without experiencing a complication (n = 13). eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.



**Figure 2.** Outcome of kidney function before and after conversion from belatacept. (a) In patients who were converted from belatacept to calcineurin inhibitors (n = 34). (b) In patients who were converted from belatacept to mTORi (n = 10). eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor.

### Patients Who Were Converted From Belatacept to CNIs

Thirty-four patients were converted from belatacept to a CNI-based regimen. eGFR decreased after belatacept cessation ( $P = 0.001$ ). Mean eGFR decreased from  $44.1 \pm 15.3$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $38.9 \pm 19.5$  ml/min per  $1.73 \text{ m}^2$  at 12 months post-conversion ( $P = 0.006$ ) and  $34.8 \pm 18.9$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P < 0.0001$ ) (Figure 2a).

### Patients Who Were Converted from Belatacept to mTORi

Ten patients were converted from belatacept to an mTORi-based regimen. No significant change in eGFR was observed after belatacept stop ( $P = 0.17$ ). Mean eGFR decrease was at  $44.6 \pm 17.4$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept,  $40.7 \pm 16.8$  ml/min per  $1.73 \text{ m}^2$  at 12 months post-conversion ( $P = 0.22$ ), and  $38.5 \pm 18.3$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.2$ ) (Figure 2b).

### Immunological and Kidney Allograft Outcomes After Conversion From Belatacept

Only one patient, who was given CNI + MPA + S, developed a *de novo* DSA (2.3%) 6 months after conversion from belatacept that led to antibody-mediated rejection and graft loss. Another patient who had a DSA at conversion to belatacept developed chronic

antibody-mediated rejection. A third patient experienced a T-cell-mediated rejection 16 months after conversion from belatacept. Thus, overall, 3 patients (6.8%) developed an acute rejection after belatacept cessation. Four patients (9.1%) lost their graft during follow-up: the first patient because of chronic antibody-mediated rejection, the second patient due to the development of the acute antibody-mediated rejection, the third one due to poor kidney function and severe interstitial fibrosis/tubular atrophy, and the last patient because of a cardiorenal syndrome. After the exclusion of patients who presented an acute rejection and/or a graft loss (n = 5), eGFR significantly decreased in the remaining 39 patients from  $46.1 \pm 14.6$  ml/min per  $1.73 \text{ m}^2$  at conversion to  $39.3 \pm 16.2$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.0002$ ).

### Clinical Outcomes After Conversion From Belatacept

During follow-up, 10 patients (22.3%) experienced an infectious episode: cytomegalovirus replication (n = 3), flu (n = 2), norovirus infection (n = 1), *pneumocystis jiroveci* pneumonitis (n = 1), pyelonephritis (n = 2), and arthritis (n = 1).

Eight patients (18.2%) developed *de novo* cancer after conversion from belatacept: 6 patients developed skin cancer 4 to 66 months after conversion from



belatacept; one patient presented lung cancer 11 months after conversion from belatacept; and one patient developed an Epstein-Barr virus–positive cerebral post-transplant lymphoproliferative disease 12 months after the conversion from belatacept.

Two patients (4.5%) developed *de novo* diabetes mellitus 1 and 3 months after belatacept cessation.

Two patients (4.5%) developed *de novo* hypertension 1 and 3 months after the conversion from belatacept, whereas a worsening of hypertension defined by adding antihypertension medications was observed in 10 other patients (22.7%).

Finally, 6 patients (13.6%) died during follow-up with a functioning graft. The causes for death were colon cancer ( $n = 1$ ), lung cancer ( $n = 1$ ), cerebral post-transplant lymphoproliferative disease ( $n = 1$ ), stroke ( $n = 1$ ), vascular dementia ( $n = 1$ ), and acute respiratory distress syndrome due to flu virus ( $n = 1$ ).

## DISCUSSION

The effect of the conversion from belatacept to another immunosuppressive regimen is underreported. The aim of the present retrospective study was to assess the effect on kidney function and the clinical outcome of the conversion from belatacept to another regimen. Our findings were threefold: (1) the conversion from belatacept to another regimen was associated with a decrease in eGFR of  $\sim 8$  ml/min per  $1.73 \text{ m}^2$ ; (2) the decrease was less significant in patients who were converted from belatacept for a reason that was not a complication, and in those who were converted to an mTORi-based CNI-free regimen; and (3) some patients developed diabetes and hypertension after conversion from belatacept.

In maintenance kidney transplantation patients, a phase II randomized controlled study showed an improvement in kidney function at 1 year in patients converted to belatacept (that was administrated with MPA and S) compared to those who were maintained on CNI ( $7 \pm 11.99$  ml/min per  $1.73 \text{ m}^2$ ).<sup>12</sup> This gain was maintained at 3 years (i.e.,  $+1.9$  ml/min per  $1.73 \text{ m}^2$  per year).<sup>10</sup> In a large retrospective real-life European multicenter study that included 219 maintenance kidney transplantation patients, mean eGFR significantly increased from  $32 \pm 16.4$  ml/min per  $1.73 \text{ m}^2$  at conversion to belatacept to  $38 \pm 20$  ml/min per  $1.73 \text{ m}^2$  at  $21.9 \pm 20.2$  months later.<sup>11</sup> In the present study, we observed another way that eGFR decreases by  $\sim 8$  ml/min per  $1.73 \text{ m}^2$  after conversion from belatacept. This decrease was observed in patients who had received belatacept at transplantation and in those who had been converted to belatacept earlier because of impaired kidney function and/or histology.

In nearly two-thirds of patients, belatacept was stopped because of a complication, mainly because of a viral infection. It was recently shown that cytomegalovirus infection is the main opportunistic infection observed in belatacept-treated kidney transplantation patients.<sup>13,14</sup> Conversely, in 30% of patients, belatacept was stopped either at the patients' request or because of belatacept shortage. In these patients in whom belatacept was stopped without having experienced any complication, eGFR also decreased from  $56.4 \pm 15.6$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept to  $47.7 \pm 20$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P = 0.07$ ). Because of the small number of patients, the decrease in eGFR was not statistically significant. An improvement in eGFR was observed in 7 patients after belatacept cessation. Most of them were converted because of a complication. Thus, we speculate that the improvement is related to the resolution of the complication.

The improvement in kidney function after stopping CNI was often attributed to the loss of CNI-associated intrarenal vasoconstriction.<sup>15</sup> In the present study, in patients converted from belatacept to CNI, eGFR decreased from  $44.1 \pm 15.3$  ml/min per  $1.73 \text{ m}^2$  to  $34.8 \pm 18.9$  ml/min per  $1.73 \text{ m}^2$  at last follow-up ( $P < 0.0001$ ), whereas in those converted from belatacept to an mTORi-based CNI-free regimen, no significant change in eGFR was observed (i.e.,  $44.6 \pm 17.4$  ml/min per  $1.73 \text{ m}^2$  at conversion from belatacept and  $38.5 \pm 18.3$  ml/min per  $1.73 \text{ m}^2$  at last follow-up;  $P = 0.2$ ). Thus, after belatacept cessation, a lesser eGFR decrease was observed in patients who stopped it without having experienced a complication and in patients who were given mTORi without CNI. Although the risk of *de novo* DSAs is increased in kidney transplantation patients who receive the latter combination,<sup>4,5</sup> several studies have shown improved kidney function in patients given an mTORi-based therapy compared to those on CNI-based immunosuppression.

The use of belatacept was associated with a decreased risk of metabolic syndrome, post-transplant diabetes mellitus, and hypertension.<sup>16,17</sup> In the present study, some patients developed *de novo* diabetes and *de novo* hypertension in the first 3 months after conversion from belatacept.

There are several limitations for the present study. It is retrospective uncontrolled study that included a small number of patients. The evolution of eGFR should be interpreted with caution because in 28 of 44 patients, belatacept was stopped because of a complication that could have had a negative impact on kidney function. Finally, we acknowledge the lack of kidney allograft histology at conversion from belatacept and at last follow-up.

In summary, ceasing belatacept is associated with a significant decrease in kidney function.

## DISCLOSURE

DD has received grants from Astellas and Neovii. CL has received lecture fees from Astellas, Novartis, Chiesi, CSL Behring, and Hansa Medical, and travel grants from Astellas, CSL Behring, and Alexion. NK has received lecture fees from Astellas, Novartis, Gilead, Neovii, MSD, Octapharma, and Amgen, and travel grants from Astellas, CSL Behring, Novartis, and Alexion. All the other authors declared no competing interests.

## AUTHOR CONTRIBUTIONS

AG collected the data from Toulouse, pooled the data from all centers, and wrote the paper. RS-S and CL collected the data from Necker Hospital and reviewed the paper. CC and DD collected the data from Besançon Hospital and reviewed the paper. DB collected the data from Rouen Hospital and reviewed the paper. ADB and AD reviewed the paper. NK designed the study, did the statistical analyses, and wrote the paper.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Supplementary Table S1.** Clinical course of all 44 patients who were included in the study.

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