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RESEARCH LETTER

The Conversion From Mycophenolic Acid to Mammalian Target of Rapamycin Inhibitor Reduces the Incidence of Cytomegalovirus Replication in Belatacept-Treated Kidney-Transplant Recipients

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INTRODUCTION

A better long-term graft survival, kidney function, and metabolic profile are observed in *de novo* kidney-transplant patients given belatacept associated with mycophenolic acid (MPA) than those receiving calcineurin-based immunosuppression.[1] Similarly, kidney function is better in kidney-transplant patients converted from calcineurins to belatacept than those who were maintained on calcineurins.[2] In addition, less *de novo* donor-specific antibodies developed in patients given belatacept.[2] Conversely, more opportunistic infections, particularly cytomegalovirus (CMV) infection, were observed in patients treated with belatacept.[3,4] Recurrent CMV infections and unusual presentations of CMV disease were also reported in patients treated by belatacept.[4,5] *In vitro* and *in vivo* data suggest that mammalian target of rapamycin inhibitors (mTORi) prevent CMV replication.[6,7] Therefore, theoretically, combining belatacept with an mTORi could allow to benefit from nonnephrotoxic effect of belatacept without increasing the risk of CMV infection. Scarce data regarding the combination of belatacept with mTORi were published until now. In the present retrospective study, we report the efficacy of replacing MPA with an mTORi in belatacept-treated kidney-transplant patients for CMV replication.

RESULTS

Between January, 2005 and December, 2020, 171 kidney-transplant patients were given belatacept-based therapy in our institution (Supplementary Methods). Among them, MPA (given at a fixed dose of 360 mg twice a day) was replaced with an mTORi (24 everolimus and 11 sirolimus) in 35 patients (Figure 1a). Patients' characteristics are presented in Table 1. All patients received low-dose steroids, and 4 patients (11.4%) also received low-dose tacrolimus (trough level 2 to 5 ng/ml). Patients were converted to mTORi for intolerance to MPA ($n = 16$), cancer ($n = 5$), or viral replication ($n = 14$, 8 recurrent CMV and 6 polyoma BK virus). Conversion to mTORi was done 28.0 (interquartile range [IQR]: 12.3–61.3) months after transplantation, and 18.0 (IQR: 8.2–41.4) months after the initiation of belatacept. The median duration of exposure to belatacept–mammalian target of rapamycin was 15.0 (IQR: 7.0–33.0) months ($P = 0.23$ with median duration of exposure to belatacept-MPA). Everolimus trough level was 5.3 ± 2.7 ng/ml (Figure 1b).

Ninety-five CMV DNAemias occurred in 14 patients (5 [IQR: 1–9] episodes/patient, 9 patients with ≥2 episodes) treated with belatacept-MPA during 1308 months of exposure (incidence: 0.072/mo of exposure), and only 32 CMV DNAemias were observed in 5 patients given

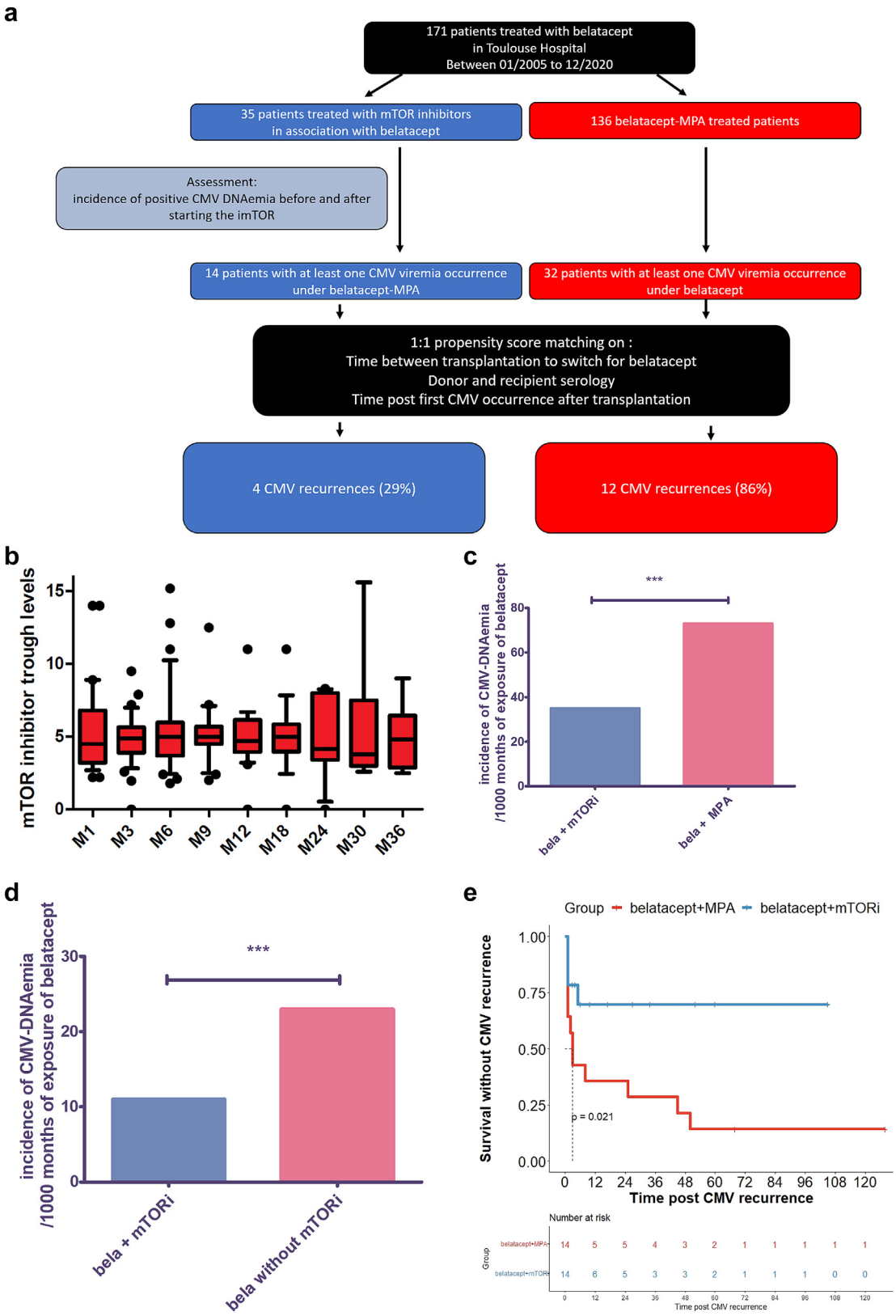

Figure 1. (a) Flow chart of the study. (b) mTOR inhibitors concentration through levels at different points during the follow-up in patients receiving belatacept. (c) Incidence of CMV DNAemia in the 35 patients treated with belatacept and converted from mycophenolic acid to mTOR inhibitors. The incidence is expressed for 1000 months of belatacept exposure. ***: $P = 0.0002$ (Chi-square test). (d) Incidence of CMV DNAemia in patients treated with belatacept who were converted from mycophenolic acid to mTOR inhibitors for recurrent CMV replication ($n = 8$). The incidence is expressed for 1000 months of belatacept exposure. ****: $P < 0.0001$ (Chi-square test). (e) Free from CMV recurrence in patients receiving mTORi, and in a 1:1-matched cohort receiving belatacept-MPA.
P-value was calculated with the log-rank test.
bela, belatacept; mTOR, mammalian target of rapamycin; mTORi, mammalian Target of Rapamycin inhibitors.

Table 1. Patients' characteristics

Variables	Patients receiving belatacept for which MPA was replaced by mTORi (n = 35)
Donors' characteristics	
Donor age (yr), mean ± SD	59 ± 15
Living donor (yes), n (%)	7 (20.0)
Recipients' characteristics	
Recipient age at transplantation (yr), mean ± SD	58 ± 15
Recipient gender (male), n (%)	22 (62.9)
Detectable DSA before belatacept initiation, n (%)	3 (8.6)
HLA A/B/DR/DQ mismatches, mean ± SD	5.2 ± 1.6
Donor and Recipient CMV status, n (%)	
D- R-	7 (20.0)
D+ R-	11 (31.4)
D- R+	7 (20.0)
D+ R+	10 (28.6)
Induction therapy (yes), n (%)	26 (74.3)
Polyclonal antibodies	9 (25.7)
Basiliximab	17 (48.6)
Rituximab	2 (5.7)
Time between transplantation and start of belatacept (mo), median (IQR)	2.0 (0.0–10.3)
Reason for the introduction of belatacept, n (%)	
Impaired renal function	22 (62.9)
Initial immunosuppression	12 (34.2)
Nonadherence to standard immunosuppression	1 (2.9)
Time between transplantation- start of belatacept + mTORi association (mo), median (IQR)	28 (12.3–61.3)
Reason for initiation of mTORi, n (%)	
Viral replications	14 (40.0)
Cancer	5 (14.3)
Mycophenolate intolerance	16 (45.7)
Duration of exposure to belatacept + MPA (mo), median (IQR)	15.0 (7.0–33.0)
Duration of exposure to belatacept + mTORi (mo), median (IQR)	18.0 (8.2–41.4)

DSA, donor-specific antibodies; IQR, interquartile range; MPA, mycophenolic acid; mTORi, mammalian Target of Rapamycin inhibitors.

belatacept-mTORi (5 [IQR: 2–5] episodes/patient, 4 patients with ≥2 episodes, Supplementary Figure S1) during 914 months of exposure (incidence: 0.035/mo of exposure; $P = 0.0002$) (Figure 1c). After the conversion to mTORi, positive CMV DNAemia was observed in only 1 of the 21 patients who did not experience a CMV DNAemia before the conversion to mTORi. For the 8 patients who were specifically switched to mTORi because of CMV replication (2 donors CMV seropositive/recipients seronegative, and 6 seropositive recipients), the incidence of CMV DNAemia was 0.233/mo of exposure under MPA, and 0.114/mo of exposure under mTORi, ($P < 0.0001$) (Figure 1d). The median CMV concentration was 5925 (IQR: 1200–46,923) copies/ml in patients treated with belatacept-MPA and 6680 (IQR: 500–81,523) copies/ml in patients treated with belatacept-mTORi ($P = 0.44$). CMV disease occurred in 3 (2 tissue invasive) and 2 (both tissue invasive) patients before and after conversion to mTORi, respectively ($P >$ 0.99). A UL97 mutation was observed in 1 patient before the conversion from MPA to mTORi. Conversion did not prevent the further recurrence of CMV for this patient.

We eventually assessed the risk of CMV DNAemia recurrence in patients receiving mTORi. A propensity score matching was used to compare those patients and patients receiving a belatacept-MPA therapy. The survival free-from CMV recurrence was dramatically lower in patients receiving belatacept-MPA (Figure 1e, Supplementary Table S1). To note, the risk for CMV recurrence was similar between patients who started mTORi during the first year posttransplantation and those who started later (Supplementary Figure S2).

Other opportunistic infections descriptions are available in the Supplementary Material (Other opportunistic infections).

One patient had experienced an acute steroid-resistant T-cell mediated rejection before conversion to mTORi (12 months posttransplantation) and 2 other patients presented with an acute steroid-resistant T-cell mediated rejection after the conversion (2 and 5 months postconversion, both occurred during the first year posttransplantation). The rejection rate during the first year posttransplantation was similar to what observed in the 68 patients who received belatacept in combination with MPA (4/68, $P = 0.69$). No *de novo* donor-specific antibody was detected after the conversion. Overall, graft survival was 80% at the end of the follow-up, 66 (IQR: 26.5–104) months post-transplantation. Four patients died with a functioning graft (1 from a cancer and 3 from lung infection), and 3 patients that received belatacept for impaired renal function returned to dialysis with progression of Interstitial fibrosis and tubular atrophy lesions.

mTORis were stopped in 16 patients (45.7%), 10.0 (5.0–28.8) months after the conversion for the following reasons: digestive disorders ($n = 6$), lymphoedema ($n = 4$), wound healing ($n = 4$), renal complications (proteinuria, $n = 1$; and rejection, $n = 1$).

The renal function before conversion and at the last follow-up was 36.0 (IQR: 30.5–50.0) and 33.0 (IQR: 25.0–47.5) ml/min per 1.73 m^2 (CKD-EPI eGFR). Urinary albumin-to-creatinine ratio before conversion and at last follow-up was 82.5 (IQR: 21.8–135.5) and 63.0 (IQR: 30.0–265.0) mg/g respectively ($P = 0.76$).

DISCUSSION

Belatacept is approved to be used in combination with MPA and steroids (Supplementary References). However, opportunistic infections, especially CMV replication, is a major concern in patients treated with belatacept.[3] Karadkhele and colleagues had showed that in high-risk CMV donor seropositive/recipient

seronegative patients, CMV DNAemia is observed in 22.1% of patients treated with belatacept-MPA versus 1.6% in patients treated with tacrolimus-MPA ($P < 0.001$).[5] The authors also found a higher number of positive CMV tests in patients treated with belatacept than in patients treated with tacrolimus. The antiviral effects of mTORi were attributed to immunologic properties (expansion of CMV-specific CD4+ and CD8+ T cells, decrease of dysfunction PD1+CD85j+ αβ and γδ T cell) and to direct viral inhibition (through Akt activation blockage, and viral protein synthesis inhibition of pUL44 and pp65).[6,7] Despite the small number of patients, the present study confirms the lower incidence of CMV DNAemia in patients given belatacept and mTORi as well as a significant reduction of the incidence of CMV DNAemia in patients converted to mTORi because of recurrent CMV DNAemia, suggesting a particular interest for those patients. The main concern is the already reported[8] high rate of mTORi discontinuation due to side-effect.

Our study presents several limitations. It is a single center retrospective study. The switch from MPA to mTORi was based on the judgment of the treating physician. The number of patients is small. We did not assess other previously tested strategies such as belatacept monotherapy[9] that could have been proposed to reduce the risk for CMV recurrence. Moreover, the absence of CMV-specific T-cell response analyses before and after the introduction of mTORi prevents us from drawing definitive conclusion regarding the causative role of such combination for CMV recurrence.

In conclusion, our data suggest that replacing MPA with an mTORi in patients treated with belatacept could significantly decrease the incidence of CMV-viremia. Thus, large prospective studies are required to confirm these data.

DISCLOSURE

ADB has received speakers' fees and participated to advisory boards for Astellas, Chiesi, Hansa, Sandoz, and Neovii. NK has received speakers' fees and participated to advisory boards for Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeViR, Hansa, Merck Sharp and Dohme, Glasgow Smith Kline, Novartis Pharma, Sanofi, Sandoz, and Takeda. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

ADB and JC collected the data. ADB and NK designed the study, analyzed data, and wrote the paper. ADB, NK, TP, and FA participated in the performance of the research.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. The course of the 5 patients who presented a CMV reoccurrence despite a combination of belatacept and mTOR inhibitors therapy.

Figure S2. Comparison of CMV -recurrence free survival between patients that received the belatacept -mTORi combination during the first year post transplantation (designed as "Early group") and those who received the belatacept -mTORi later (designed as "late group"). Regarding the number of patients included, the statistical data is purely indicative.

Table S1. Comparison of the main characteristics of patients with a past of CMV DNAemia switched for a belatacept + mTORi combination, and a matched cohort of patients receiving belatacept + MPA.

Other opportunistic infections.

STROBE Checklist.

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