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Background. Costimulatory blockade with belatacept has demonstrated long-term benefits in renal transplantation, but de novo use in liver transplant recipients has resulted in increased rejection, graft loss, and death. However, belatacept conversion as a calcineurin inhibitor (CNI) avoidance strategy has not been studied and may be of benefit in liver transplantation where CNI-induced renal dysfunction and toxicity are barriers to improved outcomes. **Methods.** Using clinical data extracted from our institutional medical record, we report on 8 patients who underwent kidney after liver transplantation and were treated with belatacept-based immunosuppression and transient CNI therapy. **Results.** All patients tolerated belatacept therapy without any patient deaths or graft losses. No episodes of rejection, de novo donor-specific antibody formation, or major systemic infections were observed, and all patients demonstrated preserved liver and excellent renal allograft function. Patients received belatacept for a median duration of 13.2 mo, and at a median follow-up of 15.9 mo post–kidney transplant, 6 of 8 patients continued on belatacept with 3 completely off and 3 poised to transition off CNI. **Conclusions.** These findings are the first evidence that in liver transplant recipients requiring subsequent kidney transplantation, belatacept-based therapy can potentially facilitate CNI-free maintenance immunosuppression. This supports the possibility of belatacept conversion in stand-alone liver transplant recipients as a viable method of CNI avoidance.

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INTRODUCTION

Since their introduction in the 1980s, calcineurin inhibitors (CNIs) have been the cornerstone of immunosuppression in solid organ transplantation, leading to dramatic improvements in patient and graft survival.[1-3] Despite their ongoing role in most immunosuppressive regimens, significant challenges associated with their use remain, leaving a subset of patients who require alternative immunosuppression strategies.[4] CNIs have been associated with a number of deleterious acute manifestations, including neurotoxicity and, in the setting of renal transplantation, thrombotic microangiopathy of the renal allograft, which can lead to significant renal dysfunction and graft loss.[5,6] Long-term use has been associated with alterations in glucose and lipid metabolism, hypertension, increased risk of cardiovascular disease, and nephrotoxicity.[7,8] The negative long-term effects of CNIs on renal function have been particularly evident in recipients of nonrenal solid organ allografts, as in liver transplantation.

Selective costimulatory blockade with belatacept has emerged as an alternative immunosuppressive strategy to CNIs in kidney transplantation, with demonstrated long-term improvements in glomerular filtration rate as well as a decreased long-term risk of death and graft loss when compared with CNI-based regimens.[9] Although its use in renal transplantation is expanding,[10-12] the use of belatacept in nonrenal solid organ transplantation is limited by a paucity of data.[13,14] In liver transplantation, chronic renal insufficiency develops in a substantial number of recipients and serves as a significant risk factor for late posttransplant mortality that has been variably associated with CNIs.[15,16] Thus, there is an unmet need for CNI-free long-term maintenance strategies in liver transplant recipients to prevent renal dysfunction, obviate the need for renal transplantation, and improve outcomes. The use of belatacept is one possible method of achieving this important goal.

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Following the early promising results of belatacept in kidney transplantation, a phase II clinical trial evaluating de novo belatacept in adult liver transplantation was conducted. Despite significantly improved renal function in belatacept-treated liver transplant patients, increased rates of acute rejection, graft loss, and death were observed in the belatacept group compared with those treated with a CNI-based regimen.[17] Consequently, the trial was terminated prematurely, and a black box warning by the US Food and Drug Administration was issued for belatacept use in liver transplantation. It is unclear whether trial design and patient selection, mechanisms of CD28 blockade, or a combination of both underlie the inferior results observed with belatacept in the phase II study.[18] Understandably, there have been few subsequent investigations evaluating belatacept in the liver transplant setting, despite the finding on post hoc analysis that liver transplant recipients in the aforementioned discontinued phase II trial experienced a significant decline in glomerular filtration rate once they transitioned from belatacept to CNIs.[19] Importantly, although this trial raises concerns about de novo use of belatacept in liver transplant recipients, posttransplant conversion to belatacept may yet be of benefit to liver transplant recipients, particularly when renal dysfunction and CNI-induced toxicity are potential barriers to improved outcomes.

At Emory University Hospital, belatacept has been used for maintenance immunosuppression in renal transplantation since its Food and Drug Administration approval in 2011.[20] Belatacept combined with transient CNI therapy has become our standard immunosuppressive regimen for eligible de novo kidney transplant recipients and achieves CNI-free long-term maintenance therapy in the majority of patients. In this study, we report on the use of this belatacept-based regimen in kidney after liver (KAL) transplantation. To the best of our knowledge, belatacept-based immunosuppression for this KAL patient population has not been previously reported, nor has belatacept conversion in a series of liver transplant recipients of this size. We demonstrate that in prior liver transplant recipients requiring kidney transplantation, belatacept-based therapy was both efficacious and safe, facilitating CNI-free maintenance immunosuppression in several recipients. These findings introduce that belatacept conversion in liver transplant recipients may be a viable method of extending the long-term benefits associated with costimulatory blockade and CNI avoidance to liver transplant recipients.

MATERIALS AND METHODS

Data Extraction

After institutional review board approval (IRB00000393), we reviewed our institutional database for patients who underwent KAL transplantation and who were managed with belatacept immunosuppression after their kidney transplant. We identified 8 recipients who met our inclusion criteria and received a kidney transplant at Emory University Hospital between January 1, 2010, and December 31, 2020. Six of these 8 recipients received a kidney transplant within the past 2 y, reflecting a change in our group practice rather than a specific patient indication as the reason for initiating belatacept. A retrospective chart review was undertaken and data were extracted from the electronic medical record. We extracted patient demographics, immunosuppression regimens, clinical history, pathology records, and laboratory investigations, including serum creatinine, estimated glomerular filtration rate, liver function tests, BK virus and cytomegalovirus (CMV) levels, and HLA antibody profiles. Visualization of the clinical data was performed using the R software platform and packages readr, dplyr, and ggplot (The Comprehensive R Archive Network, https://cran.r-project.org).

Immunosuppression Protocols

KAL transplant recipients were treated with our standard kidney transplant belatacept-based immunosuppression protocol[20] (Figure 1), which consists of basiliximab induction (20 mg intravenous [IV] intraoperatively) followed by maintenance therapy with belatacept (10 mg/kg initial intraoperative dose and 5 mg/kg monthly thereafter), corticosteroids (500 mg IV intraoperatively; 250 mg and 125 mg IV on postoperative days 1 and 2, respectively; 5 mg postoperatively daily thereafter), mycophenolate mofetil (2000 mg daily), and transient CNI therapy (low-dose tacrolimus for 9 mo posttransplant [tacrolimus troughs, 3–8 ng/mL], followed by wean and discontinuation by month 12). All patients received the above protocol with 3 exceptions. Patient 4 was initially on a CNI-based (tacrolimus) regimen but immediately converted to belatacept 5 d post–kidney transplant because of biopsy-proven thrombotic microangiopathy. She received transient low-dose cyclosporine for 9 mo before being weaned off of all CNIs. Patient 8 was also initiated on a CNI-based regimen but was transitioned to the belatacept-based protocol described above 13 d posttransplant because of delayed graft function and a history of CNI nephrotoxicity. Patient 6 received an HLA-identical living donor allograft from a full sibling and was not initiated on transient CNI therapy in accordance with our belatacept-based HLA-identical protocol.

HLA Assessment

HLA antibody assessments were performed on all patients at baseline and regular intervals per protocol thereafter. Antibody screening was performed using solid-phase flow cytometry screening (FlowPRA, One Lambda, Inc., Canoga Park, CA). Sera from patients with anti-HLA antibodies were subsequently analyzed using LABScreen single-antigen bead assay (One Lambda, Inc.) to determine antibody specificity and the presence/absence of donor-specific antibodies (DSAs) (mean fluorescence intensity). Sera are not pretreated or diluted before single-antigen bead testing. Mismatch was determined by comparing donor–recipient phenotype at the antigen/allele level for the A, B, and C class I loci and DQ and DR class II loci.

Infection Surveillance

Infection surveillance was conducted in accordance with our center's post–kidney transplant clinical protocol. KAL recipients were screened for evidence of bacterial infection using laboratory investigations, clinical exam, and urinalysis during all clinical follow-up visits. In addition, screening for BK virus and CMV was performed with monthly polymerase chain reaction testing for the first 12 mo posttransplant. Screening for Epstein-Barr virus (EBV) was performed by monthly polymerase chain reaction testing for 6 mo for any transplant where the donor was positive and the recipient was negative and again at months 9 and 12.

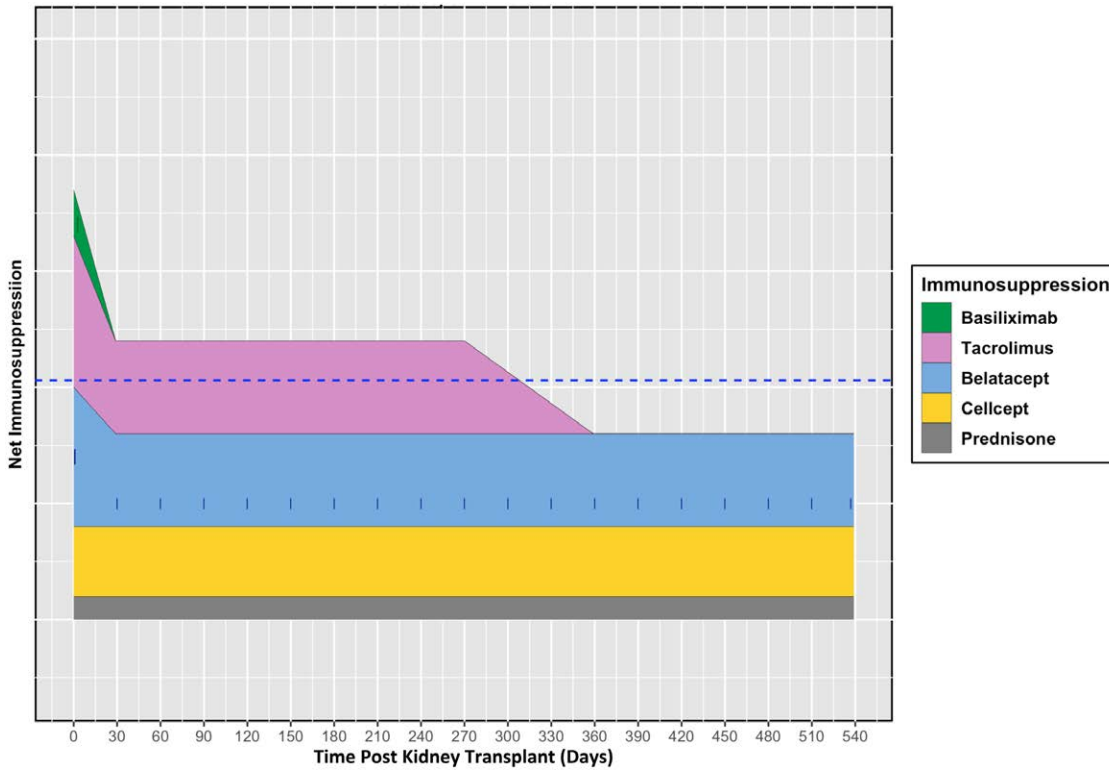

FIGURE 1. Schematic of the belatacept-based immunosuppression protocol. The protocol consists of basiliximab induction; transient, low-dose tacrolimus therapy; and belatacept, CellCept, and prednisone maintenance. Tacrolimus withdrawal initiated at 270 d (9 mo) and completed by 360 d (12 mo) posttransplant. Notably, tacrolimus is not administered in HLA-identical kidney transplants.

Statistical Analysis

Descriptive statistics were used to report on measured variables.

RESULTS

Patient Characteristics and Immunosuppression

A total of 8 patients underwent KAL transplantation and received belatacept-based immunosuppression. Patient, disease, and follow-up details are summarized in Table 1. All patients were adults at the time of kidney transplant, ranging in age from 26 to 72 y. Three patients were male and 5 patients were female. The median time post–liver transplantation was 53 mo (range, 7–285 mo). All patients received basiliximab induction and were started on belatacept either at the time of their kidney transplant according to our center's standard belatacept regimen or shortly thereafter, as described in Materials and Methods.

The patient cohort has been on belatacept for a median time of 13.2 mo (range, 2.5–51.8 mo). Two patients have not continued on belatacept post–kidney transplant: patient 1 after 12 mo due to chronic vascular access difficulties, and patient 3 after 11 mo in the context of mild asymptomatic BK viremia, which subsequently resolved. Notably, this was not standard management of BK viremia at our center but was undertaken because it coincided with the onset of the coronavirus disease 2019 pandemic and its attendant logistical challenges. At last follow-up, 6 of the 8 patients remain on belatacept therapy. Of these, 1 was never on CNI (patient 6, HLA-identical), 2 have completed their CNI wean, and 3 remain on low-dose CNI that continues to be tapered.

Patient/Graft Survival and Allograft Function

Median patient follow-up after kidney transplant has been 15.9 mo (range, 2.9–100.5). There have been no patient deaths or liver or kidney allograft losses, and all patients have exhibited excellent and stable graft function while on belatacept (Figure 2). Two patients (patients 2 and 4) experienced mild elevations in their liver transaminases (<200 U/L) early post–kidney transplant that were self-limited and resolved without intervention or adjustment in immunosuppression. Patient 1 experienced mild, asymptomatic elevation in her liver transaminases (<150 U/L) during the first year post–renal transplant, which was thought to be associated with low-level EBV reactivation (<17 000 copies/mL), for which she was treated with valganciclovir. Of note, the patient had a history of intermittent EBV reactivation and transaminase elevation that preceded the renal transplant and belatacept regimen. A liver biopsy performed 11 mo post–renal transplant was negative for rejection. All patients but 1 exhibited normal (<1.2 mg/dL) and stable total bilirubin levels postoperatively. Patient 7 exhibited a mild transient increase to 1.6 mg/dL 2 mo posttransplant, which was not associated with any other abnormalities and subsequently resolved. There were no instances of acute cellular rejection in either the kidney or the liver allografts, and there was no de novo DSA formation on belatacept (Table 2).

Safety

No liver-related complications were observed. Three patients developed BK viremia during the study period. Two of these were low-level viremias (<11 000 copies/mL) that were managed with reduced immunosuppression (patients 3 and 8).

TABLE 1.

Patient characteristics and transplant data

Patient		Liver transplant			Kidney transplant							Graft survival and follow-up			
ID	Sex	Age (y)	Cause of ESLD	Rejection	IS before KTx	Age (y)	Time post–liver Tx (mo)	IS at KTx	Cause of ESRD	Re-Tx	Donor type	Rejection	Kidney (mo)	Liver (mo)	Time on belatacept (mo)	Current IS
1	F	3	Biliary atresia	No	Tac[a] Sirolimus Pred	26	281	Bela Tac MMF Pred	CNI toxicity	Yes[b]	Living	No	100.5	381.4	12.1	Tac[c] AZT Pred
2	M	5	A1AT deficiency	No	None[d]	29	285	Bela Tac MMF Pred	Hypertension	No	Living	No	51.8	336.5	51.8	Bela MMF Pred
3	F	54	Alcoholic cirrhosis	No	Tac[a] MMF	55	7	Bela Tac MMF Pred	Hepatorenal syndrome	No	Deceased	No	18.2	25.2	10.6	Tac[e] MMF Pred
4	F	59	Cryptogenic	Yes[f]	CsA[g]	61	23	Tac MMF Pred	T2DM	No	Deceased	No	15.9	38.9	15.7	Bela MMF Pred
5	M	64	Secondary biliary cirrhosis	No	Tac[a]	66	22	Bela Tac MMF Pred	T2DM	No	Living	No	14.1	35.9	14.1	Bela Tac Pred
6	F	60	Alcoholic cirrhosis	No	Sirolimus Pred	64	53	Bela MMF Pred	CNI toxicity/TMA	No	Living	No	13.2	65.8	13.2	Bela MMF Pred
7	F	60	A1AT deficiency	No	Tac[a] MMF Pred	61	13	Bela Tac MMF Pred	Hepatorenal syndrome	No	Deceased	No	6.1	18.8	6.1	Bela Tac MMF Pred
8	M	64	NASH cirrhosis	No	Tac[a] Pred	72	103	Tac MMF Pred	CNI toxicity	No	Deceased	No	2.9	106.4	2.5	Bela Tac MMF Pred

[a]Target tacrolimus trough levels: Pt 1: 4–8 ng/mL, Pt 3: 8–10 ng/mL, Pt 5: 5–8 ng/mL, Pt 7: 6–8 ng/mL, Pt 8: 3–5 ng/mL.
[b]Previous deceased donor renal transplant that failed after 11 y due to chronic allograft failure.
[c]Belatacept discontinued after 12 mo because of chronic vascular access difficulties.
[d]Patient discontinued all immunosuppression 6 y before kidney transplant.
[e]Belatacept discontinued after 11 mo in the context of asymptomatic BK viremia.
[f]Pre-kidney, pre-belatacept.
[g]Target CsA trough levels: 150–200 ng/mL.
A1AT, alpha 1 antitrypsin; AZT, azathioprine; Bela, belatacept; CNI, calcineurin inhibitor; CsA, cyclosporine A; ESRD, end stage renal disease; IS, immunosuppression; KTx, kidney transplant; MMF, mycophenolate mofetil; NASH, nonalcoholic steatohepatitis; Pred, prednisone; Pt, patient; Re-Tx, retransplantation; T2DM, type 2 diabetes mellitus; Tac, tacrolimus; TMA, thrombotic microangiopathy; Tx, transplant.

The other patient (patient 4) developed BK nephropathy that was also resolved by decreasing the doses of mycophenolate mofetil and CNI while remaining on belatacept therapy. All patients in the cohort were CMV intermediate risk (recipients CMV immunoglobulin G seropositive), and there were no episodes of CMV viremia. Patient 4 developed a postoperative subcutaneous seroma, which became superinfected after bedside percutaneous drainage and ultimately required debridement and washout. There were no instances of posttransplant lymphoproliferative disorder or other infectious events in this group.

DISCUSSION

Despite being a cornerstone of transplant immunosuppression for the past 40 y, CNIs continue to be associated with a variety of detrimental short- and long-term side effects that include impaired renal function and cardiovascular toxicity in renal and nonrenal solid organ transplantation. CNI-related toxicities have prompted efforts to minimize or eliminate their use. In liver transplantation, CNIs result in high rates of renal insufficiency and end stage renal disease,[15,16] but optimal and widely accepted alternative immunosuppressive options are lacking. De novo use of the CNI alternative belatacept in liver transplantation did not show efficacy in a phase II study, but the potential benefit of belatacept as conversion therapy in stable liver transplant recipients has not been evaluated as a method of CNI avoidance. In this study, we report on a cohort of liver transplant recipients converted to belatacept-based immunosuppression with transient CNI therapy at the time of kidney transplantation. Overall, all 8 KAL recipients tolerated belatacept therapy without any patient deaths or graft losses. No episodes of rejection, de novo DSA formation, or major systemic infections were observed, and all patients demonstrated preserved liver and excellent renal allograft function. At a median follow-up of 15.9 mo post–kidney transplant, 6 of 8 patients remained on belatacept with a total of 3 patients completely off of CNI therapy.

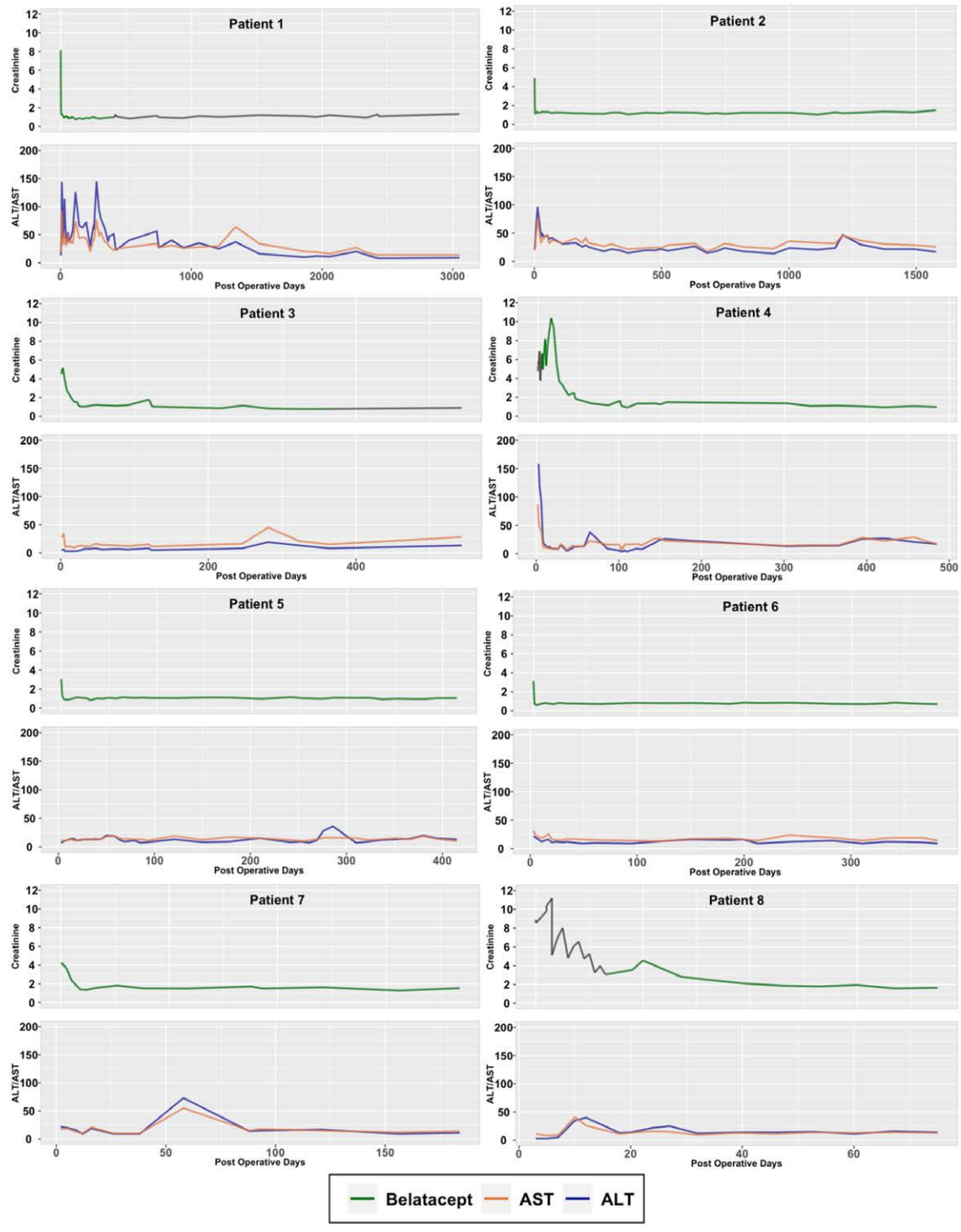

FIGURE 2. Renal and liver allograft function in the postoperative period following kidney transplantation. ALT, alanine transaminase; AST, aspartate transaminase.

The demonstrated efficacy of belatacept in preserving long-term renal function and reducing the risk of death and graft loss has led to its increased use as a maintenance agent in renal transplantation.[9-12,21] Despite these benefits, widespread uptake of belatacept has been limited because of increased rates of acute cellular rejection when compared to CNI-based regimens.[22] Mitigation strategies to overcome the increased risk of rejection include late conversion from CNI to belatacept or the use of adjunctive de novo therapies.[12,23] Whereas many centers have opted for conversion,[11] at Emory we have primarily used a transient course of low-dose tacrolimus therapy within the first year posttransplant that has reduced rejection rates to levels comparable with those of CNI-based regimens while preserving the benefits of belatacept on renal function.[9,20] As such, in this series of KAL patients, we have effectively extended late conversion to belatacept for stable liver allograft recipients using adjunctive transient CNI therapy for the kidney graft to minimize risk of rejection and ultimately achieve CNI-free maintenance immunosuppression.

TABLE 2.

Patient HLA profiles

Patient ID	HLA mismatch[a]		PRA Time of kidney transplant		PRA Most recent		DSA[b]
	Class I (A–B–C)	Class I (DR–DQ)	Class I %	Class II %	Class I %	Class II %	
1	1–1–1	1–1	00	00	00	00	No
2	0–1–1	1–1	24	00	00	00	No
3	1–2–1	2–1	00	00	00	00	No
4	1–2–1	1–2	00	00	00	00	No
5	0–1–1	1–1	00	00	00	00	No
6	0–0–0	0–0	00	00	00	00	No
7	1–2–1	2–2	00	00	00	00	No
8	0–0–0	0–0	29	11	33	08	No

[a]With reference to renal allograft.
[b]With reference to renal and liver allograft.
DSA, donor-specific antibody; PRA, panel reactive antibody.

The phase II trial evaluating the use of belatacept in de novo liver transplantation delivered disappointing results. Belatacept was associated with higher rates of early acute cellular rejection, mirroring a similar effect observed in kidney recipients in the BENEFIT trial[24] that has now been mitigated by alternative de novo immunosuppressive strategies.[10,12,20] However, belatacept was also associated with an increased risk of death and graft loss 6 and 12 mo posttransplantation, with a majority of these attributable to sepsis and multisystem organ failure.[17] Although it is not clear whether the inferior outcomes observed with belatacept were a result of patient selection and preexisting immune compromise in the liver recipients or from direct interference with the CD28 pathway and impaired protective immunity,[18] we did not observe any significant adverse outcomes in this series of KAL recipients. There were no instances of acute cellular rejection in the liver or renal allografts, no patient deaths or graft losses, and no major systemic infectious events. One episode of BK nephropathy was successfully managed with immunosuppression reduction while ultimately maintaining the patient on belatacept. It is probable that transient CNI therapy contributed to reduction of rejection risk for both grafts and that, unlike the phase II liver trial, all recipients in our cohort had a stable, functioning liver allograft at the time of kidney transplant and belatacept initiation, with a minimum of 7 mo having elapsed since the liver transplant.

The CNI avoidance strategy of early conversion to mammalian target of rapamycin (mTOR) inhibitor-based therapy has demonstrated efficacy in preserving renal function,[25] but is suboptimal and limited by the adverse outcomes characteristic of the mTOR inhibitor class (eg, pneumonitis, wound complications, metabolic toxicities). Successful posttransplant conversion to belatacept in nonrenal solid organ transplantation has been previously reported,[26,27] but very few instances have been observed in liver transplant recipients. The largest experience in liver transplantation consisted of the successful use of belatacept as a temporary bridge to renal recovery in 7 recipients with hepatitis C,[28] but the duration of belatacept treatment was short, ranging from 19 to 89 d and all patients were converted back to CNIs. More recently, Lang et al[29] described belatacept as salvage maintenance immunosuppressive therapy in a liver transplant recipient who had experienced multiple complications associated with CNI and mTOR inhibitor therapy, and Klintmalm and Gunby[30] reported on the resolution of chronic antibody-mediated rejection and a successful subsequent pregnancy in a liver transplant recipient transitioned to belatacept. Our study is unique in that all patients in our cohort received belatacept as conversion therapy in relation to the liver allograft, with 6 of 8 patients on track for long-term CNI-free maintenance therapy. Interestingly, CNI toxicity occurred either pre- or posttransplant in 4 of the 8 recipients in this study.

This study has certain limitations, most notably that it is a small single-center experience that is retrospective in nature and consists of relatively unsensitized, low immunologic risk recipients without a history of hepatocellular carcinoma or immune-mediated liver disease. Furthermore, the duration of follow-up is modest (median 15.9 mo), although a majority of patients (5 of 8) in the cohort have now been on belatacept >1 y and are beyond the period of time during which complications were observed in the phase II trial and during which transplant recipients are at most risk of immunologic or infectious complications. Three of these patients are completely off CNI and 3 others are at least on reduced dose CNI and positioned to transition off. Additionally, it is important to note that these results cannot be generalized to de novo liver transplantation, nor to recipients of simultaneous liver/kidney transplants. All recipients in this series received belatacept after a period of ≥7 mo of liver allograft stability, which may be a key factor contributing to the favorable outcomes observed to date. The time elapsed from liver to kidney transplant in our cohort varied significantly, ranging from 7 to 285 mo, with 2 of the recipients having received their liver transplants as young children. The optimal timing post–liver transplant at which to consider a transition to belatacept in the setting of KAL thus remains to be defined.

Although the long-term impact of belatacept immunosuppression in this group of patients remains to be elucidated, this series suggests that belatacept can be safe and effective in de novo renal transplant recipients with a previous history of liver transplantation and may possibly be a viable conversion option to achieve CNI-free therapy in stand-alone liver transplant recipients. Belatacept represents a potentially valuable addition to the immunosuppression armamentarium in nonrenal transplant recipients, particularly in the setting of CNI-associated renal dysfunction and as the basis for CNI

avoidance efforts. Larger prospective future studies should be considered to formally evaluate these possibilities and may open avenues for liver transplant recipients to derive benefit from the long-term renal protective effects of belatacept.

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