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The impact of belatacept on third party HLA alloantibodies in highly sensitized kidney transplant recipients

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Abstract

Recent evidence suggests that belatacept reduces the durability of pre-existing antibodies to class I and class II HLA antigens. In this case series of 163 highly-sensitized kidney transplant candidates whose calculated panel reactive antibody (cPRA) activity was ≥98–100%, the impact of belatacept on pre-existing HLA antibodies was assessed. Of the 163 candidates, 72 underwent transplantation between 12/4/2014 and 4/15/2017; 60 of these transplanted patients remained on belatacept consecutively for 6 at least six months. We observed a decrease in the breadth and/or strength of HLA class I antibodies as assessed by FlowPRA® in belatacept-treated patients compared to controls who did not receive belatacept. Specifically, significant HLA antibody reduction was evident for class I (p<0.0009). Post-transplant belatacept-treated patients also had a clinically significant reduction in their cPRA compared to controls (p<0.01). Collectively, these findings...
suggest belatacept can reduce HLA class I antibodies in a significant proportion of highly sensitized recipients and could be an option to improve pre-transplant compatibility with organ donors.

INTRODUCTION

Until recently, deceased donor (DD) kidney allocation to highly sensitized transplant candidates was infrequent due to HLA incompatibility among donors and recipients. The new kidney allocation system (KAS) prioritized candidates with calculated panel reactive HLA antibodies (cPRA) levels of 98–100% for DD kidneys. While their transplant rates increased from 2.7% to 19.1%, statistical models demonstrated that a quarter of these patients remained without a compatible donor.¹ The HLA antibodies in these patients are persistent² and thus present a formidable barrier to organ access.

The fusion protein, belatacept, is an inhibitor of T cell activation via its binding to CD80/CD86 molecules on antigen presenting cells, thereby limiting the availability of these ligands to engage T lymphocytes through their CD28/CD152 receptors.³ In recent human in vitro studies, belatacept reduced plasmablast differentiation and immunoglobulin production.⁴ In vivo primate studies revealed that belatacept suppressed donor specific antibodies at the level of the germinal center by regulating T follicular helper cells.⁵,⁶ In addition, in a dual therapy setting including bortezomib, belatacept suppressed memory B cell proliferation.⁵ However, the impact of belatacept on long-lived plasma cells (LLPC), which are likely responsible for the continuous production of pre-existing antibodies (including HLA antibodies) has not been characterized. Interestingly, murine studies revealed that CD28 is important for LLPC survival and maintenance of long-term antibody titers.⁷,⁸ Furthermore, studies in healthy human volunteers demonstrated CD28 expression on approximately 30% of LLPC.⁹ Finally, recent studies revealed decreased production of de novo donor specific HLA antibodies (DSA)¹⁰,¹¹ and elimination of pre-existing DSA¹² in minimally sensitized recipients treated with belatacept compared to those patients treated with cyclosporine. Overall, these studies suggest that belatacept could reduce the production of pre-existing HLA antibodies in highly sensitized transplant recipients. This hypothesis became testable within the Emory Transplant Center (where belatacept is routinely used as a standard maintenance immunosuppressive agent) when the new KAS was implemented. That policy resulted in a significant increase in transplantation of highly sensitized candidates with a cPRA ≥98%.¹³,¹⁴ Herein, we report that a significant proportion of highly sensitized transplant recipients treated with belatacept exhibited a decrease in their pre-existing HLA antibodies.

MATERIALS AND METHODS

Study design

An IRB-approved retrospective cohort study assessing the waitlist demographics and pre- and post-transplant HLA antibody characteristics of recipients transplanted with cPRA values ≥98% was performed upon data collected from 12/4/2014–10/23/18. Patients were transplanted only in the absence of DSA. Excluded from analysis were patients who did not
complete at least six months of monthly belatacept treatment. Also included were sera from transplant recipients with a cPRA of 98–100% receiving control immunosuppression. HLA antibodies were assessed using FlowPRA® and/or Luminex single-antigen bead assays as described below.

**HLA antigen and antibody assessment**

*HLA-A, -B, -C, -DRB1 -DQB1 and DPB1* antigens were identified by molecular typing methods. Antibody screening was performed using solid-phase flow cytometry screening (FlowPRA®, One Lambda, Inc., West Hills, CA). The presence of HLA antibodies was assessed in transplanted patients at baseline (day of transplant) and post-transplant (Figure 1). The FlowPRA® was considered positive when ≥3% of class I or class II beads displayed increased fluorescence intensity (i.e., a shift to the right on the X axis of the histogram) in comparison to a negative control from human serum containing no HLA class I or class II antibodies. FlowPRA provides data based exclusively on the total number of positive HLA antigen coated beads. Specificities of the HLA antibodies are not determined. Patient sera were further analyzed using the Luminex single-antigen bead assay (One Lambda, Inc.) to determine HLA antibody specificity and their mean fluorescence intensity (MFI), as previously described. The threshold to consider an HLA antigen unacceptable was 2000 MFI. Pre- and post-transplant cPRA values of 60 belatacept treated patients and 19 control patients were assessed using the UNOS cPRA calculator. Post-transplant charges in class I or class II antibodies were assessed when pre-transplant FlowPRA® levels were >20%. Post-transplant charges in a patient’s class I or class II antibodies were considered informative only when pre-transplant FlowPRA® levels of those antibodies were >20%. Post-transplant, a response to treatment was defined as positive only when the reduction in FlowPRA was ≥10%.

**Immunosuppression**

In accordance with the Emory Transplant Center immunosuppression protocol and as shown in Figure 2, belatacept treated recipients received induction with basiliximab and steroids (500mg IV solumedrol intraoperatively, tapered to prednisone 5mg daily upon post-operative day 3). Maintenance immunosuppression was with tacrolimus (trough target 5–8 ng/ml for months 0–6 post-transplant, 3–5 ng/ml for months 6–9 post-transplant, and tapering of tacrolimus at month 9 and eventual discontinuation by month 11), belatacept (10mg/kg intra-operatively, 5mg/kg beginning month 1 and monthly thereafter) mycophenolate mofetil (1–2g daily), and prednisone. Control group immunosuppression (Figure 1) included induction with thymoglobulin (6–7.5mg/kg) or basiliximab and maintenance immunosuppression with tacrolimus (trough target 8–12 ng/ml), mycophenolate mofetil (1–2g daily), and prednisone (5 mg daily). Figure 2

**Statistical analysis**

Data were analyzed with Student’s t-test. A *P* value < 0.05 was considered statistically significant.
RESULTS

Demographics of Waitlist Candidates and Transplant Recipients

Of 163 patients who were actively listed at Emory with a cPRA of ≥98% (average cPRA of 99.74%) during the study period; 72 (44%) patients were transplanted, while 91 (56%) remained on the waitlist. Among transplant recipients, 32 of 72 (44%) were re-transplants, 70 of 72 (97%) were from deceased donors and two were from living donors (one from a sibling, one from paired donor exchange). The majority of recipients were primary transplants (56%), female (72%), and African American (65%). The average age was 49.1 years, and the most common causes of ESRD were glomerulonephritis and hypertension (Table 1).

HLA Antibody Loss

In Supplemental Figure 1, the FlowPRA® histograms display the pre- and post-transplant results of a patient who received belatacept. As seen in Supplemental Figures 1A and 1B, the pre-transplant FlowPRA® was 5% and 99% for class I and class II, respectively, while the post-transplant FlowPRA® values were 0% and 93%. Although the absolute changes in PRA values were modest, there were clearly apparent changes in the fluorescence intensities (approximately one log) and profiles (i.e., architecture) of the pre- vs. post-transplant class II antibody samples (Supplemental Figures 1B and 1D), suggesting a reduction in antibody breadth and/or strength of reactivity. Examples of the spectrum of decreased FlowPRA® responses in four belatacept treated patients are shown in Supplemental Figure 2.

HLA Antibody Loss: Belatacept vs. Control Immunosuppression

The pre-transplant and post-transplant FlowPRA® histograms were compared among recipients receiving control and belatacept immunosuppression. Figure 3 compares three subjects from each group. Compared to the relatively unchanged profiles of these three patients treated with control immunosuppression (Figures 3A, B and C), the belatacept-treated patients displayed marked changes in the profile and/or fluorescence intensities of class I, class II, or both antibodies (Figures 3D, E and F).

FlowPRA® Changes in cPRA ≥ 98% Belatacept-Treated Recipients

The analysis of class I and II FlowPRA® profiles at pre- and post-transplant in belatacept versus control immunosuppression recipients are shown in Figure 4. A reduction of >10% in FlowPRA® class I was observed in 32% (19/59) of the belatacept treated patients. The overall differences between belatacept treated patients and controls was significant for class I antibodies (p<0.0009). There was no significant difference for class II antibodies.

Single-Antigen Bead Analysis

To determine whether reduction in FlowPRA® corresponded to reduction in cPRA, the pre- and post-transplant sera from belatacept-treated patients and control patients were assessed by Luminex single antigen bead analysis. While all pre-transplant cPRA values ranged from 98–100%, 50% of post-transplant cPRA values were <98% in belatacept treated patients, and 18% had cPRA values <90% (Figure 5). In contrast, 11% of control patients dropped
below 98% and 5% had cPRA values <90%. Post-transplant belatacept-treated patients had a significant reduction in their cPRA compared to controls (p<0.01).

DISCUSSION

In 2011, belatacept, co-stimulation blocker was introduced as an innovative and well-tolerated immunosuppressive agent. Initial reports revealed that patients receiving belatacept had higher rates of early acute rejection compared to those receiving cyclosporine. Subsequently, the BENEFIT trial demonstrated that patient survival, graft survival, and graft function were significantly higher with belatacept than with cyclosporine seven years after transplantation. Based on those data, belatacept was accepted as a safe immunosuppressive therapy. A minimally sensitized cohort of belatacept-treated patients had lower rates of de novo DSA than patients treated with cyclosporine. Recent post hoc analyses of those studies revealed that belatacept also decreased pre-existing DSA more effectively than cyclosporine. In this study, we investigated the impact of belatacept on HLA antibody levels in patients transplanted with a cPRA ≥98%.

Current options for highly sensitized patients not likely to be allocated a deceased donor kidney include: 1) “standard” desensitization (i.e., IVIG, IVIG and plasmapheresis ±Rituximab, proteasome inhibitors), 2) HLA antibody degradation with IgG-degrading proteases (IdeS), 3) transplanting across DSA, 4) paired donor exchange ± desensitization, and 5) no transplant (with its associated morbidity and mortality). The data presented here suggest there may be another option, namely, belatacept treatment, to reduce the breadth of class I alloantibody activity and increase the likelihood of finding compatible donors. In the current study, up to one third of belatacept treated patients displayed a significant reduction in class I HLA antibodies. These findings are notable when compared to patients who received control immunosuppression who had essentially no change in their class I HLA antibody profiles. Importantly, none of the recipients who received belatacept underwent any of the pre-transplant desensitizing therapies described above. These data are consistent with the studies of Young et al wherein allosensitized mice given delayed treatment of CTLA4-Ig displayed a rapid reduction in donor-specific alloantibody even after a robust germinal center response was established, compared to untreated sensitized controls. In additional murine studies, Lee et al demonstrated CD28 promoted survival of LLPC. Interestingly, recent findings in humans demonstrated that ~30% of LLPC have surface CD28. Those data are consistent with the observation here that sensitized recipients treated with belatacept present with greater loss of pre-existing HLA antibodies than patients treated with control immunosuppression.

One explanation for the apparent inability of belatacept to reduce class II antibodies (or for why all patients with class I antibodies do not respond) may be that their titers are higher than those antibodies that are susceptible. In fact, a recent study reported that antibody titer could be a surrogate marker to predict patient responsiveness to desensitizing agents. Another possibility to explain responsiveness vs non-responsiveness to belatacept comes from studies by Halliley et al who reported that plasma cells in human bone marrow are composed of four distinct subsets. These subsets display significant variability in their lifespans, which, by extension, impact how long they can produce antibodies. Each plasma
cell subset may exhibit differential responsiveness to belatacept. Additional studies are needed to address whether class I and class II HLA antibodies are produced by distinct plasma cell subsets.

The cPRA values displayed in Figure 5 were calculated post-transplant. While the reduction in cPRA appears modest in some belatacept patients (e.g., a 5% reduction from 100% to 95%; Figure 5), recent data indicate that a subgroup of cPRA=100% patients could still have significant benefit from even this small change in cPRA. Specifically, not all patients with cPRA=100% have equally benefitted from the new KAS.1,29 The current study is consistent with those data and reveals a disparity in DD transplantation among cPRA =100% patients whose precise values are above or below 99.9%. The FlowPRA test is more indicative of responsiveness to belatacept than is SAB testing as changes can be visually discerned in the former compared to the latter. Data from our laboratory (unpublished) reveal that changes in FlowPRA do not necessarily correlate with changes in cPRA (which are based on SAB results). For example, two patients can present with 50% FlowPRA and have distinctly different fluorescence intensities. However, when tested by single beads, both patients display MFI values of 20000. This is the level at which single beads become saturated in our laboratory (using a Luminex 200 instrument). Thus, changes on FlowPRA could be masked when testing by SAB. In such circumstances, differences between such patients would need to be determined by titering the samples on SABs, an expensive endeavor beyond the scope of the current study.

Among 138 transplant candidates with cPRA=100%, incremental cPRA values ranged from (99.45%–99.99%; Table 2). Forty-eight of these candidates (35%) were transplanted over 28 months, while 90 patients (65%) remained on the waitlist. At study onset, 33% of the patients had cPRA values <99.9% and 67% had cPRA values >99.9%. Among the transplanted group, 69% had cPRA levels <99.9%, while 31% had cPRA levels >99.9%. Notably, of the cPRA=100% who remained on the waitlist at the end of this study, only 14% had cPRA levels <99.9, and 86% had cPRA levels ≥99.9%. These data reflect the ongoing disparity among cPRA=100% patients regarding their access to kidney transplant offers from deceased donors.

A reasonable speculation is that pre-treatment of such highly sensitized patients with belatacept could result in increased opportunities for transplantation from deceased donors or from paired donor exchange without the need for antibody depleting therapies such as IVIG, plasmapheresis, IdeS, etc. Prior studies demonstrate that the mechanism of action for belatacept to reduce pre-existing circulating antibodies is at the level of memory B cells and/or plasma cells/plasmablasts.4,5 However, as this was a retrospective study, it was exploratory and not designed to identify underlying mechanisms. Future studies involving the administration of belatacept to highly sensitized patients on the wait list need to evaluate 1) if there is an impact of HLA antibody reduction on organ allocation, 2) the role of concurrent immunosuppression with tacrolimus, mycophenolate mofetil, and prednisone, and 3) duration, safety (i.e., infectious risks) and efficacy profiles and 4) post-transplant outcomes including incidence of de novo DSA, acute rejection, graft failure, and patient survival.
The limitations to this study include: 1) it was a retrospective analysis, subject to selection bias, 2) there were fewer patients within the control group compared the belatacept group and 3) presence of confounding variables, since all belatacept patients received multiple immunosuppressive agents. Belatacept could synergize with these other immunosuppressants to reduce HLA antibodies rather than act alone. We believe our data warrant a clinical trial wherein belatacept would be tested as a monotherapeutic agent to eliminate HLA antibodies. In such a randomized and prospective clinical trial, the issues of selection bias and confounding variables would be addressed. With regard to the limited number of controls, valid comparison was dependent on assessment of cPRA 98–100% patients receiving control immunosuppression. Historical controls were virtually nonexistent as very few patients with cPRA values of 98–100% were transplanted prior to the new KAS. Since essentially all recipients at Emory received belatacept, control samples at Emory were limited until the recent nationwide shortage of belatacept happened. New patients transplanted at Emory during that time (including those with cPRA=98–100%) received tacrolimus maintenance immunosuppression and were included in this study. Controls ultimately included the Emory cohort and samples from subjects provided by our collaborators who do not use belatacept.

In summary, the data reported here support our previous studies that belatacept can reduce HLA antibody levels in minimally sensitized transplant patients and extend these observations into a population of highly sensitized patients. It is promising that a large subset of patients showed a decrease in class I antibody levels relatively early post-transplant with the well-tolerated agent, belatacept. Our data has shown a potential relationship between alloantibody reduction and belatacept that merits further examination. Belatacept may be another desensitizing agent that could benefit highly sensitized patients who otherwise would be unlikely to find a compatible organ. Prospective studies are needed to confirm the observations of this study and to determine whether pre-transplant administration of belatacept can reduce/eliminate HLA antibodies in highly sensitized candidates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to acknowledge Patricia Brannon, Vincent Fisher and Marilyn Eisenstadt, CHS for their excellent technical assistance.

Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>cPRA</td>
<td>calculated panel-reactive antibody</td>
</tr>
<tr>
<td>CTLA4-Ig</td>
<td>cytotoxic T lymphocyte-associated protein 4-immunoglobulin</td>
</tr>
<tr>
<td>DSA</td>
<td>donor specific HLA antibodies</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
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</table>

Am J Transplant. Author manuscript; available in PMC 2021 February 01.
**HLA**  human lymphocyte antigen

**IdeS**  IgG-degrading proteases

**KAS**  kidney allocation system

**LLPC**  long-lived plasma cells

**MFI**  mean fluorescence intensity

**FlowPRA®**  flow cytometry screening panel reactive antibody

**REFERENCES**


Figure 1: A schematic representation distinguishing patients treated with belatacept from patients treated with control immunosuppression.

*= FlowPRA analysis was performed separately for class I and class II antibodies. For each class, a FlowPRA value >20% was required for patient inclusion. **cPRA values from predicated on their pre-transplant FlowPRA (class I and class II) being >20%.
Figure 2: Graphic illustration of treatment regimens for patients treated with belatacept vs control immunosuppression.
Figure 3: FlowPRA® Histograms in belatacept-treated highly sensitized recipients versus recipients treated with control immunosuppression.
Class I and II FlowPRA® histograms comparing six highly sensitized kidney transplant recipients pre- and post-transplant, who were received either receiving control immunosuppression or a regimen that included belatacept. The patients that are shown represent the spectrum of response to Belatacept: change in both fluorescence intensity and architecture (D), peak loss with minor change in fluorescence intensity (E) and change in fluorescence intensity with minor change in peak architecture.
Figure 4: Comparison of changes in FlowPRA® for Class I & II for highly sensitized recipients treated with either control immunosuppression or belatacept.

The percent change in class I & II FlowPRA® values for the control immunosuppression patients (n=33 & 32 for Class I & II, respectively) and the belatacept-treated recipients (n=59 & 49 for Class I & II, respectively). Dots represent individual patients and their percent FlowPRA® change comparing an immediately pre-transplant sample to a sample obtained post-transplant.
Figure 5: Post-transplant cPRA values in belatacept-treated highly sensitized recipients (n=60) vs patients treated with control immunosuppression (n=19).

After identifying HLA class I/class II antibodies that had MFI values ≥2000, the corresponding antigens were entered into the UNOS cPRA calculator and cPRA values were derived.
Table 1:

Demographics of cPRA 98 –100% belatacept or control immunosuppression transplant recipients

<table>
<thead>
<tr>
<th>Transplant Recipients</th>
<th>Belatacept</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>72(100)</td>
<td>44(100)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>47(65)</td>
<td>25(57)</td>
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<tr>
<td>Hispanic</td>
<td>4(6)</td>
<td>4(9)</td>
</tr>
<tr>
<td>White</td>
<td>21(29)</td>
<td>12(27)</td>
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<tr>
<td>Asian</td>
<td>0(0)</td>
<td>3(7)</td>
</tr>
<tr>
<td>Transplant number, n (%)</td>
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<td></td>
</tr>
<tr>
<td>First</td>
<td>40(56)</td>
<td>20(44)</td>
</tr>
<tr>
<td>Second</td>
<td>31(43)</td>
<td>19(43)</td>
</tr>
<tr>
<td>Third</td>
<td>1(1)</td>
<td>4(9)</td>
</tr>
<tr>
<td>Sixth</td>
<td>0(0)</td>
<td>1(2)</td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52(72)</td>
<td>35(80)</td>
</tr>
<tr>
<td>Male</td>
<td>20(28)</td>
<td>9(20)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>46.9(25)</td>
<td>45.1(10)</td>
</tr>
<tr>
<td>Male</td>
<td>50(25)</td>
<td>52.8(13)</td>
</tr>
<tr>
<td>Etiology of ESRD, n (%)</td>
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<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>11(15)</td>
<td>10(23)</td>
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<tr>
<td>Hypertension</td>
<td>18(25)</td>
<td>8(18)</td>
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<tr>
<td>Polycystic Kidney</td>
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<td></td>
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<tr>
<td>Disease</td>
<td>11(15)</td>
<td>2(3)</td>
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<tr>
<td>Lupus</td>
<td>6(8)</td>
<td>5(11)</td>
</tr>
<tr>
<td>IgA Nephropathy</td>
<td>5(7)</td>
<td>3(7)</td>
</tr>
<tr>
<td>FSGS</td>
<td>8(11)</td>
<td>5(11)</td>
</tr>
<tr>
<td>Other, GN, etc.</td>
<td>13(18)</td>
<td>11(25)</td>
</tr>
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</table>
Table 2:

Comparison of transplanted and waitlist patients according to cPRA 99.9%

<table>
<thead>
<tr>
<th>cPRA</th>
<th>Total transplant candidates (n = 138)</th>
<th>Transplanted (n = 48)</th>
<th>Waitlist after 28 months (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 99.9%</td>
<td>33% (45)</td>
<td>69% (33)</td>
<td>14% (13)</td>
</tr>
<tr>
<td>&gt; 99.9%</td>
<td>67% (93)</td>
<td>31% (15)</td>
<td>86% (77)</td>
</tr>
</tbody>
</table>