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From bench to bedside: reversing established antibody responses and desensitization

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Abstract

Purpose of review: Basic transplant immunology has primarily focused on the definition of mechanisms, but an often-stated aspirational goal is to translate basic mechanistic research into future therapy. Pre-transplant donor specific antibodies (DSA) mediate hyperacute as well as early antibody-mediated rejection (AMR), while DSA developing late post-transplantation may additionally mediated chronic rejection. While contemporary immunosuppression effectively prevents early cellular rejection after transplant in non-sensitized patients, it is less effective at controlling pre-existing HLA antibody responses or reversing DSA once established, thus underscoring a need for better therapies.

Recent Findings: We here review the development of a bench-to-bedside approach involving transient proteasome inhibition to deplete plasma cells, combined with maintenance co-stimulation blockade, with CTLA-4Ig or belatacept, to prevent the generation of new antibody-secreting cells (ASCs).

Summary: This review discussed how this a treatment regimen that was rationally designed and validated to reverse established DSA responses in mouse models, translated into reversing active AMR in the clinic, as well as desensitizing highly-sensitized patients on the transplant waitlist.

Keywords

Donor-specific antibodies; antibody-mediated rejection; desensitization; proteasome inhibition; co-stimulation blockade

Introduction

Seminal studies by Billingham and colleagues established a critical role for T cells in mediating skin allograft rejection(1, 2), while studies by Terasaki and colleagues established a role for humoral immunity in mediating kidney rejection in the clinic (3, 4). Additional direct evidence for antibodies mediating kidney rejection came from Feucht and colleagues

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Conflict of interest

The authors have no additional conflicts of interest.

who reported on complement C4d deposits in the peritubular capillaries of rejected kidney allografts(5, 6). These and subsequent studies firmly establish the pathogenicity of high-titer DSA pre-existing at the time of transplantation, or when produced early post-transplantation, in mediating hyperacute and early AMR of kidney and heart allografts.

While there is a strong clinical correlation between DSA and poor graft outcomes (7-9), some controversy exists as to whether DSA is the initiator and/or driver of ongoing chronic rejection or is serving simply as a biomarker for an uncontrolled cellular response that is actually mediating graft rejection (10). One way to resolve this uncertainty would be to test if reversing DSA responses improves graft outcome. However, currently there is no treatment that reliably reverses established DSA responses especially in a chronic setting. In this review, we will discuss a mechanistic-based bench-to-bedside approach we took to developing an effective therapeutic strategy, involving co-stimulation blockade and proteasome inhibition, to reverse established donor-specific responses that is applicable to treating clinical AMR and in desensitization (Figure 1).

Preventing and reversing primary DSA responses

The T-cell dependent nature of the anti-donor HLA IgG response is clinically underscored by the fact that calcineurin inhibitor (CNI) withdrawal leads to an unacceptably high incidence of DSA(11, 12) and by the observation that non-adherence and CNI minimization, as is necessary to reduce CNI toxicities, increases the risk of developing DSA especially in patients where the antigenic eplet mismatch is high (13-15). T-dependent B cell responses develop in two phases: an earlier extrafollicular B cell phase that generates short-lived plasmablasts and memory B cells, and a later germinal center (GC) phase that generates short-lived plasmablasts and long-lived plasma cells (PC), as well as memory B cells. While extrafollicular and post-GC memory B cells and PCs exhibit somatic hypermutation (SHM) and class-switching, post-GC B cells tend to have higher levels of somatic mutation and undergo affinity maturation that is driven by limited access to GC Tfh help(16).

Our early studies into the splenic architecture after allogeneic heart transplantation revealed a significant increase in the T cell zones and GCs compared to isografted rats, whereas the B-cell follicles and MZ were not statistically different(17). Those observations are consistent with allografts preferentially eliciting T-dependent GC B cell responses with minimal extrafollicular and MZ responses, whereas significant increases in the B-cell follicles and MZ were observed after xenografting with hamster hearts. These observations prompted us to investigate if established GC responses could be dissolved and developing antibody responses halted with co-stimulation blockade that interferes with T:B cell activation. Indeed, anti-CD154 or CTLA-4Ig starting on day 7 after allogeneic donor splenocyte immunization rapidly dissolved established GCs and halted further development of the alloantibody response(18). Furthermore, delaying the initiation of CTLA-4Ig treatment until day 6 after a fully mismatched heart transplantation inhibited alloantibody production and prevented acute rejection, while the adoptive transfer of immune sera reversed the effects of delayed CTLA-4Ig. These observations underscored the efficacy of co-stimulation blockade at inhibiting ongoing B cell responses even when graft-specific T cell and GC B cell

responses had been established(19, 20). Furthermore, delaying CTLA-4Ig treatment to day 7 post-sensitization was able to prevent the generation of memory B cells(20) (Figure 1).

In contrast, when CTLA-4Ig was administered starting on day 14 post-immunization, it no longer was able to reduce donor-specific IgG responses. The lack of efficacy was not due to the inability of CTLA-4Ig to dissolve late GC responses, but because plasmablasts had already been generated and CTLA-4Ig was not able to inhibit their production of donor-specific IgG(19). These observations suggested that inhibiting the production of donor-specific IgG by newly generated plasmablasts is necessary. One way to accomplish this is by adding a proteasome inhibiter such as bortezomib, to CTLA-4Ig therapy. Indeed, transient bortezomib in combination with sustained CTLA-4Ig, starting at day 14 after donor splenocyte immunization or allogeneic skin-transplantation was able to prevent further increase in DSA(21). Most impressively, this treatment combination starting as late as day 35 post-skin transplant was still able to reduce circulating DSA levels. This raises the intriguing question of whether the combination of a proteasome inhibitor and co-stimulation blockade could be translated to the clinical setting to halt and/or reverse established DSA responses.

Preventing and reversing recall DSA responses

Recent studies by Mesin et al.(22) using prime-boost models in mice showed that, contrary to expectation, secondary B cell responses were characterized by a bottleneck that restricted the engagement of the large diversity of memory B cell clones generated in the primary response. In fact, only a few higher-affinity memory B cell clones accounted for the majority of secondary antibody responses, whereas GC responses observed with secondary antigen encounter were predominantly populated by B cells without prior GC experience and are most likely naïve. One possible explanation for this observation was suggested by the early studies of Pape et al.(23), where the presence of high-affinity neutralizing serum immunoglobulin prevented low affinity memory B cells from participating in the recall response.

We investigated the fate of memory B cells upon re-encounter with the same alloantigen as in the primary sensitizing event, and showed that recall class-switched DSA responses were associated with memory B cells responding to donor-MHC Class I or Class II antigens by rapidly differentiating into plasmablasts, with minimal involvement of GC responses(20, 24). The appearance of donor-specific plasmablasts occurred more quickly in sensitized compared to naïve mice, correlating with more rapid increases in DSA, and was inhibited by CTLA-4Ig administration started at the time of transplant. Thus the recall B cell response upon re-encounter of the same alloantigens was extrafollicular and T cell-dependent. When CTLA-4Ig treatment was delayed for 14 days until the recall DSA was at its peak, and combined with transient administration of bortezomib, a significant and rapid reversal of the recall DSA response was also observed(21), suggesting a therapeutic treatment for sensitized patients undergoing AMR early post-transplantation. Similarly, Burghuber et al. (25) reported that the combination of co-stimulation blockade and transient bortezomib was able to significantly reduce AMR in sensitized non-human primates, through the targeting of both PC and upstream GC responses.

Investigations into the B cells participating in recall antibody responses in humans have only recently become possible through the use of ultrasound-guided fine needle aspiration to serially sample the draining lymph nodes and investigate the dynamics and specificity of GC B cell and PC responses after influenza vaccination(26). In response to seasonal influenza vaccination, GC responses were detected in 3 of 8 individuals, and between 12% and 88% of the responding GC B cell clones overlapped with B cells detected among early circulating plasmablasts. The shared B cell clones had high frequencies of somatic hypermutation consistent with memory B cells differentiation into PC and undergoing affinity maturation in the GC for new influenza epitopes. For the remaining vaccine-induced B cell clones detected only in the GC but not as plasmablasts, the GC B cells exhibited significantly lower frequencies of somatic hypermutation and predominantly encoded strain-specific antibodies consistent with naive B cells originating the GC. A reasonable explanation for the high frequency of memory B cells entering the GC is that the response is driven by new epitopes in the seasonal influenza vaccine, and that for identical epitopes, the entry of memory B cells into the GC response might be substantially reduced. An inference from these observations is that reencounter of identical HLA alleles might preferentially induce memory alloreactive B cells to differentiate into plasmablasts, but challenge with non-identical HLA epitopes/eplets might result in memory B cells entering into a GC response. In either case, susceptibility to co-stimulation blockade is predicted (Figure 1).

Based on the potency of CTLA-4Ig in combination with transient bortezomib in reversing established B cells primary or recall responses in our model, we conducted in a series of proof-or-principle investigation to test whether co-stimulation blockade with belatacept, in combination with transient bortezomib, was able to reverse established DSA responses and AMR in 6 kidney transplant recipients (21). Compassionate use of this regimen was initiated for the first patient who developed early, severe acute AMR after his third kidney transplant that was unresponsive to steroids, plasmapheresis, and intravenous immunoglobulin. Remarkably, belatacept in combination with two doses of bortezomib resulted in a rapid reversal of AMR and the reduction of 3 of 4 (including presumed anamnestic) DSA within 30 days. A 30-month follow-up showed sustained control of DSA responses and a well-functioning graft. These early observations prompted the treatment of five additional patients who also resolved their acute AMR episodes and had sustained disappearance of circulating DSA. Notably, case 4 was treated successfully with bortezomib and belatacept on post-transplant day 11, and DSA become undetectable by day 17. However, DSA was again detected on post-transplant day 31, and positive C4d deposition detected 50 days later prompted a second round of bortezomib on post-transplant day 115. This resulted in loss of all DSA within 119 days, and remained controlled at 18 months post-transplant follow-up. Likewise, case 6 presented with DSA and biopsy confirmed AMR at routine follow-up on day 291 post-transplantation. Treatment with bortezomib and belatacept also rapidly reversed 3 of 4 DSAs within 9 days. This small case series confirm that a strategy combining plasmablast and PC depletion with co-stimulation blockade is effective at reversing antibody responses in both an acute and subacute settings, thus raising the possibility that it might be efficacious in desensitization.

Targeting serological memory to HLA

Long-lived serological memory has long been thought to be mediated by long-lived PCs that reside in the bone marrow(27). An important feature of the long-lived PC cells is that they are not intrinsically long-lived, but depend on continually receiving survival signals from the microenvironment. In the bone marrow, this comprises soluble components such as cell-releasing (cytokines, growth factors, and chemokines) and extracellular matrix (ECM) components (fibronectin, collagen, laminin, and heparan sulfate (HS), and cellular components such as mesenchymal stromal/stem cells, dendritic cells (DC), monocyte/macrophages, megakaryocytes, eosinophils, basophils, and regulatory T cells. These cells support PC longevity through their production of survival cytokines, such as CXCL12, APRIL, and/or IL-6, and contact-dependent signals by CD138, CD28, CD44, VLA-4, and CD93. Notably, CD28 facilitates PC survival by stimulating IL-6 production by dendritic cells upon CD80/86 engagement(28, 29), and by promoting PC metabolic fitness through upregulating IRF4 and inducing ROS production(30).

Antibody producing cells (ASCs) are comprised of the short-lived plasmablasts produced by extrafollicular and GC responses, and long-lived PCs. In mice, Wilmore et al.(31) used B220, CD138 and Sca-1 (detecting Ly6A/E) to identify ASCs, while Pracht et al. (32) distinguished plasmablasts from PC based on expression of CD19 and B220, CD138 and TACI, with plasmablasts expressing $TACI^{+}CD138^{+}B220^{int}CD19^{int}$, and PC further down-regulating the B cell markers, B220 and CD19. PCs are a heterogenous population of cells that can reside in secondary lymphoid organs and sites of inflammation, in addition to the bone marrow(33). Studies by Halliley et al.(27) used the markers CD19, CD38, and CD138 to identify four PC subsets in human bone marrow (BM), with the CD19(−)CD38(hi)CD138(+) subset being the longest-lived population that expressed CD28 and genes enriched in the autophagy pathway, that has been reported to be critical for the survival and function of mouse PCs.

The unique properties of PC provide opportunities for depleting these cells in the transplantation setting. To this point, PC are vulnerable to proteasome inhibition, due to their vigorous production of secreted antibodies and propensity to accumulate misfolded immunoglobulins, resulting in endoplasmic reticulum stress, a misfolded protein response, and cell apoptosis (Figure 1)(34). There are a number of reports confirming the ability of proteasome inhibitors, such as bortezomib and carfilzomib, to reduce circulating DSA(35-38). However, the major caveat of these studies was the incomplete reduction of anti-HLA antibodies and their rebound when treatment was stopped. One hypothesis for the resistance to proteasome inhibition is differential susceptibility of PC subsets, with the long-lived PC being the most resistant. We tested this hypothesis in mice treated with bortezomib, and demonstrated, unexpectedly, that it was the more mature PC in the BM that were most sensitive to bortezomib compared to the proliferating plasmablasts(21). We reasoned that this susceptibility could be explained by the PC being more efficient producers of antibody compared to plasmablasts. Furthermore, investigations into resistance to carfilzomib by human $CD138^{+}$ PC using a transcriptomic profiling revealed an acquired genomic signature, including increased expression of the immunoproteasome that mediated resistance to the proteasome inhibitors carfilzomib, bortezomib, and ixazomib(39).

Experimental and clinical data indicate that proteasome inhibition alone cannot sustainably reduce circulating anti-HLA antibodies; indeed Kwun et al.(40) reported that repeated bortezomib monotherapy of allosensitized non-human primates resulted in humoral compensation that manifested as a rapid but transient induction of circulating IgG^+ B cells and increased GC responses in the lymph nodes. We reasoned that CTLA-4Ig or belatacept would work synergistically with proteasome inhibition to not only inhibit memory B cells differentiation into plasmablasts and PC, but also to deplete long-lived $CD28^+$ PC. Indeed, non-human primate and clinical data are consistent with this possibility, where long-term treatment with belatacept results in the gradual reduction of pre-transplant donor-specific as well as third-party HLA alloantibody in highly sensitized kidney transplant recipients(35, 41-43). Furthermore, Jain et al.(21) reported that sustained belatacept treatment after acute AMR resulted in the gradual reduction of anti-donor HLA Class I and Class II IgG. These observations raised the possibility that this approach of transient proteasome inhibition in combination with belatacept might be successful in desensitizing highly-sensitized patients on the transplant waitlist. This possibility was affirmed by the observations in non-human primates by Kwun, Knechtle and colleagues(25, 44-46).

Successful desensitization using this approach has recently been suggested in a small cohort of highly sensitized (cPRA>99%) heart transplant candidates(47). All four patients were female, multiparous, had a history of prior blood transfusions, and three were supported on a left ventricular assist device (LVAD) all with complications related to the device. Desensitization with multiple cycles of a proteasome inhibitor (with or without plasmapheresis) under continuous co-stimulation blockade with belatacept sequentially reduced the mean fluorescence intensity of both class I and II HLA antibodies, and allowed for transplant with a negative CDC crossmatch across multiple historically C1q binding DSA.

In this case series, participants received consecutive cycles of bortezomib and/or carfilzomib along with belatacept that was continued after each cycle was completed. Bortezomib, a boronic acid dipeptide, is a reversible first-generation proteasome inhibitor associated with off-target effects including peripheral neuropathy(48, 49). Carfilzomib has an epoxyketone as its active moiety, binds irreversibly offering a potential efficacy advantage, and has less neurotoxic effects but has been associated with cardiotoxicity in the myeloma literature raising concern for its use in desensitization(50). The rapid rebound observed with carfilzomib-based desensitization without costimulation blockade(38) reinforces the need for synergistic therapies that prevent ASC differentiation. A desensitization study in kidney transplantation combining carfilzomib with belatacept (NCT05017545, Table 1) will help further address both safety and efficacy of the approach. Recently, the results of a phase 2 study using the second-generation oral proteasome inhibitor, ixazomib, in highly sensitized kidney transplant recipients suggested a reduction in class I and II HLA antibodies in some participants although the effect was not consistent across all specificities (51). Its use in combination with belatacept has yet to be determined but this strategy, if successful, would simplify the regimen and potentially reduce some of the cost associated with infusions or injections required for carfilzomib and bortezomib, respectively. Finally, proteasomal adaptations may limit efficacy over time and thus, alternative options are warranted(39).

Daratumumab, a human IgG1 kappa monoclonal anti-CD38 antibody has successfully been used to target malignant plasma cells in treatment-refractory multiple myeloma and AL amyloidosis through a variety of Fc-dependent effector mechanisms, as well as directly inducing apoptosis(52-54). Its distinct mechanism of action from proteasome inhibitors may afford less off-target systemic effects (neurological, cardiac, and gastrointestinal). Daratumumab has also shown efficacy in cases of refractory lupus where both clinical improvement and a reduction in autoantibodies was observed(55), and in a case of pure red-cell aplasia after allogeneic stem-cell transplant(56). In the non-human primate sensitization model, daratumumab with plerixafor (anti-CXCR4) reduced circulating DSA and lymph node plasmablasts but not T follicular helper cells or proliferating germinal center B cells. DSA rebound was observed after transplant (57) emphasizing the need for synergistic strategies as are being studied in two clinical desensitization trials using daratumumab with belatacept in highly sensitized kidney transplant candidates (NCT04827979, NCT05145296; Table 1).

Daratumumab also reduces the frequency of CD38 expressing NK cells, suggesting a potential adjunctive therapeutic effect. However, the remaining NK cells may continue to be functional and promote immune cell priming, and the implications for allogeneic transplantation are unclear(58, 59). CD38 is additionally expressed on suppressor lineages including regulatory B cells, myeloid cells, and a subset of Tregs with enhanced suppressive function, further suggesting that off-target effects could be of concern (60). In heavily pre-treated multiple myeloma patients enrolled in two clinical trials, the CD8+ T cell: Treg ratio, CD8+ T cell clonality, and response to viral antigens increased during treatment with daratumumab suggesting immune activation(60). Indeed, in the aforementioned non-human primate model acute T-cell mediated rejection was observed(57). Consistent with this observation, cellular rejection or tubulointerstitial inflammation have also been described in select cases where daratumumab was used to treat AMR (61, 62). The implications for desensitization will be defined in ongoing clinical trials (Table 1). Other plasma cell therapies with the potential to be used in synergistic desensitization strategies have been discussed elsewhere(63).

Although this review focuses on the rational and evidence for combining plasma cell depletion with costimulation blockade to block the development of new antibody secreting cells, the implications for infection and protective immunity are also noteworthy. In the non-human primate models, CMV infection was a limiting factor while pre-desensitization vaccine-induced protective immunity remained intact(25, 46). In our case series, there were two mild infections (C. difficile and E.coli urinary tract infection), both of which responded to treatment after which desensitization was resumed without recurrence(47). Consistent with our proposed mechanism and supported by the poor response to primary vaccine series under costimulation blockade(64), in our program, we recommend comprehensive vaccination prior to desensitization while acknowledging that some reduction in protective immunity may occur with multiple cycles of desensitization.

Implications of the approach for thoracic organ transplantation

The importance of sustaining the response to treatment in the pre-transplant setting is critical for thoracic organ transplant candidates as desensitization is optimally undertaken when the patient is clinically stable and the timing of transplant cannot be ascertained *a priori*. Thus, the brisk rebound following proteasome inhibitor-based desensitization(38) presents a major challenge to this population. The sustained response to CTLA4-Ig in the mouse model, inhibition of proteasome inhibitor mediated homeostatic proliferation in the non-human primate studies(40), combined with the clinical observation that belatacept can constrain pre-existing DSA (65) and reduce non-DSA in the clinical setting(43), along with our preliminary experience(47) suggests that continuing belatacept in the pre-transplant setting may help overcome this limitation.

End-stage heart and lung disease is unique in its urgent need for effective desensitization strategies to permit life-saving organ transplantation where, unlike patients with chronic kidney disease, living donor or paired exchange is not an option. While left ventricular support devices (LVADs) may be an alternative for some heart transplant candidates, not all patients qualify and complications limit duration of support, thus transplantation remains the gold-standard. Moreover, LVADs further drive sensitization serving as a unique risk factor to this population(66). Immunologically, LVAD-related sensitization is often characterized by a robust HLA antibody response early after implant that decays over time(67). Nonetheless, memory persists as suggested by the increased risk of rejection (both cellular and antibody mediated) after transplant. This raises the possibility that targeting the plasmablast/early PC subsets could be particularly effective and that long-term inhibition of memory T cell – B cell interactions is required. Consistent with the mechanistic principles discussed above, belatacept may be particularly efficacious in this setting reducing plasmablasts(68) as well as memory and isotype switched B cell responses(44, 46, 68). Multiple cycles of plasma cell targeted therapies are likely to be needed to effectively control long-lived plasma cells, particularly when there are additional risk factors, such as remote pregnancies, as was the situation in all our cases.

HLA sensitization related to congenital heart disease (CHD) repair with allogeneic homograft material is often considered a formidable barrier to transplant yet CHD is now the 2nd most common indication for heart transplant between 18-39 years of age(69). Chronic exposure to foreign HLA in the absence of immunosuppression results in immunological sensitization implying an important role for targeting long-lived plasma cells and preventing rebound in the setting of established memory and ongoing presence of the homograft. While the dose and dosing strategy of belatacept in our protocol was modeled after the FDA licensed approach in de novo kidney transplant recipients for rejection prophylaxis, whether higher or more frequent dosing would enhance the effect or improve tissue penetration in the setting of established HLA sensitization, remains to be defined.

Conclusion

There is an urgent need for effective, mechanistically-driven strategies to treat established HLA antibody responses both in the pre- and post-transplant setting. Herein we review

a bench-to-bedside approach to addressing this unmet need. Building on the pre-clinical efficacy of CTLA4-Ig at inhibiting memory B cell responses and reversing established DSA, we address the clinical limitation of rebound seen with proteasome-inhibitor based strategies by combining costimulation blockade with proteasome inhibition first in mouse models and in the clinical setting to treat AMR and for desensitization in highly sensitization heart transplant candidates. This approach is further supported by work in non-human primate models. Collectively, this review highlights the utility of a rational, collaborative, mechanistically-driven approach to humoral desensitization to improve access to and long-term outcomes in solid organ transplantation.

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Discussion of the off-label use of belatacept and proteasome inhibitor.

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Key points

- Pre-transplant donor specific antibodies (DSA) mediate hyperacute as well as early antibody-mediated rejection (AMR), while DSA developing late post-transplantation may additionally mediated chronic rejection.
- The combination of transient proteasome inhibition to deplete plasma cells, together with maintenance co-stimulation blockade, CTLA-4Ig or belatacept, to prevent the generation of new antibody-secreting cells (ASCs), effectively reverses established DSA responses in mouse models.
- Treatment regimen of proteasome inhibition and belatacept reverses active antibody-mediated rejection in the clinic and is an effective desensitizing strategy for highly-sensitized patients on the transplant waitlist.

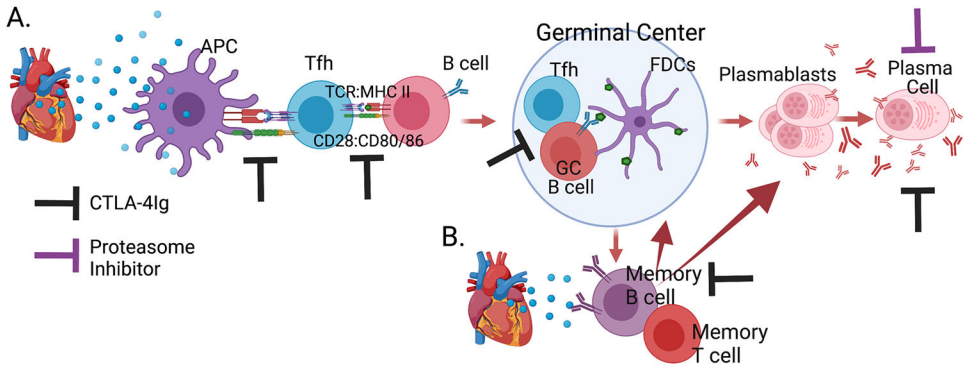

FIGURE 1.

(a) The cellular interactions that result in the differentiation of naive alloreactive B cells into antibody-secreting plasmablasts and plasma cells. CTLA-4Ig interferes with CD28 binding to CD80/CD86, which facilitates cognate T-cell : B-cell interactions at the T: B interface and in the germinal center. As a result, the differentiation of extrafollicular and postgerminal center memory B cells and antibody-secreting cells is prevented. (b) Upon alloantigen reencounter, memory B cells preferentially differentiate into antibody-secreting cells in a T-cell-dependent manner. CTLA-4Ig inhibits memory B-cell differentiation into antibody-secreting cells. Proteasome inhibitors rapidly deplete plasma cells, whereas CTLA-4Ig induces a more gradual depletion of plasma cells. APC, antigen presenting cells; FDC, follicular dendritic cells presenting intact antigen complexes to B cells in the germinal center; GC, germinal center; MHC, major histocompatibility complex; Tfh, T-follicular helper; TCR, T-cell receptor.

Table 1.

Clinical trials of HLA antibody reduction with belatacept and plasma cell targeting therapies

Carfilzomib and Belatacept for Desensitization (ADAPT)	Desensitization	NCT05017545	Recruiting	Phase 1/2 open-label non-randomized clinical trial to address the safety and efficacy of belatacept and carfilzomib in highly HLA sensitized kidney transplant candidates.
Lung Transplant Plasmapheresis/ Belatacept/Carfilzomib for Antibody Mediated Rejection and Desensitization	Desensitization and AMR	NCT03805178	Withdrawn	Phase 2 open-label non-randomized clinical trial to address safety and tolerability in highly sensitized lung transplant candidates and lung transplant recipients with antibody mediated rejection (AMR).
Novel Desensitization Kidney Transplantation	Desensitization	NCT05345717	Recruiting	Open-label pilot study to test the safety and effectiveness of desensitization therapy with belatacept and proteasome inhibitor to increase the likelihood of finding an acceptable donor for highly HLA sensitized kidney transplant candidates.
Daratumumab and Belatacept for Desensitization (ATTAIN)	Desensitization	NCT04827979	Recruiting	Phase 1/2 open-label non-randomized, clinical trial to assess the safety and efficacy of daratumumab and belatacept in highly HLA sensitized kidney transplant candidates.
The Safety/Efficacy Of Daratumumab With Belatacept In Highly HLA-Sensitized Patients Awaiting Kidney Transplantation (COMBAT)	Desensitization	NCT05145296	Recruiting	Non-randomized, single-center pilot trial assessing the safety and efficacy of targeting peripheral and central humoral alloimmune memory with daratumumab and belatacept in highly HLA sensitized patients awaiting kidney transplantation.

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