Evaluating the Use of Bortezomib and Eculizumab in Desensitization of Transplant Patients

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Abstract

Objective: To systematically review the existing literature concerning the utilization of bortezomib and eculizumab to determine if there is enough evidence to warrant their routine use in desensitization protocols for high-risk transplant candidates. **Data Sources:** PubMed, Google Scholar, and ClinicalTrials.gov were searched using the terms bortezomib, eculizumab, desensitization, transplant, highly-sensitized, pre-sensitized, and antibody-mediated rejection (AMR). The articles included were published between January 2009 and August 2012. **Study Selection and Data Extraction:** All English-language articles involving human subjects were assessed for inclusion. The search included articles evaluating the use of these agents in desensitization and the prevention of AMR, but excluded articles investigating these drugs in the treatment of established AMR. **Data Synthesis:** Highly sensitized transplant candidates are at an increased risk of developing AMR after transplant; desensitization potentially reduces this risk. The addition of bortezomib and eculizumab to current desensitization protocols may enhance outcomes. The bortezomib search produced 3 efficacy trials, 1 safety trial, 2 in-progress trials, 14 patient cases from 8 published case reports, and 3 efficacy study abstracts. **Conclusions:** Much of the available literature assessing the efficacy of bortezomib and eculizumab for use in desensitization exists as restricted clinical trials and incomplete case reports. Bortezomib and eculizumab appear to be potentially effective additions to current desensitization protocols. However, we are unable to determine at this time whether these agents improve the most clinically relevant outcome of successful transplantation. Further well-designed clinical trials are needed to determine their true clinical efficacy in highly sensitized transplant candidates.

Keywords

desensitization, bortezomib, eculizumab, transplant, highly sensitized

Introduction

Transplantation is a potentially life-saving measure for individuals with diseases in which there are limited alternatives for treatment. It requires critical evaluation of the donor and recipient, vast resources, and a dedicated health care team to care for the patient. The waiting period for a patient to receive a transplant can be long, and in some cases may be extended even further. One reason for an increase in wait time is the presence of donor-specific antibodies (DSA) in the recipient's blood. DSAs can be divided into major histocompatibility complex anti-human leukocyte antigen (HLA) antibodies and non-HLA minor histocompatibility complex antibodies.¹ These antibodies are directed to the major histocompatibility complex class I and II antigens on the allograft's endothelial cells and can lead to rejection of the transplanted organ. Detection of these antibodies is accomplished by testing the recipient's serum with common HLA antigens from the general population, resulting in a

collective percentage, described as panel reactive antibody (PRA). The higher the PRA for a recipient, the greater likelihood there will be a positive crossmatch with a donor allograft, thus limiting the donor pool for the recipient and increasing the time the recipient will have to wait for a suitable donor.

Desensitization is the process of removing the transplant recipient's circulating antibodies or modifying the recipient's immune system prior to transplantation in an attempt to decrease the likelihood of organ rejection.² Desensitization can be desired because wait times on the transplant list are

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considerably longer for those patients who are highly sensitized, and it is hypothesized that reducing the time to transplantation may enhance patients' quality of life, save health care costs, and improve long-term mortality. Successful outcomes of desensitization include reducing PRA and HLA antibodies to increase the chance of receiving a suitable transplant organ with a negative crossmatch and reduce time to transplant, decreasing the risk of antibody-mediated rejection (AMR) to improve the probability of survival of the transplanted organ, and reducing long-term mortality.³

Current methods of desensitization include removal of antibodies using plasmapheresis (PP) or immunoadsorption, B-cell reduction, and inhibition of antibody response using rituximab, and reduction of immune response using intravenous immune globulin (IVIg) or a splenectomy.² These methods are attempted as monotherapies or in different combinations and are used in a variety of different dosing regimens. Due to the variability of success with these methods, new medications are being researched to optimize the desensitization process. Proteasome inhibition offers an additional mechanism for decreasing anti-HLA antibody production by inhibiting DSA plasma cells.⁴ Bortezomib (Velcade, Millennium Pharmaceuticals, Cambridge, MA), a drug approved by the United States Food and Drug Administration (US FDA) for the treatment of multiple myeloma and mantle cell lymphoma, is a 26S proteasome inhibitor that has also shown efficacy in desensitization of transplant patients.^{4,5} Another mechanism involves complement cascade blockade. AMR can result from complement activation in patients with high DSA levels. Eculizumab (Soliris, Alexion Pharmaceuticals, Cheshire, CT), a C5 terminal complement blocker approved by the US FDA for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, has been studied to evaluate its usefulness in preventing AMR in highly sensitized transplant patients.^{6,7}

The objective of this article is to systematically review the existing clinical trials (including those in progress), case reports, and study abstracts concerning the utilization of these new therapies and determine if there is enough evidence to warrant their routine use in practice specifically for desensitization.

Methods

PubMed, Google Scholar, and ClinicalTrials.gov searches were used, employing different combinations of the search terms bortezomib, eculizumab, desensitization, transplant, highly-sensitized, pre-sensitized, and antibody-mediated rejection. Search results were limited to those written in English and involving human subjects. Following the search, articles evaluating the use of these agents in desensitization and the prevention of AMR were included, but articles investigating these drugs in the treatment of established AMR

were excluded. Additional primary literature was identified after evaluating the references of the review articles and clinical trials produced by the original search. The search and selection of articles were conducted by the primary and secondary authors, and discrepancies were resolved by the third and fourth authors. Final included articles were clinical trials (including those in-progress), case reports, and oral abstracts from clinical transplant conferences. All included articles were published between January 2009 and August 2012, but no date limits were applied to the literature search.

Results

The bortezomib search produced 3 efficacy trials, 1 safety trial, 14 patient cases from 8 published case reports, 3 efficacy oral abstracts, and 2 in-progress trials. The 3 bortezomib efficacy trials reported on the drug's ability to decrease DSA, PRA, and T-cell and B-cell crossmatch, respectively, whereas the safety trial evaluated the toxicity profile associated with bortezomib. The bortezomib case reports describe the use of bortezomib in individual situations and represent a large portion of the available evidence.

The eculizumab search produced 1 efficacy trial investigating eculizumab's ability to prevent AMR, 5 in-progress trials, and 1 efficacy oral abstract. Although several published clinical trials and case reports exist, some of the available evidence for bortezomib and eculizumab originates from oral abstracts that represent topics addressed at recent clinical transplant conferences. Additionally, there are several in-progress trials that describe emerging areas of research.

Bortezomib

In a prospective, nonrandomized trial, Diwan and colleagues compared overall reduction in B-cell flow crossmatch channel shift (BFXM-CS), a marker of serum DSA, in 5 patients receiving both bortezomib and PP to a historical control of 8 patients who had received PP alone.⁴ Because terminally differentiated plasma cells are the greatest producers of anti-HLA antibodies, investigators also examined the impact of bortezomib on the number of DSA-plasma cells (DSA-PCs) in the bone marrow of 8 bortezomib-treated subjects. All patients enrolled had end-stage renal disease, qualified for a renal transplant, had identifiable antibodies with specificities for at least one donor HLA type, and possessed a B-cell flow crossmatch (BFXM) > 450. Two bortezomib dosing strategies were used with 4 patients receiving a single cycle of bortezomib (1.3 mg/m² on days 1, 4, 8, and 11) while the remaining 4 patients received a 4-cycle regimen with at least 10 days between cycles. Patients undergoing PP received at least 7 daily treatments with a BFXM goal of less than 300; however, subjects unable to reach this endpoint received up

to 7 additional PP treatments before being considered a treatment failure. It was determined that treatment with bortezomib enhanced the reduction in BFXM-CS when concomitantly administered with PP (BFXM-CS was reduced by 272.6 ± 92.1 in the bortezomib-PP group and by 95.4 ± 72.2 in the PP-monotherapy group; $P = .008$). Additionally, patients receiving bortezomib experienced a decrease in DSA-PC concentrations from baseline as pretreatment and posttreatment DSA-PC values were found to be 16.7 ± 14.5 DSA-PCs/mL and 6.2 ± 3.6 DSA-PCs/mL, respectively ($P = .048$). Infection of the central line was the only adverse event reported and occurred in 2 patients receiving bortezomib. No effect on patient or organ outcome was reported as a result of this.

In 2011, Patel and investigators evaluated bortezomib's ability to reduce PRA in 7 patients awaiting cardiac transplantation in a nonrandomized, uncontrolled, observational study.⁸ Highly sensitized patients were enrolled if they possessed a baseline PRA > 50%. Six out of 7 patients received treatment with bortezomib 1.3 mg/m^2 on days 1, 4, 7, and 10 in conjunction with PP for 2 days prior to bortezomib administration as well as acetaminophen, diphenhydramine, and metoclopramide or ondansetron to reduce adverse effects. In these 6 subjects, bortezomib therapy was initiated after patients proved refractory to desensitization treatment with IVIg, rituximab, and PP. The seventh sensitized subject required bortezomib for the treatment of amyloidosis and received 14 cycles of bortezomib and 9 cycles of PP prior to transplantation as well as additional cycles of bortezomib postoperatively as prescribed by an oncologist. Patients who went on to be transplanted eventually received antithymocyte globulin as part of their induction therapy along with maintenance immunosuppression with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. After treatment with bortezomib, 6/7 patients experienced a decrease in PRA from baseline with mean PRA decreasing from 62% to 35% ($P = .001$). Of these 6 patients, 5 were able to undergo transplantation. Infection was the most common adverse event associated with bortezomib with 2 patients dying from sepsis. No confounding reasons for these deaths were reported. Additional adverse events included anemia, mild leucopenia, slight nausea, and neuropathy.

A prospective study in 2011 by Kute and colleagues evaluated the efficacy and safety of bortezomib-based desensitization therapy in 34 highly sensitized patients prior to renal transplantation.⁹ Patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11. Concurrent desensitization therapy included PP, antithymocyte globulin, MMF, and IVIg. After 1 month, serological testing was performed, and if results indicated continued sensitization, additional treatment included another cycle of bortezomib (1.3 mg/m^2 on days 29, 33, 37, and 40), PP, IVIg, calcineurin inhibitors, and rituximab. In 1 month (after only the first desensitization cycle), 67.7% of

patients had responded; in these responders, therapy decreased T-cell crossmatch (TCXM) from 122.4 ± 91.4 to 24.7 ± 19.4 median channel shift (MCS) and BFXM from 279 ± 142.9 to 74.7 ± 34.8 MCS. After a follow-up of 0.8 ± 0.32 years, patient survival was 100%, graft survival was 88.2%, and mean serum creatinine was $1.27 \pm 0.32 \text{ mg/dL}$. Of the 34 patients, 2 developed neuropathy, 8 had gastrointestinal (GI) side effects, 5 had thrombocytopenia, 2 developed herpes, and 2 had altered liver function tests.

In 2012, Schmidt and colleagues conducted a prospective evaluation of toxicities associated with bortezomib used for desensitization prior to renal transplantation in 19 patients.¹⁰ All patients received at least 1 cycle of bortezomib ($1.3 \text{ mg/m}^2 \times 4$ doses given 72 hours apart) and received methylprednisolone prior to each bortezomib administration. After desensitization, a reduction in bortezomib dose was required in 5.3% of patients due to neuropathy and 8.6% due to thrombocytopenia, but no anemia, neutropenia, or GI adverse events necessitated bortezomib dose reduction. Additionally, no opportunistic infections or malignancies were reported in patients receiving bortezomib for desensitization.

Eight published case report articles described the use of bortezomib in desensitization in 14 individual patients.¹¹⁻¹⁸ The majority of patients received bortezomib in a cyclical regimen. Most cycles consisted of 4 doses of 1.3 mg/m^2 administered over an 11-day period; however, the number of cycles each patient received varied. In addition to bortezomib, patients received desensitization using a variety of treatments including IVIg, PP, rituximab, antiproliferative agents, and dexamethasone. Results from case reports were sporadic, as reported outcomes varied between investigators. Authors reported PRA response in 7/14 cases, and bortezomib reduced PRA levels in a majority of these patients (6/7). Most cases reported bortezomib's effect on anti-HLA antibodies; however, the presence or extent of this response varied greatly between cases. Of the 14 cases, 10 published the patients' transplant status after desensitization. One of 10 patients was unable to undergo transplantation while 6/14 underwent successful transplantation and 7/14 patients remained as potential transplant candidates. Bortezomib was generally well tolerated, with the most common side effects including neuropathy, nausea, vomiting, and diarrhea. Table 1 summarizes these case reports.

In addition to the above-mentioned clinical trials, bortezomib's use as a desensitization agent has been assessed in several oral abstracts that were presented at the 2009, 2010, and 2011 American Transplant Congress (ATC) meetings. All 3 oral abstracts investigated bortezomib's efficacy in desensitization by evaluating endpoints surrounding bortezomib's ability to reduce antibody-mediated posttransplant complications.¹⁹⁻²¹ Though there was some variability in results, the first oral abstract reported bortezomib effectively removed DSA, while the second demonstrated a significant reduction

Table 1. Bortezomib Case Reports.

Author	Patient Demographics	Txp Organ(s)	Bortezomib Desensitization ^a	Additional Desensitization Therapy	Immunosuppression Regimen	Txp Status ^b	PRA (Baseline → After Bortezomib Desensitization)	HLA Response to Bortezomib	Toxicities
Hartono et al (2009) ¹¹	44 yom	Kidney	1.3 mg/m ² (POD 3, 7)	IVIg x7; PP x3; RTX x1	ATG, MMF, PRED, TAC	Successful txp	92% to 87%	HLA: A32 (80% decrease), B61 (67% decrease), B51 (86% decrease), DP14 (75% decrease), DP10 (87% decrease) HLA-Ab reduction of 50% at 1 month; rebound to 20% above baseline at 6 months	No SE
Marino-Vázquez et al (2010) ¹²	57 yof	Kidney	1.3 mg/m ² (days 1, 3, 7, 10)	PP x3	NR	Successful txp	57/67% to NR	HLA-Ab reduction of 50% at 1 month; rebound to 20% above baseline at 6 months	NR
Marino-Vázquez et al (2010) ¹²	32 yof	Kidney	1.3 mg/m ² (days 1, 3, 7, 10)	PP x3; RTX x1	NR	Still awaiting txp	95/89% to NR	HLA: MFIs between 1000 and 10 000 increased following bortezomib; MFIs > 10 000 decreased 40% over 4 months	NR
Marino-Vázquez et al (2010) ¹²	41 yom	Kidney	1.3 mg/m ² (days 1, 3, 7, 10)	PP x3; RTX x1	NR	Still awaiting txp	44/66% to NR	HLA-Ab reduction of 30% at 30 days	NR
Marino-Vázquez et al (2010) ¹²	34 yom	Kidney	1.3 mg/m ² (days 1, 3, 7, 10)	None	NR	Still awaiting txp	55/80% to NR	No initial HLA-Ab response; HLA increase after 30 days	NR
Marino-Vázquez et al (2010) ¹²	53 yom	Kidney	1.3 mg/m ² (days 1, 3, 7, 10)	PP x3; RTX x1	NR	Still awaiting txp	58/45% to NR	No HLA response	NR
Guthoff et al (2012) ¹³	21 yom	Kidney	1.3 mg/m ² (days 1, 4, 8, 11)	None	None	NR	No change	No HLA response	No SE
Guthoff et al (2012) ¹³	46 yof	Kidney	1.3 mg/m ² (days 1, 4, 8, 11)	None	None	NR	44% to 20%	Decrease in non-DSA up to day 40. No difference in HLA-Ab levels at day 100	No SE
Raghavan et al (2009) ¹⁴	33 yom	Kidney	1.3 mg/m ² x 3 cycles (cycle 1: 4 doses in 11 days; cycles 2 and 3: 4 doses in 11 days initiated 17 days after previous cycle)	MMF x2; RTX x?	MMF, PRED, TAC, ATG	Successful txp	55% to 30%	HLA: A24 (MFI baseline <4000; decreased after therapy); other HLA-Ab had similar response	No SE
Zhu et al (2009) ¹⁵	33 yom	Kidney	1.3 mg/m ² (2 doses in 3 days)	IVIg x2; PP x2	ATG, MMF, TAC	Successful txp	NR	General reduction in HLA-Ab	No SE

(continued)

Table 1. (continued)

Author	Patient Demographics	Txp Organ(s)	Bortezomib Desensitization ^a	Additional Desensitization Therapy	Immunosuppression Regimen	Txp Status ^b	PRA (Baseline → After Bortezomib Desensitization)	HLA Response to Bortezomib	Toxicities
Wahrmann et al (2010) ¹⁶	65 yom	Kidney	1.3 mg/m ² × 2 cycles (cycles 1 and 2: 4 doses in 11 days, separated by 4 months)	DXM × 2	None	NR	87% to 80% after cycle 2	No HLA response; decrease in MFI	No SE
Wahrmann et al (2010) ¹⁶	41 yof	Kidney	1.3 mg/m ² × 2 cycles (cycles 1 and 2: 4 doses in 11 days, separated by 3 months)	DXM × 2	None	NR	35% to 13%	No effect on HLA or MFI	No SE
Lonze et al (2010) ¹⁷	43 yof	Kidney	1.3 mg/m ² (10 doses in 63 days)	IVlg × 8, PP × 3, RTX × 1	ATG, DXM, ECZ, PRED	Successful txp	100% to NR	Some reduction in HLA-Ab observed at 2 months	NR
Patel et al (2009) ¹⁸	63 yom	Heart/kidney	No dose strength reported (4 doses in 14 days)	IVlg × 2; PP × 2; RTX × 4	ATG	Successful txp	54% to 23%	Reduction in MFI values	No SE

Abbreviations: ATG, antithymocyte globulin; CSP, cyclosporine; DXM, dexamethasone; ECZ, ecuzimab; HLA-Ab, human leukocyte antigen antibody; HLA, human leukocyte antigen; IVlg, intravenous immunoglobulin; MFI, mean fluorescence intensity; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; non-DSA, non-donor specific antibody; NR, not reported; N/V/D, nausea/vomiting/diarrhea; POD, postoperative day; PP, plasmapheresis; PRA, panel reactive antibody; PRED, prednisone; RTX, rituximab; SE, side effects; TAC, Tacrolimus; txp, transplant; yof, year old female; yom, year old male.

^aAll bortezomib administered pretransplant unless otherwise noted by POD date.

^bTransplant status at time of case report publication.

? = Unknown number of doses.

in total anti-HLA antibody serum levels after bortezomib treatment.^{19,20} In the final abstract, bortezomib reduced or removed DSA in most patients after a median time of 37 days posttreatment, but authors noted many patients experienced a reappearance of DSA in 6 to 7 months, questioning the sustainability of bortezomib's effect.²¹

Eculizumab

In 2011, Stegall and colleagues conducted an open-label study comparing eculizumab therapy ($n = 26$) to a historical control group ($n = 51$) in highly sensitized renal transplant recipients who had a positive BFXM against their donor.⁶ The treatment group received eculizumab 1200 mg immediately prior to surgery, 600 mg on postop day 1 (POD-1), followed by 600 mg weekly for 4 weeks; after week 4, eculizumab 1200 mg every other week was administered based on BFXM-CS levels. Both groups received induction therapy with antithymocyte globulin, tacrolimus, MMF, and prednisone. Twelve percent of the eculizumab group and 76% of the control group received PP treatments. Incidence of AMR in the first 3 months following transplant was significantly reduced in the eculizumab-treated group compared to the control group (7.7% and 41%, respectively; $P = .0031$). Graft survival was similar between the groups at 1 year (100% in the eculizumab group and 96% in the control group; $P = 1.00$). In the eculizumab group, 1 patient developed a wound infection, and 1 patient died of Burkitt's lymphoma 2.5 years after transplant.

At the 2009 ATC, one oral abstract assessing the efficacy of eculizumab for desensitization was presented.²² In this abstract, eculizumab was found to prevent endothelial activation following transplantation, and this effect is believed to correlate with the prevention of acute humoral rejection.

Discussion

Desensitization is the process of removing a transplant recipient's circulating antibodies or modifying the recipient's immune system prior to transplantation in an attempt to decrease the likelihood of organ rejection.² Current protocols include a variety of treatments such as PP, IVIg, and rituximab. The introduction of the 26S proteasome inhibitor bortezomib and the anti-C5 antibody agent eculizumab offers potential new strategies to enhance desensitization protocols. Through investigation of various outcomes such as PRA reduction, T-cell and B-cell crossmatch, and others, literature evaluating the use of these agents in desensitization demonstrates their potential as valuable additions to current desensitization practices.

While both bortezomib and eculizumab are being investigated for use in transplant desensitization, much more evidence exists assessing the use of bortezomib for this indication. This may be due to the fact that bortezomib was

made available to the public first, when it was approved for use in multiple myeloma on May 13, 2003.²³ Eculizumab was not available until it was approved to treat paroxysmal nocturnal hemoglobinuria on March 16, 2007.²⁴

Results from clinical trials make up much of the evidence supporting the use of bortezomib and eculizumab in desensitization. Although these clinical trials used different endpoints, most authors concluded the agents were associated with positive outcomes in desensitization. The reductions in PRA, T-cell and B-cell crossmatch, DSA, or frequency of AMR demonstrate these agents may decrease the time sensitized patients are on the waiting list and increase the likelihood of a successful transplantation although this has not been directly measured in the available studies to date. There were many limitations associated with these studies that warrant discussion. For example, each trial in this review used treatment groups with populations of less than 35; unfortunately, small sample sizes are common among trials involving organ transplantation. These small sample sizes limit the clinician's ability to extrapolate results to the general transplant population. The design of the studies also serves as a weakness as trials either lacked a control group or simply used a historical control. A final consideration is the lack of patient randomization between study groups.

Some of the published findings surrounding the use of bortezomib for desensitization exist as published case reports. Patients represented in these case reports experienced varying levels of success. The case reports include diverse outcomes (eg, change in PRA, HLA response), lack certain details (eg, posttransplant immunosuppression, living/deceased donor, time between desensitization and transplantation), and do not allow for long-term follow-up of endpoints (eg, transplant status over time, delayed adverse events). Drawing conclusions based on the results of these cases can be difficult, but due to the fact that all applicable clinical trials have significant limitations, evidence derived from these case reports should be taken into consideration. For example, the majority of patients received at least 1 cycle consisting of 4 doses of bortezomib at a strength of 1.3 mg/m². In most cases, bortezomib was not administered as monotherapy, but instead patients received concurrent desensitization and posttransplant immunosuppression consisting of pharmacological and PP interventions. The majority of case reports noted an overall reduction in PRA or a positive HLA response following bortezomib desensitization, potentially contributing to the patients' probability of successful transplantation.

A limitation shared by both clinical trials and case reports was the inconsistency in concomitant desensitization and immunosuppression regimens, as each patient may have received different therapies in addition to bortezomib or eculizumab. This variation may have confounded results and does not allow practitioners to identify an optimal desensitization

Table 2. In-Progress Clinical Trials Evaluating Bortezomib and Eculizumab for Transplant Desensitization.

ClinicalTrials.gov Identifier	Sponsor/Collaborator	Primary Outcome	Expected Date of Completion
Bortezomib			
NCT01502267 ²⁷	Seoul National University Hospital/Roche	Rate of kidney transplantation	January 2016
NCT01556347 ²⁸	Providence Health & Services/NR	Anti-HLA alloantibody reduction in heart transplant candidates ^a	April 2018
Eculizumab			
NCT00670774 ²⁹	Stegall/Alexion	Preventing AMR in positive crossmatch LDKTX patients	August 2013
NCT01567085 ³⁰	Alexion/NR	Posttransplantation treatment failure rate	September 2015
NCT01106027 ³¹	Mayo/Alexion	AMR in DDKTX patients up to 1 year posttransplant	December 2015
NCT01399593 ³²	Alexion/NR	Week 9 posttransplantation treatment failure rate	April 2016

Abbreviations: Alexion, Alexion Pharmaceuticals; AMR, antibody-mediated rejection; DDKTX, deceased donor kidney transplant; LDKTX, living donor kidney transplant; NR, collaborator not reported; Roche, Roche Pharma AG.

^aNot all primary outcomes listed.

regimen. Additionally, it should be noted that clinical trials and case reports only assessed the use of these therapies in kidney, heart, lung, and pancreas transplants. Thus, results may not apply to the transplant of other organs.

An additional consideration for the use of these agents in desensitization is the cost associated with treatment. The average wholesale price (AWP) of bortezomib is currently \$1807.20 for a 3.5 mg vial.²⁵ Using a dose of 1.3 mg/m² (the typical dose used in several studies and case reports reviewed), only 1 vial would be required for a patient with a body surface area of less than 2.7 m². However, bortezomib was typically administered in a regimen that consisted of 2 to 4 doses, and this regimen could be repeated in additional cycles. Eculizumab has an AWP of \$6830.40 for a 300 mg vial.²⁶ Using the dosing regimen in the study by Stegall and colleagues, the first dose alone (1200 mg) would cost \$27321.60. Patients went on to receive a minimum of 5 additional 600 mg doses (\$13660.80/600 mg dose) with some subjects receiving further doses depending on the patient's BFXM-CS. Since neither drug currently has an FDA-approved indication for desensitization, obtaining reimbursement for these high treatment costs could also be a challenge for providers.

Beyond the published clinical trials, there are 6 additional ongoing studies evaluating this emerging area of research.²⁷⁻³² Results from these trials hope to provide additional evidence to substantiate the use of these drugs in desensitization. Table 2 summarizes these trials. It is recommended that clinicians follow this research to further establish the role of these therapies in potential desensitization regimens. Future research should offer insights on the optimal dosing of these agents, determine which combination of desensitization regimens presents maximum value,

identify ideal patients for use of these therapies, recognize the presence of long-term efficacy and safety, and validate that the benefits of these drugs truly outweigh the costs.

Conclusion

Much of the available literature assessing the efficacy of bortezomib and eculizumab for use in desensitization exists as restricted clinical trials and incomplete case reports. Limitations associated with these types of literature reduce the clinician's ability to extrapolate results to the general transplant population. Bortezomib and eculizumab appear to be potentially effective additions to current desensitization protocols. However, we are unable to determine at this time whether these agents contribute to the most clinically relevant outcome of successful transplantation and cannot confidently recommend their routine use in current desensitization protocols. Further well-designed clinical trials are needed to determine their true clinical efficacy in highly sensitized transplant candidates.

Declaration of Conflicting Interests

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References

1. Barbari A, Abbas S, Jaafar M. Approach to kidney transplant in sensitized potential transplant recipient. *Exp Clin Transplant*. 2012;10:419-427.

2. Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol*. 2011;6:922-936.
3. Montgomery R, Lonze B, King K, et al. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med*. 2011;365:318-326.
4. Diwan TS, Raghavaiah S, Burns JM, Kremers WK, Gloor JM, Stegall MD. The impact of proteasome inhibition on allo-antibody-producing plasma cells in vivo. *Transplantation*. 2011;91:536-541.
5. Velcade [Package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc; 2012.
6. Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant*. 2011;11:2405-2413.
7. Soliris [Package insert]. Cheshire, CT: Alexion Pharmaceuticals, Inc; 2012.
8. Patel J, Everly M, Chang D, Kittleson M, Reed E, Kobashigawa J. Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. *J Heart Lung Transplant*. 2011;30:1320-1326.
9. Kute VB, Vanikar AV, Trivedi HL, et al. Desensitization protocol for highly sensitized renal transplant patients: a single-center experience. *Saudi J Kidney Dis Transpl*. 2011;22:662-669.
10. Schmidt N, Alloway RR, Walsh RC, et al. Prospective evaluation of the toxicity profile of proteasome inhibitor-based therapy in renal transplant candidates and recipients. *Transplantation*. 2012;94:352-361.
11. Hartono C, Lubetzky M, Aull MJ, et al. Use of bortezomib for prevention and treatment of rejection in sensitized patients. *Clin Transpl*. 2009:499-503.
12. Marino-Vázquez LA, Leyva S, Alberú J, Morales-Buenrostro LE. Bortezomib for desensitization of patients on a waiting list for deceased donor kidney transplant: experience in Mexico City. *Clin Transpl*. 2010:363-367.
13. Guthoff M, Schmid-Horch B, Weisel KC, Häring HU, Königsrainer A, Heyne N. Proteasome inhibition by bortezomib: effect on HLA-antibody levels and specificity in sensitized patients awaiting renal allograft transplantation. *Transpl Immunol*. 2012;26:171-175.
14. Raghavan R, Jeroudi A, Achkar K, et al. Bortezomib in kidney transplant desensitization: a case report. *Clin Transpl*. 2009:339-342.
15. Zhu L, Lin Z, Xiang Y, Liu S, Chen G. Successful desensitization in a crossmatch positive living-related kidney transplant recipient using a bortezomib-based protocol. *Clin Transpl*. 2009:359-360.
16. Wahrmann M, Haidinger M, Kormoczi G, et al. Effect of proteasome inhibitor bortezomib on humoral immunity in two presensitized renal transplant candidates. *Transplantation*. 2010;89:1385-1390.
17. Lonze BE, Dagher NN, Simpkins CE, et al. Eculizumab, bortezomib and kidney paired donation facilitate transplantation of a highly sensitized patient without vascular access. *Am J Transplant*. 2010;10:2154-2160.
18. Patel JK, Everly MJ, Kittleson M, Kobashigawa JA. Use of bortezomib as adjunctive therapy for desensitization in combined heart and kidney transplantation—a case report. *Clin Transpl*. 2009:347-349.
19. Everly MJ, Trivedi HL, Terasaki PI, et al. Optimizing bortezomib to reduce donor specific HLA antibodies prior to allograft dysfunction. *Am J Transplant*. 2009;9:383.
20. Walsh RC, Rike Shields A, Wall GE, et al. A prospective, staged trial of proteasome inhibitor-based therapy for reduction of HLA sensitization in kidney transplant candidates. *Am J Transplant*. 2010;10:44.
21. Everly MJ, Terasaki PI, Trivedi HL, et al. Durability of donor specific antibody removal following bortezomib-based therapy. *Am J Transplant*. 2011;11:124.
22. Cornell LD, Burns JM, Stegall MD, et al. Prevention of endothelial activation with C5 inhibition in positive-crossmatch kidney transplants (+XMKTx). *Am J Transplant*. 2009;9:304.
23. Food and Drug Administration. Drugs @ FDA [Search for Bortezomib]. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed October 17, 2012.
24. Food and Drug Administration. Drugs @ FDA [Search for Eculizumab]. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed October 17, 2012.
25. Bortezomib. *RED BOOK Online*. Greenwood Village, CO: Thomson Micromedex. <http://thomsonhc.com>. Accessed October 16, 2012.
26. Eculizumab. *RED BOOK Online*. Greenwood Village, CO: Thomson Micromedex. <http://thomsonhc.com>. Accessed October 16, 2012.
27. US National Institutes of Health. Desensitization protocol for highly sensitized patients on the waiting list for kidney transplant. <http://www.clinicaltrials.gov/ct2/show/NCT01502267?term=bortezomib+and+desensitization&rank=2>. Accessed October 17, 2012.
28. US National Institutes of Health. Multi-drug desensitization protocol for heart transplant candidates. <http://www.clinicaltrials.gov/ct2/show/NCT01556347?term=bortezomib+and+desensitization&rank=1>. Accessed October 17, 2012.
29. US National Institutes of Health. Dosing regimen of eculizumab added to conventional treatment in positive cross match living donor kidney transplant. <http://www.clinicaltrials.gov/ct2/show/NCT00670774?term=eculizumab+and+transplant&rank=4>. Accessed October 17, 2012.
30. US National Institutes of Health. An open-label, single-arm, multicenter trial to determine safety and efficacy of eculizumab in the prevention of antibody mediated rejection (AMR) in sensitized recipients of a kidney transplant from a deceased donor. <http://www.clinicaltrials.gov/ct2/show/NCT01567085?term=eculizumab+and+transplant&rank=8>. Accessed October 17, 2012.
31. US National Institutes of Health. Dosing regimen of eculizumab added to conventional treatment in positive crossmatch living donor kidney transplant. <http://www.clinicaltrials.gov/ct2/show/NCT01106027?term=eculizumab+and+transplant&rank=5>. Accessed October 17, 2012.
32. US National Institutes of Health. Safety & efficacy of eculizumab to prevent AMR in living donor kidney transplant recipients requiring desensitization. <http://www.clinicaltrials.gov/ct2/show/NCT01399593?term=eculizumab+and+transplant&rank=6>. Accessed October 17, 2012.