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Bortezomib for Reduction of Proteinuria in IgA Nephropathy

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Introduction: IgA nephropathy is the most common glomerulonephritis in the world. We conducted a pilot trial (NCT01103778) to test the effect of bortezomib in patients with IgA nephropathy and significant proteinuria.

Methods: We treated 8 consecutive subjects from July 2011 until March 2016 with 4 doses of bortezomib. All subjects had biopsy-proven IgA nephropathy and proteinuria of greater than 1 g per day. They were given 4 doses of bortezomib i.v. at 1.3 mg/m^2 of body surface area per dose. Changes in proteinuria and renal function were followed for 1 year after enrollment. The primary endpoint was full remission defined as proteinuria of less than 300 mg per day.

Results: All 8 subjects received and tolerated 4 doses of bortezomib over a 2-week period during enrollment. The median baseline daily proteinuria was 2.46 g (interquartile range: 2.29–3.16 g). At 1-year follow-up, 3 subjects (38%) had achieved the primary endpoint. The 3 subjects who had complete remission had Oxford classification T scores of 0 before enrollment. Of the remaining 5 subjects, 1 was lost to follow-up within 1 month of enrollment and 4 (50%) did not have any response or had progression of disease.

Conclusion: Proteasome inhibition by bortezomib may reduce significant proteinuria in select cases of IgA nephropathy. Subjects who responded to bortezomib had Oxford classification T score of 0 and normal renal function.

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IgA nephropathy is the most common glomerulonephritis in the world.[1] Renin-angiotensin-aldosterone system blockade is accepted as first-line therapy.[2] However, select patients treated with renin-angiotensin-aldosterone system blockade remain at risk for worsening of renal function.[3] For severe disease, existing treatment options, such as corticosteroids, cyclophosphamide, and azathioprine, potentially confer more risk without significant benefit.[4,5] IgA nephropathy is an autoimmune disease whereby the pathogenesis involves autoantibodies directed against galactose-deficient IgA1 (Gd-IgA1) or other endogenous proteins that act as autoantigens.[6,7] Immortalization of cell lines from peripheral blood of patients with IgA nephropathy demonstrated production of the aberrant glycosylation of IgA1 antibodies from B cells.[8] In a murine model, an increase in the number of intestinal IgA-producing plasma cells and decreased excretion of IgA into the intestinal lumen also could contribute to elevated serum IgA level and deposition in the kidney.[9] Abrogating the production of Gd-IgA1 by antibody-producing cells could be a promising strategy to treat IgA nephropathy.

Bortezomib is a proteasome inhibitor that targets plasma cells, which are professional antibody-producing cells and is approved by the Food and Drug Administration for the treatment of multiple myeloma by inhibiting transcriptional factor nuclear factor kappa B and inducing apoptosis of myeloma cells via misfolded protein response.[10,11] Bortezomib, in off-label use, was shown to deplete A Disintegrin and Metalloproteinase with Thrombospondin motifs-13 antibodies in thrombotic thrombocytopenic purpura, as well as depleting alloantibodies in the setting of antibody-mediated kidney transplant rejection.[12,13] Extended bortezomib therapy was reported to be associated with the

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resolution of *de novo* IgA nephropathy in a patient with multiple myeloma.[14] We conducted a single-center open-label pilot trial to test the effect of bortezomib in patients with severe IgA nephropathy.

METHODS

The Weill Cornell Medical College institutional review board of our center approved the study protocol. The study was registered with clinicaltrials.gov, protocol NCT01103778. Informed consent was obtained before all study procedures, and the trial adhered to the Declaration of Helsinki.

Subjects

Adults with biopsy-proven IgA nephropathy were eligible for the trial. Inclusion criteria were daily proteinuria of greater than 1 g and glomerular filtration rate (GFR) via 24-hour creatinine clearance measurement of greater than 30 ml/min and administration of a stable dose of renin-angiotensin-aldosterone system inhibitors for a minimum of 30 days before screening. Fish oil was not required, but if taken before enrollment, was continued during the study. Enrollment was defined as having received 1 dose of bortezomib. Except for corticosteroids, other concurrent immunosuppression medications were not allowed after enrollment. Bortezomib was administered i.v. 1.3 mg/m^2 per dose for 4 doses over a 2-week course. We chose this dosing regimen because Perry *et al.*[13] demonstrated that it could induce apoptosis of plasma cells *in vitro*, resulting in abrogation of alloantibody production. The study period was for 1 year, whereby subjects were monitored for side effects and outcome. Signs of neuropathy were monitored for 1 year using Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity Questionnaire, version 4.0. Additional data on renal function and proteinuria were captured if available after the 1-year period. The primary endpoint was complete remission, defined as daily proteinuria of less than 300 mg analyzed via 24-hour urine collection. Partial response was defined as any reduction in daily proteinuria from baseline.

RESULTS

Patient Characteristics

We enrolled 9 consecutive subjects (number 1–9) from July 2011 until March 2016 for the trial. Subject 5 was excluded from data analysis due to a revised interpretation of renal biopsy that reclassified the biopsy from IgA nephropathy to idiopathic membranous nephropathy that occurred following enrollment. Subsequently, for 6 of the remaining 8 subjects, our pathologist (SVS) reviewed the biopsy and confirmed the diagnosis of IgA nephropathy, either before enrollment (subjects 6–9) or after enrollment (subjects 1 and 2). We could not review the biopsies for 2 subjects (subjects 3 and 4) to reconfirm the diagnosis of IgA nephropathy, as these biopsies were done 9 and 4 years prior, respectively, to enrollment.

Complete baseline data were available for all the subjects (Table 1). Mean age (±SD) was 35 ± 12 years during enrollment. Two of 8 (25%) participants were male. Three subjects were white non-Hispanic, 3 were Asian, 1 was white Hispanic, and 1 was black non-Hispanic. The median time from diagnosis to treatment was 14 months (interquartile range [IQR]: 5–63 months). At baseline, the median serum creatinine was 1.25 mg/dl (IQR: 0.72–2.07 mg/dl). The median GFR as measured by creatinine clearance was 72 ml/min (IQR: 62–108 ml/min). The median proteinuria as measured by 24-hour urine collection was 2.46 g per day (IQR: 2.29–3.16 g per day). Four of 8 (50%) participants had not received any immunosuppressive medications before enrollment. Three participants had prior exposure to corticosteroids, which failed to induce remission. At enrollment, only 1 participant, subject 3 was completing prednisone at 20 mg daily, given from 2 days before bortezomib infusion and ended on the last day of infusion. Subject 3 received a short course of tapering dose of prednisone (40 mg daily) for 7 days at 2 months after bortezomib infusion for ocular inflammation. All subjects had received renin-angiotensin-aldosterone system inhibitors at a median of 9 months (IQR: 2–30 months) before enrollment. Blood pressure was well controlled before enrollment, averaging 114/69 ± 12/11 mm Hg. All except subject 1 had received fish oil before enrollment.

IgA nephropathy was classified based on the Oxford classification schema (MEST: M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis) for 6 of 8 of the participants.[15] Of the 6 participants, 3 had T scores of 0, whereas 2 had T scores of 1 and 1 had a T score of 2. The rest of the MEST scores are shown in Table 1.

Bortezomib was given uniformly to all participants at a dose of 1.3 mg/m^2 of body surface area. All participants tolerated 4 doses over a 2-week period. Subject 6 had shown additional signs of the nephrotic syndrome (hypoalbuminemia, hyperlipidemia, and edema) (Supplementary Figure S1).

Outcomes

Data were available for 7 of the 8 participants for analysis; 1 patient (subject 7) was lost to follow-up after 1 month (Table 2). Three of the 8 participants (38%) fulfilled criteria for complete remission (Table 2).

Table 1. Baseline data for subjects with IgA nephropathy treated with bortezomib

Study subjects	Age (yr)/sex	Race	MEST	Previous immunosuppression	Diagnosis to treatment (mo)	Serum creatinine (mg/dl)	GFR (ml/min)	Proteinuria (g)
1	53/Female	WNH	1,1,1,1	Steroids	5	2.13	61	2.52
2	22/Female	WNH	1,1,1,0	NA	6	0.59	122	1.17
3	49/Male	WH	NA	Steroids	108	2.63	46	4.55
4	22/Female	BNH	NA	NA	48	1.35	64	2.70
6	28/Female	A	1,1,1,0	NA	3	0.54	138	4.96
7	30/Male	A	0,1,1,2	Unknown	144	2.05	62	2.13
8	44/Female	A	1,1,0,0	NA	3	0.76	103	2.40
9	32/Female	WNH	1,1,0,1	Steroids	21	1.14	79	2.34

GFR and proteinuria assessed by 24-hour urine collection.
A, Asian; BNH, black non-Hispanic; GFR, glomerular filtration rate; MEST Oxford Classification, M: mesangial hypercellularity, E: endocapillary hypercellularity, S: segmental glomerulosclerosis, T: tubular atrophy/interstitial fibrosis; NA, not applicable; WH, white Hispanic; WNH, white non-Hispanic.

Subject 2 achieved the primary endpoint at 9 months, subject 6 at 6 months, and subject 8 at 6 months. The median baseline 24-hour proteinuria excretion for those participants who achieved the primary endpoint was 2.4 g (IQR: 1.8–3.7 g) and the median baseline serum creatinine was 0.59 mg/dl (IQR: 0.57–0.68 mg/dl) (Table 2). In subjects who achieved complete remission, the median time for reduction of proteinuria to less than 300 mg per day was 6 months (range: 6.0–7.5 months) after 4 doses of bortezomib (Table 2). All 3 participants who have reached the primary endpoint were women with 1 white non-Hispanic and 2 Asian individuals. They all had Oxford classification T scores of 0 and the median time to receiving bortezomib from diagnosis was 3 months (IQR: 3–4.5 months) (Table 1). Despite the severity of the IgA nephropathy based on proteinuria, all 3 participants were treatment naïve without exposure to immunosuppression therapy before enrollment. Similarly, no corticosteroids were given to the participants after enrollment.

Subject 6 first noticed leg edema, foamy urine, and weight gain 2 months before a kidney biopsy (Supplementary Figure S1). The kidney biopsy showed IgA nephropathy without extensive podocyte effacement. The total cholesterol was 310 mg/dl, triglyceride was 228 mg/dl, and serum albumin was 2.1 g/dl at 5 days before the renal biopsy. She received the maximum tolerated dose of lisinopril (10 mg) daily for 2 months before screening. Within 3 months of treatment with bortezomib, the daily proteinuria had decreased to 500 mg per day and the serum albumin had improved to 3.8 g/dl (Supplementary Figure S1).

Resolution of hematuria was not a study endpoint. However, we observed on urinalysis that subject 2 from a baseline of 20 red blood cells (RBCs) per high power field (HPF) had 10 RBCs per HPF (reference 0–4 per HPF) at 9-month follow-up when she achieved the primary endpoint. The RBC count was 6 per HPF at 1-year follow-up. From a baseline of 27 RBCs per HPF, subject 6 had 18 RBCs per HPF at 6-month follow-up when she achieved the primary endpoint. The RBC count had improved to 3 per HPF by 16 months and 4 per HPF by 27-month follow-up. Subject 8 had 30 RBCs per HPF at baseline and 6 RBCs per HPF at 6-month follow-up when she achieved the primary endpoint. The RBC count was 3 per HPF at 13 months and 5 per HPF at 25-month follow-up.

Three of 8 participants did not respond, and 1 had a partial response to bortezomib at 1-year follow-up. The initial median baseline 24-hour proteinuria was 2.6 g (IQR: 2.5–3.2 g) for this group of participants, which was similar to those who had achieved the primary endpoint (see previously) (Table 2). In contrast to subjects who had reached the primary endpoint, this group had a median baseline serum creatinine of 1.74 mg/dl (IQR: 1.30–2.26 mg/dl) and the median time to receiving

Table 2. Treatment data and outcome for subjects with IgA nephropathy treated with bortezomib

Study subjects	Doses of bortezomib (*n*)	Duration of follow-up (mo)	Proteinuria (g/24 h)						Outcome at 1 yr
			Pre-bortezomib	1-mo	3-mo	6-mo	9-mo	12-mo	
1	4	12	2.52	NA	0.48	2.80	1.99	1.43	Partial response
2	4	12	1.17	0.90	1.08	0.63	0.30	0.28	Complete response
3	4	12	4.55	3.62	4.23	3.54	4.23	4.23	No response
4[a]	4	12	2.70	NA	NA	4.06	NA	2.84	No response
6	4	12	4.96	3.00	0.50	0.00	0.20	0.10	Complete response
7	4	1	2.13	3.48	NA	NA	NA	NA	Unknown
8	4	12	2.40	1.68	1.91	0.18	0.53	0.42	Complete response
9	4	12	2.34	1.53	3.57	2.67	2.10	2.53	No response

NA, not available.
[a]Subject did not show up for follow-up visits at months 1, 3, and 9.

bortezomib from diagnosis was 34.5 months (IQR: 17–63 months). The pretreatment biopsy showed T scores of 1 in 2 of the 4 participants according to the Oxford classification for IgA nephropathy in the group. Before enrollment, 3 of 4 of this group of participants had prior exposure to immunosuppressive agents (Table 1).

We observed that all of the participants tolerated 4 doses of bortezomib without any serious adverse events. Signs of neuropathy were monitored for all participants and none developed any neuropathy at the end of the study period (1 year after exposure to bortezomib). Participants (subjects 4 and 6) did have a mild reversible decline in platelet count during the 2-week course of bortezomib, which was not clinically significant (data not shown). We did not observe any opportunistic infections or mortality during the 1-year monitoring period.

Whereas our study had a 1-year follow-up design, we had the opportunity to obtain long-term data in 6 participants. The remission was durable without relapse in the 3 participants who had complete remission with minimal to no proteinuria and stable renal function extending out to 5, 4, and, 2 years, respectively, after initial treatment with bortezomib (Table 3). For participants who had partial or no response to treatment, 2 developed end-stage renal disease and 2 had worsening renal function (Table 3).

DISCUSSION

Immunosuppressive agents have been shown to be the mainstay for treatment of severe IgA nephropathy.[16,17] The risk for not treating patients with significant proteinuria is progression to end-stage renal disease.[18] Recent studies, however, have informed that conventional immunosuppressive agents, such as corticosteroids, cyclophosphamide, and azathioprine, might not be superior when compared with supportive care alone in preventing disease progression.[4] Because IgA nephropathy is an autoimmune disease elicited by Gd-IgA1 antibodies, which are produced by B cells,[6] B-cell depletion can be considered as an effective strategy. However, a randomized multicenter trial investigating rituximab in IgA nephropathy did not show expected efficacy.[19] The rituximab for IgA trial had 16 participants in the rituximab arm and 15 participants in the control arm.[19] No spontaneous remissions were observed in the control arm. Despite B-cell depletion, rituximab could not abrogate serum levels of or antibodies against Gd-IgA1.[19] Including various possibilities, the authors posited that autoantibodies could have originated from antibody-producing cells or plasma cells in the bone marrow and were immune to B-cell depletion by rituximab.[19] We elected to investigate bortezomib due to its attractive properties of targeting antibody production from plasma cells.

In the rituximab trial, 3 of 16 participants in the rituximab arm (19%) had 50% or greater reduction in proteinuria from baseline.[19] In comparison, 3 participants (38%) in our study achieved complete remission without relapse (Tables 2, 3). When examining their therapeutic courses, we confirmed that no other immunosuppressive medications had been administered, strengthening the conclusion that bortezomib was the most probable explanation for the disease remission. However, because of the small sample size and without a control group, we acknowledge that we could have observed spontaneous remissions in the 3 participants. Spontaneous remission for IgA nephropathy has been reported in children[20] and in adult patients, although this is not common.[4] The remission might have been induced by supportive care, such as fish oil, angiotensin-converting enzyme inhibition, statins, and control of blood pressure. The STOP-IgAN study demonstrated that patients with IgA

Table 3. Long-term outcome of subjects after treatment with bortezomib[a]

Study subjects	Age (yr)/sex	Baseline serum creatinine (mg/dl)	Year completed bortezomib	Outcome at 1 yr	Long-term kidney function (serum creatinine, mg/dl)				
					1-yr	2-yr	3-yr	4-yr	5-yr
1	53/Female	2.13	2011	Partial response	2.08	2.38	ESRD[b]	ESRD	ESRD
2	22/Female	0.59	2011	Complete remission	0.52	0.56	0.68	0.65	0.70[c]
3	49/Male	2.63	2012	No response	2.75	2.94	3.57	5.17	4.18
4	22/Female	1.35	2012	No response	1.86	NA	6.62	ESRD	Kidney transplant
6	28/Female	0.54	2013	Complete remission	0.63	0.52	0.59	0.55[d]	NA
7	30/Male	2.05	2015	Unknown	NA	NA	NA	NA	NA
8	44/Male	0.76	2015	Complete remission	0.73	0.59[e]	NA	NA	NA
9	32/Male	1.14	2016	No response	1.52	NA	NA	NA	NA

ESRD, end-stage renal disease; NA, not available.
[a]Subject 1 received bortezomib in July 2011; subject 9 completed bortezomib in March 2016; outcomes measured as serum creatinine (mg/dl) when available.
[b]Listed for kidney transplantation.
[c]Urinalysis showed trace proteinuria.
[d]Spot urine protein was less than 1.1 mg/dl.
[e]Spot urine albumin-to-creatinine ratio of 450 mg/g Cr.

nephropathy and proteinuria of less than 3.5 g per day could respond to supportive care.[4] Except for subject 6 who had the nephrotic syndrome, both subjects 2 and 8 may have qualified for enrollment in the STOP-IgAN trial. Spontaneous remission of the nephrotic syndrome in patients with IgA nephropathy has been described in a retrospective series wherein 10% of cases presented with the nephrotic syndrome.[21] Among patients with the nephrotic syndrome, 20% had spontaneous remission in the series.[21]

Several other findings are novel in our pilot trial. Foremost, many of our participants found the steroid-free feature and short duration of bortezomib therapy very appealing. This was not unanticipated, because the TESTING trial in IgA nephropathy demonstrated that although it reduced the risk of disease progression, corticosteroid treatment was associated with higher risk of adverse events compared with placebo.[5] When corticosteroids are prescribed for IgA nephropathy, they are often given for a prolonged period, with the risk of disease relapse if stopped. Subject 9 experienced this scenario before enrollment. Importantly, we observed that for our 3 subjects with complete remission, the response was durable without relapse, with the longest remission lasting for 5 years (Table 3).

Participants who had complete remission in our study had Oxford classification T scores of 0 and low baseline serum creatinine (median of 0.59 mg/dl; IQR: 0.57–0.68 mg/dl). They also had received bortezomib within 6 months of diagnosis. In contrast, the rituximab study[19] enrolled subjects with more advanced renal insufficiency (median creatinine of 1.4 mg/dl; IQR: 0.8–0.2.4 mg/dl). Subjects who failed to respond to bortezomib had a higher grade of Oxford classification T scores (Tables 1, 2) despite having a baseline GFR of greater than 30 ml/min. This finding was consistent with the observation of others and could be an important factor when designing future trials.[19,22] Nonresponders generally did poorly in our study, with 2 of 4 participants developing end-stage renal disease at 3 and 4 years after treatment. We feel that the Oxford classification T score is more reliable than serum creatinine or GFR when predicting risk of progression or response in our limited sample size. However, the VALIGA study suggested that treatment with corticosteroids could benefit patients with estimated GFR of less than or equal to 50 ml/min per 1.73 m^2,[23] although none of our participants with baseline serum creatinine of greater than 2.0 mg/dl responded to bortezomib.

Based on our experience in using bortezomib for treating antibody-mediated kidney transplant rejection, we did not anticipate major side effects (data not shown). Similar to our bortezomib-treated kidney transplant recipients, participants in the trial did not develop neuropathy from exposure to 4 doses of bortezomib (1 cycle). However, our observation could be limited by sample size and duration of monitoring. Because all our participants received only 1 cycle of bortezomib, our pilot study could not address dosing effect on efficacy.

Our pilot study has several significant limitations, including small sample size, no control group, and nonrandomization. Without posttreatment kidney biopsy, we did not show definitively the resolution of IgA nephropathy. Similarly, without mechanistic studies, we could only speculate that bortezomib was useful by abrogating production of Gd-IgA1 antibodies and inhibiting nuclear factor kappa B expression.

In summary, we have gained more insight into the appropriate timing for bortezomib therapy in patients with active IgA nephropathy. Subjects who had benefited from bortezomib had normal renal function with Oxford classification score of T0. The strength of our study is the hypothesis-generating observations of proteasome inhibition by bortezomib for reducing proteinuria in patients with IgA nephropathy. We recommend performing a larger trial to further explore the efficacy of proteasome inhibition in severe IgA nephropathy and to define if early treatment is preferable for this disease.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Figure S1. Treatment course and laboratory results before and after bortezomib for subject 6. Patient first noticed leg edema, foamy urine, and weight gain 2 months before kidney biopsy. A timed 24-hour urine collection revealed protein excretion at study screening of 4.96 g, which was obtained 17 days before the first dose of bortezomib. The timed 24-hour proteinuria was 0.04 g at 6 months and 0.10 g at 1 year after bortezomib.

Supplementary material is linked to the online version of the paper at http://www.kireports.org/.

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