Use of Bortezomib in the Treatment of C3 Glomerulonephritis Refractory to Eculizumab and Rituximab

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Received 6 February 2020; revised 14 March 2020; accepted 17 March 2020; published online 30 March 2020

Kidney Int Rep (2020) 5, 951–954; https://doi.org/10.1016/j.ekir.2020.03.022
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INTRODUCTION

C3 glomerulopathy (C3G) is a chronic kidney disease defined by the predominance of C3 deposition in the renal glomeruli.1 C3G is caused by dysregulation of the alternative pathway of complement activation. The majority of C3G is caused by acquired factors—circulating IgG that stabilize the formation of the alternative pathway C3 convertase, C3bBb, which are referred to as C3 nephritic factor (C3NeF).2 In a smaller subset of C3G, autoantibodies that bind to and interfere with factor H, a protein that competes with factor B for C3 binding and acts as a cofactor for factor I, are present.3 The remaining patients have genetic dysregulation of the alternative pathway. C3G is currently treated by a combination of immunosuppression and complement pathway inhibition with mycophenolate, prednisone, eculizumab, and rituximab.4,5 Little is known regarding treatment options for the many patients with incomplete response or unacceptable side effects with these therapies. In this report, we describe the use of bortezomib to induce factor H autoantibody remission in a patient with longstanding C3G.

CASE PRESENTATION

We report the case of a young man with refractory C3 glomerulonephritis. He initially presented with the clinical picture of postinfectious glomerulonephritis at 6 years of age. He was subsequently lost to follow up for 3 years and, when re-evaluated, was found to have persistently depressed C3 level and nephrotic-range proteinuria (Table 1). He started prednisone, and although the C3 level remained below the assay limit of detection, the proteinuria normalized. Following the discontinuation of prednisone 2 years later, the proteinuria became severe, and a renal biopsy sample showed hypercellular, lobular glomeruli consistent with membranoproliferative glomerulonephritis (Figure 1a). Additional blood studies were performed at that time: factor H autoantibody was detected by enzyme-linked immunosorbent assay, fluid-phase C3 convertase stabilization was detected by immunofixation electrophoresis, and C3 convertase stabilization assay results were positive (Iowa University Molecular Otolaryngology and Renal Research Laboratories). Sequencing alternative pathway component genes was unrevealing. The patient was treated with mycophenolate 750 mg twice daily and prednisone 20 mg every other day, and the remained stable until the age of 16 years, when he developed worsening proteinuria. At that time, mycophenolate was discontinued and eculizumab was added. He had subsequent improvement of proteinuria, normalization of his soluble membrane attack complex, and improved appearance of the glomerular basement membrane on ultrastructural examination (Figure 1b).

At 19 years of age, despite being on eculizumab, his proteinuria worsened, and he was noted to have significant T-cell lymphopenia. Four doses of rituximab were administered and prednisone was discontinued. After 4 months, there was no improvement in proteinuria, and the C3 level remained below the assay limit of detection. Prednisone was restarted. The patient subsequently received 12 sessions of plasmapheresis and 2 additional doses of rituximab. His urine demonstrated a decrease in RBC, but he continued to have significant proteinuria with low serum albumin,
and the C3 level remained below the assay limit of detection. Mycophenolate was restarted. Despite these interventions, he deteriorated clinically and developed anasarca requiring diuretics, worsened hypertension, and grossly bloody urine. The factor H autoantibodies had declined (Figure 2) following treatment with rituximab; however, because the C3 level remained below the limit of detection, we hypothesized that autoantibody continued to dysregulate the alternative complement pathway. To further decrease autoantibody production, we decided to target plasma cells with bortezomib. Mycophenolate and prednisone were stopped, and shortly thereafter, at 21 years of age, bortezomib was started at 1.6 mg twice weekly for 2 weeks, followed by 1 week off, with dexamethasone 20 mg taken prior to each treatment. The patient quickly

Table 1. Key clinical parameters

| Age (yr) | Eculizumab Started | Rituximab 4 doses | Rituximab 2 doses | Bortezomib started | Kidney biopsy Present day |
|----------|-------------------|------------------|------------------|-------------------|-------------------------|
| Creatinine (mg/dl) | 0.3 | 0.6 | 0.6 | 0.6 | 0.8 | 0.5 |
| Albumin (g/dl) | 2.2 | 2.8 | 2.5 | 1.7 | 3.2 | 3.5 |
| Urine Protein/creatinine | 2.41 | 2.55 | 7.82 | 13.05 | 2.82 | 2.37 |
| C3 (mg/dl) | <15 | <15 | <15 | <15 | 110 | 131 |
| UA blood (mg/dl) | 1 | 1 | 1 | 1 | 0.2 | 0.2 |

Figure 1. Renal biopsy sample images at presentation and throughout the treatment course. (a) (Left) Hematoxylin–eosin staining demonstrating hypercellular, lobular glomeruli, and (right) electron microscopy demonstrating mesangial and subendothelial deposits (arrows). (b) Persistent glomerular hypercellularity on hematoxylin–eosin staining and (right) electron microscopy with decreased deposits in the basement membrane (arrow points at persistent mesangial dense deposits). (c) Immunofluorescence microscopy showing improvement of C3 staining from (left) 2 years before, and (right) 1 year after, starting bortezomib.
stabilized, with significant improvement of his nephritic and nephrotic clinical features. He no longer required diuretics and remained on only 1 antihypertensive agent, lisinopril.

After 4 months of therapy, his serum C3 level increased to the normal range, which was the first time that it had been detectable in 15 years (Figure 2, Table 1). Subsequent renal biopsy at the age of 22 years showed no glomerular endocapillary hypercellularity, stable mesangial hypercellularity, mild interstitial fibrosis, and evolving changes of focal segmental glomerular sclerosis with 10% global and 15% segmental sclerosis. Glomerular basement membrane C3 deposition was less prominent than in prior biopsy samples (Figure 1c). Despite the much-improved glomerular C3 deposition, the patient continues to have significant proteinuria (Table 1). He remains on bortezomib on the dosing schedule of 1.6 mg once weekly for 2 weeks, then 1 week off. Side effects of the treatment have been limited to nausea and decreased appetite, but no peripheral neuropathy.

DISCUSSION

To our knowledge, this is the first report of the use of bortezomib for the treatment of factor H autoantibody—associated C3G. Thus far, the use of plasma cell targeted therapies such as bortezomib has been limited to renal pathology associated with myeloma, monoclonal gammopathy, or monoclonal immune deposits. Treatment of C3G associated with nephritic factor or factor H autoantibody, on the other hand, typically involves the use of plasmapheresis, mycophenolate, prednisone, rituximab, and eculizumab. With the exception of rituximab, these therapies do not address the underlying cause of complement dysregulation in autoantibody-associated C3G. This case presentation provides preliminary evidence that plasma-cell directed therapies could reverse the alternative pathway abnormality in patients with factor H autoantibodies and C3G, particularly if targeting B cells with rituximab was ineffective (Table 2). Given this patient’s course, it is warranted to study this treatment in a larger cohort of C3G patients.

DISCLOSURE

BHR is on the advisory board of Admirx, Aurinia Pharmaceuticals, Biogen Idec, Bristol Myers Squibb, Callidatis, Chugai Pharma, EMD Serono, Genentech, Janssen, Lupus Foundation of America, AstraZeneca, MorphoSys, Novartis, Omeros, Pfizer, and Retrophin. He is a clinical trial principal investigator for Aurinia Pharmaceuticals, Biogen Idec, Genentech, Astra Zeneca, Retrophin, LuCIN, Human Genome Sciences, and ChemoCentryx. All the other authors declared no competing interests.

ACKNOWLEDGMENT

Funding was provided by the National Institutes of Health (K08AI141734) (JKA).

REFERENCES

1. Pickering MC, D’Agati VD, Nester CM, et al. C3 glomerulopathy: consensus report. Kidney Int. 2013;84:1079–1089.
2. Daha MR, Fearon DT, Austen KF. C3 nephritic factor (C3NeF): stabilization of fluid phase and cell-bound alternative pathway convertase. J Immunol. 1976;116:1–7.
3. Durey M-AD, Sinha A, Togarsimalemath SK, Bagga A. Anti-complement-factor H-associated glomerulopathies. *Nat Rev Nephrol*. 2016;12:563–578.

4. Avasare RS, Canetta PA, Bomback AS, et al. Mycophenolate mofetil in combination with steroids for treatment of C3 glomerulopathy: a case series. *Clin J Am Soc Nephrol*. 2018;13: 406–413.

5. Welte T, Arnold F, Kappes J, et al. Treating C3 glomerulopathy with eculizumab. *BMC Nephrol*. 2018;19:7.

6. Hirashio S, Satoh A, Arima T, et al. Favorable effect of bortezomib in dense deposit disease associated with monoclonal gammopathy: a case report. *BMC Nephrol*. 2018;19:108.

7. Huang J, Sun C, Su H, Zhang C, Xiong J. Bortezomib-based chemotherapy with autologous stem cell transplantation for monoclonal gammopathy of renal significance: a case report and literature review. *Kidney Blood Press Res*. 2019;44: 858–869.

8. Gumber R, Cohen JB, Palmer MB, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Kidney Int*. 2018;94:199–205.