DARATUMUMAB IN PATIENTS WITH BORTEZOMIB-REFRACTORY PROLIFERATIVE GLOMERULONEPHRITIS WITH MONOCLONAL IMMUNOGLOBULIN DEPOSITS

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Monoclonal gammopathy describes the presence of a monoclonal immunoglobulin (mIg) in the serum or urine that is secreted by a clonal population of the B-cell lineage.1–3 The clonal population can cause organ damage via a variety of mechanisms such as tumor burden, immunomodulation, and mIg deposition. The term monoclonal gammopathy of renal significance is used to describe kidney involvement that is not due to tumor burden. Patients with monoclonal gammopathy of renal significance often develop progressive renal dysfunction that can progress to end-stage kidney disease, and it commonly recurs after kidney transplantation.4,5 Thus, management of monoclonal gammopathy of renal significance has shifted from supportive therapy to aggressive treatment directed toward the presumptive underlying B cell or plasma cell clone if one is identified.4

Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) is a unique form of monoclonal gammopathy of renal significance, where kidney damage occurs as the result of deposition of mIg in kidney glomeruli.1–3 Patients with PGNMID typically present with proteinuria (often in the nephrotic range), microscopic hematuria, and abnormal kidney function. Only 30% of patients will have a detectable clonal population of B cells.4 Histologically, a membranoproliferative glomerulonephritis pattern is most common, but PGNMID may also exhibit an endocapillary proliferative or membranous (MN) pattern of injury.4 Around 50% of patients have IgG3 monoclonal glomerular deposits, and almost all have C3 deposits by immunofluorescence.4 Around 20% of patients with PGNMID progress to end-stage kidney disease.4 The treatment strategy for PGNMID relies on targeting the B cell or plasma cell clone if one is identified. The therapeutic approach to patients without an identifiable clone is not clear. In many centers including ours, patients are initially treated with a plasma cell–targeted regimen such as bortezomib and dexamethasone (with or without cyclophosphamide). Other centers use B cell–targeted agents such as rituximab.

Daratumumab is an anti-CD38 human IgG1k monoclonal antibody that depletes plasma cells, which are the major antibody-secreting cells in multiple myeloma (MM). Daratumumab is increasingly being used for refractory and/or relapsed MM.5 In addition, because of its favorable safety and tolerability profile, it is also being incorporated into regimens for treatment-naïve MM,6 and hence it represents a potential therapeutic option for patients with PGNMID. Until recently, data describing the use of daratumumab in patients with PGNMID were scarce. Zand et al. reported the outcome of 10 patients with PGNMID, 7 of which were treatment naïve.7 During the course of the 12-month study, all patients achieved a partial response and 4 achieved a complete response. Additionally, there were no serious infections, grade 3 or 4 anemia, leukopenia, or thrombocytopenia in the PGNMID patients. However, a decrease in immunoglobulin levels was observed in most patients. Data describing the efficacy of daratumumab for PGNMID patients resistant to traditional
Demographics and clinical characteristics

| Patient | Age, yr | Sex | Bone marrow biopsy | Bone marrow examination | Monoclonal gammopathy at diagnosis | Monoclonal gammopathy at first | Monoclonal protein (sIFE) | Prior therapy | Time on Vd (mo) | Proteinuria at last 24 h (mg/24 h) | Proteinuria at last 24 h (mg/24 h) | eGFR start (at last f/u) | eGFR last f/u (at last f/u) | Adverse events | F/u time while on Dara (mo) |
|---------|---------|-----|--------------------|-------------------------|-------------------------------|-------------------------------|-----------------------------|----------------|-------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|----------------|-------------------|
| 1       | 29      | F   | P/B cell flow, IHC, cytogenetics | No                      | Yes                          | IgG-k                        | MFM/Itux/Tac/Vd             | 4             | 7292          | 4817                        | 120                        | 113                        | 19                          | None                        | Recurrent vaginal yeast infections | 12.4                     |
| 2       | 29      | F   | P/B cell flow, IHC, FISH | No                      | Yes                          | IgG-k                        | MMF/Itux/Itux/Vd             | 19            | 10,072        | 2695                        | 19                         | ESRD                       | N/A                         | None                        | None                           | 9.0                      |
| 3       | 49      | F   | Monoclonal kappa restricted plasma cells (5%–10%) | Yes | Yes | IgG-k | Itux/Vd | 1 | 9346 | 247 | 46 | 80 | N/A | 19.1 | None | None | 19.1 |
| 4       | 30      | F   | P/B cell flow, IHC, cytogenetics | No | Yes | IgG-A | Vd | 7 | 3220 | 1404 | 114 | 112 | N/A | N/A | None | 112 |
| 5       | 79      | F   | PC flow, IHC, cytogenetics | No | Yes | IgG-A | Vd | 6 | 11,896 | 8116 | 79 | 79 | N/A | N/A | None | 5.0 |

AZA, azathioprine; CYC, cyclophosphamide; Dara, daratumumab; P/B cell flow, plasma-cell and B-cell flow cytometry; FISH, fluorescence in situ hybridization; F/u, follow-up; IHC, immunohistochemistry; MFM, mycophenolate mofetil; Itux, rituximab; sIFE, serum immunofixation; Tac, tacrolimus; Vd, combination bortezomib and dexamethasone; Voclo, voclosporin.

*All patients underwent serial hematologic evaluation with serum protein electrophoresis, serum immunofixation, and serum light-chain measurement.

**Values are in milliliters per minute per 1.73 m² using CK-EPI not adjusted for race.

**Detected monoclonal protein believed to be daratumumab which is an IgG1κ monoclonal antibody.
from 7.3 to 4.8 g/d); however, her repeat biopsy demonstrated resorbing immune deposits but significant damage to the glomerular basement membrane (Supplementary Figure S1), which might explain her persistent proteinuria. Patient 5 did not achieve renal response but had limited follow-up time (5 months). Patient 2 had advanced renal dysfunction at the time of infusion and suffered reactions at the time of infusion. Three patients achieved renal response at some point during treatment, and a fourth demonstrated resolving immune deposits suggestive of histologic improvement. The patient achieving complete proteinuric response was also the only patient with a detectable plasma cell clone, and achieved a hematologic response, supporting the efficacy of clone-directed therapy. Our results are encouraging for several reasons. First, none of the patients progressed to end-stage kidney disease due to PGNMID. The patient who did progress to end-stage kidney disease was improving prior to suffering from sepsis-induced acute tubular necrosis. Second, all patients had a decrease in proteinuria level, and 2 patients demonstrated improvement in kidney histology. Only 1 patient suffered from a severe adverse effect, and none of the patients suffered reactions at the time of infusion.

In conclusion, this study supports and extends the recently reported prospective clinical trial findings by Zand and colleagues. Despite the small number of patients included in these cohorts, daratumumab appears to be effective and well-tolerated. Daratumumab appears to be a viable option for both treatment-naive and treatment-resistant PGNMID and deserves evaluation in larger trials as a single agent or in combination with other B cell–targeted therapies.

**Table 2. Kidney biopsy findings**

| Patient | Predominant histologic pattern | Age at biopsy, yr | Predominant Ig (IIF) | Predominant light chain (IIF) | Location of immune-type deposits (EM) | Vascular findings (LM) | Concomitant ATN |
|---------|-------------------------------|------------------|----------------------|------------------------------|--------------------------------------|------------------------|----------------|
| 1       | MN                            | 25.82            | <25                  | IgG1                         | M, subEpi, IM                        | Normal                 | No            |
| 2       | MN                            | 21.20            | <25                  | IgG1                         | M, subEpi                            | Normal                 | No            |
| 3       | MN                            | 24.09            | <25                  | IgG1                         | M, subEpi, subEndo                   | Arteriolar wall thickening | No            |
| 4       | MPGN                          | 26.68            | <25                  | IgG1                         | M, subEpi, subEndo                   | Moderate intimal thickening of arteries, hyaline changes in arterioles | No            |
| 5       | MesangioPGN                   | 28.29            | <25                  | IgG1                         | M, IM, subEpi                        | Moderate intimal thickening of arteries, hyaline changes in arterioles | Yes           |
| 6       | MPGN                          | 48.75            | <25                  | IgG1                         | subEpi, subEndo                      | Moderate intimal thickening of arteries, hyaline changes in arterioles | No            |
| 7       | MPGN                          | 50.18            | <25                  | IgG1                         | subEpi, IM                           | Normal                 | Yes           |
| 8       | MPGN                          | 28.12            | <25                  | IgG1                         | subEpi, IM                           | Normal                 | No            |
| 9       | MPGN                          | 30.56            | <25                  | IgG1                         | subEpi, subEndo                      | Moderate intimal thickening of arteries, hyaline changes in arterioles | No            |

ATN, acute tubular necrosis; EM, electron microscopy; IIF, indirect immunofluorescence; LM, light microscopy; M, mesangial; MesangioPGN, mesangiproliferative glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; subEndo, subendothelial; subEpi, subepithelial.

*Subclass staining was not performed.

**Repeat kidney biopsy revealed resolving immune deposits but extremely damaged basement membrane.

**Patient had strong C3 staining in all of her biopsies.
DISCLOSURE
All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS
SA, SP, YE, and IA designed the research. SA analyzed the data. SA wrote the paper. AA provided the pathology input. SP, AA, NB, BR, NS, YE, and IA reviewed and edited the manuscript.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Figure S1. Patient 1’s first kidney biopsy, electron microscopy.

REFERENCES
1. Fermand JP, Bridoux F, Dispenzieri A, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018;132:1478–1485.
2. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. Nat Rev Nephrol. 2019;15:45–59.
3. Jain A, Haynes R, Kothari J, Khera A, Soares M, Ramasamy K. Pathophysiology and management of monoclonal gammopathy of renal significance. Blood Adv. 2019;3:2409–2423.
4. Nasr SH, Satoskar A, Markowitz GS, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009;20:2055–2064.
5. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375:1319–1331.
6. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019;380:2104–2115.
7. Zand L, Rajkumar SV, Leung N, Sethi S, El Ters M, Fervenza FC. Safety and efficacy of daratumumab in patients with proliferative GN with monoclonal immunoglobulin deposits. J Am Soc Nephrol. 2021;32:1163–1173.