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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 IgG3κ monotypic 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 IgG1κ 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

plasma cell–targeted therapy are lacking. Thus, we performed an institutional case review analysis assessing the safety and efficacy of daratumumab in PGNMID patients who did not respond to a bortezomib-based regimen.

We identified five patients who were treated with daratumumab after not responding to a bortezomib-based regimen. For most of the patients, multiple immunomodulatory therapies were tried in addition to bortezomib, without success prior to initiation of Daratumumab (Table 1). All patients were females with a median age of 25.8 years (interquartile range 21.2–46.8) at the time of first kidney biopsy demonstrating PGNMID. All patients underwent serial hematologic evaluation and a bone marrow biopsy. Only 1 patient (patient 3) had a detectable serum monoclonal protein and a monoclonal plasma cell population on bone marrow biopsy at diagnosis. After treatment with daratumumab, all patients developed a circulating IgGκ monoclonal protein that was sometimes different from the monoclonal protein detected in the kidney and likely represented daratumumab itself. For example, patient 4 developed a serum IgGκ gammopathy despite having IgG3-λ glomerular deposits.

A variety of histologic patterns including membranoproliferative glomerulonephritis, membranous, and mesangioproliferative glomerulonephritis (MesangioPGN) were identified on kidney biopsy (Table 2). Three patients had more than 1 kidney biopsy (patients 1, 2, and 4). The histologic pattern did not change with repeated biopsies in patients 1 and 4; however, patient 2 presented initially with a membranous pattern that evolved into a membranoproliferative glomerulonephritis pattern and later a MesangioPGN pattern at biopsy 4. The majority of patients had nephrotic-range proteinuria at the start of daratumumab therapy with a median of 9.3 g/d (interquartile range 7.2–10.0). The median eGFR was 46 ml/min per 1.73 m^2 (interquartile range 29–114). The median follow-up time was 11.2 months (interquartile range 9–12.4).

Overall, 1 patient (patient 3) achieved a complete proteinuric response (defined in the Methods section, Supplementary Material), with proteinuria decreasing from 9.3 to 0.2 g/d. This patient also achieved hematologic response with resolution of urine monoclonal protein and normalization of the serum light-chain levels and ratio. Another patient (patient 4) developed renal response (defined in the Methods section, Supplementary Material), with proteinuria decreasing from 3.2 to 1.4 g/d. Her most recent kidney biopsy demonstrated disappearance of IgG staining; however, she had persistent strong C3 staining suggesting potential overlap with C3 glomerulopathy. Patient 1 did not achieve a renal response (proteinuria decreased

Table 1. Demographics and clinical characteristics

Patient	Age, yr	Sex	Bone marrow biopsy	Bone marrow examination	Monoclonal gammopathy at diagnosis[a]	Monoclonal gammopathy ever[a]	Monoclonal protein (sIFE)	Prior therapy	Time on Vd (mo)	Proteinuria at Dara start (mg/24 h)	Proteinuria at last f/u (mg/24 h)	eGFR[b] at start	eGFR[b] at last f/u	Adverse events	F/u time while on Dara (mo)
1	29	F	Normocellular	P/B cell flow, IHC, cytogenetics	No	Yes[c]	IgG-κ	MMF/Ritux/Tac/Vd	4	7292	4817	120	113	Recurrent vaginal yeast infections	12.4
2	29	F	Normocellular	P/B cell flow, IHC, FISH	No	Yes [c]	IgG-κ	MMF/CYC/ritux/AZA/voclo/Vd	19	10,072	2695	19	ESRD	N/A	9.0
3	49	F	Monoclonal kappa restricted plasma cells (5%–10%)	P/B cell flow, IHC, cytogenetics, FISH (gains of 1q, 3q, and 17p and loss of 14q)	Yes	Yes	IgG-κ	Ritux/Vd	1	9346	247	46	80	N/A	19.1
4	30	F	Hypocellular, 1%–2% plasma cells	P/B cell flow, IHC, cytogenetics	No	Yes [c]	IgG-λ	AZA/Vd	7	3220	1404	114	112	N/A	11.2
5	79	F	Normocellular	PC flow, IHC, cytogenetics	No	Yes [c]	IgG-κ	Vd	6	11,896	8116	79	79	N/A	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; MMF, mycophenolate mofetil; Ritux, rituximab; sIFE, serum immunofixation; Tac, tacrolimus; Vd, combination bortezomib and dexamethasone; Voclo, voclosporin.
[a]All patients underwent serial hematologic evaluation with serum protein electrophoresis, serum immunofixation, and serum light-chain measurement.
[b]Values are in milliliters per minute per 1.73 m^2 using CKE-EPI not adjusted for race.
[c]Detected monoclonal protein believed to be daratumumab which is an IgG1κ monoclonal antibody.

Table 2. Kidney biopsy findings

Patient	Predominant histologic pattern	Age at biopsy, yr	Glomeruli with sclerosis (LM), %	Interstitial fibrosis and tubular atrophy (LM), %	Predominant Ig (IIF)	Predominant light chain (IIF)	Location of immune-type deposits (EM)	Vascular findings (LM)	Concomitant ATN
1	MN	25.82	58	25–50	IgG1	κ	M, subEpi, IM	Normal	No
	MN	28.56	40	25–50	IgG[a]	κ	IM—resolving[b]	Moderate intimal thickening of arteries, hyaline changes in arterioles	No
2	MN	21.20	0	<25	IgG1	κ	M, IM, subEpi	Normal	No
	MN	24.09	56	25–50	IgG1	κ	M, subEpi, IM, subEndo	Arteriolar wall thickening	No
	MPGN	26.68	25	25–50	IgG1	κ	M, subEpi, subEndo	Moderate intimal thickening of arteries, hyaline changes in arterioles	No
	MesangioPGN	28.29	63	25–50	IgG1	κ	M, IM, subEpi	Moderate intimal thickening of arteries	Yes
3	MPGN	46.75	10	<25	IgG1	κ	subEpi, subEndo	Moderate intimal thickening of arteries, hyaline changes in arterioles	No
4	MPGN[c]	17.95	0	<25	IgG3	λ	M, subEpi, IM, subEndo	Normal	Yes
	MPGN [c]	23.49	0	<25	IgG[a]	Equal	subEpi, IM, subEndo	Normal	No
	MPGN [c]	28.12	4	<25	IgG3	λ	subEpi, IM, subEndo	Mild intimal thickening of arteries	No
	MPGN [c]	30.56	8	<25	None	None	Minimal subEpi	Mild intimal thickening of arteries	No
5	MesangioPGN	78.14	13	<25	IgG3	κ	M, subEpi, subEndo	Moderate intimal thickening of arteries, hyaline changes in arterioles	No

ATN, acute tubular necrosis; EM, electron microscopy; IIF, indirect immunofluorescence; IM, intramembranous LM, light microscopy; M, mesangial; MesangioPGN, mesangioproliferative glomerulonephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; subEndo, subendothelial; subEpi, subepithelial.
[a]Subclass staining was not performed.
[b]Repeat kidney biopsy revealed resolving immune deposits but extremely damaged basement membrane.
[c]Patient had strong C3 staining in all of her biopsies.

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 starting daratumumab (eGFR 19 ml/min per 1.73 m^2). After 2 months of treatment, she developed sepsis from multifocal pneumonia and acute kidney injury due to acute tubular necrosis (noted on repeat biopsy), resulting in end-stage kidney disease and dialysis dependence. However, before developing sepsis, she appeared to be responding to daratumumab with improvement in eGFR from 19 to 28 ml/min per 1.73 m^2 and improvement in 24-hour urine protein from 10 to 2.8 g/d, thus achieving renal response prior to her hospitalization. Aside from the infectious complication noted in patient 2, daratumumab was well tolerated with no additional major adverse effects.

In our cohort of bortezomib-resistant PGNMID, 4 of 5 patients demonstrated some improvement after treatment with daratumumab. 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.[7] 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-naïve and treatment-resistant PGNMID and deserves evaluation in larger trials as a single agent or in combination with other B cell–targeted therapies.

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.

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