Safety and Efficacy of Daratumumab in Patients with Proliferative GN with Monoclonal Immunoglobulin Deposits

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ABSTRACT

Background Treatment of proliferative GN with monoclonal Ig deposits (PGNMID) is not established. A monoclonal anti-CD38 antibody (daratumumab) is effective in treating multiple myeloma. Abnormal plasma cell clones may play a role in the pathogenesis of PGNMID.

Methods We evaluated daratumumab’s safety and efficacy in an open-label, phase 2 trial in 11 adults with PGNMID and one with C3 glomerulopathy (C3G) with monoclonal gammopathy. Patients had an eGFR >20 ml/min per 1.73 m² and proteinuria >1 g/d. They received daratumumab intravenously (16 mg/kg) once weekly for 8 weeks, and then every other week for eight additional doses. Primary outcome was safety, defined as major infections, grade 3 or 4 anemia, leukopenia, or thrombocytopenia. Secondary outcomes were rate of complete remission (proteinuria <500 mg/d with <15% decline in baseline eGFR) or partial remission (>50% reduction in 24-hour proteinuria with <30% decline in eGFR) and proteinuria at 6 and 12 months.

Results One patient with C3G had GN unrelated to the monoclonal gammopathy, and one with PGNMID did not complete the first infusion. Five serious adverse events occurred. During the 12 months of the trial, six of the ten patients with PGNMID who received at least one dose of daratumumab had a partial response, and four had a complete response (an overall response rate of 100%). Three patients experienced relapse, two of whom re-entered partial remission after resuming daratumumab therapy. Proteinuria declined significantly, from a median of 4346 mg/d to 1264 mg/d by 12 months.

Conclusions Daratumumab demonstrated an acceptable safety profile and resulted in significant improvement in proteinuria while stabilizing kidney function in patients with PGNMID, suggesting the drug merits further investigation.

Clinical Trial registry name and registration number: Daratumumab in Treatment of PGNMID and C3 GN, NCT03095118

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deposition of the monoclonal proteins in the kidney, as documented by monotypic Ig staining and light-chain restriction on immunofluorescence microscopy, with associated inflammation. 3-5 Another is C3 glomerulopathy (C3G) (including C3 GN [C3GN] and dense deposit disease [DDD]), in the setting of MG, in which the monoclonal protein results in activation of the alternative complement pathway and indirectly causes kidney injury. 6-9 In the absence of any treatment, most patients with PGNMID and C3G associated with MG progress to ESKD. 3,10-13 These patients often have disease recurrence after kidney transplantation, which is associated with a high rate of allograft failure. 1,14 However, there is currently no standardized treatment for these patients. Most agree that the treatment should be directed toward the pathologic clone (known as clone-directed therapy) when a clone is detected. 1,8,11 However, up to 70% of patients with PGNMID do not have an identifiable clone on bone marrow biopsy specimens and have negative serum or urine protein electrophoresis and immunofixation, and normal serum free light chain ratios. 5 This poses a challenge for the hematologist and the nephrologist alike as to how to treat these patients. The current practice is to treat patients empirically with therapies that are traditionally used in patients with MM or lymphocytic or lymphoplasmacytic lymphoma. These include treatment with a combination of cyclophosphamide, bortezomib, and dexamethasone (known as CyBorD) or rituximab-based therapy. 5 The effectiveness of the current therapeutic strategy has not been well established and can be associated with significant side effects. 8,12 There remains a need for additional therapeutic options in this population.

Daratumumab is a human IgGk monoclonal anti-CD38 antibody that has shown effectiveness as a single agent, or in combination with other agents, in treating patients with relapsed and newly diagnosed MM. 16-20 We hypothesized that patients with PGNMID and C3G associated with MG may respond to daratumumab. In this prospective, phase 2, pilot study, we evaluated the safety and efficacy of daratumumab in treating patients with PGNMID or C3G associated with MG.

METHODS

Study Design
This was a single-center, open-label, phase 2, clinical trial conducted at the Mayo Clinic (Rochester, MN). The study was approved by the institutional review board at the Mayo Clinic. Written informed consent was obtained from all participants.

Participants
Adults (≥18 years of age) with biopsy specimen–proven PGNMID or C3G considered secondary to MG were recruited. All kidney biopsy specimens were reviewed by a Mayo Clinic pathologist to confirm the diagnosis. In patients with a diagnosis of C3G, a positive serum protein electrophoresis (SPEP) and serum immunofixation (SIF) were required. Inclusion criteria were proteinuria ≥1 g/24 h with an eGFR of ≥20 ml/min per 1.73 m². Exclusion criteria were hepatitis B and C, HIV, pregnancy, or breastfeeding. A pregnancy test was obtained before each infusion in females of reproductive age. Patients with MM or hemoglobin <8.5 g/dl, platelet <100×10⁹/L or white blood cells (WBC) <3.5×10⁹/L were excluded. Patient could not have received cyclophosphamide within 6 months of enrollment, or oral prednisone or glucocorticoid equivalent within 6 weeks of enrollment; however, prednisone or its equivalent at a dosage of ≤10 mg daily for a condition unrelated to PGNMID or C3G (e.g., asthma or gout) was allowed. Patients on mycophenolate mofetil (MMF), cyclosporine, tacrolimus, or azathioprine were eligible if proteinuria was not improving or if kidney function was declining despite treatment with these medications. However, once therapy with daratumumab was started, these medications had to be discontinued. In patients who had received rituximab therapy, reconstitution of their B cells (CD19 count >5 cells/dl) was required.

Procedures
Daratumumab was given intravenously (IV) at a dose of 16 mg/kg once weekly for 8 weeks, followed by once every 2 weeks for eight additional doses. Before the first infusion, patients also received 100 mg of methylprednisolone IV in addition to 1000 mg of acetaminophen and 50 mg of diphenhydramine orally. In the absence of infusion-related reactions, 1000 mg of acetaminophen and 50 mg of diphenhydramine was given orally before the subsequent infusions. All patients received 4 mg dexamethasone orally once daily for 2 days, beginning the day after the daratumumab infusion, for delayed infusion-related reactions. In addition, all patients received 400 mg of acyclovir orally twice daily, beginning within 1 week of starting daratumumab, up to 3 months after the last daratumumab infusion. Single-strength trimethoprim/sulfamethoxazole once a day (or its equivalent) was given up to 6 months after the last daratumumab infusion. The dosing

**Significance Statement**

Treatment of proliferative GN with monoclonal Ig deposition (PGNMID), in which direct deposition of the monoclonal proteins damages the kidney, is not established. Daratumumab, a monoclonal anti-CD38 antibody, has shown effectiveness as multiple myeloma therapy. In an open-label, phase 2 study, the authors evaluated safety and efficacy of a 6-month course of intravenous daratumumab in 11 patients with PGNMID and one with C3 glomerulopathy with monoclonal gammopathy. Five episodes of serious adverse events (two of which were infection related) occurred. All ten patients with PGNMID who received at least one daratumumab dose experienced a significant reduction in proteinuria at 6 months, which was sustained in seven patients by 12 months. Overall, in this pilot study, daratumumab’s acceptable toxicity profile and significant improvement in proteinuria, while stabilizing kidney function, suggest further investigation is warranted.
and frequency of daratumumab infusions were determined on the basis of prior efficacy studies in patients with MM.\textsuperscript{16} Follow-up visits were organized on days 49, 77, 161, 264, and 365 for complete physical examination, evaluation of adverse events, blood work (including complete blood count, chemistry tests, SPEP, SIF, serum free light chains, Ig levels), and urine studies (including urinary protein electrophoresis [UPEP], urinary immunofixation [UIF], urinary protein, and urinalysis with microscopy).

Outcomes

The primary outcome was a safety outcome, specified as the incidence of major infections (defined as the development of pneumonia, severe urinary tract infection [UTI]/pyelonephritis, sepsis, or meningitis); grade 3 or 4 anemia; leukopenia or thrombocytopenia; or a decrease in hemoglobin, WBC count, or platelet count from baseline to 6-month and 12-month time points. The severity of the serious adverse events (SAE) and infectious adverse events was classified on the basis of the Common Toxicity Criteria for Adverse Events version 5.\textsuperscript{21}

The secondary outcome was an efficacy outcome, specified as remission at 12 months. Complete remission (CR) was defined as proteinuria $<$500 mg/24 h and $<15\%$ decline in baseline eGFR, as determined by quantified creatinine clearance. Partial remission (PR) was defined as $>$50\% reduction in 24 hour proteinuria and $<30\%$ decline in baseline eGFR. No response (NR) was defined as any patient with $<50\%$ reduction in proteinuria and/or $>30\%$ reduction in baseline GFR. Other secondary outcomes included change in proteinuria, eGFR, hematuria, and C3 levels at 6 months and 12 months compared with baseline.

Statistical Analyses

This was a descriptive study, with the primary goal of determining toxicity rates associated with daratumumab in this patient population. Continuous variables are presented as mean $\pm$ SD if normally distributed, and median with interquartile ranges (IQRs) if not normally distributed. For the primary end point, the number and proportion of patients with treatment-emergent major infections, grade 3 or 4 anemia, leukopenia, or thrombocytopenia are summarized. Changes in hemoglobin, WBC count, and platelet count from baseline are analyzed using a paired $t$ test by comparing baseline values to follow-up values. The secondary efficacy end points were analyzed in a similar manner.

RESULTS

Study recruitment started in February 2018 and was completed by May 2019, and the last patient follow-up occurred in May 2020. Thirteen patients were screened for this trial. One patient was excluded because review of the kidney biopsy specimen revealed type I cryoglobulinemic GN and not PGNMID (Figure 1). A total of 12 patients with biopsy specimen–proven C3G with MG ($n=1$) and PGNMID ($n=11$) were enrolled. All 12 patients are included in the primary safety analysis. One patient with C3G and MG was recruited in the study. However, her C3G was noted to be related to MG and, therefore, she did not have true MG of renal significance. She was thus not included in the efficacy analysis. In addition, of the 11 patients with PGNMID, one patient did not complete the first infusion of daratumumab due to SAE (discussed below), was removed from the study by the principal investigator, and was not included in the efficacy analysis. The efficacy analysis presented here is of ten patients with PGNMID who received at least one infusion of daratumumab. An intent-to-treat analysis including all 12 patients, of which ten completed the 6-month treatment period, is also included.

Patients’ Baseline, Hematologic, and Kidney Biopsy–Specimen Characteristics

In the ten patients with PGNMID, the mean ($\pm$ SD) age of the cohort was 51.2 $\pm$ 22.6 years and ranged between 18 and 87 years of age. Male and females were equally divided and all patients were White. At the time of enrollment, mean ($\pm$ SD) eGFR was 61.1 $\pm$ 31.9 ml/min per 1.73 m$^2$. The median (IQR) 24-hour urinary protein was 4346 (3245–7943) mg and ranged from 2322 to 9566 mg. Only one patient had detectable monoclonal proteins in the blood and urine (IgGk), and all others had normal SPEP/SIF and UPEP/UIF. This patient did not have a detectable clone on review of their bone marrow biopsy specimen. All patients had a normal $\kappa/\lambda$ ratio in the setting of CKD. Median (IQR) time from kidney biopsy to enrollment was 8.25 (1.2–26.3) months, and there was little chronicity on the kidney biopsy specimens, with a mean ($\pm$ SD) incidence of global sclerosis of 16.9\% ($\pm$12.2\%) and of interstitial fibrosis and tubular atrophy (IFTA) of 12.5\% ($\pm$7.2\%). The most common immunofluorescence finding was IgGk ($n=6$), followed by IgGk ($n=2$). Additional baseline clinical, hematologic, and kidney biopsy–specimen characteristics are shown in Supplemental Table 1 and Table 1.

Of the ten patients, seven had not received any prior immunosuppressive therapy, two had been treated with rituximab (6 months and 24 months before the trial, respectively), and one was treated with MMF and prednisone (12 months before enrollment in the study). The patients that were treated with rituximab had evidence of reconstitution of their CD19 cells before enrollment and had shown no reduction in proteinuria.

Safety Outcomes and Adverse Events

Of the 12 patients that received daratumumab (162 infusions), there were two serious infectious complications. Both events occurred in the same patient. This patient had a diagnosis of C3G with MG. She had completed all 16 daratumumab infusions but, due to a lack of response at 6 months, she was started on 20 mg prednisone daily in addition to tacrolimus (1 mg twice daily) and MMF (500 mg twice daily). After 2 months
into treatment with the combination immunosuppression, she developed fever. Extensive infectious workup was completed and was negative. Tacrolimus and MMF were stopped and prednisone dose was reduced. Once her febrile episode resolved, she was restarted back on tacrolimus but remained off MMF. The second serious infection was due to *Clostridium difficile* colitis that required hospitalization for management of volume depletion and IV-fluid administration. The patient developed uncomplicated UTI 1 month after her febrile episode, for which she was treated with 3 days of antibiotics. However, a couple of days after completing the antibiotic course, she developed significant diarrhea (secondary to *C. difficile* infection) and volume depletion, requiring hospitalization. She was treated with oral vancomycin and her *C. difficile* resolved. Three months later, she had another uncomplicated UTI that required treatment with 3 days of antibiotics, after which she developed anotherepisode of *C. difficile* infection, for which she underwent fecal transplantation. She has not had recurrence of her UTI or *C. difficile* since.

There were no episodes of grade 3 or 4 anemia, leukopenia, or thrombocytopenia. The platelet count showed a statistically significant drop from baseline to 6 months, but not 12 months. The clinical relevance of the drop at 6 months is unclear (the lowest platelet count was $150 \times 10^9/L$ and within normal range). The hemoglobin level increased significantly from $11.7 \pm 1.9 \ g/dL$ at baseline to $12.8 \pm 1.4 \ g/dL$ at 12 months ($P=0.01$), despite receiving daratumumab.

There were total of five SAE. Two were related to infections, as discussed above. Another two SAE were eye chemosis and severe headache, which occurred in one patient. Both SAE started at the end of the first infusion of daratumumab and both resolved within 48 hours. The patient withdrew from the
study and did not receive any additional infusions. The fifth SAE was secondary to acute closed-angle glaucoma that occurred within the first 45 minutes of infusion of daratumumab. The patient developed headache, nausea, vomiting, and decreased vision. The infusion was stopped immediately and she was urgently seen by ophthalmology and diagnosed with acute closed-angle glaucoma. She was treated accordingly and her eye pressures normalized. The glaucoma was attributed to daratumumab and she was, therefore, withdrawn from the study by the principal investigator.

Other nonserious infectious complications included uncomplicated UTIs. Two occurred in the same patient, as noted above, and one in another patient that was treated with 3 days of antibiotics with resolution. There was one episode of upper respiratory infection that required no treatment.

The additional adverse events are shown in Table 2. The majority were infusion-related side effects, with the most common side effects including cough, congestion, throat irritation, and blurred vision. These were all self-limiting and were most common with the first infusion, with limited recurrence in future infusions. The majority of side effects were treated with as-needed doses of diphenhydramine.

**Efficacy Outcomes**

Overall, all ten patients with PGNMID who received at least one infusion of daratumumab responded to therapy. At 6 month follow-up (day 161), two patients had entered CR and six patients had entered PR, for an overall response rate of 80%. Two patients showed NR at 6 months. However, by 12 months of follow-up (day 365), the two patients that

| Table 1. Patients’ baseline clinical, hematologic and kidney biopsy–specimen characteristics |
|-----------------------------------------------|
| Characteristics                     | Baseline (n=10) |
|-----------------------------------------------|
| **Clinical characteristics**                 |                |
| Age (yr), mean±SD (IQR)                      | 51.2±22.6 (18–87) |
| Sex, n/M/F                                    | 5/5            |
| White race, n                                | 10             |
| BMI (kg/m²), mean±SD                         | 25.0±3.5       |
| Systolic BP (mm Hg), mean±SD                 | 125.6±21.0     |
| Diastolic BP (mm Hg), mean±SD                | 71.6±7.4       |
| Serum albumin (mg/dl), mean±SD (IQR)         | 3.23±0.6 (1.9–4.0) |
| Serum creatinine (mg/dl), mean±SD (IQR)      | 1.36±0.57 (0.6–2.56) |
| eGFR<sub>CKD-EPI</sub> (ml/min per 1.73 m²), mean±SD (median [IQR]) | 61.1±31.9 (55 [38–74]) |
| Creatinine clearance (ml/min per 1.73 m²), mean±SD (median [IQR]) | 85.3±44.9 (76.5 [53–107]) |
| Urinary protein (mg/24 h), median (IQR)      | 4346 (3245–7943) |
| Hematuria (present), n                        | 6              |
| C3 levels (mg/dl), median (IQR)              | 95 (54–110)    |
| C4 levels (mg/dl), median (IQR)              | 18 (16–30)     |
| Serum total cholesterol (mg/dl), mean±SD     | 225±43.4       |
| Serum LDL (mg/dl), mean±SD                   | 125.4±35.4     |
| Serum HDL (mg/dl), mean±SD                   | 68.1±29.5      |
| Hematologic characteristics                  |                |
| Hemoglobin (g/dl), mean±SD                   | 11.7±1.9       |
| SPEP, n normal/M-spike                       | 9/1            |
| Serum immunofixation (+), n                  | 1 IgGk         |
| UPEP, n normal/M-spike                       | 9/1            |
| Serum κ/λ ratio, mean±SD (IQR)               | 1.38±0.69 (0.54–2.93) |
| Serum IgA levels (mg/dl), mean±SD            | 141.7±60.4     |
| Serum IgM levels (mg/dl), mean±SD            | 91.6±64.9      |
| Serum IgG levels (mg/dl), mean±SD            | 556.2±201.7    |
| Kidney biopsy–specimen characteristics       |                |
| Time from biopsy to enrollment (mo), median (IQR) | 8.65 (1.2–26.3) |
| Global sclerosis (%), mean±SD                | 15.9±13.0      |
| IFTA (%), mean±SD                            | 12.5±7.2       |
| Arteriosclerosis, n none/mild/moderate        | 4/3/3          |
| Immunofluorescence, n                        |                |
| IgG3k                                         | 6              |
| IgG1k                                         | 2              |
| IgG3a                                         | 1              |
| IgA                                          | 1              |

M, male; F, female; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IFTA, interstitial fibrosis and tubular atrophy.
Table 2. Adverse events

| Adverse Event                | Severity Grade | No. Events or Patients |
|------------------------------|----------------|------------------------|
| SAE*a                        |                |                        |
| Eye chemosis                 | 2              | 1                      |
| Headache                     | 3              | 1                      |
| Acute glaucoma               | 1              | 1                      |
| Fever (? viral infection)     | 2              | 4                      |
| C. difficile infection        | 3              | 1                      |
| Infection-related AE*b       |                |                        |
| UTI                          | 2              | 3                      |
| C. difficile infection        | 2              | 2                      |
| URI                          | NG             | 1                      |
| Infusion-related AE*b        |                |                        |
| Cough                        | 7              | 7                      |
| Congestion                   | 7              | 7                      |
| Throat irritation             | 6              | 6                      |
| Blurred vision               | 4              | 4                      |
| Headache                     | 3              | 3                      |
| Myalgia                      | 3              | 3                      |
| Tingling in feet             | 3              | 3                      |
| Flushed                      | 2              | 2                      |
| Watery eyes                  | 2              | 2                      |
| Itching                      | 2              | 2                      |
| Sneezing                     | 3              | 3                      |
| Chest tightness              | 1              | 1                      |
| Vagal response               | 1              | 1                      |
| Lip tingling                 | 1              | 1                      |
| Skin itchy at IV site        | 1              | 1                      |
| Hoarse voice                 | 1              | 1                      |
| Sensation of facial swelling | 1              | 1                      |
| Other AE*b                   |                |                        |
| Fatigue                      | 3              | 3                      |
| Nausea                       | 3              | 3                      |
| Insomnia                     | 2              | 2                      |
| Night sweats                 | 2              | 2                      |
| Constipation                 | 2              | 2                      |
| Sore throat                  | 2              | 2                      |
| Leg cramps                   | 2              | 2                      |
| Sore scalp                   | 2              | 2                      |
| Chills                       | 2              | 2                      |
| Restless legs                | 1              | 1                      |
| Sore in mouth                | 1              | 1                      |
| Acne                         | 1              | 1                      |
| Rectal bleeding              | 1              | 1                      |
| Urinary frequency            | 1              | 1                      |
| Tinnitus                     | 1              | 1                      |
| Foot pain                    | 1              | 1                      |
| Low back pain                | 1              | 1                      |
| Bloating                     | 1              | 1                      |

SAE, serious adverse events; AE, adverse events; URI, upper respiratory infection; NG, not graded.

*aValues provided are number of events.

*bValues provided are number of patients.

Other AE were considered nonresponders had entered PR, and two additional patients that had achieved PR had entered CR. However, one patient that had achieved CR and two patients that had achieved PR at 6 months had relapsed. Therefore, at 12 months, there were three CRs, six PRs, and one NR. The best response at 12 months was a PR rate of 100%, and a CR rate of 40%. On an intent-to-treat basis, including all patients who were treated, the PR rate was 83% (ten of 12 patients), and the CR rate was 33% (four of 12 patients). Of note, three patients had serum albumin levels <30 g/L at baseline and all achieved remission (two PRs; one CR) at 12 months. Overall proteinuria reduced significantly from median (IQR) baseline proteinuria of 4346 (3245–7943) to 702 (435–3057) mg/24 h by 6 months ($P=0.001$), and 1264 (463–3645) mg/24 h by 12 months ($P=0.004$) (Figure 2). There was no statistically significant difference in proteinuria between 6 and 12 months. There were three patients that, by 12 months, were considered to have relapsed, and two patients were reinitiated on daratumumab. The first patient relapsed with proteinuria increased to 5.1 g/24 h, which improved to 0.9 g/24 h after 3 months of therapy with daratumumab. At the last follow-up, 15 months after relapse, proteinuria remained at 0.8 g/24 h. The patient remains on 16 mg/kg daratumumab IV every 2 months. The second patient relapsed to a proteinuria of 9.9 g/24 h, which improved to 2.1 g/24 h 4 months later after therapy with daratumumab. At the last follow-up, 10 months after relapse, proteinuria remains at 2.0 g/24 h. The patient continues treatment with 16 mg/kg daratumumab IV every 2 months. The third patient relapsed to a proteinuria of 5.6 g/24 h and was treated with CyBorD for a total of 16 cycles, with proteinuria remaining at 5.1 g/24 h.

The improvement in proteinuria occurred in conjunction with an improvement in serum albumin from 3.23±0.60 g/dL to 3.9±0.50 mg/dL at 6 months ($P=0.003$), and 3.94±0.63 g/dL at 12 months ($P=0.007$). Similarly, there was significant reduction in LDL cholesterol at 6 and 12 months. Hematuria also improved, with disappearance of hematuria at 6 months in all six patients who had evidence of hematuria at baseline, from a mean±SD of 10.0±8.6 to 0 red blood cells per high-power field (RBC/HPF) at 6 months ($P=0.05$) and 3.3±2.6 RBC/HPF at 12 months ($P=0.08$). There was no significant change in kidney function on the basis of creatinine, eGFR, or 24 hour creatinine-clearance measurements from baseline to 6 month and 12 month follow-up, as shown in Table 3. There were two patients with PGNMID who had low C3 levels at baseline, and both had normalization of their C3 levels at follow-up. One patient with IgG3κ had a baseline C3 level of 45 mg/dL (reference range, 54–100 mg/dL) and C4 level of 31 mg/dL (reference range, 14–40 mg/dL). A second patient with IgG3κ had a baseline C3 level of 6 mg/dL and C4 level of 18 mg/dL. This may reflect the fact that IgG1 and IgG3 are the most effective IgG subclasses at complement activation at the surface level. It is unknown whether the monoclonal IgG3 is also triggering complement activation in the fluid in these patients. Both patients went into CR with normalization of C3 complement levels at 12 months.

Notable is the patient with PGNMID who received only one infusion of daratumumab and subsequently withdrew from the study due to SAE of headache and eye chemosis. This patient, despite not having received any additional infusions, had...
resolution of his proteinuria (0 mg/24 h) at 6 months, which remained at 12 months, and serum creatinine that improved from a baseline of 1.37 to 0.96 mg/dl at 6 months and 0.9 mg/dl at 12 months.

We monitored SPEP/SIF and UPEP/UIF during the study period. Overall, there were no changes except for the time period at which an M-spike was detected on SPEP and SIF in patients who were receiving daratumumab, which showed IgGκ for all patients, consistent with the presence of the drug. This resolved after 6 months when the infusions were stopped. There was no change in the κ/λ ratio from baseline to 6 and 12 month follow-up, however, the absolute value of κ and λ reduced significantly at 6 months and the effect lasted by 12 months (Table 3). All Ig levels (IgG, IgA, and IgM) decreased significantly with daratumumab use.

There was only one patient with C3G and MG (IgGλ). This patient completed all 16 infusions within the first 6 months. However, at the end of the infusions, her proteinuria had increased from 3180 to 6634 mg/24 h, hematuria had increased from 41–50 to 51–100 RBC/HPF, in addition to a rise in serum creatinine from 1.17 to 1.33 mg/dl, all consistent with lack of response. During this time, her M-spike decreased from 0.8 to 0.4 g/dl. Given the lack of response to daratumumab despite a reduction in her M-spike, it was postulated that the overactivation of her alternative complement pathway triggering her C3G was unrelated to the MG. The functional complement pathway analysis showed an elevation in her levels of soluble membrane attack complex (344 ng/ml; normal levels are <251 ng/ml) and she was found to carry four copies of CFHDDD/C3GN-associated risk alleles (p.Val62 and p.His402) and two copies of C3DDD/C3GN-associated risk alleles (p.Gly102 and p.Leu314) on genetic testing. As a result, 12 months after enrolling in the trial, and after failing additional immunosuppressive therapy as previously described, she was initiated on eculizumab therapy and her tacrolimus and prednisone were stopped. Since initiation of eculizumab she has gone into CR. On her last evaluation (a year after starting eculizumab), her proteinuria had resolved (160 mg/24 h), hematuria disappeared (<3 RBC/HPF), and her serum creatinine remained stable at 1.33 mg/dl.

**DISCUSSION**

This is the first study to evaluate the safety and efficacy of daratumumab in patients with PGNMID. Overall, daratumumab presented an acceptable toxicity profile and resulted in significant improvement in proteinuria while stabilizing kidney function. PGNMID has been recognized as a distinct entity over the last decade and yet the best therapeutic approach remains unclear. Small case series suggest that clone-directed therapy may provide the best chance of entering PR or CR. However, in up to 70% of patients with PGNMID, a clone cannot be identified and, therefore, the majority of the patients are treated empirically. Given the success of daratumumab in treatment of patients with refractory MM and increased expression of CD38 on plasma cells in these patients, we hypothesized that daratumumab may be effective in treating patients with PGNMID. This was on the basis of the hypothesis that patients with PGNMID have plasma cell clones that result in production of monoclonal proteins that deposit in the kidneys and elicit inflammation. Therefore, eliminating the pathologic clone and preventing production of the monoclonal protein should result in renal response.
Indeed, all ten patients with PGNMID in this trial entered either CR or PR during the course of the study. In the majority of the patients, improvement in proteinuria was evident within the first month of infusion, by 6 months two patients had entered CR, and an additional two patients had entered CR by 12 months. Seven patients continued to have progressive improvement in their proteinuria throughout the trial. In addition, there was an overall significant improvement in serum albumin, hemoglobin, total and LDL cholesterol, and C3 levels, while serum creatinine remained stable. This clinical response was consistent with the fact that only one patient had a monoclonal protein detected on serum and urine studies and none had a detectable clone on review of their bone marrow biopsy specimens. A retrospective study of patients with PGNMID showed that, in nontransplant patients who were treated empirically with either rituximab, CyBorD, or a combination of the two, the rate of CR and PR was 75%. Similarly, in a study that evaluated effectiveness of rituximab in this patient population, the response rate was 54%, which is significantly lower than in those with MM. In PGNMID, it is yet to be determined whether the effect of daratumumab is related to specific depletion of a true plasma cells clone, depletion of oligoclonal plasma cells, or other effects of the drug.

The relapse in these three patients, two of which were re-started on daratumumab, raises the question of what should be the appropriate duration and frequency of therapy. We were not able to answer this question in this trial. The dosing and frequency of the infusions in this study were determined on the basis of prior trials of daratumumab in other autoimmune disorders, such as SLE and autoimmune hemolytic anemia. In patients with lupus, the effect has been attributed to the depletion of autoantibody, long-lived plasma cells, in addition to modification of IFN type I activity and modulation of effector T–cell responses. In PGNMID, it is yet to be determined whether the effect of daratumumab is related to specific depletion of a true plasma cells clone, depletion of oligoclonal plasma cells, or other effects of the drug.

Table 3. Clinical and hematologic characteristics of patients at baseline and 6 month and 12 month follow-up

| Characteristics                      | Baseline       | 6 Months     | P Value      | 12 Months    | P Value      |
|--------------------------------------|----------------|--------------|--------------|--------------|--------------|
| Serum albumin (mg/dl) (3.5–5.0 g/dl), mean±SD | 3.23±0.60     | 3.90±0.50    | 0.003        | 3.94±0.63    | 0.007        |
| Serum creatinine (mg/dl), mean±SD   | 1.36±0.57     | 1.25±0.44    | 0.15         | 1.25±0.52    | 0.16         |
| eGFR by the Cockcroft-Gault equation | 61.1±31.9     | 65.0±28.4    | 0.4          | 65.0±31.7    | 0.4          |
| Creatinine clearance (ml/min per 1.73 m², mean±SD) | 85.3±44.9     | 84.3±33.1    | 0.7          | 88.5±30.6    | 0.7          |
| Proteinuria (mg/24 h), median (IQR) | 4346 (3245–7943) | 702 (435–3057) | 0.001       | 1264 (463–3645) | 0.004       |
| Hematuria (present), n               | 6              | 0            | 0.06         | 2.5±2.6      | 0.15         |
| Hematuria (RB/C, HPF), mean±SD      | 6.0±8.0       | 0±0          | 0.06         | 2.5±2.6      | 0.15         |
| C3 levels (mg/dl) (75–175 mg/dl), median (IQR) | 95 (54–110) | N/A          | 0.06         | 95 (85–117) | 0.06         |
| C4 levels (mg/dl) (14–40 mg/dl), median (IQR) | 18 (16–30) | N/A          | 0.002        | 20 (17–38) | 0.2          |
| Serum total cholesterol (mg/dl), mean±SD | 225±43.4      | N/A          | 0.005        | 200.9±46.9   | 0.005        |
| Serum LDL (mg/dl), mean±SD          | 125.4±35.4    | N/A          | 0.004        | 109.8±42.0   | 0.04         |
| Serum HDL (mg/dl), mean±SD          | 68.1±29.4     | N/A          | 0.004        | 68.5±22.3    | 0.95         |

| Hematologic characteristics, mean±SD |                |              |              |              |              |
|--------------------------------------|----------------|--------------|--------------|--------------|--------------|
| Hemoglobin (g/dl)                    | 11.7±1.9       | 12.3±1.3     | 0.07         | 12.8±1.4     | 0.01         |
| WBC (×10³ cells)                     | 6.39±1.51      | 6.00±1.67    | 0.70         | 6.27±1.63    | 0.71         |
| Platelets (×10⁹/L)                   | 248.2±56.0     | 223.5±37.8   | 0.04         | 235.0±60.2   | 0.35         |
| Serum albumin (mg/dl)                | 0.03–1.94 mg/dl| 0.75±0.40    | 0.02         | 0.87±0.48    | 0.01         |
| Serum IgA levels (61–263 mg/dl)      | 1.98±0.97      | 0.65±0.30    | 0.002        | 0.72±0.33    | 0.002        |
| Serum IgA ratio (0.26–1.65)          | 1.38±0.69      | 1.10±0.35    | 0.34         | 1.24±0.45    | 0.42         |
| Serum IgG levels (61–356 mg/dl)      | 141.7±60.4     | 28.90±18.75  | 0.0003       | 41.30±23.00  | 0.0005       |
| Serum IgG levels (37–286 mg/dl)      | 91.6±64.9      | 43.90±29.60  | 0.0009       | 57.80±38.70  | 0.02         |
| Serum IgG levels (767–1590 mg/dl)    | 556.2±201.7    | 334.4±132.1  | 0.03         | 365.5±141.4  | 0.04         |

N/A, not available.
Most notable was one patient who only received one dose of daratumumab but entered CR within a month and remained in CR by 12 months. This highlights the notion that, in certain patients, a shorter duration of therapy may be just as effective. On the other hand, three patients had an initial response but relapses occurred within 6 months of stopping therapy, suggesting that, in a subset of patients, a longer-term therapy (perhaps once monthly similar to the MM population) is needed.27 At this point, it is unclear as to which patients can have a long-lasting effect from daratumumab and which patients require further infusions to remain in remission. Future studies are required to answer this question and determine the optimal frequency of daratumumab.

One notable change with the use of daratumumab was the significant reduction in the absolute amount of k and l light chains. This is likely a reflection of the effect of daratumumab on all plasma cells. Another significant change was the reduction in the Ig levels after therapy at 6 months which persisted by 12 months. This, however, was not associated with an increased risk of infection. The two serious infections that occurred in this study were in the same patient who was receiving additional immunosuppression (including steroids, calcineurin inhibitors, and MMF) and it is likely that the combination therapy was responsible for this increased risk. It should be noted that patients in this trial were treated with acyclovir for 9 months, and trimethoprim/sulfamethoxazole for 12 months, and these measures may have been effective in lowering the risk of infection; patients who receive daratumumab should be monitored closely for risk of infection.

The most common side effect in this trial was the infusion-related reaction, but the majority of patients tolerated the infusion and only one patient decided to withdraw from the study due to the side effects. Acute closed-angle glaucoma has been described with the use of daratumumab but is exceedingly rare.28,29 The mechanism is thought to be secondary to ciliochoroidal swelling that, in turn, results in shallowing of the anterior chamber of the eye, which ultimately leads to increased intraocular pressures and may be related to the effect of daratumumab on the CD38 cells that are expressed on the ciliary body.30 Another common infusion-related side effect was blurred vision, which resolved after the infusion and may have been related to myopic shift that can occur with daratumumab.31

There was only one patient with C3G and MG in this study, and this patient did not respond to therapy with daratumumab despite evidence of overexpression of CD38 cells on their bone marrow biopsy specimen, and despite a reduction in M-spike with the use of daratumumab. The lack of response to therapy raised the possibility that other complement pathway abnormalities were not triggered by the monoclonal protein, and that her MG was a coincidental finding. After initiation of eculizumab, this patient achieved CR, confirming our diagnostic suspicion. This case should raise awareness of the treating clinician that, although there is strong evidence that circulating monoclonal proteins can activate the alternative pathway and be responsible for the underlying pathology in some patients,11 proof that the monoclonal protein is working as an autoantibody against a protein in the complement cascade has only been provided in research settings.32 As such, in clinical practice, this is an assumption that, as illustrated by the patient with C3G included in the study, proved to be incorrect. Therefore, when treating patients with C3G in association with MG, one should be cautious and, if there is no improvement in kidney function and proteinuria after treating the MG, consideration should be given that the MG may be a coincidental finding.

Our study has several limitations. The number of patients was small, there was no comparison arm, and, therefore, the effectiveness of daratumumab cannot be directly compared with rituximab or CyBorD therapy. However, the 100% response rate is almost unheard of, with perhaps the exception of response rate to erythropoietin.33 Additionally, the frequency of dosing once the patient achieves remission could not be addressed in this trial. Confirmation of our findings is required in future studies with larger number of patients that also evaluate the frequency of dosing. This was mainly a proof-of-concept, pilot study to evaluate the safety and efficacy of daratumumab in patients with PGNMID, a disease for which there is no standard of care. Indeed, we were able to show that daratumumab was both safe and effective in treating patients with PGNMID and provide a viable alternative for treatment in patients with this disease.

**DISCLOSURES**

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Dr. Ladan Zand, Dr. S. Vincent Rajkumar, and Dr. Fernando C. Fervenza designed the study; Dr. Ladan Zand, Dr. Fernando C. Fervenza, Dr. S. Vincent Rajkumar, Dr. Nelson Leung, and Dr. Mireille El Ters recruited and followed the patients; Dr. Sanjeev Sethi reviewed kidney biopsy specimens for the study; Dr. Ladan Zand, Dr. Fernando C. Fervenza, and Dr. Nelson Leung analyzed the data; Dr. Ladan Zand and Dr. Fernando C. Fervenza drafted and revised the paper; and all authors provided input for the final version of the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/supp/doi:10.1681/ASN.2020101541/-/DCSupplemental.

Supplemental Table 1. Diagnostic kidney biopsy findings and efficacy outcomes for the 12 patients enrolled in the study.

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