Briana C. Ndife (briana.ndife@novartis.com)

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Characteristics of patients with complement 3 glomerulopathy (C3G) in a US multi-center assessment

Briana C. Ndife[1], Carolina A. Aldworth[1], Kathleen P. Murphy[1], Jennifer Nguyen[1], Irina Pivneva[2], Marie Louise Edwards[2], Annika Anderson[2], James Signorovitch[2], Pietro A. Canetta[3]

[1]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [2]Analysis Group, Boston, Massachusetts, USA; [3]Columbia University Irving Medical Center, New York, New York, USA

KEY FINDINGS & CONCLUSIONS

- In this contemporary assessment of patients with C3G from a US cohort, we identified a population with multiple comorbidities, advanced kidney disease around the time of C3G diagnosis, and high rates of CKD stage progression, highlighting a need for novel treatments to improve patient outcomes
- At the index date, 33 patients (11.6%) had post-transplant recurrent C3G
  - Close to the time of diagnosis, these patients tended to have advanced disease, poor kidney function, and high rates of comorbidities
- Of 188 patients assessed for CKD stage progression, 115 progressed during the follow-up period
  - Close to the index date, these patients tended to have advanced CKD stage and poor kidney function
  - During the baseline period, they had high rates of comorbidities, kidney transplant, and supportive care

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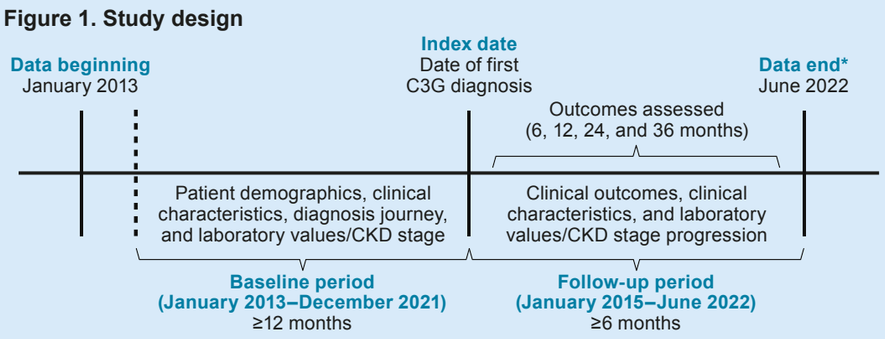
INTRODUCTION

- C3G is a rare glomerulonephritis with an estimated incidence of between 1 and 3 cases per million people in the US[1–3]
- C3G is characterized by the accumulation of C3 in the glomeruli, caused by the dysregulation of the alternative complement pathway[1,3,4]
- There are currently no validated treatment strategies or approved therapies for C3G[5]
  - Supportive care (including ACEi and ARBs) and immunosuppressive agents are recommended management strategies, based on expert opinion[5]
- Up to 50% of adults living with the disease develop kidney failure within 10 years of diagnosis[6,7]
- Contemporary cohort studies examining the clinical burden of C3G are limited, and there is a lack of data that represent a diverse US population[2,4,5]
- In this analysis of EHR data, we present the demographic and clinical characteristics of a real-world cohort of US patients diagnosed with C3G

METHODS

- This was a retrospective cohort study of patients within the US Optum Life Science Clinical EHR database who received a C3G diagnosis between January 2015 and June 2022 (**Figure 1**)
- A C3G diagnosis was identified by the presence of a diagnostic code (ICD-10-CM or SNOMED CT) for C3G; the index date was the date of the first C3G diagnosis
  - Included patients were ≥12 years of age at the index date and had ≥1 C3G diagnosis between January 2015 and June 2022
  - Patients were required to have ≥12 months of available clinical data before the index date (baseline period) and ≥6 months after the index date (follow-up period)

Figure 1. Study design



*Or patient death or end of continuous clinical activity, if before data end. C3G, complement 3 glomerulopathy; CKD, chronic kidney disease.

- Patient demographics, clinical characteristics, and laboratory values were assessed during the baseline period and/or at the index date
- Patients were stratified by kidney transplant status at the index date (post-transplant recurrent C3G or C3G in the native kidney) and CKD stage progression status (CKD stage progressors or non-progressors, as assessed during the follow-up period)
  - Post-transplant recurrent C3G was defined as documentation of a kidney transplant before C3G diagnosis at the index date
  - Progression was assessed in patients with CKD stage <5 at the index date, who had adequate data to assess progression (based on laboratory values, diagnosis codes, or dialysis procedure codes); patients with a higher CKD stage post-index date were considered progressors
- Continuous variables were summarized by mean and SD; categorical variables were summarized by counts and percentages

RESULTS

- In the US Optum Life Science Clinical EHR database, 415 patients had ≥1 diagnosis for C3G
  - A total of 284 patients met the study inclusion criteria
  - As of the index date, 33 patients had post-transplant recurrent C3G
  - Of 188 patients assessed for CKD stage progression, 115 progressed at any time after the index date

Demographic and clinical characteristics

- Demographic and clinical characteristics for the overall population, stratified by kidney transplant status and CKD stage progression status, are summarized in **Table 1**
- Overall, most patients were White (77.5%), 50% were female, and the mean age at the index date was 48.8 years (SD: 20.5)
- Of those with available data within 1 month of the index date, 59.6% had CKD stage ≥3
- Based on data closest to the end of the baseline period, 66.0% had normal C3 levels, and 86.5% had proteinuria

Patients stratified by post-transplant recurrent C3G and C3G in the native kidney

- In patients with post-transplant recurrent C3G, relative to patients with C3G in the native kidney:
  - CKD stage ≥3 at the index date was more prevalent (89.7% and 55.3%)
  - ACEi or ARB use 1 month before (and including) the index date was numerically lower (ACEi, 15.2% and 21.9%, and ARB, 0% and 15.1%)
  - At the end of the baseline period, normal proteinuria was more prevalent (28.6% and 10.5%), as were normal C3 levels (83.3% and 62.2%)

Table 1. Demographic and clinical characteristics

Characteristic	Overall N=284	Kidney status at the index date (N=284)		Patients with CKD stage progression assessed during the follow-up period* (n=188)	
		C3G in the native kidney n=251	Post-transplant recurrent C3G n=33	Non-progressors n=73	CKD stage progressors n=115
Age at the index date, years					
Mean ± SD	48.8 ± 20.5	49.2 ± 20.7	46.5 ± 19.1	48.1 ± 19.9	53.5 ± 19.8
Sex†, n (%)					
Female	142 (50.0)	128 (51.0)	14 (42.4)	36 (49.3)	54 (47.0)
Race, n (%)					
African American	30 (10.6)	26 (10.4)	4 (12.1)	4 (5.5)	16 (13.9)
Asian	6 (2.1)	6 (2.4)	0	4 (5.5)	1 (0.9)
White	220 (77.5)	196 (78.1)	24 (72.7)	54 (74.0)	90 (78.3)
Other/unknown	28 (9.9)	23 (9.2)	5 (15.2)	11 (15.1)	8 (7.0)
BMI (kg/m²)‡, n (%)					
BMI assessed	249 (87.7)	218 (86.9)	31 (93.9)	64 (87.7)	103 (89.6)
<18.5	9 (3.6)	8 (3.7)	1 (3.2)	2 (3.1)	4 (3.9)
≥18.5 to <25	67 (26.9)	60 (27.5)	7 (22.6)	19 (29.7)	22 (21.4)
≥25 to <30	73 (29.3)	61 (28.0)	12 (38.7)	24 (37.5)	23 (22.3)
≥30	100 (40.2)	89 (40.8)	11 (35.5)	19 (29.7)	54 (52.4)
CKD stage within 1 month of the index date§, n (%)					
CKD stage assessed	228 (80.3)	199 (79.3)	29 (87.9)	73 (100.0)	115 (100.0)
Stage 1	41 (18.0)	40 (20.1)	1 (3.4)	22 (30.1)	19 (16.5)
Stage 2	51 (22.4)	49 (24.6)	2 (6.9)	23 (31.5)	28 (24.3)
Stage 3	45 (19.7)	38 (19.1)	7 (24.1)	15 (20.5)	30 (26.1)
Stage 4	36 (15.8)	34 (17.1)	2 (6.9)	13 (17.8)	23 (20.0)
Stage 5/kidney failure	55 (24.1)	38 (19.1)	17 (58.6)	0	15‖ (13.0)
Treatments 1 month before (and including) the index date, n (%)					
CV-related	125 (44.0)	110 (43.8)	15 (45.5)	23 (31.5)	74 (64.3)
ACEi	60 (21.1)	55 (21.9)	5 (15.2)	15 (20.5)	34 (29.6)
ARBs	38 (13.4)	38 (15.1)	0	9 (12.3)	23 (20.0)
CS (oral/IV)	66 (23.2)	54 (21.5)	12 (36.4)	11 (15.1)	41 (35.7)
Immunosuppressive agents	39 (13.7)	20 (8.0)	19 (57.6)	4 (5.5)	21 (18.3)
Eculizumab	6 (2.1)	4 (1.6)	2 (6.1)	2 (2.7)	1 (0.9)
eGFR (mL/min/1.73m²)‡,¶, n (%)					
eGFR measured	239 (84.2)	209 (83.3)	30 (90.9)	70 (95.9)	105 (91.3)
eGFR mean ± SD	59.2 ± 37.5	62.8 ± 37.6	33.7 ± 25.3	76.5 ± 36.0	51.9 ± 31.7
Proteinuria status‡,#, n (%)					
Proteinuria status assessed	126 (44.4)	105 (41.8)	21 (63.6)	33 (45.2)	62 (53.9)
Normal (<0.2 g/g)	17 (13.5)	11 (10.5)	6 (28.6)	6 (18.2)	11 (17.7)
Subnephrotic (≥0.2 to <3.5 g/g)	76 (60.3)	64 (61.0)	12 (57.1)	21 (63.6)	32 (51.6)
Nephrotic (≥3.5 g/g)	33 (26.2)	30 (28.6)	3 (14.3)	6 (18.2)	19 (30.6)
UPCR (g/g), mean ± SD	2.9 ± 3.9	3.2 ± 4.1	1.5 ± 1.9	1.9 ± 2.5	3.5 ± 4.6
Hematuria status‡,* (RBC/HPF), n (%)**					
Hematuria assessed	101 (35.6)	82 (32.7)	19 (57.6)	30 (41.1)	47 (40.9)
Normal (<3)	30 (29.7)	25 (30.5)	5 (26.3)	12 (40.0)	14 (29.8)
Microscopic hematuria (≥3)	71 (70.3)	57 (69.5)	14 (73.7)	18 (60.0)	33 (70.2)
C3 level (mg/dL)‡, n (%)					
C3 level assessed	100 (35.2)	82 (32.7)	18 (54.5)	24 (32.9)	47 (40.9)
Decreased (<77)	34 (34.0)	31 (37.8)	3 (16.7)	9 (37.5)	15 (31.9)
Normal (≥77 to <201)	66 (66.0)	51 (62.2)	15 (83.3)	15 (62.5)	32 (68.1)

*Patients with a lower CKD stage at the index date than at the follow-up timepoint were considered progressed; †The sex of one patient in the overall population/post-transplant recurrent C3G subgroup was unknown; ‡Assessed using data closest to the end of the baseline period; §CKD stage was defined using the eGFR value closest to the index date. If eGFR data were not available within 1 month of the index date, CKD stage was defined using the CKD diagnosis code closest to the index date; CKD stage 3 includes stage 3a, stage 3b, and unspecified stage 3; ‖If a patient had a procedure code for dialysis within 1 month of the index date, their CKD stage was defined as CKD stage 5/kidney failure; 15 patients were identified as CKD stage 5 in the month after the index date; ¶eGFR values were either calculated with the CKD-EPI creatinine equation (2021) for patients ≥18 years of age or reported by Optum (Schwartz formula) for patients <18 years of age; #Proteinuria was assessed using UPCR; proteinuria status was based on the definition from Kamińska J et al[8]; **Hematuria was assessed using red blood cell count (microscopic urinalysis); hematuria status was based on the definition from Barocas DA et al.[9]
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; C3, complement component 3; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CS, corticosteroids; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HPF, high power field; IV, intravenous; RBC, red blood cells; SD, standard deviation; UPCR, urine total protein to creatinine ratio.

Patients stratified by CKD stage progression status

- In patients with CKD stage progression, relative to non-progressors:
  - The mean age at the index date was higher (53.5 years and 48.1 years)
  - Obesity was more prevalent at the end of the baseline period (BMI ≥30; 52.4% and 29.7%)
  - More patients tended to have CKD stage ≥3 at the index date (59.1% and 38.4%)
  - ACEi or ARB use 1 month before (and including) the index date was more prevalent (ACEi, 29.6% and 20.5%, and ARB, 20.0% and 12.3%)
  - Nephrotic proteinuria was more prevalent at the end of the baseline period (30.6% and 18.2%)

Clinical characteristics during the baseline period

- Clinical characteristic data during the baseline period for the overall population, stratified by kidney transplant status and CKD stage progression status, are summarized in **Table 2**
- In the overall population:
  - Hypertension was the most common C3G-related comorbidity (64.8%)
  - CV-related treatments (62.7%) and CS (oral/IV; 53.9%) were the most common C3G-related treatments

Patients stratified by post-transplant recurrent C3G and C3G in the native kidney

- In patients with post-transplant recurrent C3G, relative to patients with C3G in the native kidney:
  - The mean Charlson Comorbidity Index score was numerically higher (3.9 and 2.1)
  - C3G-related comorbidities were more prevalent, particularly hypertension (93.9% and 61.0%)
  - More tended to have received CV-related treatments (87.9% and 59.4%), CS (oral/IV; 84.8% and 49.8%), and immunosuppressive agents (81.8% and 12.7%)

Patients stratified by CKD stage progression status

- In patients with CKD stage progression, relative to non-progressors:
  - The mean Charlson Comorbidity Index score was numerically higher (2.8 and 1.8)
  - More had received a kidney transplant (10.4% and 2.7%)
  - A numerically greater proportion of patients were receiving CV-related treatments (79.1% and 52.1%), CS (oral/IV; 67.0% and 42.5%), and ACEi (51.3% and 34.2%)

Table 2. Clinical characteristics of patients with C3G during the baseline period

Characteristic	Overall N=284	Kidney status at the index date (N=284)		Patients with CKD stage progression assessed during the follow-up period* (n=188)	
		C3G in the native kidney n=251	Post-transplant recurrent C3G n=33	Non-progressors n=73	CKD stage progressors n=115
Charlson Comorbidity Index score					
Mean ± SD	2.3 ± 2.7	2.1 ± 2.4	3.9 ± 3.6	1.8 ± 2.4	2.8 ± 2.6
Comorbidities included in the Charlson Comorbidity Index score†, n (%)					
Kidney/renal disease‡	171 (60.2)	138 (55.0)	33 (100.0)	40 (54.8)	76 (66.1)
Chronic pulmonary disease	70 (24.6)	59 (23.5)	11 (33.3)	16 (21.9)	32 (27.8)
Diabetes without chronic complication	56 (19.7)	43 (17.1)	13 (39.4)	10 (13.7)	34 (29.6)
Congestive heart failure	54 (19.0)	42 (16.7)	12 (36.4)	10 (13.7)	23 (20.0)
Malignancy	46 (16.2)	37 (14.7)	9 (27.3)	8 (11.0)	23 (20.0)
Peripheral vascular disease	43 (15.1)	32 (12.7)	11 (33.3)	9 (12.3)	23 (20.0)
C3G-related comorbidities, n (%)					
Hypertension	184 (64.8)	153 (61.0)	31 (93.9)	40 (54.8)	91 (79.1)
Fatigue/tiredness	93 (32.7)	76 (30.3)	17 (51.5)	22 (30.1)	41 (35.7)
Edema	78 (27.5)	66 (26.3)	12 (36.4)	14 (19.2)	43 (37.4)
Pain	60 (21.1)	48 (19.1)	12 (36.4)	8 (11.0)	35 (30.4)
C3G-related procedures, n (%)					
Kidney biopsy	60 (21.1)	46 (18.3)	14 (42.4)	13 (17.8)	32 (27.8)
Kidney transplant§	33 (11.6)	0	33 (100.0)	2 (2.7)	12 (10.4)
Hemodialysis	27 (9.5)	18 (7.2)	9 (27.3)	1 (1.4)	11 (9.6)
Treatments, n (%)					
CV-related	178 (62.7)	149 (59.4)	29 (87.9)	38 (52.1)	91 (79.1)
ACEi	115 (40.5)	100 (39.8)	15 (45.5)	25 (34.2)	59 (51.3)
ARBs	73 (25.7)	60 (23.9)	13 (39.4)	17 (23.3)	34 (29.6)
CS (oral/IV)	153 (53.9)	125 (49.8)	28 (84.8)	31 (42.5)	77 (67.0)
Immunosuppressive agents	59 (20.8)	32 (12.7)	27 (81.8)	11 (15.1)	25 (21.7)
Eculizumab	7 (2.5)	3 (1.2)	4 (12.1)	2 (2.7)	2 (1.7)

*Patients with a lower CKD stage at the index date than at the follow-up timepoint were considered progressed; †≥15% in the overall population; ‡Kidney/renal disease includes select kidney/renal conditions as defined per the Charlson Comorbidity Index, based on the presence of an ICD-9 or ICD-10 code; §Kidney transplant during the baseline period, or diagnosis code in the baseline period indicating a prior kidney transplant.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CS, corticosteroids; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases; IV, intravenous; SD, standard deviation.

LIMITATIONS

- Due to the nature of EHR data collection, the diagnosis codes and data recorded may be subject to human or technical error or data omission
- The subgroup population sizes were small and not powered for statistical comparison
- CKD stage was derived using a combination of diagnosis codes, procedure codes, and eGFR values and therefore may not reflect the actual CKD stage for each patient; progression, which was dependent upon CKD stages, may not reflect the true disease progression of the patient
- Patients with a C3G diagnosis at the index date and documentation of a kidney transplant were assumed to have recurrent C3G and, therefore, categorized as having post-transplant recurrent C3G
- The analysis required patients to have ≥6 months of continuous clinical activity, which may lead to the underestimation of the proportions of patients with select clinical events, such as progression

Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; C3, complement component 3; C3G, complement 3 glomerulopathy; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CM, Clinical Modification; CS, corticosteroids; CT, Clinical Terms; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HPF, high power field; ICD, International Classification of Diseases; IV, intravenous; RBC, red blood cells; SD, standard deviation; SNOMED, Systematized Nomenclature of Medicine; UPCR, urine total protein to creatinine ratio; US, United States.

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Disclosures

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