Patterns of Clinical Response to Eculizumab in Patients With C3 Glomerulopathy

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Background: Cases reports and small series of patients with C3 glomerulopathy have reported variable efficacy of eculizumab.

Study Design: Case series of C3 glomerulopathy.

Setting & Participants: Pediatric and adult patients with C3 glomerulopathy treated with eculizumab between 2010 and 2016 were identified through the C3 glomerulopathy French registry database, and a questionnaire was sent to participating French pediatric and adult nephrology centers, as well as one pediatric referral center in Québec, Canada.

Outcomes: Global or partial clinical renal response.

Measurements: Evolution of serum creatinine and proteinuria values.

Results: 26 patients (13 children/adolescents) were included. 22 (85%) patients had received steroids, plasma exchange, or immunosuppressive therapy before eculizumab, and 3 of them had rapid progression of their kidney disease despite treatment. At the initiation of eculizumab therapy, 11 (42%) patients had chronic kidney disease, 7 (27%) had rapidly progressive disease, and 3 (12%) required dialysis. After eculizumab treatment (median duration, 14 months), 6 (23%) patients had a global clinical response; 6 (23%), a partial clinical response; and 14 (54%), no response. Compared with those who had a partial clinical or no response, patients who had a global clinical response had lower estimated glomerular filtration rates, a more rapidly progressive course, and more extracapillary proliferation on kidney biopsy. Age, extent of renal fibrosis, frequency of nephrotic syndrome, low serum C3 and C3 nephritic factor and elevated soluble C5b-9 concentrations, or complement gene variants did not differ between responders and nonresponders.

Limitations: Retrospective design without a control group, relatively small number of cases, inclusion of pediatric and adult cases.

Conclusions: Eculizumab appears to be a potential treatment for patients with crescentic rapidly progressive C3 glomerulopathy. Its benefit in patients with non–rapidly progressing forms seems to be limited.

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For decades, membranoproliferative glomerulonephritis (MPGN) was classified into 3 subtypes: type I and III, characterized by immunoglobulins and complement deposits, and type II (dense deposit disease [DDD]), defined as the presence of dense deposits in the basement membrane on electron microscopy study. More recently, a new classification was proposed to take into account the wide variety of pathologic patterns of MPGN on light microscopy and distinguish: (1) C3 glomerulopathies (C3Gs), a group of nephropathies with exclusive or predominant glomerular C3 deposits, with (DDD) or without (C3 glomerulonephritis) dense deposits on electron microscopy study; and (2) immunoglobulin-associated MPGN. This classification is based on data generated through animal models of C3G,[1] the pattern of immune deposits in kidney biopsies, the identification of complement dysregulation in patients with MPGN,[2,3] and the association of anti-complement antibodies,[4,5] mainly C3 nephritic factor (C3Nef), with C3G.[2] Most importantly, it has reemphasized the suspected role of complement dysregulation in the pathophysiology of these nephropathies.[6-8]

The new classification has also coincided with the availability of the first complement inhibitor, the anti-C5 monoclonal antibody, eculizumab.[9,10] A small prospective study[11] and a limited number of case series or case reports[12-18] have shown variable efficacy of eculizumab in C3G affecting the native kidneys, in sharp contrast to the dramatic effect of this drug in another complement-mediated kidney disease, atypical hemolytic uremic syndrome.[9,19-21] Moreover, case reports carry the potential bias of the preferential publication of positive results. Thus, the Francophone Working Group on C3G analyzed data from all cases of children, adolescents, and adults with C3G treated with eculizumab in France and in a referral pediatric center in Québec, Canada, to provide a more global picture of the use of eculizumab for these nephropathies in clinical practice.

Methods

We identified patients with C3G treated with eculizumab in France and in Hôpital Sainte Justine, Québec, through: (1) the C3G French registry database, which includes

nearly all cases of C3G diagnosed in France (at the Laboratory of Immunology, Hôpital Européen Georges-Pompidou in Paris, a French reference center for complement analysis); and (2) a questionnaire sent to pediatric and adult nephrology centers in France and the pediatric nephrology department at Hôpital Sainte-Justine in Québec, Canada. Patients' files were reviewed and relevant clinical, biological, and pathologic data were extracted.

Based on the previously published consensus document,[7] C3G was defined by C3 intensity staining (immunofluorescence study) in a kidney biopsy specimen 2 or more orders of magnitude more than any other immune reactant on a scale of 0 to 3. Electron microscopy is not routinely performed for kidney biopsies in France and thus subtype classification of C3G (DDD vs C3 glomerulonephritis) is not available for most of the included patients. Kidney biopsies were locally reviewed in a pathology department of a university hospital by a qualified renal pathologist familiar with the diagnosis of C3G.

Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, calculated using the MDRD (Modification of Diet in Renal Disease) Study equation[22] in adults or the Schwartz formula[23] in children and adolescents. Rapidly progressing C3G/MPGN was defined as ≥50% increase in serum creatinine concentration in less than 2 months.

Complement workup (performed <3 months before the start of eculizumab treatment, except for genetic tests performed at the diagnosis of C3G) included: (1) measurement of serum C3, C4, soluble C5b-9, factor B (FB), factor H (FH), factor I (FI), and membrane cofactor protein expression on granulocytes; (2) enzyme-linked immunosorbent assay test for anti-CFH antibodies; and (3) sequencing of all coding sequences for FH (*CFH*), FI (*CFI*), membrane cofactor protein, C3, and FB (*CFB*) and screening for rearrangements in the *CFHR1-CFHR5* region using multiplex ligation–dependent probe amplification. All techniques were performed as previously described.[24,25]

Complement genes variants were categorized as: (1) pathogenic: rare variant with a minor allele frequency (MAF) < 1% and functional data indicating that the variant affects protein function or expression; (2) likely pathogenic variant: rare variant with MAF < 1% and highly deleterious effects by in silico prediction (using the polyphen 2 tool) or in protein structure, but without available functional data; and (3) variant of uncertain significance rare variant with MAF < 1% with uncertain deleterious effects by in silico prediction (using polyphen 2) and no functional data.[26]

Nephrotic syndrome was defined as proteinuria with protein excretion > 3 g/d, serum protein concentration < 6 g/dL, and serum albumin concentration < 3 g/dL.

Response to eculizumab was characterized as: (1) global clinical response, defined as (a) >50% decrease in serum creatinine concentration and urinary protein-creatinine ratio (UPCR) and serum albumin concentration > 3 g/dL or (b) the persistence of normal serum creatinine concentration (±10%) and albumin concentration > 3 g/dL and normalization of UPCR (<150 mg/g); or (2) partial clinical response, defined as (a) <50% decrease in serum creatinine concentration, albumin concentration > 3 g/dL, and >50% decrease in UPCR; or (b) the persistence of normal serum creatinine concentration (± 10%), albumin concentration > 3 g/dL, and > 50% decrease in UPCR.

Data are presented as frequency and percentage or median and range. All analyses (χ^2, Fisher exact, Mann-Whitney, and *t* tests) with $P < 0.05$ were considered statistically significant. For this retrospective study without identifying information, informed consent and ethics committee approval were not required, but written consent for genetic analysis was obtained.

Results

Patient Characteristics

Twenty-six patients (13 children/adolescents and 13 adults) treated with eculizumab between 2010 and 2016 were included. Cases of patients 1 and 6,[27] 2,[28] 16 and 17,[16] and 13[29] have been previously reported, but are included in the present series with an extended follow-up. Patient characteristics are summarized in Table 1 (also see Fig 1).

Median age at eculizumab treatment start was 18 (range, 9-65) years. All patients received angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists, and doses were unchanged after eculizumab treatment initiation. Median time from diagnosis to eculizumab treatment initiation was 16 (range, 0.5-150) months. At eculizumab treatment initiation, median serum creatinine concentration was 0.6 (range, 0.2-4.6) mg/dL in children/adolescents and 2.3 (range, 0.6-9.9) mg/dL in adults, corresponding to median eGFRs of 110 (range, 10-150) and 28 (range, 8-111) mL/min/1.73 m^2, respectively. At eculizumab treatment initiation, 19 (73%) patients had nephrotic syndrome, 11 (42%) had CKD, 7 (27%; patients 2, 14-16, 17, 19, and 20) had a rapidly progressive form of C3G, and 3 (12%; patients 2, 17, and 19) required dialysis at eculizumab treatment initiation. None of the patients had monoclonal gammopathy. Compared with adults, children/adolescents had milder disease at eculizumab treatment initiation, as exemplified by a higher eGFR (110 vs 36 mL/min/1.73 m^2; $P = 0.001$; Table 1).

Before eculizumab treatment initiation, 20 (77%) patients had received steroids with or without plasma exchanges (n = 2) or an immunosuppressive treatment (mycophenolate mofetil [MMF; n = 8], rituximab [n = 4], cyclophosphamide [n = 2]; or tacrolimus [n = 1]). Median time between these treatments and eculizumab use was 18 (range, 1-58) months. Eculizumab treatment was initiated for persistent nephrotic syndrome in 15 patients; for rapidly progressing disease in 7 patients, including 3 (patients 2, 15, and 16) in whom C3G had rapidly