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Case Report

Eculizumab for Treatment of Rapidly Progressive C3 Glomerulopathy

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C3 glomerulopathy (C3G) is a prototypic complement-mediated kidney disease. Rapidly progressive forms of C3G usually respond poorly to conventional treatments. We report on the efficacy of the terminal complement inhibitor eculizumab in 3 adult patients with rapidly progressive C3G. In all 3 patients, serum creatinine levels had increased by >50% in the 2 months preceding initiation of eculizumab treatment despite the use of conventional immunosuppressive drugs and/or plasma exchanges in 2 of these individuals. Of note, 2 patients had long-standing nephrotic syndrome. Kidney biopsy performed prior to eculizumab treatment disclosed marked glomerular inflammatory changes and increased C5b-9 deposition in all patients. Eculizumab use was associated with significant improvement in kidney function, with estimated glomerular filtration rates of patients increasing 22 to 38 mL/min/1.73 m^2. Eculizumab use also was associated with remission of nephrotic syndrome in the 2 affected patients, an effect observed as early as one week after treatment initiation. Repeat kidney biopsy disclosed regression of glomerular inflammatory changes and decreases in glomerular staining for C5b-9 in all patients. These results warrant further assessment of eculizumab for treatment of rapidly progressive forms of C3G with markedly increased glomerular C5b-9 deposits.
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INDEX WORDS: C3 glomerulopathy (C3G); C5b-9 deposits; complement; complement alternative pathway; eculizumab; rapidly progressing glomerulonephritis; acute kidney injury (AKI).

A recently described nephropathy, C3 glomerulopathy (C3G), is characterized by exclusive or predominant glomerular C3 deposits[1] with or without dense deposits.[1,2] Pathologic features of C3G include not only various aspects of membranoproliferative glomerulonephritis (MPGN; eg, "double contours" and mesangial expansion), but also those of mesangial proliferative glomerulonephritis, crescentic or acute proliferative glomerulonephritis, and exudative glomerulonephritis.[3,4] C3G is a prototypic complement-mediated disease linked to complement alternative pathway dysregulation. This link is supported by animal models (mice[5] and pigs[6]) in which deficiency of complement alternative pathway regulatory factor H leads to uncontrolled activation of alternative C3 convertase and ultimately to C3G development. Autoantibodies targeting the alternative C3 convertase (C3 nephritic factor [C3NeF] and antifactor B) and mutations in genes coding for C3 or complement alternative pathway inhibitors (factor H, factor I, or membrane cofactor protein [MCP]) have been detected in patients with C3G.[3,7-9]

C3G conveys a poor renal prognosis that is not restricted to patients with dense deposit disease (DDD).[10] About half the patients with C3G reach end-stage renal disease and half of these may experience disease recurrence in the kidney transplant.[3,4] Treatment of C3G remains ill defined; therapies have included mycophenolate mofetil, cyclophosphamide, and plasma exchanges. Rapidly progressive forms of C3G, which account for up to 20% of cases,[1,2] usually respond poorly to conventional treatments; thus, treating such cases remains highly challenging. However, eculizumab, a terminal complement inhibitor, has changed perspectives on managing complement-mediated diseases, including paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.[11] Even so, eculizumab treatment of C3G and MPGN (mainly in chronic forms) has produced conflicting results.[12-15] We report on the efficacy of eculizumab in 3 adult patients with rapidly progressive C3G.

CASE REPORTS

We report on 3 patients followed up in 3 French university hospitals (Hôpital Foch, Centre Hospitalier Universitaire de

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Nantes, and Centre Hospitalier Régional Universitaire de Lille) who were treated with eculizumab for rapidly progressive C3G. The main clinical and biological features of each patient are summarized in Table 1 and displayed in Figs 1 to Figs 3. Item S1 contains detail on definitions used for diagnosis and on assay methods. Two patients (1 and 3) had C3G affecting native kidneys, whereas one had C3G recurrence in her transplanted kidney. One patient had DDD. None had features of autoimmune disease or serum or urine monoclonal component. In all 3 patients, serum creatinine levels had increased by >50% in the 2 months preceding initiation of eculizumab treatment despite the use of conventional immunosuppressive drugs and/or plasma exchanges in 2 of these individuals (Table 1). Two patients also had long-standing nephrotic syndrome.

Kidney biopsies were performed during the acute kidney injury phase and after eculizumab treatment on either the native or transplanted kidney. Prior to eculizumab treatment, glomerular inflammatory changes were found in all biopsy specimens. In patients 1 and 3, for whom initial kidney biopsy specimens had been obtained during a more chronic phase of the disease, we observed markedly increased glomerular deposition of C5b-9 in the native kidney specimen from the acute kidney failure phase compared to the initial specimens (Figs 1 and 3; Table S1). As seen in Fig 2, early deposition of C5b-9 was found in the transplanted kidney. Complement assays (Table S2) showed features of complement alternative pathway activation (decreased serum C3 and CH50 and normal C4 levels) in all patients and C3NeF was detected in one patient. Soluble C5b-9 levels were elevated in 2 patients. No mutation was detected in the tested complement genes.

After receiving meningococcal vaccine and long-term antibiotic prophylaxis (penicillin), patients were started on 4 weekly 900-mg eculizumab infusions, followed by a single 1,200-mg eculizumab infusion every 2 weeks. In all patients, eculizumab use was associated with a significant improvement in kidney function (increase in estimated glomerular filtration rate by 22-38 mL/min/1.73 m^2), observed as early as the first week after starting eculizumab treatment. Complete or partial remission of nephrotic syndrome was noted in the 2 patients who initially had presented with heavy proteinuria. Complement inhibition (CH50 < 10%) was achieved in all patients. No side effects were observed during follow-up. Persistently decreased serum C3 levels were observed in 2 patients, and C3NeF was detectable in patient 1 before and after eculizumab treatment. Soluble C5b-9 levels returned to the reference range in the 2 patients who had increased levels prior to eculizumab treatment. Repeat kidney biopsies performed 3 to 13 months after starting eculizumab treatment revealed regression of glomerular inflammatory changes and a decrease in glomerular staining for C5b-9 in all patients (Table S1; Figs 1-3). Glomerular C3c deposits had completely disappeared in one patient, but persisted in 2 patients.

DISCUSSION

In 3 patients with rapidly progressive C3G, we found that eculizumab use was associated with significant improvement in kidney function and with complete or partial remission of nephrotic syndrome in the 2 patients who had presented with long-standing heavy proteinuria. Improvement in kidney function was most striking in the 2 patients who experienced rapid progressive decreases in kidney function despite conventional treatment (one patient received steroids and mycophenolate mofetil, whereas the other

Table 1. Clinical and Biological Characteristics of 3 Patients With Rapidly Progressive C3 Glomerulopathy

	Patient 1	Patient 2	Patient 3
Sex	F	F	M
Age (y)	27[a]	63	45
Biopsy specimen	Native kidney	Transplanted kidney	Native kidney
Previous treatments	ACEi/ARB	Cs, PE	ACEi/ARB, Cs, MMF
At eculizumab initiation			
Time from diagnosis (mo)	8	5	15
Scr (mg/dL)	6	2.2	4.1
eGFR (mL/min/1.73 m^2)	9	24	17
Serum albumin (g/dL)	1.8	3.5	2.2
UPCR (g/mmol)	1.42	0.16	1.3
NS	+	−	+
Duration of eculizumab treatment (mo)[b]	19	32	6
At last follow-up			
Scr (mg/dL)	2	0.9	1.7
eGFR (mL/min/1.73 m^2)	31	62	44
Increase in eGFR (mL/min/1.73 m^2)	22	38	27
Serum albumin (g/dL)	4	3.7	3
UPCR (g/mmol)	0.08	0.09	0.78
NS	CR	−	PR

Note: Conversion factors for Scr in mg/dL to μmol/l, ×88.4.

Abbreviations and definitions: ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CR, complete remission; Cs, corticosteroids; eGFR, estimated glomerular filtration rate (calculated using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation); MMF, mycophenolate mofetil; NS, nephrotic syndrome; PE, plasma exchange; PR, partial remission; Scr, serum creatinine; UPCR, urinary protein-creatinine ratio.

[a]The patient's kidney disease was discovered shortly after the end of her first pregnancy.

[b]At the time of writing, eculizumab treatment in all patients was ongoing.

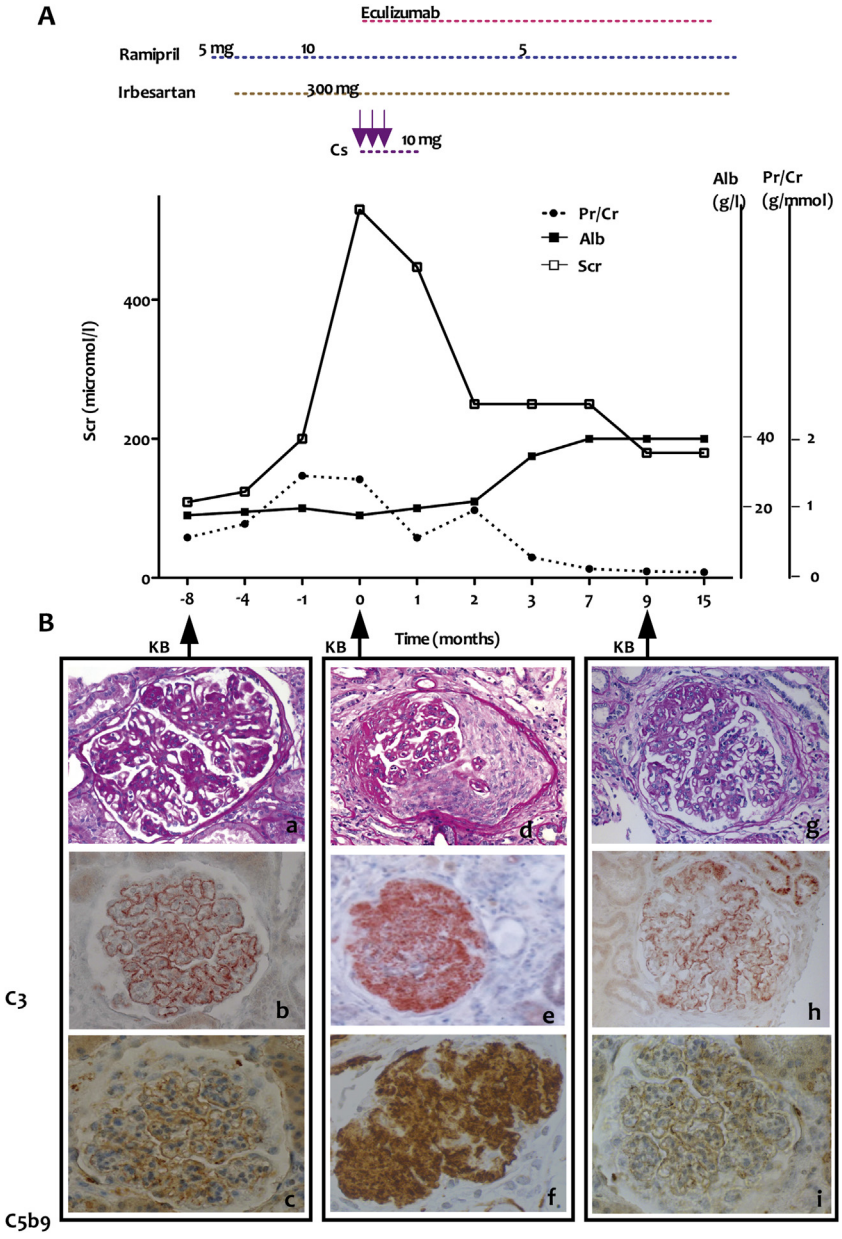

Figure 1. Laboratory values and kidney biopsy images for patient 1. (A) Changes in serum creatinine (Scr), urine protein-creatinine ratio (Pr/Cr), and serum albumin (Alb) values before and after eculizumab initiation. (B, a-c) First kidney biopsy (KB). (a) Photomicrograph (periodic acid–Schiff [PAS] stain; original magnification, ×400); presence of mild mesangial expansion. (b) Immunohistochemical stain (anti-C3; original magnification, ×400); presence of significant C3 deposits. (c) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); presence of mild C5b-9 deposits. (d-f) Second kidney biopsy. (d) Photomicrograph (PAS stain; original magnification, ×400); presence of intense extracapillary proliferation. (e) Immunohistochemical stain (anti-C3; original magnification, ×400); increased C3 deposits compared to the previous biopsy specimen. (f) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); presence of intense C5b-9 deposits. (g-i) Third kidney biopsy. (g) Photomicrograph (PAS staining; original magnification, ×400); absence of extracapillary proliferation and persistence of mild mesangial expansion. Segmental tuft scarring is present. (h) Immunohistochemical stain (anti-C3; original magnification, ×400); C3 staining intensity is similar to that noted in the first biopsy specimen. (i) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); marked decrease in C5b-9 deposits compared to the second biopsy specimen. Abbreviation: Cs, corticosteroids.

received these treatments along with tacrolimus and plasma exchanges). The beneficial effect of eculizumab was observed as early as the first week after treatment initiation, suggesting that eculizumab induces rapid and potent inhibition of the complement terminal pathway that translates into rapid clinical improvement. These observations contrast those made in eculizumab-treated patients with non–rapidly progressive forms of C3G or MPGN: one study showed that complement inhibition led to a rather modest and delayed reduction in proteinuria and serum creatinine level in only 60% of patients.[12]

The patients reported here had 2 common features that may predict and explain eculizumab efficacy in this population. First, prior to eculizumab therapy initiation, all patients had features of marked activation of the terminal complement pathway (increased soluble C5b-9 levels and/or an increase in or appearance of intrarenal deposition of C5b-9 compared with previous kidney biopsies performed during chronic phases of the disease) that normalized after treatment. These parameters were discrepant in patient 1, who had a normal soluble C5b-9 level contrasting with intense glomerular C5b-9 deposition. This patient presented with severe nephrotic syndrome that may have accounted for urinary loss of soluble C5b-9. However, in patient 3, who had nephrotic syndrome of similar severity, soluble C5b-9 levels were elevated. Interestingly, the evolution of glomerular C5b-9 deposition paralleled changes in kidney function. Thus, the kinetics of

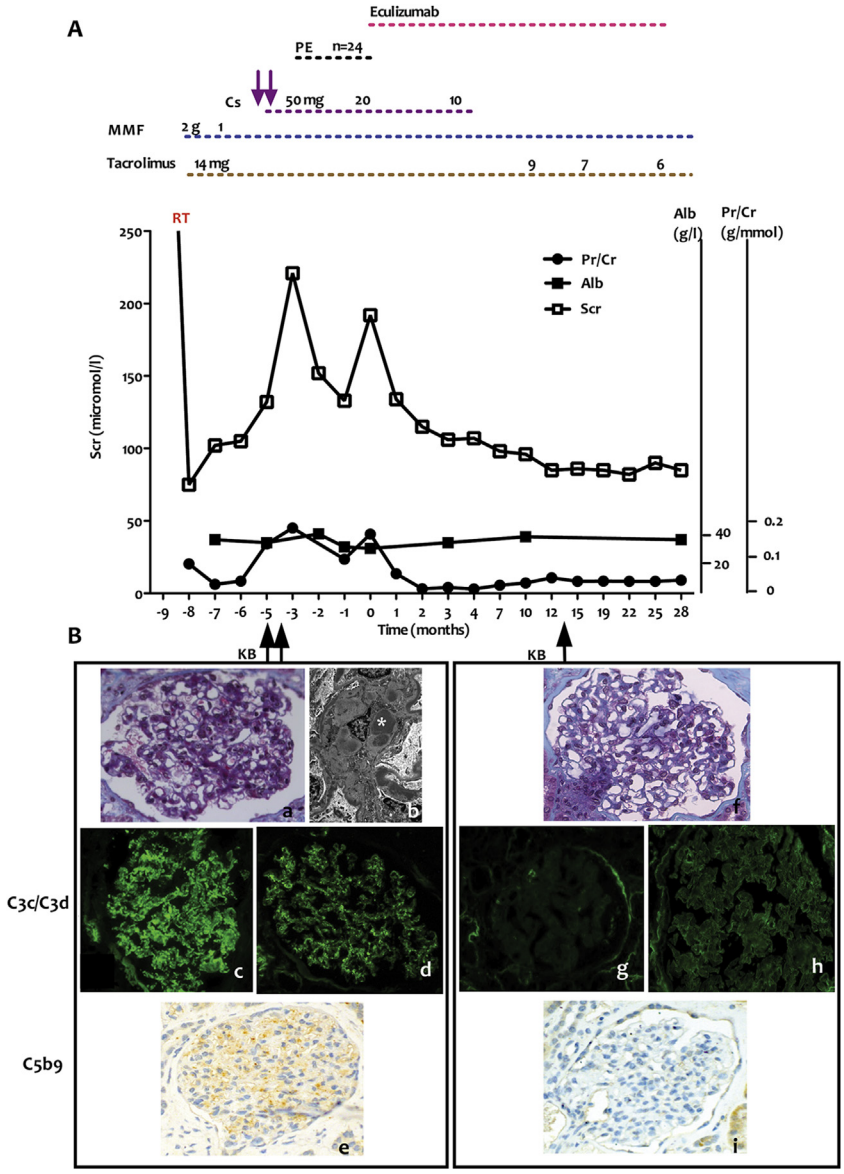

Figure 2. Laboratory values and kidney biopsy images for patient 2. (A) Changes in serum creatinine (Scr), urine protein-creatinine ratio (Pr/Cr), and serum albumin (Alb) levels before and after eculizumab initiation. (B, a-e) First kidney biopsy (KB). (a) Photomicrograph (Masson trichrome; original magnification, ×400); presence of mesangial expansion and inflammatory cells in the glomerulus. (b) Electron micrograph (lead citrate, uranyl acetate; original magnification, ×5,000); dense deposits (*) within the basement membrane and mesangium. (c, d) Immunofluorescence stain (c: anti-C3; original magnification, ×400) and (d: anti-C3d; original magnification, ×400); presence of intense C3 and C3d glomerular deposits. (e) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); moderate C5b-9 deposits in glomeruli. (f-i) Second kidney biopsy. (f) Photomicrograph (Masson trichrome; original magnification, ×400); glomerular inflammatory changes have clearly improved compared to the initial biopsy specimen. (g, h) Immunofluorescence stain (g: anti-C3; original magnification, ×400) and (h: anti-C3d; original magnification, ×400); C3 deposits have disappeared, whereas C3d has noticeable decreased. (i) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); disappearance of glomerular C5b-9 deposits. Abbreviations: Cs, corticosteroids; MMF, mycophenolate mofetil; PE, plasma exchange.

C5b-9 accumulation in glomeruli may be one of the best predictors of a patient's response to eculizumab.

Second, all patients had marked inflammatory changes (crescents, inflammatory cell infiltration, and endocapillary proliferation) revealed by the kidney biopsies performed prior to eculizumab use; these inflammatory changes resolved after treatment. Our data thus provide clinical evidence that C5 activation products, C5a and C5b-9, trigger the inflammatory changes seen in rapidly progressive forms of C3G/MPGN. This is consistent with experimental data from factor H–deficient mice in which prevention of C5 activation improves spontaneous or induced glomerular inflammation and reduces proteinuria, but does not alter C3 glomerular deposition.[16] In 2 patients, impressive clinical improvement contrasted with the persistence of low serum C3 levels and unchanged C3 glomerular deposits. However, in patient 2, who was treated soon after disease recurrence in her kidney transplant, eculizumab was associated with complete disappearance of C3c deposits, as well as a marked reduction in C3d deposits. These observations are striking and suggest that the renal pathologic features of C3G are reversible, as previously demonstrated in animal studies. Even so, the exact mechanisms leading from complement terminal blockade to effective upstream control of the alternative C3 convertase remain elusive. Eculizumab also inhibits the release of C5a, a potent proinflammatory anaphylatoxin. Thus, the decrease in inflammation within glomeruli induced by eculizumab may lead to a reduction in C3 deposition and/or accelerated clearance of C3 from glomeruli.

Glomerular accumulation of eculizumab (which is a monoclonal immunoglobulin G [IgG], subclass 1, κ

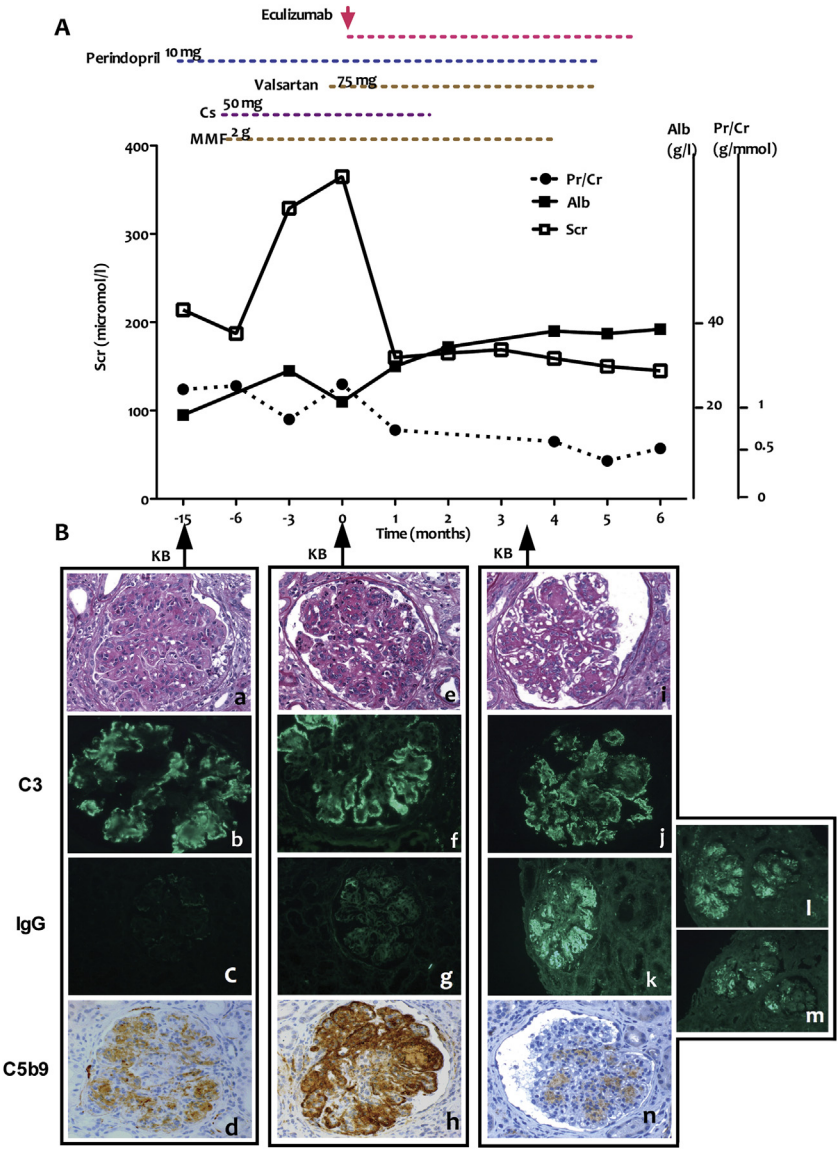

Figure 3. Laboratory values and kidney biopsy images for patient 3. (A) Changes in serum creatinine (Scr), urine protein/creatinine ratio (Pr/Cr), and serum albumin (Alb) values before and after eculizumab initiation. (B, a-d) First kidney biopsy (KB). (a) Photomicrograph (Masson trichrome; original magnification, ×400); presence of marked mesangial expansion and subendothelial deposits in the glomerulus. (b) Immunofluorescence stain (anti-C3; original magnification, ×400); presence of C3 glomerular deposits. (c) Immunofluorescence stain (anti–immunoglobulin G [IgG]; original magnification, ×400); no IgG deposits were detected. (d) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); moderate subendothelial C5b-9 deposits in glomeruli. (e-h) Second kidney biopsy. (e) Photomicrograph (Masson trichrome; original magnification, ×400); persistence of glomerular inflammatory changes although subendothelial deposits are less marked compared to the initial biopsy specimen. (f) Immunofluorescence stain (anti-C3; original magnification, ×400); persistence of C3 glomerular deposits. (g) Immunofluorescence stain (anti-IgG; original magnification; original magnification, ×400); absence of IgG deposits. (h) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); intense C5b-9 deposits present in glomeruli. (i-n) Third kidney biopsy. (i) Photomicrograph (Masson trichrome; original magnification, ×400); improvement of glomerular inflammatory changes, but with the presence of segmental sclerotic lesions. (j) Immunofluorescence stain (anti-C3; original magnification, ×400); C3 deposits were unchanged compared with the 2 previous biopsy specimens. (k) Immunofluorescence stain (anti-IgG; original magnification, ×400); IgG deposits in glomeruli with a predominance of κ (l: original magnification, ×40) compared to λ light chain (m: original magnification, ×40). (n) Immunohistochemical stain (anti-C5b-9; original magnification, ×400); significant decrease in C5b-9 glomerular deposits compared to the second biopsy specimen. Abbreviations: Cs, corticosteroids; MMF, mycophenolate mofetil.

light chain) has been documented previously.[17] In 2 of our patients, no glomerular IgG deposits were detected after eculizumab treatment. In the remaining patient, glomerular IgG deposits appeared in the repeat biopsy specimen after eculizumab treatment initiation, with the coexistence of κ and λ light chains. Although κ chains predominated, it is unclear whether the IgG deposits reflect a shift in the subtype of C3G or, at least partially, the accumulation of eculizumab. The latter may vary according to the intensity of proteinuria and the time between kidney biopsy and the last eculizumab infusion.

Only one of the patients had dense deposits typical of DDD on electron microscopy. Thus, whether eculizumab will prove to be similarly effective in other rapidly progressive cases of DDD remains to be assessed. Moreover, cases of rapidly progressing C3G in which eculizumab has been unsuccessful probably are under-reported. Finally, the optimal duration of eculizumab treatment in this setting is unknown. Thus, a prospective trial is needed to establish the effectiveness and optimal use of eculizumab in patients with rapidly progressive forms of C3G.

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SUPPLEMENTARY MATERIAL

Table S1: Kidney pathology features before and after eculizumab initiation.

Table S2: Complement assays before and after eculizumab initiation.

Item S1: Detailed methods.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.09.025) is available at www.ajkd.org

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