Eculizumab in the Treatment of Membranoproliferative Glomerulonephritis

Andrew S. Bomback

Department of Medicine, Division of Nephrology, Columbia University Medical Center, New York, N.Y., USA

Key Words

Eculizumab · Membranoproliferative glomerulonephritis · C3 glomerulopathies

Abstract

A major shift in our understanding of the membranoproliferative glomerulonephritis (MPGN) lesion is the focus on which components of the complement pathway are involved in mediating renal injury. Hence, MPGN is no longer classified solely by ultrastructural findings on biopsy but instead divided into immune complex-mediated lesions versus complement-mediated lesions. This emphasis on complement, in turn, leads to interest in therapies that target complement as potential disease-modifying agents. Eculizumab, the first available anticomplement therapy, blocks at the level of C5 and has revolutionized the treatment of complement-mediated diseases such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Whether this agent will work equally well for the far more heterogeneous complement-mediated MPGN lesions, also known as C3 glomerulopathy, remains unclear. To date, the experience and published data on using eculizumab in MPGN suggests this agent will work for some, but not all, patients with this pathologic lesion.

© 2014 S. Karger AG, Basel

Introduction

The last decade has witnessed a transformation in the approach to and understanding of the membranoproliferative glomerulonephritis (MPGN) lesion. Our understanding of the role that abnormalities in the alternative complement pathway play in the pathogenesis of some forms of MPGN has led to a reclassification of the lesion into immune complex-mediated versus complement-mediated disease. Simultaneously, the advent of anti-complement therapy with eculizumab, a monoclonal antibody that binds with high affinity to C5 and which has drastically altered the treatment paradigm of diseases like atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH), has fostered interest in using this therapeutic strategy in MPGN. The ability to selectively target components of the complement pathway offers unique avenues to change the natural history of glomerular diseases. However, this treatment strategy may also be associated with unforeseen consequences, including unintended infectious adverse events, stimulation of earlier components of the

Biologic Treatment in Glomerular Disease

D. Jayne, Cambridge

V. Tesar, Prague

complement pathway, and the potential need for life-long therapy. This review surveys current data on the role of eculizumab in treating MPGN and attempts to identify which MPGN patients might benefit from this therapy.

What Is a C3 Glomerulopathy?

The complement system is divided into three initiating pathways – the classical, lectin, and alternative pathways – that all converge at C3 to generate an enzyme complex, the C3 convertase, which cleaves C3 into C3a and C3b. The association of C3b with C3 convertase results in generation of C5 convertase, which cleaves C5 into C5a and C5b. This cleavage triggers the terminal complement cascade, which is comprised of C5b, C6, C7, C8, C9, and regulators of these terminal complement proteins, such as clusterin and vitronectin. The terminal complement cascade culminates in the assembly of the membrane attack complex (MAC; also known as C5b-9) and subsequent cell lysis. While all three pathways converge at a similar level and have, therefore, similar downstream targets, the pathways are distinct in their points of origin. Furthermore, the alternative pathway is constitutively active, and thus enhanced activity of this system is generally due to a loss of regulation. In contrast, the classical and lectin pathways are not constitutively active and need a ‘trigger’ to stimulate activity.

Until recently, the traditional view of complement’s role in glomerulonephritides such as MPGN was focused on the classical complement pathway. Immune complex deposition on immunofluorescence microscopy signaled that antigen-antibody interactions had triggered the classical complement pathway. More specifically, the presence of both immunoglobulin (IgG, IgM, and/or IgA) and complement (C1q and/or C3) on immunofluorescence microscopy inferred that the classical pathway had been activated by an inciting cause or event that generally fell into one of three major categories: infectious, autoimmune, or malignancy associated [1]. Treatment of these lesions, therefore, was appropriately focused on the trigger for the classical pathway, exemplified by the use of antiviral therapy in hepatitis C-associated MPGN compared to high-dose and relatively nonspecific immunosuppression in ‘idiopathic’ (presumed autoimmune) MPGN.

During this time, however, pathologists began emphasizing in their reports the presence of isolated deposits of C3 in examples of MPGN type I and type III that

were similar to the C3-only staining pattern of dense deposit disease (DDD; formerly termed MPGN type II, a misnomer given that many patients demonstrate the classic ultrastructural changes of electron densities along the glomerular basement membrane of DDD without a MPGN pattern on light microscopy). These immunoglobulin-negative cases were distinct from the more common variants of type I and type III MPGN, which contained immunoglobulin, and were initially called idiopathic MPGN with isolated C3 deposits. The name C3 glomerulonephritis (C3GN) eventually took hold to mesh these cases with others without MPGN histologic patterns by light microscopy (e.g. mesangioproliferative GN, crescentic GN) [2]. Finally, the term C3 glomerulopathy, which encompasses both DDD and C3GN, has been proposed as an umbrella classification for any GN with isolated C3 staining that signals an antibody-independent means of complement deposition and, subsequently, dysregulation of the alternative complement pathway [3].

Eculizumab: Anticomplement Therapy Targeting C5

The alternative complement pathway is constitutively active at a low level. The term ‘tickover’ has been used to describe this basal, physiologic activation of the alternative pathway by spontaneous hydrolysis of C3 and the production of C3b, which binds factor B to yield a fluid phase C3 convertase (C3bBb) [4–6]. This alternative pathway C3 convertase, though, is under tight modulation by soluble or membrane-bound regulating proteins, including complement factor H, complement factor I, and membrane cofactor protein (MCP) (fig. 1). Thus, a genetic or acquired (i.e. via autoantibodies) defect in either the activation or modulation of the C3 convertase could lead to a transformation from low-grade physiologic activity (‘tickover’) to unrestrained hyperactivity (diseases of complement dysregulation) [5–12]. In these instances, therapies aimed at specific components of the alternative complement pathway may prove to be effective, targeted therapies.

The first available anticomplement therapy was eculizumab, a fully humanized monoclonal antibody that binds with high affinity to C5 and prevents the generation of MAC. Eculizumab was first approved for the treatment of PNH [13] and, more recently, for treatment of aHUS based on treatment data from 27 patients treated in off-label studies and 37 patients in two phase II trials [14]. The success of eculizumab in treating PNH and aHUS

has raised expectations that the drug may prove equally beneficial in the C3 glomerulopathies, which share many of the same abnormalities in alternative pathway regulation as aHUS and PNH. The literature to date on using eculizumab for C3 glomerulopathies is limited to 8 case reports [15–22] and the results from a 1-year, open-label study of eculizumab therapy in 6 subjects [23, 24]. All but 1 of the 8 case reports document beneficial effects of eculizumab in treating patients with C3 glomerulopathies with improvements in serum creatinine, serum albumin, and/or proteinuria (table 1) [15–22]. Notably, the one case report that did not show clinical improvement when treating recurrent C3GN in the allograft with eculizumab was supported by protocol biopsies at 6 and 12 months of treatment, which demonstrated progression of disease at the histopathologic level [20].

C3GN, 3 with disease recurrent in allograft kidney) was published in two parts, one focusing on clinical response to therapy [23] and one focusing on the results of biopsies done before and after treatment [24]. All subjects were treated with eculizumab for 1 year with the same dosing schedule used for aHUS. Subjects had proteinuria >1 g/day and/or acute kidney injury (serum creatinine $\geq 150\%$ baseline) at enrollment. After 1 year of therapy, 2 subjects demonstrated significantly reduced serum creatinine with decreased mesangial and/or endocapillary proliferation on light microscopy, 1 subject attained remission of nephrotic syndrome with reduced mesangial proliferation on light microscopy and partial resorption of deposits on EM, and 1 subject had stable laboratory parameters but significantly reduced mesangial and endocapillary proliferation on light microscopy. The 2 remaining patients, however, demonstrated steeply declining renal function during treatment.

Table 1. Case reports of eculizumab therapy in C3 glomerulopathies

Reference	n	Disease	Native/transplant	C3Nef	Response
McCaughan et al. [18], 2012	1	DDD	transplant	(+)	↓ Scr ↓ proteinuria
Daina et al. [17], 2012	1	DDD	native	(+)	↓ Scr ↓ proteinuria ↑ Salb
Vivarelli et al. [16], 2012	1	DDD	native	(+)	↓ proteinuria ↑ Salb
Radhakrishnan et al. [15], 2012	1	MPGN type 1	native	(+)	↓ Scr ↓ proteinuria ↑ Salb
Gurkan et al. [20], 2013	1	C3GN	transplant	(+)	progression of disease ¹
Kerns et al. [19], 2013	1	C3GN	native	not reported	↓ proteinuria
Rousset-Rouviere et al. [21], 2014	1	DDD	native	(+)	↓ Scr ↓ proteinuria
Ozkaya et al. [22], 2014	1	DDD	native	(+)	↓ proteinuria ↑ Salb

C3Nef = C3 nephritic factor; Salb = serum albumin; Scr = serum creatinine. ¹ Creatinine and proteinuria levels were unchanged during 1 year of therapy while repeat allograft biopsies at 6 and 12 months showed continuously active GN with increased chronicity.

Taken together, the results of the case reports and open-label study indicate that eculizumab may be an appropriate treatment for a subgroup of patients with DDD and C3GN, but clearly does not fit all patients with C3 glomerulopathies and may carry the potential for worsening of disease in some patients. This variation in response to C5 blockade highlights the differences between C3 glomerulopathies and aHUS. Some investigators have suggested that aHUS should be considered part of a spectrum that includes DDD and C3GN, given the overlap in genetic abnormalities (e.g. mutations in factor H, factor I, MCP, C3 and factor B) and autoantibodies (e.g. anti-factor H autoantibodies) reported in these diseases [7, 25–27]. Yet, aHUS differs from the C3 glomerulopathies in *where* the alternative pathway dysregulation occurs. The alternative pathway consists of a network of complement proteins in either the fluid phase, as soluble plasma proteins, or in the solid phase, as cell membrane proteins. The underlying defect in most instances of the C3 glomerulopathies (and in all cases of DDD) is felt to be excessive activation of the alternative complement pathway in the fluid phase [28–30]. In contrast, the endothelial damage that is the hallmark of aHUS is due to

dysregulation at the level of the cell membrane, or in the solid phase [4]. This solid-phase dysregulation makes aHUS a more homogenous disease than the C3 glomerulopathies in terms of prognosis and response to anti-C5 therapy.

The solid-phase dysregulation in aHUS translates to C5 convertase dysregulation being at least equal and often greater than C3 convertase dysregulation. Hence, blockade of C5 in this disease is expected to yield improvement. In contrast, the heterogeneity of fluid-phase dysregulation in C3 glomerulopathies in *some* cases is associated with C3 convertase dysregulation being greater than C5 convertase dysregulation and in *other* cases with C5 convertase dysregulation being greater than C3 convertase dysregulation [31]. Only the latter cases would be expected to respond to eculizumab, and the former cases, due to a feedback effect on C3 convertase activity, could potentially be aggravated by C5 blockade. Therefore, one of the major challenges in treating patients with C3 glomerulopathies with anticomplement therapy is how to distinguish the patient with primarily C3 convertase dysregulation from the patient with primarily C5 convertase dysregulation. Speculatively, the

mass spectrometry techniques reported by Sethi et al. [32], which have shown components of the alternative and terminal complement pathway in glomeruli of patients with C3 glomerulopathies that were neither seen in glomeruli of normal controls nor, to the same extent, in glomeruli of patients with immune complex-mediated MPGN, hold the potential to distinguish deposits primarily composed of breakdown products from C3 convertase hyperactivity versus C5 convertase hyperactivity. Levels of soluble MAC (sMAC), which can be measured from whole blood samples, may also be informative, as elevated levels in a patient with C3 glomerulopathy likely implicate a high degree of C5 convertase dysregulation [31]. Indeed, in the open-label study of eculizumab for DDD and C3GN, the sMAC levels of the responders normalized immediately on therapy and paralleled improvements in serum creatinine and proteinuria, while the nonresponders had normal levels of sMAC prior to therapy [23]. These observations hold forth the promise that elevated sMAC prior to eculizumab treatment may be a predictor of response. Conversely, normal sMAC levels may be a contraindication to using this therapy.

Duration of Therapy with Eculizumab

Eculizumab was engineered to target C5 while minimizing its own potential to elicit an inflammatory response. The C5-specific variable regions were fused to a kappa light chain and a hybrid heavy chain created from portions of IgG2 and IgG4. IgG2 constant region 1 and hinge region were chosen because they do not bind Fc receptors or activate complement. IgG4 constant regions 2 and 3 were selected for their inability to activate complement [33]. Dosed intravenously, eculizumab has a half-life of approximately 11 ± 3 days, allowing for a maintenance dosing of every other week once the drug has been loaded. Effective and complete complement blockade by the drug can be monitored by conventional CH50 assays [33].

Despite such well-defined pharmacokinetics and pharmacodynamics, a major and still unresolved issue for eculizumab therapy is whether the drug must be considered lifelong therapy. This question, which applies to use of eculizumab in its approved indications (aHUS and PNH) as well as its off-label use in C3 glomerulopathies, is influenced heavily by the exceedingly high cost of treatment and the increased potential for infection with prolonged complement suppression. Nonetheless, prior experience with eculizumab in treating PNH has involved

prolonged, often lifelong, courses of therapy due to the relapsing nature of the disease, a similar phenomenon seen with aHUS [34, 35]. Currently, most patients who begin therapy with eculizumab for PNH or aHUS are presumably embarking upon a lifelong course of therapy. However, a recent series from Ardissino et al. [36] reported 10 patients with aHUS who voluntarily discontinued eculizumab maintenance therapy and concluded that careful home monitoring for relapse may allow such a maneuver. Three of the 10 patients relapsed within 6 weeks of stopping therapy but, with immediate resumption of therapy, experienced complete clinical recovery; the other 7 patients, with follow-up times up to 2 years, appeared by clinical parameters to be free of TMA off therapy.

As described above, all but 1 patient from the 8 published case reports on eculizumab therapy of C3 glomerulopathies showed clinical signs of response; these 7 patients remained on therapy at the time of publication. We have more available information on outcomes after discontinuing eculizumab from the open-label study of eculizumab therapy at Columbia University Medical Center. Four of 6 subjects with C3 glomerulopathies were considered responders to eculizumab after 1 year of therapy, at which point treatment was discontinued with close clinical follow-up. Two of these 4 subjects required almost immediate resumption of therapy. One subject, with DDD in the native kidney, demonstrated a rising creatinine (1.2 mg/dl to 1.5 to 1.7) within 8 weeks of stopping eculizumab, accompanied by a rise in sMAC levels from the normal range (<0.30 mg/l) to 1.26 mg/l. Eculizumab was started and, after an additional 2 years of therapy, creatinine is in the range of 1.1–1.2 mg/dl. A second subject, with recurrent C3GN in the allograft kidney, demonstrated stable renal function 3 weeks after eculizumab was discontinued, but at 7 weeks after treatment his creatinine had risen to 8.4 mg/dl. Repeat renal biopsy showed recurrent, active C3GN with crescents. He was treated with plasma exchange, pulse steroids, and resumption of eculizumab, with some improvement in renal function (creatinine 3.8 mg/dl within 2 months after restarting eculizumab). He has remained on eculizumab, but has progressed to end-stage renal disease.

In contrast, the investigators from this study recently presented (in abstract form) [37] the results of the other two responders (both with recurrent C3 glomerulopathy after kidney transplantation), who to date have remained off eculizumab with no evidence of relapse. Both patients were diagnosed with recurrent C3 glomerulopathy

within 2 months prior to initiating eculizumab therapy. Maintenance immunosuppression of mycophenolate mofetil and tacrolimus continued unchanged while on and off eculizumab. Biopsies done at completion of therapy and 1 year *after* completion of therapy showed mild mesangial proliferation with no evidence of endocapillary proliferation or exudative features. On electron microscopy, the resorption of electron dense deposits seen at the termination of therapy continued in biopsies done after being 1 year off therapy. Notably, in both patients, the *de novo* immunofluorescence staining for kappa-restricted IgG₂ and IgG₄ (suggesting binding of the monoclonal eculizumab to C5 in renal tissues) that was present in biopsies performed at completion of therapy was no longer detectable 1 year after therapy. Thus, these patients appear to have persistence of clinical and histopathologic remission of disease after discontinuation of therapy, although, it must be noted, under the auspices of dual immunosuppression for transplant rejection prophylaxis.

Conclusion

The improved understanding of the role of alternative complement dysregulation in the pathogenesis of a subgroup of MPGN, coupled with the advent of anticomplement therapies, has engendered hope that the natural history of this disease can be modified. Eculizumab, which targets complement at the level of C5, has shown some promising results in treating C3 glomerulopathies in native and allograft kidneys. Nonetheless, the 'game changing' results of this drug in aHUS likely will not extend to the more heterogeneous entities of C3GN and DDD. Indeed, as we further delineate the causes of C3GN and DDD, one of the crucial searches is identification of patients who will benefit from C5 blockade.

Disclosure Statement

None.

References

- Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011;31:341–348.
- Sethi S, Nester CM, Smith RJ: Membranoproliferative glomerulonephritis and C3 glomerulopathy: resolving the confusion. *Kidney Int* 2012;81:434–441.
- Fakhouri F, Fremeaux-Bacchi V, Noel LH, Cook HT, Pickering MC: C3 glomerulopathy: a new classification. *Nat Rev Nephrol* 2010;6:494–499.
- Roumenina LT, Loirat C, Dragon-Durey MA, Halbwachs-Mecarelli L, Sautes-Fridman C, Fremeaux-Bacchi V: Alternative complement pathway assessment in patients with atypical HUS. *J Immunol Methods* 2011;365:8–26.
- Zhang Y, Meyer NC, Wang K, et al: Causes of alternative pathway dysregulation in dense deposit disease. *Clin J Am Soc Nephrol* 2012;7:265–274.
- Licht C, Fremeaux-Bacchi V: Hereditary and acquired complement dysregulation in membranoproliferative glomerulonephritis. *Thromb Haemost* 2009;101:271–278.
- Skerka C, Licht C, Mengel M, et al: Autoimmune forms of thrombotic microangiopathy and membranoproliferative glomerulonephritis: indications for a disease spectrum and common pathogenic principles. *Mol Immunol* 2009;46:2801–2807.
- Zand L, Kattah A, Fervenza FC, et al: C3 glomerulonephritis associated with monoclonal gammopathy: a case series. *Am J Kidney Dis* 2013;62:506–514.
- Sethi S, Sukov WR, Zhang Y, et al: Dense deposit disease associated with monoclonal gammopathy of undetermined significance. *Am J Kidney Dis* 2010;56:977–982.
- Servais A, Noel LH, Roumenina LT, et al: Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int* 2012;82:454–464.
- Servais A, Fremeaux-Bacchi V, Lequintrec M, et al: Primary glomerulonephritis with isolated C3 deposits: a new entity which shares common genetic risk factors with haemolytic uraemic syndrome. *J Med Genet* 2007;44:193–199.
- Sethi S, Fervenza FC, Zhang Y, et al: C3 Glomerulonephritis: clinicopathologic findings, complement abnormalities, glomerular proteomic profile, treatment and follow-up. *Kidney Int* 2012;82:465–473.
- Hillmen P, Young NS, Schubert J, et al: The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006;355:1233–1243.
- Zuber J: Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. *Nat Rev Nephrol* 2012;8:643–657.
- Radhakrishnan S, Lunn A, Kirschfink M, et al: Eculizumab and refractory membranoproliferative glomerulonephritis. *N Engl J Med* 2012;366:1165–1166.
- Vivarelli M, Pasini A, Emma F: Eculizumab for the treatment of dense-deposit disease. *N Engl J Med* 2012;366:1163–1165.
- Daina E, Noris M, Remuzzi G: Eculizumab in a patient with dense-deposit disease. *N Engl J Med* 2012;366:1161–1163.
- McCaughan JA, O'Rourke DM, Courtney AE: Recurrent dense deposit disease after renal transplantation: an emerging role for complementary therapies. *Am J Transplant* 2012;12:1046–1051.
- Kerns E, Rozansky D, Troxell ML: Evolution of immunoglobulin deposition in C3-dominant membranoproliferative glomerulopathy. *Pediatr Nephrol* 2013;28:2227–2231.
- Gurkan S, Fyfe B, Weiss L, Xiao X, Zhang Y, Smith RJ: Eculizumab and recurrent C3 glomerulonephritis. *Pediatr Nephrol* 2013;28:1975–1981.
- Rousset-Rouviere C, Cailliez M, Garaix F, Bruno D, Laurent D, Tsimaratos M: Rituximab fails where eculizumab restores renal function in C3nef-related DDD. *Pediatr Nephrol* 2014;29:1107–1111.
- Ozkaya O, Nalcacioglu H, Tekcan D, et al: Eculizumab therapy in a patient with dense-deposit disease associated with partial lipodystrophy. *Pediatr Nephrol* 2014;29:1283–1287.
- Bombach AS, Smith RJ, Barile GR, et al: Eculizumab for dense deposit disease and C3 glomerulonephritis. *Clin J Am Soc Nephrol* 2012;7:748–756.
- Herlitz LC, Bombach AS, Markowitz GS, et al: Pathology after eculizumab in dense deposit disease and C3 GN. *J Am Soc Nephrol* 2012;23:1229–1237.

- 25 Noris M, Remuzzi G: Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;361:1676–1687.
- 26 Maga TK, Nishimura CJ, Weaver AE, Frees KL, Smith RJ: Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. *Hum Mutat* 2010;31:E1445–E1460.
- 27 Lorcy N, Rioux-Leclercq N, Lombard ML, Le Pogamp P, Vigneau C: Three kidneys, two diseases, one antibody? *Nephrol Dial Transplant* 2011;26:3811–3813.
- 28 Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis – a new look at an old entity. *N Engl J Med* 2012;366:1119–1131.
- 29 Pickering M, Cook HT: Complement and glomerular disease: new insights. *Curr Opin Nephrol Hypertens* 2011;20:271–277.
- 30 Smith RJ, Harris CL, Pickering MC: Dense deposit disease. *Mol Immunol* 2011;48:1604–1610.
- 31 Nester CM, Smith RJ: Treatment options for C3 glomerulopathy. *Curr Opin Nephrol Hypertens* 2013;22:231–237.
- 32 Sethi S, Gamez JD, Vrana JA, et al: Glomeruli of dense deposit disease contain components of the alternative and terminal complement pathway. *Kidney Int* 2009;75:952–960.
- 33 Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L: Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat Biotechnol* 2007;25:1256–1264.
- 34 Parker C: Eculizumab for paroxysmal nocturnal haemoglobinuria. *Lancet* 2009;373:759–767.
- 35 Kose O, Zimmerhackl LB, Jungraithmayr T, Mache C, Nurnberger J: New treatment options for atypical hemolytic uremic syndrome with the complement inhibitor eculizumab. *Semin Thromb Hemost* 2010;36:669–672.
- 36 Ardissino G, Testa S, Possenti I, et al: Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. *Am J Kidney Dis* 2014;64:633–637.
- 37 Hogan JJ, Bombach AS, Herlitz LC, et al: Remission off eculizumab in two patients with recurrent C3 glomerulopathy. *J Am Soc Nephrol* 2013;24:773A.