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Treatment Options for C3 Glomerulopathy

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Abstract

Purpose of review—The purpose of this review is to discuss emerging nomenclature, review the salient clinicopathological features and describe the therapeutic options available for the treatment of C3 Glomerulopathy.

Recent findings—C3 Glomerulopathy is minimally responsive to traditional immune suppression and randomized controlled trials to support therapy are absent. The burgeoning understanding of the role of the alternate complement pathway in C3 Glomerulopathy combined with animal data supporting the use of terminal complement blockade and a few reports suggesting that the anti-complement drug eculizumab may offer a therapeutic advantage has triggered great interest in the field of complement-mediated renal disease.

Summary—Anti-cellular immune suppression and plasma therapy have limited efficacy in C3G. Data suggest that eculizumab may ameliorate disease in some C3G patients. The limited, recently published cohort data highlight crucial aspects of this group of diseases and support the need for extensive genetic and biomarker research to validate the pathologic mechanisms, delineate the spectrum of disease, and guide the design of the rigorous trials to identify effective therapies for the treatment ofC3 Glomerulopathy.

Keywords

C3 Glomerulopathy; alternate pathway of complement; C3 Glomerulonephritis; Dense Deposit Disease; membranoproliferative glomerulonephritis

Introduction

C3 Glomerulopathy (C3G) is a newly recognized term used to encompass glomerular diseases that are distinguished by isolated C3 deposits along the glomerular basement membrane in the absence of significant deposition of immunoglobulin[1-3]. While C3G awaits a formal clarification of its pathological boundaries (i.e. how much if any immune globulin

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is allowed and how does the isolated C3, post-infectious lesion fit into the current concept of disease, etc.), the current assumption is that there will be a spectrum of diseases. Over the last five years it has become clear that there are at least two identifiable types: *Dense Deposit Disease* (DDD – critically defined by the electron microscopic findings of glomerular basement membrane intramembranous dense deposits[4] and *C3 Glomerulonephritis* (C3GN) (defined currently as isolated C3 immune deposits that are not of the classic intramembranous type). The C3G designation is irrespective of light or electron microscopy (EM) findings.

Pathology

Dense Deposit Disease

DDD is an ultra-rare renal disease that predominates in children and young adults and classically carries a poor renal prognosis[5,6] It was the first recognized C3G. The essential and distinguishing characteristic of DDD as a subset of C3G is the EM pattern of dense deposits within the glomerular basement membrane, and not the presence or absence of the membranoproliferative pattern of glomerular injury – making the historical term membranoproliferative glomerulonephritis type II (MPGN II) obsolete. The dense deposits of DDD contain components of the alternative pathway of complement including C3b and the breakdown products iC3b, C3dg, and C3c, as well as components of the terminal complement cascade[7]. A complete understanding of the pathological basis of DDD remains elusive however there are multiple lines of evidence supporting an abnormality of fluid-phase complement control as central to this disease. DDD is characterized by alternate complement pathway dysregulation[8]. Mutations in complement factor H(CFH)[9-11], complement factor C3 (C3)[12] and the complement factor H related 5 gene (CFHR5)[13] have been identified in DDD. Most DDD patients do not have disease-causing mutations but instead carry specific polymorphisms of multiple complement genes (i.e. *CHF* H402[14,15]) that collectively form a complex ‘complotype’ of risk alleles[16]. In addition, the majority of DDD patients develop an autoantibodies called C3 nephritic factors (C3Nefs) that stabilize C3 convertase, the key enzyme in alternative pathway activation. C3Nefs facilitate the dysregulation of complement that is characteristic of DDD but how they are related to the common genetic ‘complotype’ remains unclear [3].

C3 Glomerulonephritis

The concept of C3GN was first considered in 2007 when Servais et al. characterized a group of patients with a glomerular lesion they termed “primary glomerulonephritis with isolated C3 deposits” (referred to by other authors as proliferative glomerulonephritis with C3 deposits[17]). The major diagnostic criterion for this lesion as with DDD was the requirement for isolated C3 deposits on immune fluorescence[2]. However, this group of patients did not have the classic dense deposits on electron microscopy and therefore despite the isolated C3 deposits were distinct from DDD pathologically.

Since 2007, there have been several more publications describing C3GN patients[1,17-25] however the greatest phenotypic and genotypic contributions have been made by two

recently published cohorts: a large, cohort from the Island of Cypress[25,26] and a 134 patient French Cohort[27] (both to be discussed in more detail below).

Servais et al. also gave us our first hint at the pathological mechanism behind C3G. Thirty one percent of their cohort had a mutation in either CFH, CFI or membrane cofactor protein (MCP - another alternate complement pathway regulator). From this cohort, we have also learned that the C3Nefs are less commonly found in C3GN patients than in DDD patients (45.3% versus 86.4%).

Presentation

Dense Deposit Disease

The majority of DDD patients present with proteinuria and hematuria. Fifty percent of DDD patients with disease for 10 years or greater progress to end-stage renal disease (ESRD), with young females having the greatest risk for renal failure[28]. Forty five percent of renal allografts are lost within 5 years of transplant[28]. Greater than 80% of DDD patients have C3Nefs. A low C3 is common in all forms of C3G (59% in DDD and 40% in C3GN).

C3GN - Cypriot Cohort

Gale et al. reported on 26 patients with a familial glomerulopathy. This cohort has subsequently been expanded to include 91 patients and 61 families [25]. Genetic evaluation has confirmed that this glomerular lesion is caused by a founder mutation in the CFHR5 gene in patients of Cypriot descent and this entity has been referred to as CFHR5 nephropathy[29]. CFHR5 nephropathy is characterized by microscopic hematuria however some patients manifest macroscopic hematuria associated with intercurrent illness. Proteinuria was reported in 38% of the original cohort with the majority of proteinuric patients progressing to chronic renal failure. Interestingly, of mutation carriers, men were by far more likely to progress to chronic renal failure (80%) than women (21%) and similarly men were more likely to progress to ESRD than women (78% versus 22%). From this report, it became clear that C3GN is not a benign disease.

C3GN French Cohort

From the French Cohort, (85 C3G patients; 29 with DDD and 56 with C3GN) we have a view of the phenotypic differences within the C3G disease family – this time from a broader geographical population and with increased genetic diversity. Greater than 60% of patients presented with microscopic hematuria (range 64.3-75.8%) and the urine protein appeared to be slightly lower for C3GN than for DDD (3.6g ± 3.3 versus 5.6 ± 4.5). The male-to-female ratio was essentially equal between the two groups and the age-at-onset was statistically higher for C3GN than for DDD (30.3 ± 19.3 versus 18.9 ± 17.7), although both glomerulonephritides present frequently in a relatively young population.

A total of 53 patients presented with a low C3 level. C3Nefs were more likely to be abnormal in DDD as compared to C3GN (86.4% versus 45.3%), and of key importance, mutations in the *CFH* and *CFI* genes were identified in 24 patients. As has been reported, the complement factor H H402 variant was significantly increased in DDD. An additional

at-risk membrane cofactor protein (MCP) haplotype was found in a C3GN patient. Case reports have documented the recurrence of C3GN in a renal transplant.

Treatment

Supportive Measures

There have been no major advances in the supportive treatments for C3G. No specific evidence supports the use of angiotensin converting enzyme (ACE) inhibitors in this setting, however these agents will likely continue to be used based on extrapolations from other proteinuric renal diseases and from the limited data offered from the French C3G Cohort[27,30,31]: by univariate analysis, the use of ACE inhibitors or angiotensin receptor blockers (ARBs) was associated with a better renal survival ($P < 0.0001$). Similarly, lipid lowering agents are likely to be useful as needed in C3G[32].

Plasmatherapy

There are no new data to support the use of plasmatherapy. The support for this intervention in DDD relies on case reports. Licht et al., reported efficacy of plasma therapy in a sibling pair with DDD and a factor H deficiency secondary to a mutation in *CFH*[33] while both Banks and Krmar et al. reported recovery of acute kidney injury in DDD with plasmapheresis[34,35] On the other hand McCaughan et al. reported an inability to establish a DDD remission despite the documented removal of C3Nefs via plasmapheresis[36]. Plasmatherapy will likely continue to be used on a case-by-case basis but should be used with concurrent biomarker studies of the alternative and terminal complement pathways to monitor disease.

Cellular Immune suppression

Similarly there are no controlled trials to support the use of anti-cellular immune therapy in C3G and publication bias is likely to color substantially our perception of the relative effectiveness of any given agent. From a global standpoint, Servais et al.[27] reported that renal survival was not associated with the use of immunosuppressive agents. Historically steroid therapy has not been effective in DDD[3] and Daina et al. reinforced this impression with their report of the failure of glucocorticoids to establish remission in a patient after 5 years[37]. Strategies to reduce C3Nef either by the use of anti-cellular therapy such as mycophenolate mofetil or rituximab have not been studied formally however anecdotally these agents have not been uniformly successful. This failure may reflect in part the complexities of the multiple assays for C3Nefs. McCaughan reported a failure to respond to glucocorticoid, mycophenolate mofetil and rituximab therapy[36]. Finally, one patient with C3GN in the study reported by Bomback et al. failed both prednisone and mycophenolate mofetil treatment despite dose escalation of these agents[38].

Anti-complement Therapy

As data have begun to accumulate supporting the pivotal role of abnormalities in the alternate pathway of complement in C3G, attention has focused on anti-complement therapy as a potential directed therapy for this class of diseases. C3G anti-complement response has been predicted by animal models[39] and case reports have indicated that there may be some

utility in anti-C5 therapy in C3G. In particular, eculizumab was seen to mitigate disease in three case reports and in one small trial[37,38,40,41]

Case Reports (Table 1)

Vivarelli et al. presented the case of a 17 year-old female with normal renal function, blood pressure and genetic screen[42]. The patient had a seven-year history of DDD and was noted to have 40% glomerular sclerosis on renal biopsy. She was started on eculizumab when she developed a worsening of nephrotic-range proteinuria and was continued on therapy for 18 months with a remarkable improvement in her urine protein. When eculizumab was stopped, she had a recrudescence of her urine protein with a reestablished of a relative remission with the restart of eculizumab. Two subsequent renal biopsies showed a progressive reduction of C3 and C5b-9 immunofluorescence and a progressive reduction in mesangial proliferation and glomerular capillary loop thickness[42].

Daina et al. report the case of a 22 year-old female with DDD on renal biopsy and a long standing history of nephrotic syndrome non-responsive to 5 years of steroids. The patient carried two DDD risk polymorphisms in *CHF* (V62 and H402) but otherwise had no genetic abnormalities. She had a low C3, elevated C3Nefs and normal renal function. Her terminal complement complex assay was elevated. She was treated with Rituximab with some decrease in C3Nefs however there was no renal response and five months into her therapy her creatinine began to rise. She was then treated with 48 weeks of eculizumab during which time her serum albumin normalized and her creatinine decreased. No post treatment renal biopsy was reported.

Finally, *McCaughan* et al. reported on the efficacy of eculizumab in a case of recurrent DDD post-renal transplant. They reported a case of 29 year-old DDD patient who had recurrence of disease 4 weeks post-transplant (heralded by 6g of urine protein) while on prednisone, mycophenolate mofetil and tacrolimus. She had a low C3, a positive C3Nef, and normal *CFH*, *CFI* and *MCP* mutational analysis. Despite rituximab and plasmapheresis (with a subsequent normalization of her C3Nef) her disease progressed and 13 weeks after transplant she was started on eculizumab (length of therapy not reported). Her creatinine recovered to 1.9mg/dl from 4.93mg/dl. A post-treatment biopsy was not reported.

Trial Data

A single trial exists for the treatment of C3G. Bomback et al. performed an open-label, proof-of-concept, efficacy-and-safety study in which they treated 3 DDD (one with a renal transplant) and 3 C3GN patients (two with a renal transplant) with eculizumab every other week for 1 year. All had proteinuria >1 g/d and/or acute kidney injury (AKI) at enrollment. Genetic and complement function testing revealed a mutation in *CFH* and *MCP* in one subject each and C3Nefs in three subjects.

After 12 months of therapy two subjects showed significantly reduced serum creatinine (DDD1 and C3GN3), one subject achieved marked reduction in proteinuria (DDD3), and one subject had stable laboratory parameters but histopathologic improvements (C3GN3) (Table 1 and 2). Not surprising given the mechanism of action of eculizumab, if serum

membrane attack complex (sMAC) levels were elevated prior to treatment, they normalized on therapy. The authors concluded that there was a response to eculizumab in some but not all subjects, and that an elevation of sMAC appeared to be a potentially useful marker of a responder (Table 1).

Conclusions

The finding that many cases of C3G are marked by an underlying abnormality of proteins controlling the alternative pathway of complement activation has played a role in attempts to treat disease. This fact is likely to play an even larger role in the future treatment of C3G now that anti-complement therapies are becoming available for clinical use. However, the rarity of these diseases ensures that there are likely to be no randomized control data to support a given therapy, and to date there is only a single, small numbered trial to rely upon. Undoubtedly, therefore, treatment recommendations will be influenced by retrospective data or case reports.

The pathological spectrum of C3G has yet to be fully defined and will be the work of the pathology team involved in the International C3 Glomerulopathy Focus Meeting (Hinxton, UK, August 2012). Following the lead of the C3 Glomerulopathy Focus Meeting, (disease definition consensus statement pending) the following terminology should be adopted: C3 *Glomerulopathy* as the disease category, with Dense Deposit Disease and C3 *Glomerulonephritis* as subcategories of the larger category.

The optimal disease-directed treatment for the C3Gs has yet to be determined. Per Servais et al., it may be reasonable to consider anti-cellular therapies as part of the treatment plan, however given the current understanding of the relationship of these diseases to the alternate pathway of complement, this treatment alone is likely to be insufficient. The result of the trial of eculizumab as reported by Bomback et al., and the isolated case reports using this agent in C3G suggests that anti-complement therapy directed at the terminal complement cascade may be useful however to what extent remains unclear. Inactivation of C5 in the Cfh −/− mouse does not prevent C3 deposition, capillary wall changes or reduce proteinuria, however it dose significantly decrease glomerular inflammation[43]. Limited available pathological data have shown that eculizumab decreased endocapillary proliferation and inflammatory cell infiltration in three of five patients who underwent repeat kidney biopsy[36,38,40]. Therefore, it may well be that some forms of C3 glomerulopathy, particularly those with a high inflammatory component and an elevation of sMAC, respond to eculizumab.

The use of eculizumab led to an improvement in renal parameters in six out of ten treated patients[36-38,40]. Preliminarily, it appears that response does not depend on whether the patient has the DDD or C3GN pathological. Speculatively, response may be related to the specific etiology of the C3 deposits, to the chronicity of disease prior to anticomplement therapy start, the degree of glomerular inflammation present, and/or the relative terminal complement activity in any given patient.

Setting parameters for patient enrollment in future studies and determining the answers to the above questions will become important when evaluating successes and failures in treatment modality, as it remains unclear which patient laboratory characteristics will classify a patient as a responder to a given therapeutic option. However, the advances in our understanding of the mechanistic cause of C3G opens the possibility to combinations of therapies that include anti-complement therapy. Two very large tasks remain: the continued need to expand the definition of the genetic background for these diseases (as most genetic studies have been extremely narrow) and how best to phenotype patients to make legitimate conclusions about the success and failures of therapeutic interventions. The clearance of C3 fragments from glomeruli in *Cfh*-deficient mice through the restoration of complement regulation suggests that the initial process leading to C3 glomerulopathy is dynamic may be reversible[44,45]. Trials must come – therefore, we must better understand the patients we are placing on therapy with the assumption that either the patient's genotype or phenotype will predict response to therapy. We would support the implementation of a registry akin to our oncology partners. Scientists must continue to study the yet unanswered questions of C3G, and clinicians must enroll patients in formal trials, collaborating to make consistent laboratory and clinical assessments before, during and after therapy such that the resulting data may be interpreted scientifically. It is only with rigorous study of the various disease components that we will we be able to truly facilitate improved health for patients with C3Gs.

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Table 1

Treatment of C3 Glomerulopathy with Ecullzumab#

Diagnosis	Creatinine at Start	Effect on C3	Pretreatment Terminal Complement Activity	Mutation	C3 Nephritic Factor	+ Response
Bomback et al (J. Am. Soc. Nephrol. 7, 748–756, 2012] 1 Year of Eculizumab treatment per protocol#						
DDD 1	1.8	None	+ (sMAC 1.08)	+ (CFH)	−	Creatinine 1.8 to 1.4
DDD2	2.1	None	No	−	+	
DDD3	1.2	Normalization	NA	−		Urine Protein 5.93 to 1.76
C3GN1	1.6	None	No	−	−	
C3GN2	1.7	None	+ (sMAC 0.71)	−	+	Pathology Improved*
C3GN3	1.8	None	+ (sMAC 0.32)	+ (MCP)	+	Creatinine 1.8 to 1.4
Vivarelli et al. (N. Engl. J. Med. 366, 1163–1165, 2012) 18 months of Eculizumab treatment followed by a 6-month break with restart of treatment when UP/C increased to 5g off medication#						
DDD	1.2	None	+ (Elevated sMAC)	*CFB* polymorphism		Urine Protein 5.5g to 0.9g Urine Protein 5g to 0.96g
Daina et al. (N. Engl. J. Med. 366, 1161–1163, 2012)						
DDD	1.9	None	+ (Elevated sMAC)	−	+	Urine Protein 6g to 2.5g
McCaughan etal. (Am. J. Transplant 12, 1046–1051, 2012)						
DDD	4.9	None	NA	−	+	Urine Protein 0.755mg/mmol to 0.229mg/mmol

There are four published of eculizumab use in C3G, treating a total of 9 patients (6 with DDD and 3 with C3GN). Six patients had some indication of clinical response - either improvement in creatinine or in urine protein. Five of nine patients had evidence of elevation of sMAC (data not available on two) with four showing a clinical response. Response appeared to correlate with increased terminal complement pathway activity with only a single patient with an elevated sMAC and no response after treatment with eculizumab. sMAC, soluble membrane attack complex; normal sMAC = ≤ 30; NA = Not available .

*See Table 2 for pathology.

Table 2

Renal Pathology after Eculizumab Therapy (as reported by authors)

Bomback[1] **DDD 1**	Decreased activity with no evidence of endocapillary proliferation
Bomback **DDD2**	Subject withdrew from the study and declined repeat biopsy.
Bomback **DDD3**	Decreased mesangial proliferation and less extensive deposits on electron microscopy.
Bomback **C3GN1**	Increased chronicity, with 85% of glomeruli globally sclerotic (increased from 50% in previous biopsy), and continuously active GN in the few open glomeruli with persistent membranoproliferative changes and large subendothelial deposits.
Bomback **C3GN2**	Reduced mesangial and endocapillary proliferation, with a significantly decreased mean number of inflammatory cells.
Bomback **C3GN3**	No change: mild mesangial proliferation with no endocapillary proliferation or exudative features.
Vivarelli[2] **DDD**	Reduction in mesangial proliferation and a reduction in the thickness of glomerular capillary loops
Daina[3] **DDD**	Not Reported in original manuscript.
McCaughan[4] **DDD**	Not Reported in original manuscript.

The repeat biopsies were done at 1 year in the Bomback study. Vivarelli et al. reported a repeat renal biopsy at both 6 and 18 months. Highlighted biopsies are in patients with elevated pre-transplant sMAC.