Kidney Disease Caused by Dysregulation of the Complement Alternative Pathway: An Etiologic Approach

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ABSTRACT

Kidney diseases caused by genetic or acquired dysregulation of the complement alternative pathway (AP) are traditionally classified on the basis of clinical presentation (atypical hemolytic uremic syndrome as thrombotic microangiopathy), biopsy appearance (dense deposit disease and C3 GN), or clinical course (atypical postinfectious GN). Each is characterized by an inappropriate activation of the AP, eventuating in renal damage. The clinical diversity of these disorders highlights important differences in the triggers, the sites and intensity of involvement, and the outcome of the AP dysregulation. Nevertheless, we contend that these diseases should be grouped as disorders of the AP and classified on an etiologic basis. In this review, we define different pathophysiologic categories of AP dysfunction. The precise identification of the underlying abnormality is the key to predict the response to immune suppression, plasma infusion, and complement-inhibitory drugs and the outcome after transplantation. In a patient with presumed dysregulation of the AP, the collaboration of the clinician, the renal pathologist, and the biochemical and genetic laboratory is very much encouraged, because this enables the elucidation of both the underlying pathogenesis and the optimal therapeutic approach.


The complement system contributes indispensably to immunologic homeostasis in at least three major ways. First, this system is an essential part of innate immunity that serves as the first-line defense against infections and nonmicrobial forms of stress. Second, it provides an interface between the innate and adaptive immunity, and third, it contributes to immune surveillance by clearing foreign or apoptotic cells.1,2

The key step in the complement cascade is the cleavage of C3 to C3a and C3b affected by C3 convertase activity; the latter may originate from the classic, lectin, or alternative pathways (APs) (Figure 1). The C3 convertases continuously cleave C3 in a powerful amplification loop. The terminal complement cascade is initiated by the C5 convertase and ultimately, generates the membrane attack complex inducing cell lysis. The C3 convertase amplification loop requires rigorous control to prevent inadvertent tissue inflammation and damage (Figure 2). Certain regulatory proteins reside on the cell surface and provide cytoprotection, whereas others exist in plasma and limit fluid-phase complement activation.

PATHOGENESIS

Kidney diseases caused by dysfunction of the AP comprise atypical hemolytic uremic syndrome (aHUS), C3 glomerulopathies, and atypical postinfectious GN. aHUS is a thrombotic microangiopathy (TMA) typified by the triad of AKI, microangiopathic hemolytic anemia, and thrombocytopenia, and clinically, it is often indistinguishable from thrombotic thrombocytopenic purpura. The C3 glomerulopathies are characterized by C3 accumulation, with absent or scanty glomerular Ig deposition on immunofluorescence examination.3 This recently coined group includes both C3 GN and dense deposit disease (DDD), which are discriminated from each other by the location and appearance of the glomerular deposits on electron microscopy.4,5 Atypical postinfectious GN refers to a clinical course where the diagnosis of postinfectious GN is not followed by resolution but by signs of persisting glomerular damage.6 Inappropriate activation or modulation of the C3 convertase is the pathophysiologic process common to all of these diseases and the one that instigates tissue injury.

C3 glomerulopathies are typically characterized by uncontrolled activation of the AP in the fluid phase (i.e., in the circulation) and/or at tissue surfaces that lack membrane–anchored complement

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The normal complement cascade. The complement system can be activated by the classic pathway, the lectin pathway, and the AP, all resulting in the formation of C3 convertases. The classic pathway is initiated by immune complexes that interact with C1q, ultimately leading to the formation of the classic pathway C3 convertase C4b2a. The lectin pathway generates the same C3 convertase C4b2a but is activated by the binding of mannose-binding lectins (MBLs) to carbohydrate moieties found primarily on the surface of microbial pathogens. The AP is the same C3 convertase C4b2a but is activated by the binding of mannose-binding lectins (MBLs) to carbohydrate moieties found primarily on the surface of microbial pathogens. The AP is capable of autoactivation by a mechanism called tick over of C3. Tick over occurs spontaneously at a low rate, generating a conformationally changed C3, which is referred to as C3(H2O). C3(H2O) is capable of binding CFB, resulting in the cleavage of CFB by complement factor D (CFD) and generating Bb and Bb and the formation of the AP C3 convertase C3(H2O)Bb. Any of the C3 convertases can cleave C3 to C3a and C3b. The C3b fragment can bind to CFB. After the cleavage of CFB by CFD, the C3 convertase C3bBb is formed. This C3 convertase cleaves more C3 to C3b to generate even more C3 convertase in a powerful amplification loop, resulting in the full activation of the complement system. The plasma protein properdin stabilizes C3bBb and provides a platform for its in situ assembly on microbial surfaces, apoptotic cells, and malignant cells. C3b also initiates the terminal complement cascade by the formation of the C5 convertase through association with either of the C3 convertases (C4b2aC3b or C3bBbC3b). The C5 convertase then cleaves C5 to C5a and C5b. C5b subsequently binds to C6, facilitating the binding of C7, C8, and C9 and culminating in the formation of the C5b-9 terminal membrane attack complex (MAC). The latter forms pores in the membrane of pathogens and damaged self-cells, thus promoting cell lysis. C3a and C5a are anaphylatoxins and among the most powerful effectors of complement activation capable of inducing chemotaxis, cell activation, and inflammatory signaling. MASP, mannose-binding lectin–associated serine protease.

The predilection for the kidney of disorders of the AP is incompletely understood but may be related to the presence of the fenestrae continuously exposing the acellular subendothelial tissues to complement activators, a lower baseline expression of complement regulators, and/or differences in the composition of the glycoscalix. Transitions between glomerulopathies included in this spectrum can occur during the disease course, after kidney transplantation, or among members of the same family, adding another layer of complexity to AP pathophysiology. The cause of this potential variation between phenotypes is presently unknown.

The overactivation of the AP may be either constitutive or triggered. The AP is constitutively active owing to the slow spontaneous tick over of C3, leading to the formation of the AP C3 convertase. A genetic or acquired defect in the regulators of complement activation may lead to unchecked spontaneous activation of the AP. In some instances, the defect is not severe enough to cause dysregulation in baseline circumstances, but a trigger may lead to overactivation of the complement pathway. In these patients, sustained complement activation occurs in what otherwise would have been a self-limiting event. The eliciting condition is most often an infection, a well known trigger for aHUS. A similar mechanism likely is at play in the C3 glomerulopathies. In patients originally diagnosed with postinfectious GN, AP abnormalities were detected, and subsequent biopsies were consistent with C3 glomerulonephritis. In patients originally diagnosed with postinfectious GN, AP abnormalities were detected, and subsequent biopsies were consistent with C3 glomerulonephritis. Other triggers include vaccinations, immunosuppressive or antineoplastic drugs, oral contraceptives, pregnancy, and childbirth. The development of a monoclonal gammopathy, possibly acting as an autoantibody, may also be a precipitating event.

The expression of disease may also be determined by the site of the defect in the AP. The presence of several defects may be required to instigate clinical disease, which was illustrated by the finding of genetic abnormalities in clinically unaffected relatives. Such combinations include more than one mutation, a mutation and...
However, recent data show that these diseases share a common pathophysiology and should be considered as disorders of the AP. In this section, we define different sites in the AP where dysregulation may occur. Within each mechanistic category, different clinical phenotypes may present. Unraveling the site of AP dysfunction is important, because it may assist in appropriate management.

Figure 2. Normal regulation of the complement AP. CFI is responsible for the proteolytic inactivation of C3b to iC3b (inactive C3b) and ultimately, the C3 breakdown products C3d and C3g, thus irreversibly preventing reassembly of the C3 convertase. MCP (CD46) is a surface-expressed regulator that has decay accelerating activity and acts as a cofactor for CFI. CFH is one of the most important regulators of the AP, controlling complement activation in several ways. It decreases the formation of C3b by competing with CFB in binding to C3b and accelerating the dissociation of the C3bBb convertase complex (decay accelerating activity). In addition, it acts as a cofactor for CFI in the cleavage of C3b to iC3b in concert with MCP. CFH protects against complement-mediated damage both in the fluid phase and on the host cell surface. Additional control of the cascade occurs through the CFHR protein family. CFHR consists of five proteins that are structurally and functionally related to CFH: CFHR1, CFHR2, CFHR3, CFHR4, and CFHR5. These CFHR proteins compete with CFH for binding to C3b but have no direct complement inhibiting actions.

Although the CFH-C3b interaction prevents further C3b generation, the CFHR protein-C3b interaction enables C3b amplification to proceed unhindered. This process is termed CFH deregulation. The ratio between CFH and CFHR proteins is, thus, critical for fine tuning complement regulation.

SITES OF AP DYSREGULATION

Historically, patients have been grouped into clinical syndromes (C3 glomerulopathies versus TMA) as a logical approach from the point of view of the clinician. However, recent data show that these diseases share a common pathophysiology and should be considered as disorders of the AP. In this section, we define different sites in the AP where dysregulation may occur. Within each mechanistic category, different clinical phenotypes may present. Unraveling the site of AP dysfunction is important, because it may assist in appropriate management.

Deficiency or Dysfunction of CFH

CFH is a single-polypeptide chain glycoprotein composed of 20 repetitive units of 60 amino acids each termed short consensus repeats. Insight into its structure-function relationship contributes to the understanding of CFH–associated renal disease (Figure 5); >160 mutations in CFH are currently identified (www.FH-HUS.org), resulting in deficiency or dysfunction of CFH (Figure 6A). Mutations that lead to complete absence of CFH (type I mutations)24–27 or a CFH that is expressed in plasma but lacks complement regulatory activities (type II mutations)28–30 generally located at the N terminus—result in uncontrolled complement activation in the fluid phase and GBM. The phenotypic expression is that of a proliferative GN,6,23,25,31–34 However, the majority of the aHUS-associated mutations cluster in the C-terminal recognition domain,9,20,26 The mutant CFH proteins generally show normal regulatory activity in the fluid phase but display defective recognition and regulatory functions at the surface of endothelial cells, eventuating in TMA. The majority is heterozygous missense mutations associated with normal CFH plasma levels.

Functional Inactivation of CFH by an Autoantibody

The presence of an autoantibody directed against CFH results in functional CFH deficiency and occurs in 6%–25% of Europeans35–38 and 56% of Indians with aHUS.39 These antibodies bind with the C-terminal region of CFH, where also, the majority of aHUS–associated
CFH mutations cluster, thus affecting the surface binding and recognition function of CFH.\(^{37,38}\) However, a subsequent extensive characterization of the autoantibodies in 19 patients with aHUS showed that the antibodies bind multiple epitopes on CFH and perturb both fluid–phase and cell surface complement control.\(^{40}\)

In most patients, the presence of the anti-CFH autoantibodies is associated with a homozygous deletion of the genes for complement factor H–related (CFHR) proteins CFHR1 and CFHR3 and the absence of CFHR1 and CFHR3 in plasma.\(^{22,35,37–40}\) This association has been labeled deficiency of CFHR proteins and CFH autoantibody–positive (DEAP)–hemolytic uremic syndrome (HUS; deficiency of CFHR proteins and CFH autoantibody–positive HUS).\(^{37}\) CFHR1/CFHR3 deficiency is, however, a common polymorphism found in 2%–8% of the normal population.\(^{40}\) Family members of patients with DEAP-HUS who exhibit homozygous deficiency for CFHR1/CFHR3 but lack the anti-CFH autoantibodies do not develop aHUS. Complete deficiency of CFHR1 is most likely the significant factor associated with the generation of the anti-CFH autoantibodies, possibly because of the failure of immune tolerance to the homologous region in CFH.\(^{38}\)

In a patient with DDD, a monoclonal light–chain dimer with CFH-inhibiting effects was discovered.\(^{41}\) The mini autoantibody was later shown to interfere with the regulatory domain of CFH, entailing uncontrolled complement activation in the fluid phase.\(^{42}\) Anti-CFH autoantibodies have been described in other patients with DDD,\(^{43,44}\) with a similar predilection for the N-terminal complement regulatory domain of CFH.\(^{45}\) Interestingly, in a patient with anti-CFH autoantibodies, membranoproliferative glomerulopathy occurred in the native kidneys and recurred rapidly after the first kidney transplant but transitioned to aHUS in a second transplant\(^{46}\); such clinical observations indicate that the presence of the antibody itself does not predict phenotypic expression.

**Mutations Affecting CFHR Proteins**

The CFH gene and the genes encoding the five CFHR proteins show large degrees of sequence identity favoring genomic rearrangements, including deletions, duplication, and generation of hybrid genes.\(^{45}\) The CFHR proteins are highly related in structure, and CFHR1, CFHR2, and CFHR5 share a common dimerization motif. The formation of homodimers and heterodimers promotes the binding to ligands and permits the CFHR proteins to act as competitive antagonists of CFH, a property termed CFH deregulation.\(^{46}\) However, generation of mutant CFHR proteins by internal duplication or gene fusion leads to unusual CFHR protein dimers and multimers with enhanced avidity for ligands, enabling the CFHR proteins to outcompete CFH and amplify the degree of CFH deregulation\(^{46}\) (Figure 6B). This genetic scenario is recognized in families with C3 glomerulopathy\(^{47–52}\) (Table 2).

Several hybrid genes deriving from the CFH/CFHR region have also been
identified in familial and sporadic aHUS, including hybrid CFH/CFHR1–56 and CFH/CFHR3 genes (Table 2). The resultant hybrid protein acts as a competitive antagonist of CFH but lacks CFH regulatory activity at the cell surface. A case of persistent GN after a streptococcal infection (atypical postinfectious GN) was reported in a patient with a heterozygous mutation in CFHR5 causing premature truncation (Table 2). How this mutation is associated with the disease is currently unknown.

Stabilization of the C3 Convertase
Gain-of-Function Mutations in Complement Factor B
In aHUS, different gain-of-function mutations in complement factor B (CFB) are recognized. The mutant proteins form a hyperfunctioning C3 convertase that is resistant to decay by CFH, thereby activating the AP on the cell surface and in the fluid phase. CFB mutations, however, are not uniformly pathogenic.

Gain-of-Function Mutations in C3
Gain-of-function mutations in C3 occur in aHUS. These mutations impair regulation by MCP and confer resistance to cleavage by complement factor I (CFI) with increased affinity for CFB. Dysfunctional C3 molecules resistant to inhibition by CFH also occur in C3 glomerulopathies. Such mutant C3 convertases resist inactivation by CFH but are regulated normally by decay-accelerating factor and MCP. These characteristics cause a fluid phase–restricted AP dysregulation and a normal regulation on the cell surface, explaining the DDD phenotype. In a family with mutations in both C3 and MCP, some family members present with aHUS, whereas others exhibit C3 GN.

C3 Nephritic Factor
C3 nephritic factors (C3Nefs) comprise IgG and IgM autoantibodies that bind directly to the C3 convertase or its components, thereby rendering it resistant to spontaneous or CFH- and CFI-mediated decay. The prolonged survival of the C3 convertase massively consumes C3 and markedly reduces C3 levels. C3Nefs exist in >80% of patients with DDD and 40%–50% of patients with C3 GN. C3Nefs may also occur in acute poststreptococcal GN and atypical postinfectious GN.

The specific contribution of C3Nefs to the pathophysiology of AP disorders remains undefined. C3Nefs occur in...
Table 1. Examples of variable phenotypic expression of CFH mutations

<table>
<thead>
<tr>
<th>Mutation in CFH</th>
<th>Phenotypical Expression</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro621Thr</td>
<td>Patient with C3 glomerulopathy later develops aHUS</td>
<td>12</td>
</tr>
<tr>
<td>Tyr899Stop</td>
<td>Patient with aHUS develops C3 glomerulopathy (CFHR5 nephropathy)</td>
<td>15</td>
</tr>
<tr>
<td>Ala161Ser; Arg1210Val; Arg53Cys</td>
<td>Identified in patients with aHUS and C3 glomerulopathy</td>
<td>23</td>
</tr>
<tr>
<td>Asn1117Ser</td>
<td>Crescentic and necrotizing GN in the region where aHUS mutations cluster</td>
<td>34</td>
</tr>
</tbody>
</table>

healthy individuals and asymptomatic family members of patients with DDD. Furthermore, C3Nef levels do not seem to correlate with the course of the GN. Treatment directed at the autoantibody, including high-dose steroids and rituximab, does not consistently reduce C3Nef activity and/or induce clinical remission. Finally, the presence of C3Nef often coincides with mutations in AP proteins—most often CFH and CFI and MCP. Genetic abnormalities may, thus, promote autoimmune phenomena directed against neo epitopes exposed on activated complement components.

Other Autoantibodies
Some patients with DDD lack C3Nefs but have autoantibodies against CFB44,77 or C3b and CFB, with a similar stabilizing effect on the C3 convertase (Figure 6C).

Impaired Inactivation of C3b to iC3b
Mutations in CFI
Heterozygous mutations in the CFI gene leading to reduced CFI levels or functional deficiency of CFI incur an increased risk for aHUS. CFI mutations previously identified in aHUS were later reported in C3 GN, thereby underscoring the fact that the clinical phenotype is not simply determined by the presence of these mutations. Mutations in CFI also occur in patients with immune complex GN. In some patients, the presence of positive antinuclear antibodies, ant_DOUBLE-STRANDED DNA, or rheumatoid factor suggests the presence of an underlying autoimmune process, and the latter may synergize with CFI mutations, thereby generating C3b from C3. Interestingly, CFI mutations have not been reported in DDD. Although CFH knockout mice acquire subendothelial C3 deposits, combined CFH and CFI knockout mice do not develop C3 glomerulopathy. Taken together, these results indicate that CFI and the C3 degradation products generated by CFI are essential for the pathogenesis of DDD.

Mutations in MCP
Loss of function of MCP leads to decreased protection of host cells—in particular, glomerular endothelial cells—from complement lysis without significantly affecting complement control in the fluid phase. Mutations in MCP resulting in either decreased expression or impaired cofactor function are found in 7%–13% of patients with aHUS and generally associated with a favorable prognosis. Another MCP mutation of uncertain functional significance occurs in C3 GN, HemolyS Elevated Liver enzymes and Low Platelets syndrome, and Shiga toxin–associated HUS.

Clinical disease associated with MCP mutations exhibits highly variable penetrance and commonly requires some type of endothelial stress. Suboptimal MCP activity may adequately defend host cells from inappropriate complement activation in unstimulated states but fails to provide protection in the presence of an endothelial insult (such as infection, drugs, or pregnancy). Alternatively, the concomitant presence of other mutations or disease-promoting polymorphisms may be required for full-blown manifestation of the disease. For example, a homozygous mutation with total lack of MCP expression is described in not only a patient with aHUS but also, a completely healthy sibling (Figure 6D).

Monoclonal Gammopathy
In adult patients with C3 GN and DDD, compared with the general population, the prevalence of monoclonal gammopathy is greatly increased. Importantly, glomerular deposits contain C3 and complement debris but not monoclonal proteins, thereby indicating that the disease is not caused by direct deposition of the monoclonal Ig. Additionally, evidence of AP activation is present in such patients. Although in some patients, a permissive genetic background was reported, mutations in CFH, CFI, and MCP were not identified. Overall, available evidence would suggest that the monoclonal Ig may promote complement activation by acting as an autoantibody against CFH or another AP component. The plausibility of this scenario was elegantly

Table 2. Overview of mutations in CFHR protein genes

<table>
<thead>
<tr>
<th>Genetic Defect</th>
<th>Phenotypical Expression</th>
<th>Systemic C3 Levels</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplication in the CFHR5 gene</td>
<td>C3 glomerulopathy (CFHR5 nephropathy)</td>
<td>Normal</td>
<td>47, 49, 51</td>
</tr>
<tr>
<td>Duplication in the CFHR1 gene</td>
<td>C3 glomerulopathy</td>
<td>Mildly decreased</td>
<td>52</td>
</tr>
<tr>
<td>Hybrid CFHR3/CFHR1 gene</td>
<td>C3 glomerulopathy</td>
<td>Normal</td>
<td>50</td>
</tr>
<tr>
<td>Hybrid CFHR2/CFHR5 gene</td>
<td>C3 glomerulopathy</td>
<td>Decreased</td>
<td>48</td>
</tr>
<tr>
<td>Hybrid CFH/CFHR1 gene</td>
<td>aHUS</td>
<td>Mildly decreased or normal</td>
<td>53–56</td>
</tr>
<tr>
<td>Hybrid CFH/CFHR3 gene</td>
<td>aHUS</td>
<td>Normal</td>
<td>57</td>
</tr>
<tr>
<td>Mutation in the CFHR5 gene</td>
<td>Atypical postinfectious GN</td>
<td>Decreased</td>
<td>58</td>
</tr>
</tbody>
</table>
showed in a patient with DDD, which was discussed above.41,42

TREATMENT

A standard therapeutic regimen that fits a particular clinical phenotype does not exist. On the basis of current understanding, salient therapeutic strategies and their underlying rationale are now outlined.

Nonspecific Treatment

The clinical presentation of the C3 glomerulopathies is more heterogeneous than that of aHUS. Some patients with C3 glomerulopathy are characterized by a slow progression.69 In these patients, nonspecific treatment measures, such as BP control, proteinuria reduction and lipid-lowering agents, can be used on the basis of extrapolations from data in other chronic glomerular diseases. In C3 glomerulopathy cohorts, the use of renin-angiotensin-aldosterone system blockade was associated with a better renal survival,23 and the combined use of renin-angiotensin-aldosterone system blockade and immunosuppression was better than either agent alone.90

Replace Deficient Gene Products

Plasma Infusion

Patients with type I mutations in complement regulatory plasma proteins may benefit from replacement of the deficient factor. Because recombinant CFH is currently not available, functionally intact CFH can only be administered through plasma therapy. The efficacy of this approach is attested to by successful outcomes with long-term intermittent plasma infusion in patients with C3 glomerulopathy28,29 or aHUS93 caused by complete CFH deficiency. In these patients, however, persistent disease control requires lifelong substitution therapy.

In contrast, plasma therapy is ineffective in patients with a single MCP mutation, an outcome consistent with the fact that MCP is a membrane-bound and not a circulating protein.94 Indeed, in patients with aHUS, the outcome of those with MCP mutations was equally beneficial regardless of whether they were treated with plasma.81,95

In patients with gain-of-function mutations in complement activation proteins, plasma infusion may also be ineffective or even counterproductive, because it provides additional complement substrate for the hyperfunctioning mutant protein. In a DDD pedigree with a novel mutation in the C3 gene characterized by a mutant C3 convertase resistant to CFH control, replacement therapies providing CFH are futile.67 In DDD caused by a hybrid CFHR2/CFHR5 protein that renders the C3 convertase refractory to inhibition and decay by CFH, plasma infusion proved detrimental.48

Liver Transplantation

Patients with mutations in the complement regulatory proteins have a very high risk for loss of the transplanted kidney caused by thrombosis or recurrent disease. Because CHF, CFI, CFB, and C3 are predominantly synthesized by the liver, simultaneous liver-kidney transplantation can correct the genetic abnormality. To avoid perioperative hepatic failure caused by uncontrolled hepatic complement activation, patients are prepared for surgery with intensive plasma therapy and recently, eculizumab as well.96,97 Although short-term complications remain substantial, with mortality rates up to 15%, the overall success rate (defined as good function of both grafts and cure of the disease) with this approach is 80% in experienced centers.96 Considering the growing experience with eculizumab and its success in preventing disease recurrence post-transplant, in each individual patient, the advantages and disadvantages of combined liver-kidney transplantation should be carefully weighed against those of kidney transplantation followed by chronic eculizumab prophylaxis.

Eliminate Autoantibodies and/or Mutant Proteins

Plasma Exchange

The rationale for plasma exchange is 3-fold: (1) it replaces deficient or defective regulatory proteins, (2) it removes autoantibodies and/or mutant proteins that may compete with the functional proteins, and (3) it enables the administration of higher volumes of plasma.

Before the availability of eculizumab, plasma therapy was the therapeutic mainstay in aHUS, although controlled trials showing its effectiveness are lacking. In general, no difference in response to plasma infusion versus plasma exchange has been consistently observed.22,39,98 With the availability of specific complement inhibitors, the role of plasma therapy will likely be restricted to bridging the period between clinical presentation and initiation of targeted treatment.

Few reports address the efficacy of plasma exchange in C3 glomerulopathy. In three patients with DDD,99–101 a beneficial effect of plasma exchange was seen, but all patients also received aggressive immunosuppression. In a patient with DDD caused by a CFHR2/CFHR5 deregulating hybrid protein, plasma exchange was initiated with the intent of reducing the levels of the mutant protein. Although the levels decreased substantially, the response was short lived, and within 1–2 days, complement activation rebounded.48

Immunosuppression

Direct effects of immunosuppression on the AP components have not been shown. This approach rests heavily on the view that acquired antibodies contribute to the pathophysiology of the disease and that the production of these antibodies can be attenuated by immunosuppression. An added potential benefit may be the suppression of anaphylatoxin–induced glomerular inflammation. In DEAP-aHUS, anti–CFH antibody titers correlate with disease activity.35,36,39 Accordingly, the combination of immunosuppression (prednisone with or without cyclophosphamide or rituximab) with plasma exchange benefits clinical outcome35,39,102 along with the sustained reduction of the anti–CFH antibody titers.102 Subsequent maintenance therapy with prednisone and mycophenolate mofetil or azathioprine reduces the risk of relapse by 91%.39
In the absence of controlled trials, support for immunosuppression in C3 glomerulopathy relies on case reports and case series that show variable efficacy, the latter being susceptible to inflation by publication bias. The uncertain/unsatisfactory effects of immunosuppression are clearly illustrated by the high recurrence rates of this disease in allografts. In our opinion, a trial of immune suppression should be restricted to those patients with increasing proteinuria, progressive loss of kidney function, or severe inflammation on renal biopsy (e.g., crescentic GN), and it should be interrupted in the absence of a rapid response.

**Treatment of Plasma Cell Dyscrasia**

Although a causal relationship between a monoclonal gammopathy and dysregulation of the AP has yet to be rigorously shown, therapy directed at the clonal disorder should be considered in patients with an AP disorder, in whom a monoclonal protein is detected. In patients with a C3 glomerulopathy associated with a documented monoclonal gammopathy, chemotherapy resulted in improvement of renal function in some but not all patients.

**Inhibit Complement Activation**

The appropriate complement–inhibiting strategy is determined by the underlying mechanism of complement dysregulation. Many complement inhibitors are in clinical development, but so far, only eculizumab has been approved for clinical use.

**Eculizumab**

Eculizumab (Soliris; Alexion Pharmaceuticals) is a recombinant, fully humanized mAb that binds with high affinity to the human C5 complement protein and efficiently blocks C5 cleavage, regardless of the upstream trigger. It thwarts propagation of the terminal complement cascade and generation of the membrane attack complex. Because it also prevents the generation of the powerful anaphylatoxin C5a and subsequent leukocyte infiltration, it has additional anti–inflammatory effects. Eculizumab may, thus, be expected to be (at least partially) effective in any disease where activation of the terminal complement pathway is pathogenic. However, blockade of the complement cascade at the level of C5 preserves the early complement components, thereby leaving unchecked the potential dysregulation of the C3 convertase.

Eculizumab has revolutionized the treatment of aHUS. Mainly given as rescue therapy because of resistance to or complications with plasma therapy, eculizumab caused complete remission in 21 patients from a compilation of 24 patients from the literature (11 children and 13 adults). A query sent to all nephrology centers in France retrospectively identified 19 adults with aHUS that received eculizumab as first-line or rescue therapy. The risk of reaching ESRD was reduced by one half compared with recent historical controls. Finally, in a prospective phase II trial in 37 patients (31 adults and 6 adolescents) with aHUS, eculizumab was associated with substantial renal recovery. The response to eculizumab was similar in patients with and without identified complement mutation or anti-CFH autoantibodies. Earlier intervention was associated with improved renal function. These data have led to the recommendation that eculizumab should be the first-line therapy when the diagnosis of aHUS is unequivocal (i.e., in children, familial forms, relapses, and recurrences posttransplantation), regardless of the results of the complement investigations. Screening of anti-CFH autoantibodies, however, is indicated, because positive results may dictate the need for additional immunosuppression. Whether patients with DEAP-HUS respond better to immunosuppression, eculizumab, or the combination of both has yet to be assessed.

Approximately 15% of patients with aHUS are refractory to eculizumab. It is currently unclear whether this is caused by a mutation in C5, thereby rendering eculizumab ineffective (as shown in paroxysmal nocturnal hemoglobinuria) to disease dominantly driven by C3 convertase cleavage products, or abnormalities in the coagulation cascade.

So far, the effects of eculizumab have been described in only 14 patients with C3 glomerulopathy, of which 9 patients were diagnosed with DDD and 5 patients were diagnosed with C3 GN. Eight individual patients were reported, showing success in seven patients. These optimistic results may be influenced by publication bias and contrast with the more modest effects obtained in an open–label proof-of-concept study in six patients. In three of these six patients, there was a clinical response to eculizumab: a decrease in either serum creatinine or proteinuria. In four of eight patients who underwent a biopsy, decreased mesangial proliferation, endocapillary proliferation, or inflammatory cell infiltration. In the other patients, there was stable or progressive disease. Interestingly, after treatment with eculizumab, all biopsies showed IgG–κ staining of the glomeruli, tubular basement membrane, and vessel wall, consistent with deposition of eculizumab itself. The long–term clinical effects of such binding of eculizumab to renal tissue are unclear.

The phenotypic expression (DDD or C3 GN) does not seem to predict the response to treatment although biomarker studies have suggested a greater terminal pathway activity in C3 GN compared with DDD. In contrast, elevated soluble membrane attack complex was found to be a marker of response in accordance with the mechanism of action of eculizumab on terminal pathway activation. However, in a series of 32 patients with biopsy–proven DDD, sMAC was elevated in only 3 (9%) patients. Because C3 glomerulopathies are mainly characterized by persistent fluid–phase C3 convertase activity without predominant contribution of the terminal complement pathway, eculizumab may not be the therapy of choice in the majority of patients. This was shown in a patient with a C3 glomerulopathy caused by a hybrid CFHR2/CFHR5 protein resulting in increased CFH deregulation. When eculizumab was added to the serum of the patient, it effectively blocked C5.
Inhibition of the C3 Convertase
Conceptually, complement inhibition at the level of the C3 convertase or its components should be effective in any disorder driven by dysregulation of the C3 convertase, particularly in diseases caused by a stabilized C3 convertase. However, the benefits of upstream inhibition of the complement cascade must be weighed against the potential of significant adverse effects, especially those that pertain to the critical role of C3b in innate immunity.

Compstatin, a synthetic peptide that potently binds to C3 and its active fragment C3b, is currently in clinical development for age-related macular degeneration and paroxysmal nocturnal hemoglobinuria. Recently described is an mAb that binds C3b (but not native C3), thereby preventing the formation of the C3 convertase (and the generation of iC3b); indeed, this antibody blocks C3 cleavage induced by a C3Nef–stabilized C3 convertase.

Another potential approach to complement inhibition is the creation of soluble recombinant forms of complement regulatory proteins. Complement receptor 1 (CR1) regulates both the C3 and C5 convertases and is the only cofactor of CFI that can cleave iC3b into smaller fragments (C3c and C3dg). A soluble form of CR1 prevented dysregulation of the C3 convertase when administered in vitro to sera of patients with DDD with and without C3Nef. In a murine model of C3 glomerulopathy, the soluble form of CR1 restored serum C3 levels to normal and cleared iC3b from the GBMs.

DISCLOSURES
None.

REFERENCES

CONCLUSION
Recent progress in the availability of biomarkers and genetic tests for the complement cascade has unveiled the pathophysiologic heterogeneity of glomerular diseases caused by AP dysregulation. In a subset of patients, a mutation in one of the key regulators may reveal itself as childhood C3 glomerulopathy or aHUS. However, rather than a specific single defect, more than one genetic predisposition commonly underlies AP dysregulation. Novel amino acid epitopes may be exposed and facilitate the formation of autoantibodies against regulatory proteins. Triggering factors disrupt the fragile balance between activating and restraint, thereby instigating sustained and inordinate activation of the AP. Such considerations account for the varied presentations that include atypical postinfectious GN, adult C3 glomerulopathy, or aHUS.

The new level of understanding of AP pathophysiology heralds a paradigm shift in the classification of these disorders. Traditional clinical assessment and renal pathology are not sufficiently informative to guide us in treatment decisions. In this review, we have defined pathophysiological categories with mechanistic and therapeutic significance. When the clinical history or renal biopsy hints at a disorder of complement regulation, a biochemical analysis of the different steps in the complement cascade and a complete genetic workup should be performed. Deciphering the relative pathologic role of the genetic and environmental factors can direct therapy to the site of dysregulation. As specifically targeted anticomplement molecules become increasingly available, tailored therapy to shift complement back into balance will truly become feasible.


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BRIEF REVIEW


