The management of steroid-resistant FSGS is controversial. Traditionally, tacrolimus or cyclosporine are the first-line therapy to manage adult steroid-resistant FSGS. With the sustained evolution of genetic testing, up to 60% of the patients with steroid-resistant FSGS have genetic mutations in podocyte and non-podocyte genes (5). Data from the pediatric population suggest that over three-fourths of the patients with non-genetic-associated, steroid-resistant FSGS respond favorably to cyclosporine therapy (17). With the unceasing expansion of the library of genes incriminated in the development of steroid-resistant FSGS, experts recommend genetic testing in all steroid-resistant FSGS, hence procrastinating ineffective treatment (18). As per the current consensus, all steroid-resistant FSGS patients need to be started on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and lipid lowering with statin therapy. Both the disease and its treatment affect the bone and cardiovascular system adversely. Hence, future research needs to solicit safeguards for bone and cardiovascular health in patients with steroid-resistant FSGS.

To conclude, the management of adult podocytopathy graduates from steroids (only) to steroid-minimized or steroid-free therapies, primarily involving tacrolimus/mycophenolate sodium and rituximab, thus offering a new perspective to the management of SD or FR podocytopathy. Genetic testing is the key to manage steroid-resistant FSGS, at least before subjecting it to toxic second-line agents. Admittedly, adult nephrologists worldwide with renewed interest in glomerular diseases need to collaborate and examine a steroid-free or steroid-minimized protocol for managing MCD/FSGS. Understandably, the TURING and RIFIREINS trials are steps in the right direction. ■

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C3 Glomerulopathy: Update on Pathogenesis and Treatment

By Shikha Wadhwani and Samir V. Parikh

C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), collectively known as C3 glomerulopathy (C3G), are rare glomerular diseases presenting with microscopic hematuria, proteinuria, and often, abnormal kidney function. Low serum C3 is present in 70%–80% of patients with DDD and 50% with C3GN (1). Effective therapies are lacking, and prognosis is poor (2). Disease recurrence after kidney transplantation is common and leads to graft loss in 30%–40% of affected patients (3, 4).

Pathogenesis of C3G

C3G is characterized by dysregulation of the alternative complement pathway and defined by C3-dominant staining on immunofluorescence (IF) of a kidney biopsy. DDD is differentiated from C3GN histologically: the former has characteristic ribbon-like, electron-dense, intramembranous deposits on electron microscopy, whereas the latter has mesangial, subendothelial, and rarely, subepithelial deposits (5). Despite the histological differences, the clinical presentation, outcomes, and alternative complement pathway abnormalities are similar between C3GN and DDD.

Figure 1 provides an overview of the alternative complement pathway in healthy and disease states. Briefly, in physiologic states, the alternative complement pathway maintains low-level activation through spontaneous hydrolysis of C3 to C3b ("tick over") and controlled generation of C3 convertase (C3bBb). The C3 convertase amplifies the alternative complement pathway by producing more C3b through C3 cleavage and drives C5 convertase (C3bBbC3b) generation. C5 convertase cleaves C5 to form the anaphylatoxin C5a and C5b—the latter forming the membrane attack complex (MAC), C5b-9, which induces cell lysis (5). In healthy states, fluid phase (factor H and factor I) and cell surface (factor H, membrane cofactor protein [MCP], decay-accelerating factor [DAF], and complement receptor 1 [CR1]) regulators of complement activity keep the alternative complement pathway under tight control. Genetic or acquired defects of these complement regulators or activators are responsible for alternative pathway dysregulation in C3G (Table 1). Accordingly, a complete complement workup is recommended for all patients. The most common defect in C3G is an acquired C3 nephritic factor (C3Nef), a C3 convertase-stabilizing immunoglobulin G (IgG) autoantibody that dramatically increases its half-life and hence perpetuates alternative pathway dysregulation (5, 6). Genetic variants are identified in up to 25% of C3G cases; however, the functional significance of these variants is often unclear (1, 3).

Management in C3G

There are no approved therapies for C3G, and current treatment regimens are based on retrospective case series and expert opinion. Blockade of the renin-angiotensin system is recommended for all patients with proteinuria. Corticosteroids and non-specific immunosuppressive agents are often used but have shown variable success. Perhaps the best available evidence for treatment of C3G comes from two independent cohort studies (combined n=132), which demonstrated efficacy of corticosteroids plus mycophenolate mofetil (MMF) as compared to steroids alone, other immunosuppressive therapies, or supportive care (7, 8). These studies, however, are limited by their retrospective, uncontrolled design and heterogeneity in both treatment duration and steroid dosing. Notably, MMF showed minimal response in another cohort (n = 78), possibly due to a greater number of patients with genetic variants (9). Nonetheless,

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a MMF-based regimen has been proposed as first-line treatment for C3G with proliferative glomerulonephritis (2, 10).

Advancements in the field of complement therapeutics have led to the development of several anti-complement therapies for C3G (Table 2). Given efficacy in other alternative complement pathway-mediated diseases, such as atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria, eculizumab, a monoclonal antibody against C5, was tested in C3G. In a pilot study, four of six patients treated with eculizumab had stabilization or improvement in kidney function after 1 year of treatment (11). In this study, patients with elevated baseline levels of soluble C5b-9 (soluble MAC [sMAC]) responded to treatment, suggesting sMAC could be a potential biomarker for response to eculizumab. In a subsequent prospective single-arm trial, 10 patients with C3G or immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) were treated with eculizumab for two sequential, 48-week treatment periods separated by a 12-week washout period. In this cohort, all patients had elevated sMAC and nephrotic-range proteinuria at baseline. However, only three patients (all negative for C3Nef) had sustained proteinuria reduction despite effective terminal complement blockade in all patients (12). The variable results with eculizumab suggest that more proximal alternative complement pathway blockade may be needed to achieve disease control in C3G.

A small molecule inhibitor of factor D (ACH-0044471) was recently tested in a proof-of-concept study in four patients (three with C3GN; one with IC-MPGN) who all had low serum C3. Preliminary results showed that factor D inhibition suppressed alternative complement pathway fragments Bb and Ba and increased serum C3 after 2 weeks of treatment (13). Importantly, the urine albumin-to-creatinine ratio decreased by 50% in this small cohort, although results from the entire cohort are needed before strong conclusions can be drawn.

A phase II, open-label trial of small molecule oral factor B inhibitor, iptacopan (LNP023), is currently ongoing with a primary endpoint of proteinuria reduction at 12 weeks. Promising interim results demonstrated a 49% reduction in urine total protein-to-creatinine ratio from baseline and estimated glomerular filtration rate (eGFR) stabilization without a safety/tolerability signal in 12 patients (14). An open-label extension study evaluating response at 9 months is underway.

The DISCOVERY trial, a phase II open-label study of APL-2 (a small molecule inhibitor of C3), evaluated the safety and efficacy of proximal alternative complement pathway blockade in several glomerular diseases including C3G. Preliminary results noted reduction in proteinuria, stabilization of eGFR, and improvement in serum C3 and C5b-9 levels in eight patients over the 12-week treatment period (15). Long-term follow-up and safety data are pending.

Finally, avacopan (formerly CCX168), an oral C5aR inhibitor that has shown promising results in antineutrophil cytoplasmic antibody (ANCA) vasculitis (16), is presently being studied in C3G. An interim analysis of the ACCOLADE study demonstrated statistically significant improvement in both eGFR and a novel C3G histologic chronicity index when comparing avacopan to placebo (17). This index was recently developed and found to correlate with prognosis in two independent cohorts (18, 19). Although the primary endpoint of change in the C3G histologic activity index at 26 weeks was not statistically significant, there was a trend toward improvement in the avacopan group.

As we eagerly await results of these complement inhibitor trials, many salient questions emerge. Will blockade of alternative complement pathway components actually translate into improved outcomes? Will treatment response depend on an individual patient's alternative complement pathway defect, and how will this response be measured? Will sequential blockade of alternative complement pathway factors lead to greater efficacy or just increase the risk/frequency of adverse events? Although we presently have more questions than answers, one thing is clear: there is a desperate need for complement biomarkers that can accurately reflect disease status, inform treatment, and predict response. Only with continued progress toward understanding disease pathogenesis in C3G can we truly pave the way for personalized, target-directed therapies. ■

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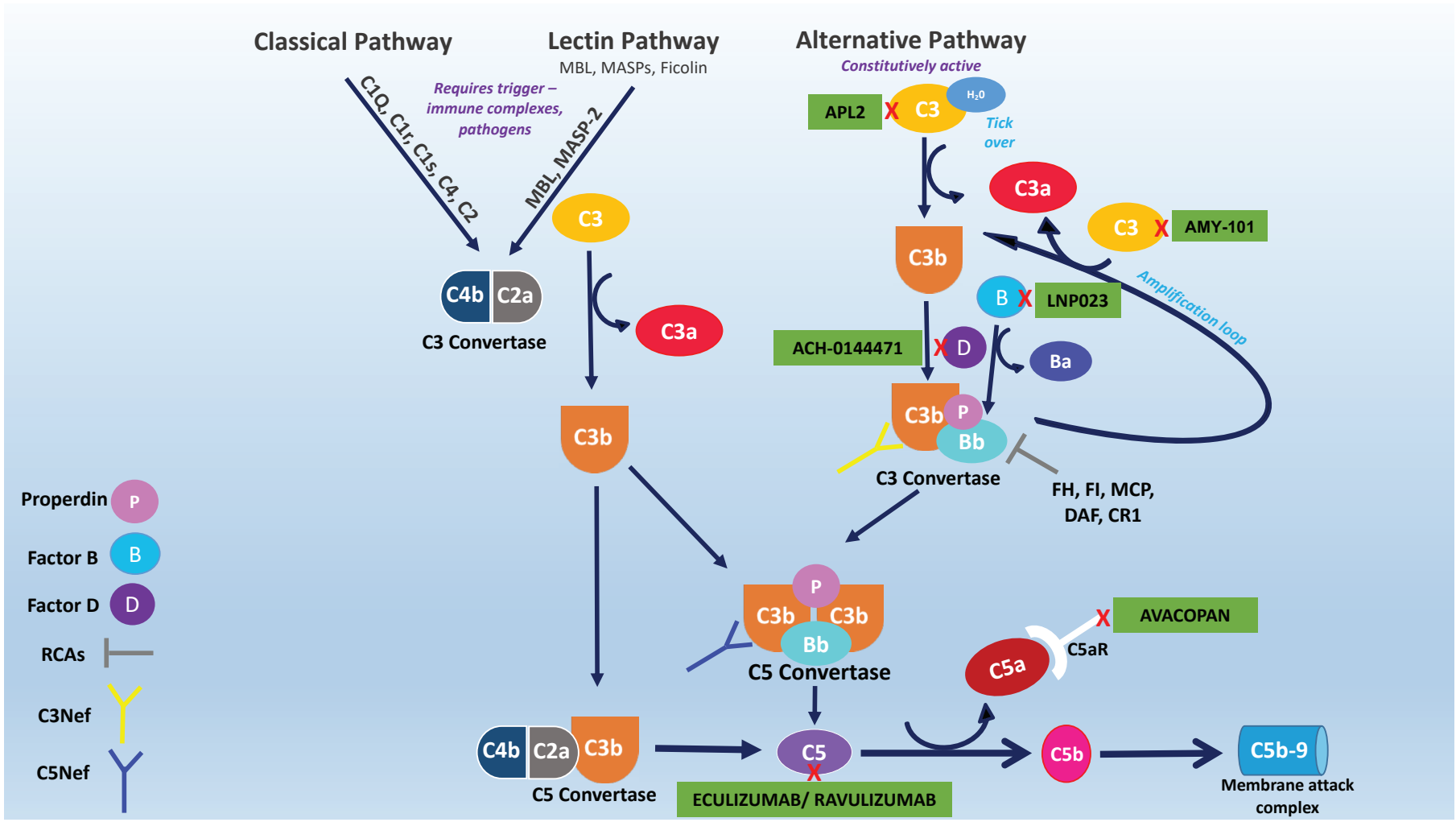
Figure 1. Alternative complement pathway dysregulation in C3 glomerulopathy



Complement is activated through the classical, lectin, and alternative pathways. Whereas the classical and lectin pathways are triggered by foreign actors or immune complexes, the alternative pathway maintains low-level activation through spontaneous hydrolysis of C3 to the anaphylatoxin C3a and C3b ("tick over"). Production of C3b leads to controlled generation of C3 convertase (C3bBb), which amplifies the alternative pathway by producing more C3b through C3 cleavage and also drives C5 convertase (C3bBbC3b) generation. C5 convertase cleaves C5 to form the anaphylatoxin C5a and C5b—the latter forming the membrane attack complex (MAC), C5b-9, which induces cell lysis. The alternative pathway is kept under tight control by regulators of complement activity (RCAs). In C3 glomerulopathy, the alternative pathway becomes dysregulated due to either genetic or acquired defects in RCAs or complement activators. Multiple novel anti-complement therapies for C3 glomerulopathy are being tested in clinical trials, and their primary targets are shown in the figure.

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Table 1. Genetic and acquired complement defects in C3 glomerulopathy

Genetic variant	Frequency (ref. 20)	Acquired defect	Frequency
C3	11%	C3 nephritic factor	80% DDD; 50% C3GN
Complement factor H	12%	C5 nephritic factor	50% of C3G
CFHR1, -1/5, -3/1, or -5	Rare	C4 nephritic factor	Rare
Complement factor B	1%	Anti-factor H autoantibody	4%–12% of C3G
Complement factor I	5%	Anti-C3B autoantibody	2%–3% of C3G

CFHR, complement factor H-related protein.

Table 2. Clinical trials of complement-directed therapies

Drug	Target	Sponsor	Treatment population	Trial phase	Clinical trial #	Status
Eculizumab	C5	Alexion	C3GN or IC-MPGN	2	NCT02093533	Completed
Avacopan (CCX168)	C5aR	ChemoCentryx	C3G, native or post-transplant	2	NCT03301467	Recruitment completed; study ongoing
ACH-0144471	Complement Factor D	Alexion	C3G or IC-MPGN	2	NCT03124368	Completed
ACH-0144471	Complement Factor D	Alexion	C3G or IC-MPGN	2	NCT03459443	Recruitment completed; study ongoing
ACH-0144471	Complement Factor D	Alexion	C3G	2	NCT03369236	Recruitment completed; study ongoing
Iptacopan (LNP023)	Complement Factor B	Novartis	C3G and recurrent C3G in transplant	2	NCT03832114, NCT03955445	Recruiting
APL-2	C3	Apellis	C3G, IgAN, LN (class III, IV, or V), primary MN	2	NCT03453619	Recruitment completed; study ongoing
AMY-101	C3	Amyndas	Healthy males	1	NCT03316521	Completed
Narsoplimab (OMS721)	MASP-2	Omeros	C3G, IgAN, LN, MN	2	NCT02682407	Recruiting

C5aR, complement component 5a receptor; IgAN, immunoglobulin A nephropathy; LN, lupus nephritis; MN, membranous nephropathy; MASP-2, mannose-binding lectin serine protease 2.