Transplantation Reviews 38 (2024) 100839

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Recurrent C3 glomerulopathy after kidney transplantation

Shota Obata [a], Pedro A.S. Vaz de Castro [b], Leonardo V. Riella [c], Paolo Cravedi [a,*]

[a] Precision Immunology Institute, Translational Transplant Research Center, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America
[b] Interdisciplinary Laboratory of Medical Investigation, Unit of Pediatric Nephrology, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Brazil
[c] Division of Nephrology and Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States of America

ARTICLE INFO

Keywords:
C3 glomerulopathy
Recurrent glomerulonephritis
Renal transplantation
Complement-mediated glomerulonephritis
eculizumab
C3
C5
C3aR
C5aR1
MAC

ABSTRACT

The complement system is part of innate immunity and is pivotal in protecting the body against pathogens and maintaining host homeostasis. Activation of the complement system is triggered through multiple pathways, including antibody deposition, a mannan-binding lectin, or activated complement deposition. C3 glomerulopathy (C3G) is a rare glomerular disease driven by complement dysregulation with high post-transplantation recurrence rates. Its treatment is mainly based on immunosuppressive therapies, specifically mycophenolate mofetil and glucocorticoids. Recent years have seen significant progress in understanding complement biology and its role in C3G pathophysiology. New complement-tergeting treatments have been developed and initial trials have shown promising results. However, challenges persist in C3G, with recurrent post-transplantation cases leading to suboptimal outcomes. This review discusses the pathophysiology and management of C3G, with a focus on its recurrence after kidney transplantation.

1. Introduction

C3 glomerulopathy (C3G) is a complement-mediated renal disease known for its high rates of recurrence post-transplantation [1–3]. The last decade has witnessed remarkable advancements in our understanding of complement biology and the emergence of therapeutic interventions targeting complement dysregulation. Notably, eculizumab, a C5 inhibitor, has revolutionized renal transplantation for patients diagnosed with atypical hemolytic uremic syndrome (aHUS) [4] – another complement-associated nephropathy once deemed unsuitable for transplantation, while the ideal treatment for C3G remains unclear. Recently, novel therapies, especially those targeting the C3, offer hope, with various clinical trials underway. This review delves into the therapeutic approaches to C3 nephropathy, emphasizing its management post-transplantation.

2. Method

To ensure a comprehensive understanding of C3G and its recurrence post-kidney transplantation, as well as to review the available treatment options, a comprehensive literature search was conducted using PubMed. The keywords employed for this search included “C3 glomerulopathy”, “C3 glomerulonephritis”, “Dense deposit disease” and “kidney transplant,”. The timeframe for the publications was between January 1, 2020 until Dec 31 December2023.

2.1. Histological and clinical features

C3G is a rare disease caused by dysregulation of the alternative complement pathway. It is characterized by the sole or dominant C3 deposition in the glomeruli with little or no immunoglobulin (Ig) deposition on immunofluorescence (IF) staining. Electron microscopy (EM) findings subclassify C3G into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on the presence or absence of characteristic intramembranous high electron-dense deposits, respectively [5]. Light microscopy findings vary greatly, showing patterns of mesangial proliferative, membranoproliferative, and endocapillary proliferative glomerulonephritis with or without crescents [6].

The presentation of C3G can vary from asymptomatic hematuria/proteinuria to an acute onset with classic signs and symptoms of glomerulonephritis, such as proteinuria, hematuria, and hypertension [7]. C3G is associated with chronic deterioration of kidney function, resulting in kidney failure within ten years of diagnosis in 36.5% of the cases [8]. The recurrence rate of C3GN and DDD after transplantation is

* Corresponding author at: Icahn School of Medicine at Mount Sinai, 1 Levy Place, 10029 New York, NY, United States of America.
E-mail address: paolo.cravedi@mssm.edu (P. Cravedi).

https://doi.org/10.1016/j.trre.2024.100839
Received 25 January 2024; Received in revised form 17 February 2024; Accepted 19 February 2024
Available online 21 February 2024

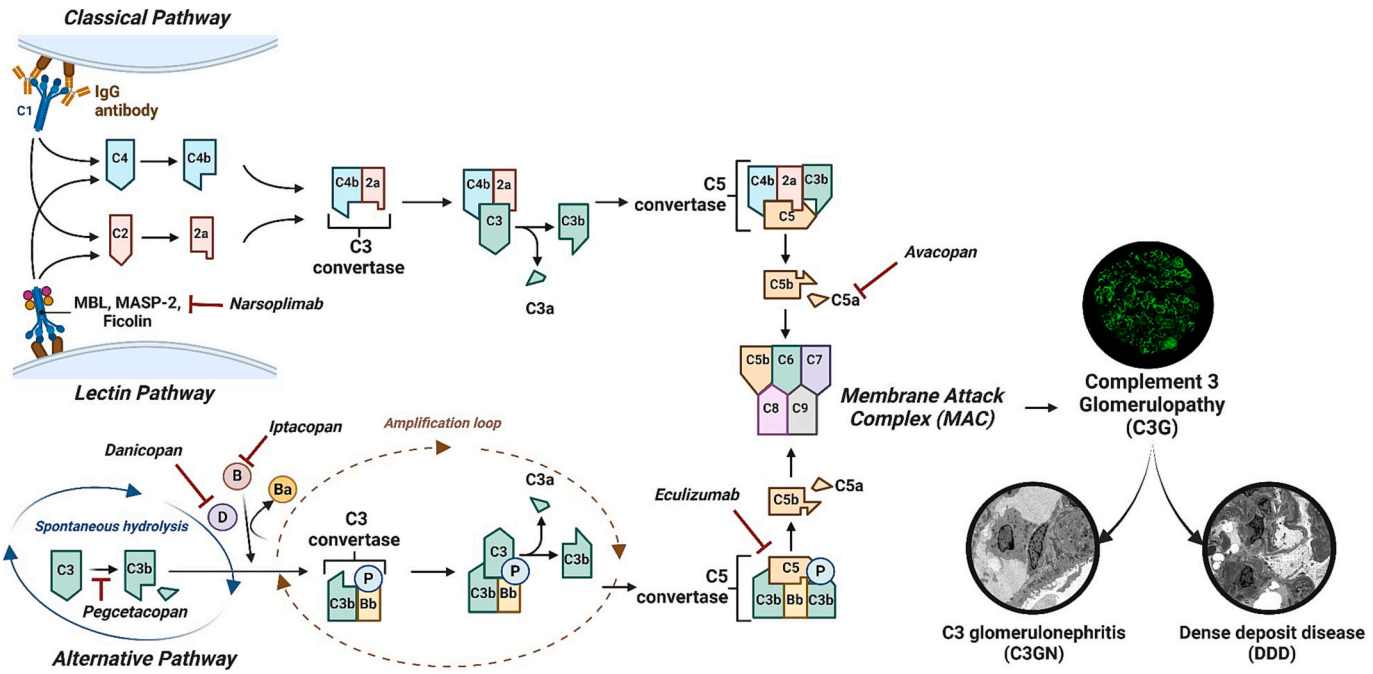

Fig. 1. Complement 3 glomerulopathy (C3G), its pathogenesis and potential therapeutic targets.
The complement system can be activated through three different pathways: the classical, lectin, and alternative pathways. The classical and lectin pathways are triggered when foreign agents or immune complexes are detected (e.g., MBL, MASP-2, ficolin). In contrast, the alternative pathway maintains a state of low-level activation through the spontaneous breakdown of C3 into the anaphylatoxin C3a and C3b (referred to as "tick over" by spontaneous hydrolysis). The production of C3b initiates the controlled formation of C3 convertase (C3bBb), which not only enhances the alternative pathway by generating more C3b through C3 cleavage but also facilitates the creation of C5 convertase (C3bBbC3b). C5 convertase, in turn, cleaves C5 to produce the anaphylatoxin C5a and C5b. C5b combines with other complement split products to form the membrane attack complex (MAC), known as C5b-9, which causes cell lysis and is directly associated with the pathogenesis of C3G. The alternative pathway is tightly regulated by complement activity regulators. However, in C3 glomerulopathy, this regulatory control becomes disrupted due to genetic or acquired defects in complement regulators or complement activators. Multiple innovative anti-complement therapies for C3Gare currently undergoing clinical trials, with their primary targets depicted in the figure. C3G can be divided in two subtypes: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). In C3GN, C3 fragment deposition and deposits with similar electron density to matrix components are present. On the other hand, in DDD the electron microscopy reveals highly electron-dense, sausage-shaped and osmiophilic deposits that promote thickening of the lamina densa of the glomerular basement membrane. Electron microscopy images retrieved from Pathology Outlines. This figure is created by BioRender.

60% to 86% and 55% to 86%, respectively [9].

2.2. C3 glomerulopathy classification

Initially described in 1965, DDD is characterized by dense intramembranous deposits [10]. The discovery of C3 nephritic factor (C3NeF), an antibody against Complement Factor H (CFH), along with familial cases of DDD, has led to the understanding that DDD results from dysregulation of the alternative complement pathway [11]. Concurrently, C3GN, characterized by proliferative glomerulonephritis with isolated C3 deposits but without dense deposits on electron microscopy, was proposed as a separate clinical entity. The recognition of genetic variants in complement-regulating genes in most C3GN cases [8] and familial nephritis in Cyprus due to CHFR5 gene mutations underscored the genetic underpinnings in this condition [12]. Thus, C3G, a new disease entity consisting of C3GN and DDD, was proposed in a 2013 consensus statement as complement-mediated nephropathy characterized by genetic and acquired abnormalities in the alternative pathway [5].

C3GN and DDD may present as membranoproliferative glomerulonephritis (MPGN), a glomerular injury pattern characterized by mesangial hypercellularity, endocapillary proliferation, and duplication of the glomerular basement membrane (GBM). In the past, MGPN cases were classified into three types based on EM findings: type I MPGN with immune deposits in the mesangium and subendothelial space, type III MPGN with immune deposits in subepithelial besides the subendothelial area, and type II MPGN (DDD) with highly dense deposits along the GBM [13]. However, MPGN can also be secondary to various underlying diseases, such as autoimmune disease, paraproteinemia, infectious disease, and thrombotic microangiopathy (TMA). In 2011, the IF-based classification was introduced to classify the disease based on the underlying etiology[14]. This classification divided MPGN mainly into immunocomplex-mediated MPGN (IC-MPGN), complement-mediated MPGN or C3G, and the no deposits group. Glomerular Ig and complement deposition characterize IC-MPGN, while C3G is characterized by dominant glomerular C3 deposition with little or no Ig deposition. This IF-based classification is based on the idea that immune complexes activate the classical complement pathway in IC-MPGN, resulting in the deposition of immune complex and C3 fragments in the glomeruli. In contrast, dysregulation of the alternative pathway in the fluid-phase plays a primary role in the development of C3G.

However, this classification does not clearly distinguish IC-MPGN and C3G based on pathophysiology. [15]. [16,17].

To further untangle this convoluted classification of the diseases, Iatropoulus et al. performed a cluster classification in which 173 patients with IC-MPGN and C3G were divided into four clusters based on histologic, genetic, and clinical data regarding serum and plasma complement parameters [17]. Clusters 1 and 2 were characterized by low C3 levels and high C5b-9, reflecting the activation of both the alternative and terminal complement pathways. What differentiated Cluster 1 from Cluster 2 is that Cluster 2 also demonstrated staining of C1q and IgG on IF, highlighting the involvement of the classical pathway. In contrast, Cluster 3, into which 84% of the patients with DDD were classified, was characterized by low C3 levels and normal or mildly increased C5b-9 levels, suggesting the dysregulation in the fluid-phase alternative pathway but not the terminal pathway. Cluster 4 was characterized by

bright C3 glomerular staining but normal C3 and C5b-9 levels. This cluster is less associated with complement gene mutations and autoantibodies than the other three. Of note, 6 of 7 patients diagnosed with C3G or IC-MPGN on the biopsy later presented with TMA, suggesting that the alternative pathway in the fluid-phase was considered unaffected, but abnormalities in the cell-membrane phase were suspected in Cluster 4 patients. This cluster analysis was validated by a different group, showing similar results [18]. This cluster classification may allow us to differentiate pathophysiology within the heterogeneous C3G/IC-MPGN entity.

2.3. Pathophysiology

2.3.1. The complement cascade

The complement system is essential to innate and adaptive immunity, killing pathogens, clearing immune complexes and apoptotic cells, and boosting the humoral response. This system comprises over 50 individual proteins or activation fragments to be activated in three pathways: the classical, lectin, and alternative pathways (Fig. 1). Activation of the classical pathway begins with the binding of C1q to an antibody attached to an antigen, activating C1r and C1s [19,20], which degrade C2 and C4 into C2a and C2b and C4a and C2b. C4b and C2a fragments form C4b2a, known as the C3 convertase [21]. The lectin pathway occurs without Ig involvement when mannose-binding lectin (MBL) or ficolins recognize pathogen-associated molecular patterns and then activate the MBL-associated serine proteases (MASPs), which in turn degrade C2 and C4 in the same fashion as the classical pathway [22,23]. Similarly, this process results in the formation of the C3 convertase (C4b2a).

In contrast to these two pathways, the alternative pathway starts with C3, which is continuously hydrolyzed to form C3(H_2O), an analog of C3b [24]. Once C3(H_2O) deposits on the cell membrane, it cleaves Complement Factor B (CFB) into Bb and Ba in the presence of Complement Factor D (CFD), resulting in the formation of C3(H_2O)Bb [25], the initial alternative pathway C3 convertase. This C3 convertase degrades C3 into C3a and C3b, which can bind to cell surfaces and from C3bBb [26], the dominant form of the alternative pathway C3 convertase. This complex is stabilized by properdin (P), further activating the complement pathway [27]. These two C3 convertases amplify the production of C3a and C3b [28]. C3a works as anaphylatoxins, triggering smooth muscle cell contraction and leukocyte recruitment and increasing the permeability of blood capillaries [29]. Extra C3b production can also lead to the formation of C5 convertase (C3bBbC3b/C4bC2aC3b), which cleaves C5 into C5a and C5b. C5a is also an anaphylatoxin. C5b forms the membrane attack complex (MAC or C5b-9) on the cell-membrane with C6, C7, C8, and several C9 molecules to lyse cellular membranes [30]. This final process is called the terminal pathway [31,32].

2.3.2. Regulation of complement activation

The alternative pathway, on standby in the bloodstream, is instantly activated to initiate a cascade of reactions when exposed to pathogens. This powerful system is carefully controlled by a wide array of regulators of complement activation (RCAs) to prevent self-damage [33].

CFH is composed of 20 short consensus repeat (SCR) domains. In the C-terminal of CFH, SCR 19 and 20 have a surface-binding role, whereas four SCRs in the N-terminal of CFH bind to C3b to prevent FB from forming C3 convertase. CFH also works as a cofactor for Complement Factor I (CFI), a serine protease that inactivates C3b into iC3b, which is unable to bind to FB [34]. Similarly, membrane cofactor protein (MCP) and decay-accelerating factor (DAF) work as cofactors for CFI-mediated cleavage of C3b on cell surfaces. In the glomeruli, the endothelial cells have membrane-bound RCAs, but the fenestrations between the glomerular endothelial cells lack these RCAs [35]. Thus, CFH is a pivotal regulator of complement activation in the glomerulus. Once C3b convertases are generated, CFH, DAF, and complement receptor 1 (CR1) accelerate their decay [35].

Complement Factor H-related proteins (CFHRs) are also involved in regulating the alternative pathway. There are five CFHRs: type 1 CFHRs (CFHR1, CFHR2, and CFHR5), which form homodimers or heterodimers, and type 2 CFHRs (CFHR3, CFHR4A, and CFHR4B) [36], which exist as a monomer in serum. Although CFH and CFHRs functionally compete due to these similarities, the function of each CFHR remains unclear [37,38]. Deletions, duplications, or hybrid genes induced by genetic rearrangements in CFHRs result in pathologic diseases such as aHUS and C3G [39].

2.3.3. Acquired factors

Dysregulation in the alternative complement pathway is considered the cause of C3G and is driven by genetic or acquired factors [7]. As acquired factors, C3NeF is the most commonly found autoantibody, which is reportedly identified in 50–80% of DDD patients and 44–50% of C3GN patients [16,37,40,41]. C3NeF IgG or IgM stabilize C3 convertase in the fluid-phase and extend its half-time, resulting in uncontrolled activation of the alternative pathway. Another antibody is the C5 nephritic factor (C5NeF), which stabilizes C5 convertase (C3bBbC3b) [42]. Less frequently, C4 nephritic factor (C4NeF) and autoantibodies against CFH and CFB are reported to cause C3G [43–45].

Monoclonal gammopathy is also associated with C3G. Ravindran et al. investigated 95 patients with C3G based on the presence and absence of monoclonal Ig [6]. In this study, 37.9% of patients were positive for monoclonal Ig. The most common autoantibody in patients with monoclonal Ig was C3NeF, which was detected in 45% of patients. Two patients showed CFH and CFHR genetic abnormalities. C3NeF was detected in 37% of patients without monoclonal Ig, and genetic abnormalities were found in 58.5% of patients with heterozygous mutations in the *CFH, C3*, *CFI*, *CFHR2*, and *CFHR5* genes. The marked difference in the detection rate of genetic testing between C3G with monoclonal Ig and without monoclonal Ig suggests that monoclonal Ig stimulates the activation of the alternative pathway. This theory is supported by the fact that renal function is preserved in patients who achieve hematologic remission [46].

2.3.4. Genetic abnormalities

Up to 25% of patients diagnosed with C3G have rare variants in genes involved in the alternative pathway, such as *C3*, *CFB*, *CFI*, and *CFFR* [7,8,47,48]. The *CFHR* region needs to be investigated by multiplex-ligation-dependent probe amplification to investigate genomic rearrangements since novel fusion genes are amongst the most common genetic abnormalities in C3G. The first found fusion genes by rearrangement came from Cypriot familial nephritis, named CFHR5 nephropathy. Duplication of exons in the *CFHR5* gene generates a novel CFHR5, resulting in complement activation [12,49]. Since this discovery, it has been reported that various cases of C3G are driven by a hybrid gene between *CFH-CFHR* or within *CFHR* and by duplication within *CFHR1* or *CFHR5* [50–53]. As with other examples of genetic mutations leading to C3G, a familial case of DDD induced by heterozygous C3 mutation was reported [54]. This mutated C3 cannot form C3b convertase except for the initial C3b convertase, C3(H_2O). C3(H_2O) is not degraded by CFH-mediated cleavage due to the mutation. Thus, it continuously degrades the wild-type C3 into C3b, activating the alternative pathway [55,56]. Several C3G from mutations in *CFH* are reported. Complete or functional loss of CFH due to mutations has also been reported to cause C3G. Homozygous nonsense and missense mutations in *CFH* result in an undetectable CFH level in the blood [57]. Homozygous mutation in *CFH* causing deletion of lysine in the area of SCR4 results in functional loss of CFH, although CFH is detectable in the blood [58]. These mutations were responsible for unregulated C3 consumption and activation of the alternative pathway.

2.4. Treatment of recurrent C3G after transplantation

C3G is one of the most frequently recurrent forms of

Table 1
Epidemiology of C3 glomerulopathy (C3G) recurrence after kidney transplant.

Author and year	Number of C3G transplant patients	Time to recurrence	C3G recurrence rate	Graft loss due to C3G recurrence	Complement abnormality or genetic mutation	Study design
Caravaca-Fontán et al., 2023 [1]	34	14 months	62%	35%	10 variants were considered pathogenic (29%, 4 in the *C3* gene, 3 in the *CHF*, 1 in the *CFB*, 1 in the *CFHR1,* and 1 in the *CFHR5*) and 1 as a variant of unknown significance (3%), whereas in 8 patients no genetic abnormalities were found (24%). 4 (11.7%) had C3NeF	Retrospective cohort
Regunathan-Shenk et al., 2019 [9]	19 (7 DDD and 12 C3GN)	14–15 months	68.4%	76.9%	6 (31.6%) patients had C3NeF, 3 (15.7%) patients had pathogenic variants (*CD46*, *CFHR5*, *CFI*)	Case series
Ravindran et al. 2019 [6]	6 (1 DDD and 5 C3GN)	22.6 and 38.8 months, respectively (only two recurrent cases)	33.3%	–	No information on pathogenic variants for recurrent patients, only for all C3G patients	Retrospective cohort
Kumar et al., 2019 [89]	18 (9 DDD and 9 C3GN)	3 days	50%	11.1%	No information on pathogenic variants for recurrent patients, only for all C3G patients	Retrospective cohort
Frangou et al., 2019 [2]	17	165 ± 59 months	29.4%	15.5%	All patients had pathologic variants of the *CFHR5* gene	Retrospective cohort
Wong et al., 2016 [59]	5	0.5 to 101 months	60%	40%	All patients had hybrid *CFHR3–1* gene	Case series – all patients are from the same family
Alasfar et al., 2016 [60]	5	–	40%	50%	–	Only C3GN patients Retrospective cohort
Zand et al., 2014 [61]	21	2.3 years	66.7%	50%	–	Only C3GN patients Retrospective cohort
Le Quintrec et al., 2013 [62]	15	–	33.3%	20%	–	Only DDD patients Case series
Andresdottir et al., 1999 [63]	13	2.9 months	84.6%	72.7%	–	Only DDD patients Retrospective cohort
Droz et al., 1979 [64]	11	–	81.8%	–	–	Only DDD patients Retrospective cohort

C3G: C3 glomerulopathy; C3GN: C3 glomerulonephritis; DDD: dense deposit disease; C3NeF: C3 Nephritic Factor.

glomerulonephritis after kidney transplantation, leading to graft loss. As C3G represents a relatively new medical condition, the studies on C3G recurrence after transplant are still limited.. (Table 1) [1–3,6,9,59–64].

Zand et al. identified 21 patients who underwent kidney transplantation due to C3GN. The median time to develop kidney failure or undergo kidney transplantation from diagnosis was 32 months. Seven patients did not have recurrence C3GN after a median post-transplant follow-up period of 162 months, while 14 patients (66.7%) developed recurrent C3GN with a median time from transplantation to recurrence of 28 months (ranging from 9 days to over 11 years), and 7 out of them (50%) developed lost their graft. The limitation of this study is that the population includes patients with and without monoclonal gammopathy, indicative of a heterogeneous population [61].

In a small cohort study, Servais et al. reported a recurrence rate after transplantation of 60% in both DDD and C3GN patients (6 out of 10 in DDD and 6 out of 10 in C3GN), but the median follow-up period was not reported [8]. Shenk et al. reported a similar case series of 19 patients (12 of C3GN and 7 of DDD) who underwent transplantation due to C3G. Of those, 16 patients (84%) developed recurrent disease with a median time after transplantation of 14 months in C3GN and 15 months in DDD. The overall graft failure rate was 47% over the median follow-up period of 76 months, ranging from 9 to 203 months [9]. Fernando et al. performed the largest multicenter retrospective cohort of 220 patients who underwent kidney transplantation due to MPGN in 11 hospitals. 21 out of 34 patients diagnosed with complement-mediated MPGN developed recurrence disease, which is a higher rate of recurrence in comparison with IC-MPGN (62% and 18%, respectively; 10/100 versus 2/100 patient-years, respectively). Furthermore, 12 out of 21 patients (57%) had graft loss [65].

In summary, C3G has a high risk of recurrence after kidney transplantation (60% to 84%), and almost half of the patients with recurrent disease have accelerated graft loss. Nevertheless, it is essential to note thatlarger studies are needed to accurately define the incidence of disease recurrence in this population.

2.4.1. MMF and steroids

In native C3G, a combination of MMF and steroids can be effective, but this approach tends to be less effective in managing recurrent C3G after transplant, given that patients recur even when treated with those immunosuppressive agents used to prevent rejection. A case series from Mayo Clinic reported that most patients between 1996 and 2010 showed that, despite ongoing MMF and steroids, the rate of graft loss in patients with recurrent disease is about 50% [61]. Shenk et al. reported a case series on recurrent C3G after transplant [9]. In this report, patients were treated by increasing the dose of MMF, adding steroids, or changing the CNI to belatacept, besides eculizumab and plasma exchange. However, 10 out of 16 patients with recurrent C3G after transplantation developed graft failure. Overall, the outcomes using MMF and steroids to treat C3G are disappointing, suggesting that additional treatments for recurrent disease are needed.

2.4.2. Eculizumab

Eculizumab, a C5 blocking antibody, has shown promising results in treating native kidney C3 glomerulopathy (C3G) and recurrent C3G post-transplant [9,66–69]. Bomback et al. reported that three patients treated with eculizumab for recurrent C3G exhibited improved kidney function, reduced proteinuria, and decreased C5b-9 levels, although one patient experienced a relapse after discontinuing treatment [66]. Shenk et al. found varied responses; out of seven treated patients, four responded positively, but the remaining three suffered re-transplantation or kidney failure [9]. A systematic review of 12 studies involving 122 patients with post-transplant recurrent C3G revealed that the graft loss rate was 33% with eculizumab, 42% with plasma exchange, and 81% with rituximab [70]. Of note, 80% of the patients who responded to treatment exhibited initially increased C5b-9 levels, which normalized post-treatment [70]. In a case report by

Table 2
Complement inhibitors for C3 glomerulopathy (C3G) recurrence after kidney transplant.

Treatment	Mechanism of action	Status
Eculizumab	Long-acting humanized monoclonal antibody targeted against complement C5, inhibiting the cleavage of C5 into C5a and C5b and preventing the formation of MAC	Approved, potential treatment for crescentic rapidly progressive C3 glomerulopathy and has been tested in transplant recipients [67–69,90–95].
Pegcetacoplan	Cyclic peptide related to compstatin, which blocks C3, preventing the generation of C3b and subsequent C3b loading of the red blood cells	Ongoing phase III. Phase II with positive results, showing the reduction in proteinuria with stabilized creatinine [82].
Iptacopan	Selective inhibitor of CFB, which is essential to form C3 convertase and C5 convertase	Shown to reduce proteinuria and to improve eGFR in native C3G [73]. Ongoing phase II for kidney transplant recipients [74].
Danicopan	CFD inhibitor that prevents CFD cleavage of factor B from forming C3 convertase	Phase II published for native C3G, limited clinical response [76].
Avacopan	Anti-C5a receptor antagonist, blocking the effect of C5a	Phase II was published for native C3G, with mild improvement of C3HI, but still no data on clinical improvement [79].
Narsoplimab	Monoclonal antibody to MASP-2, blocking the activation of the lectin pathway	Ongoing phase II for native C3G, still pending data [86].

C3G: Complement 3 glomerulopathy; CFB: Complement Factor B; CFD: Complement Factor D; MAC: membrane attack complex; MASP-2: mannose-binding protein-associated serine protease 2.

Gurkan et al., a patient with recurrent C3G with positive C3NeF showed renal function recovery with eculizumab treatment. However, despite the improvement in renal function, kidney biopsies at six and twelve months after treatment displayed persistent MPGN patterns with mild worsening of chronic changes such as fibrosis. These findings led the authors to suggest that eculizumab might be more effective in patients with elevated C5b-9 and low or no C3NeF activity [69].

In conclusion, eculizumab is a promising treatment option for recurrent C3G after transplant. However, it remains unclear which patients will effectively respond to eculizumab, partly due to the heterogeneous nature of C3G. Advances in understanding the pathophysiology of the disease are expected to lead to more tailored treatments based on the specific complement abnormalities in individual patients. There is also anticipation for improved treatment outcomes with emerging drugs targeting the upstream complement pathway, which are currently in clinical trials.

2.4.3. Plasma exchange

The efficacy of plasmapheresis for recurrent C3G after transplant varies. Kurtz et al. reported a 15-year-old girl with a history of DDD who experienced recurrent C3G three months after the transplantation. C3NeF activity was strongly positive, and plasma exchange was performed for 63 weeks, maintaining her kidney function [71]. Similarly, Kumar et al. reported the outcomes of plasma exchange in four patients with early recurrent C3G after kidney transplantation. All four patients displayed positive autoantibodies against regulators of the complement pathway. Among these patients, plasma exchange was effective in 50% of the cases (two out of four), while the remaining two experienced graft loss. Notably, one patient who initially responded to plasma exchange faced a relapse of the disease upon cessation of the treatment, a decision driven by financial limitations [3]. Conversely, several cases or cohort studies showed a lack of responsiveness to plasma exchange [9,63,72] and a meta-analysis showed that 42% of post-transplant patients treated with plasma exchange developed graft loss [70].

It is difficult to fully evaluate the efficacy of plasma exchange since patients receive steroid pulses or rituximab besides plasma exchange in most cases. Nevertheless, plasma exchange is worth considering for treating C3G recurrence, especially in cases with pathogenic antibodies, such as C3NeF, in the circulation.

2.4.4. Rituximab

The efficacy of rituximab, a B cell depleting antibody, seems limited in C3G treatment. The evidence primarily comes from case series and observational studies with mixed outcomes. Zand et al. conducted an observational study on C3GN post-transplant recurrence, where rituximab was administered in three cases. Of these, only one case showed a positive response to the treatment, while the remaining two led to graft loss [61]. Similarly, Shenk et al. reported the use of rituximab in recurrent C3G post-transplant cases, all of which were positive for C3NeF or Anti-Factor-H antibodies, yet resulted in graft loss [9]. Furthermore, no reports support the efficacy of rituximab in preventing recurrent C3G after transplant when administered at the time of transplantation.

2.4.5. New complement-targeting therapies

As a complement-targeting treatment, eculizumab was expected to have a better therapeutic effect on C3G than conventional immunosuppressive agents. However, eculizumab does not inhibit the activation of C3, which is a critical factor in the pathogenesis of C3G. This may account for the poor therapeutic responses to eculizumab in a subset of patients. Various new complement inhibitors against the upstream complement pathway are being tested in ongoing clinical trials (Table 2).

Iptacopan is an oral selective inhibitor of CFB. CFB is degraded by CFD to a serine protease domain (Bb), forming a component of C3 convertase (C3bBb) and C5 convertase (C5bBbC5b). The phase II trial of iptacopan for C3G enrolled two cohorts: (1) patients with C3G and (2) post-transplant patients with recurrent C3G. Iptacopan was shown to reduce proteinuria by 45% and to improve eGFR in patients with native C3G after 84 days of treatment. For recurrent C3G after transplant, the median C3 deposit score decreased from baseline (3.0) to day 84 (0.5) (80% confidence interval − 3.75, −0.75; $P = 0.03$). Sustained normalization of serum C3 levels was also observed in most patients [73]. The APPEAR-C3G trial is ongoing; it is a randomized, double-blind, and placebo-controlled trial. The study will enroll 68 native adult C3G patients [74]. The results of this trial may help in future decision-making regarding C3G treatment.

Danicopan is a small-molecule inhibitor of CFD that prevents CFD cleavage of CFB, inhibiting the alternative pathway C3 convertase formation [75]. Two phase II proof-of-concept clinical studies with patients with native C3G and IC-MPGN were recently conducted to evaluate a change from baseline in biopsy score and a reduction of proteinuria as the primary outcome. However, danicopan did not inhibit the alternative pathway sufficiently, leading to limited clinical response [76]. None of the patients treated with danicopan had a significant change in proteinuria or eGFR, and most presented severe adverse events.

Pelecopan (BCx9930), another small molecule CFD inhibitor, was tested in a phase II trial (RENEW trial) enrolling 42 patients with native complement-mediated kidney diseases, including C3G, IgA nephritis, and primary membranous nephropathy [77]. However, this trial was discontinued for commercial reasons.

Avacopan is an oral anti-C5a receptor antagonist. After excellent results in a trial with ANCA-vasculitis patients [78], avacopan was evaluated in ACCOLADE trial, a phase II trial enrolling 57 patients with native C3G. The primary outcome was a C3 histological index (C3HI) change at week 24. The mean change from baseline in the C3HI was 0.8% with C3G vs. 1.6% with placebo ($P = 0.04$), indicating that avacopan attenuated C3G progression [79]. Nonetheless, there were no significant changes in proteinuria and eGFR between the study groups (NCT03301467) [80].

Table 3
Treatment for C3 glomerulopathy (C3G) recurrence after kidney transplant.

	Mild disease	Moderate disease	Severe disease
Definition	Stable eGFR with proteinuria <1.5/day	eGFR slowly declining or proteinuria between 1.5 and 3.5 g/day	Rapidly declining eGFR or proteinuria >3.5 g/day
Treatment	Supportive treatment (ACEi or ARBs for proteinuria and hypertension, statins for cardiovascular risk)	Treatment based on specific causes of complement dysregulation (e.g., eculizumab)	MMF (1500 mg orally twice a day) with glucocorticoids (intravenous methylprednisolone 500 mg daily for three days followed by oral prednisone, 1 mg/kg/day with a maximum dose of 60 mg per day) Eculizumab, rituximab, or plasma exchange can be used on a case-by-case basis (e.g., patients with autoantibodies or complement gene variants)
Goal	Decrease proteinuria to <1 g/d and BP of <130/80 mmHg	Decrease proteinuria to <1 g/d and BP of <130/80 mmHg	Until remission or for a maximum of 12 weeks

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker (ARB); BP: blood pressure; eGFR: estimated glomerular filtration rate; MMF: mycophenolate mofetil.

Pegcetacoplan (APL-2) is a cyclic peptide C3 inhibitor that can bind to C3 and C3b, a C3 and C5 convertase component, inhibiting the activation of the alternative and the terminal pathways [81]. A phase 2 open-label study evaluated the efficacy and safety of pegcetacoplan in patients with complement-mediated glomerulopathies, including 8 patients with C3G. The study showed a 65% reduction in proteinuria with stabilized creatinine [82]. The VALIANT phase 3 study, a randomized, placebo-controlled, double-blinded, multicenter study, is underway to evaluate pegcetacoplan efficacy and safety in 90 patients aged 12 or older with primary IC-MPGN or C3G. The primary endpoint of this study is a reduction in proteinuria >50% at weeks 26 and 52 compared to baseline (NCT03301467) [83]. The NOBLE phase II study, an open-label randomized controlled study, is underway, enrolling 12 patients with recurrent C3G or IC-MPGN after transplantation. The primary outcome endpoint is to evaluate the efficacy of reducing C3c staining on renal biopsy after 12 weeks of treatment and reduction of C3 staining on biopsy at 52 weeks (NCT04572854) [84]. To date, no results from this trial in transplant patients have been published.

Narsoplimab (OMS721) is a humanized monoclonal antibody to MASP-2 (mannose-binding protein-associated serine protease 2), which inhibits the lectin pathway [85]. Underway is a phase II trial enrolling patients with native C3G, IgA nephropathy, lupus nephritis, and membranous nephropathy to evaluate the safety and effect on proteinuria of narsoplimab (NCT02682407) [86].

The rarity of the disease results in limited participants in clinical trials and an even smaller number in post-transplant patients. Nevertheless, it is anticipated that as the efficacy of native C3G becomes more established, clinical trials dedicated to transplant patients will also advance.

3. Conclusion

Managing recurrent C3G after transplant presents significant challenges. Table 3 is derived from expert consensus and guidelines, summarizing the discussed treatments in this review. [6,87,88].

The recurrence of C3G post-transplant often occurs despite ongoing immunosuppression, limiting the choice of therapeutic options. C3G is a heterogeneous group of diseases, and it is not yet clear which patients will benefit from treatments like eculizumab or plasma exchange. The lack of consistent efficacy in patients treated with eculizumab underscores the importance of targeting upstream components of the alternative pathway. There is growing anticipation for new drugs targeting the complement pathway, which is currently under development.

Declaration of competing interest

Paolo Cravedi reports financial support was provided by Chinook Therapeutics Inc. for consulting and research projects. Paolo Cravedi is associate Editor for Transplantation Reviews and American Journal of Transplantation. The other authors have no relevant conflicts of interest to declare.

References

[1] Caravaca-Fontán F, Polanco N, Villacorta B, Buxeda A, Coca A, Ávila A, et al. Recurrence of immune complex and complement-mediated membranoproliferative glomerulonephritis in kidney transplantation. Nephrol Dial Transplant 2023;38:222–35. https://doi.org/10.1093/ndt/gfac148.
[2] Frangou E, Varnavidou-Nicolaidou A, Petousis P, Soloukides A, Theophanous E, Savva I, et al. Clinical course and outcome after kidney transplantation in patients with C3 glomerulonephritis due to CFHR5 nephropathy. Nephrol Dial Transplant 2019;34:1780–8. https://doi.org/10.1093/ndt/gfz021.
[3] Kumar A, Bharati J, Nada R, Singh S, Sharma A, Gupta K, et al. Utility of plasma exchange in early recurrent C3 glomerulopathy. Indian J Transplant 2019;13:122. https://doi.org/10.4103/ijot.ijot_78_18.
[4] Legendre CM, Licht C, Muus P, Greenbaum LA, Babu S, Bedrosian C, et al. Terminal complement inhibitor Eculizumab in atypical hemolytic–uremic syndrome. N Engl J Med 2013;368:2169–81. https://doi.org/10.1056/NEJMoa1208981.
[5] Pickering MC, D'Agati VD, Nester CM, Smith RJ, Haas M, Appel GB, et al. C3 glomerulopathy: consensus report. Kidney Int 2013;84:1079–89. https://doi.org/10.1038/ki.2013.377.
[6] Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S. C3 glomerulopathy: 10-years experience at the Mayo Clinic. Mayo Clin Proc 2018;93:991–1008. https://doi.org/10.1016/j.mayocp.2018.05.019.
[7] Smith RJH, Appel GB, Blom AM, Cook HT, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy — understanding a rare complement-driven renal disease. Nat Rev Nephrol 2019;15:129–43. https://doi.org/10.1038/s41581-018-0107-2.
[8] Servais A, Noël L-H, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey M-A, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int 2012;82:454–64. https://doi.org/10.1038/ki.2012.63.
[9] Regunathan-Shenk R, Avasare RS, Ahn W, Canetta PA, Cohen DJ, Appel GB, et al. Kidney transplantation in C3 glomerulopathy: a case series. Am J Kidney Dis 2019;73:316–23. https://doi.org/10.1053/j.ajkd.2018.09.002.
[10] Habib R, Gubler M-C, Loirat C, Maïz HB, Levy M. Dense deposit disease: a variant of membranoproliferative glomerulonephritis. Kidney Int 1975;7:204–15. https://doi.org/10.1038/ki.1975.32.
[11] Smith RJH, Alexander J, Barlow PN, Botto M, Cassavant TL, Cook HT, et al. New approaches to the treatment of dense deposit disease. J Am Soc Nephrol 2007;18:2447–56. https://doi.org/10.1681/ASN.2007030356.
[12] Gale DP, de Jorge EG, Cook HT, Martinez-Barricarte R, Hadjisavvas A, McLean AG, et al. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis. Lancet 2010;376:794–801. https://doi.org/10.1016/S0140-6736(10)60670-8.
[13] Ferrario F, Rastaldi MP. Histopathological atlas of renal diseases. Membranoproliferative glomerulonephritis. J Nephrol 2004;17:483–6.
[14] Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. Semin Nephrol 2011;31:341–8. https://doi.org/10.1016/j.semnephrol.2011.06.005.
[15] Hou J, Markowitz GS, Bomback AS, Appel GB, Herlitz LC, Barry Stokes M, et al. Toward a working definition of C3 glomerulopathy by immunofluorescence. Kidney Int 2014;85:450–6. https://doi.org/10.1038/ki.2013.340.
[16] Iatropoulos P, Noris M, Mele C, Piras R, Valoti E, Bresin E, et al. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. Mol Immunol 2016;71:131–42. https://doi.org/10.1016/j.molimm.2016.01.010.
[17] Iatropoulos P, Daina E, Curreri M, Piras R, Valoti E, Mele C, et al. Cluster analysis identifies distinct pathogenetic patterns in C3 glomerulopathies/immune complex–mediated membranoproliferative GN. J Am Soc Nephrol 2018;29:283–94. https://doi.org/10.1681/ASN.2017030258.
[18] Garam N, Prohászka Z, Szilágyi Á, Aigner C, Schmidt A, Gaggl M, et al. Validation of distinct pathogenic patterns in a cohort of membranoproliferative glomerulonephritis patients by cluster analysis. Clin Kidney J 2020;13:225–34. https://doi.org/10.1093/ckj/sfz073.

[19] Bally I, Rossi V, Lunardi T, Thielens NM, Gaboriaud C, Arlaud GJ. Identification of the C1q-binding sites of human C1r and C1s: a refined three-dimensional model of the C1 complex of complement. J Biol Chem 2009;284:19340–8. https://doi.org/10.1074/jbc.M109.004473.
[20] Brier S, Pflieger D, Le Mignon M, Bally I, Gaboriaud C, Arlaud GJ, et al. Mapping surface accessibility of the C1r/C1s tetramer by chemical modification and mass spectrometry provides new insights into assembly of the human C1 complex. J Biol Chem 2010;285:32251–63. https://doi.org/10.1074/jbc.M110.149112.
[21] Krishnan V, Xu Y, Macon K, Volanakis JE, Narayana SVL. The structure of C2b, a fragment of complement component C2 produced during C3 convertase formation. Acta Crystallogr D Biol Crystallogr 2009;65:266–74. https://doi.org/10.1107/S0907444909000389.
[22] Frederiksen PD, Thiel S, Larsen CB, Jensenius JC. M-ficolin, an innate immune defence molecule, binds patterns of acetyl groups and activates complement. Scand J Immunol 2005;62:462–73. https://doi.org/10.1111/j.1365-3083.2005.01685.x.
[23] Krarup A, Thiel S, Hansen A, Fujita T, Jensenius JC. L-ficolin is a pattern recognition molecule specific for acetyl groups. J Biol Chem 2004;279:47513–9. https://doi.org/10.1074/jbc.M407161200.
[24] Pangburn MK, Schreiber RD, Müller-Eberhard HJ. Formation of the initial C3 convertase of the alternative complement pathway. Acquisition of C3b-like activities by spontaneous hydrolysis of the putative thioester in native C3. J Exp Med 1981;154:856–67. https://doi.org/10.1084/jem.154.3.856.
[25] Isenman DE, Kells DI, Cooper NR, Müller-Eberhard HJ, Pangburn MK. Nucleophilic modification of human complement protein C3: correlation of conformational changes with acquisition of C3b-like functional properties. Biochemistry 1981;20:4458–67. https://doi.org/10.1021/bi00518a034.
[26] Milder FJ, Gomes L, Schouten A, Janssen BJC, Huizinga EG, Romijn RA, et al. Factor B structure provides insights into activation of the central protease of the complement system. Nat Struct Mol Biol 2007;14:224–8. https://doi.org/10.1038/nsmb1210.
[27] Fearon DT, Austen KF. Properdin: binding to C3b and stabilization of the C3b-dependent C3 convertase. J Exp Med 1975;142:856–63. https://doi.org/10.1084/jem.142.4.856.
[28] Lachmann PJ. The amplification loop of the complement pathways. Adv Immunol 2009;104:115–49. https://doi.org/10.1016/S0065-2776(08)04004-2.
[29] Shivshankar P, Li Y-D, Mueller-Ortiz SL, Wetsel RA. In response to complement anaphylatoxin peptides C3a and C5a, human vascular endothelial cells migrate and mediate the activation of B-cells and polarization of T-cells. FASEB J 2020;34:7540–60. https://doi.org/10.1096/fj.201902397R.
[30] Bubeck D. The making of a macromolecular machine: assembly of the membrane attack complex. Biochemistry 2014;53:1908–15. https://doi.org/10.1021/bi500157z.
[31] Dunkelberger JR, Song W-C. Complement and its role in innate and adaptive immune responses. Cell Res 2010;20:34–50. https://doi.org/10.1038/cr.2009.139.
[32] Bexborn F, Andersson PO, Chen H, Nilsson B, Ekdahl KN. The tick-over theory revisited: formation and regulation of the soluble alternative complement C3 convertase (C3(H2O)bb). Mol Immunol 2008;45:2370–9. https://doi.org/10.1016/j.molimm.2007.11.003.
[33] Łukawska E, Polcyn-Adamczak M, Niemir ZI. The role of the alternative pathway of complement activation in glomerular diseases. Clin Exp Med 2018;18:297–318. https://doi.org/10.1007/s10238-018-0491-8.
[34] Lambris JD, Lao Z, Oglesby TJ, Atkinson JP, Hack CE, Becherer JD. Dissection of CR1, factor H, membrane cofactor protein, and factor B binding and functional sites in the third complement component. J Immunol 1996;156:4821–32.
[35] Merle NS, Church SE, Fremeaux-Bacchi V, Roumenina LT. Complement system part I – Molecular mechanisms of activation and regulation. Front Immunol 2015;6.
[36] Skerka C, Chen Q, Fremeaux-Bacchi V, Roumenina LT. Complement factor H related proteins (CFHRs). Mol Immunol 2013;56:170–80. https://doi.org/10.1016/j.molimm.2013.06.001.
[37] Heiderscheit AK, Hauer JJ, Smith RJH. C3 glomerulopathy: understanding an ultra-rare complement-mediated renal disease. Am J Med Genet C Semin Med Genet 2022;190:344–57. https://doi.org/10.1002/ajmg.c.31986.
[38] Poppelaars F, Goicoechea de Jorge E, Jongerius I, Baeumner AJ, Steiner M-S, Józsi M, et al. A family affair: addressing the challenges of factor H and the related proteins. Front Immunol 2021;12:660194. https://doi.org/10.3389/fimmu.2021.660194.
[39] Piras R, Breno M, Valoti E, Alberti M, Iatropoulos P, Mele C, et al. CFH and CFHR copy number variations in C3 glomerulopathy and immune complex-mediated membranoproliferative glomerulonephritis. Front Genet 2021;12:670727. https://doi.org/10.3389/fgene.2021.670727.
[40] Servais A, Noël L-H, Roumenina LT, Le Quintrec M, Ngo S, Dragon-Durey M-A, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. Kidney Int 2012;82:454–64. https://doi.org/10.1038/ki.2012.63.
[41] Zhang Y, Meyer NC, Wang K, Nishimura C, Frees K, Jones M, et al. Causes of alternative pathway dysregulation in dense deposit disease. Clin J Am Soc Nephrol 2012;7:265–74. https://doi.org/10.2215/CJN.07900811.
[42] Marinozzi M-C, Chauvet S, Le Quintrec M, Mignotet M, Petitprez F, Legendre C, et al. C5 nephritic factors drive the biological phenotype of C3 glomerulopathies. Kidney Int 2017;92:1232–41. https://doi.org/10.1016/j.kint.2017.04.017.
[43] Marinozzi MC, Roumenina LT, Chauvet S, Hertig A, Bertrand D, Olagne J, et al. Anti-factor B and anti-C3b autoantibodies in C3 glomerulopathy and Ig-associated membranoproliferative GN. J Am Soc Nephrol 2017;28:1603. https://doi.org/10.1681/ASN.2016030343.
[44] Zhang Y, Meyer NC, Fervenza FC, Lau W, Keenan A, Cara-Fuentes G, et al. C4 nephritic factors in C3 glomerulopathy: a case series. Am J Kidney Dis 2017;70:834–43. https://doi.org/10.1053/j.ajkd.2017.07.004.
[45] Blanc C, Togarsimalemath SK, Chauvet S, Le Quintrec M, Moulin B, Buchler M, et al. Anti-factor H autoantibodies in C3 glomerulopathies and in atypical hemolytic uremic syndrome: one target, two diseases. J Immunol 2015;194:5129–38. https://doi.org/10.4049/jimmunol.1402770.
[46] Chauvet S, Frémeaux-Bacchi V, Petitprez F, Karras A, Daniel L, Burtey S, et al. Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy–associated C3 glomerulopathy. Blood 2017;129:1437–47. https://doi.org/10.1182/blood-2016-08-737163.
[47] Iatropoulos P, Noris M, Mele C, Piras R, Valoti E, Bresin E, et al. Complement gene variants determine the risk of immunoglobulin-associated MPGN and C3 glomerulopathy and predict long-term renal outcome. Mol Immunol 2016;71:131–42. https://doi.org/10.1016/j.molimm.2016.01.010.
[48] Bu F, Borsa NG, Jones MB, Takanami E, Nishimura C, Hauer JJ, et al. High-throughput genetic testing for thrombotic microangiopathies and C3 glomerulopathies. J Am Soc Nephrol 2016;27:1245–53. https://doi.org/10.1681/ASN.2015040385.
[49] Malik TH, Gitterman DP, Lavin DP, Lomax-Browne HJ, Hiemeyer EC, Moran LB, et al. Gain-of-function factor H–related 5 protein impairs glomerular complement regulation resulting in kidney damage. Proc Natl Acad Sci U S A 2021;118:e2022722118. https://doi.org/10.1073/pnas.2022722118.
[50] Togarsimalemath SK, Sethi SK, Duggal R, Le Quintrec M, Jha P, Daniel R, et al. A novel CFHR1-CFHR5 hybrid leads to a familial dominant C3 glomerulopathy. Kidney Int 2017;92:876–87. https://doi.org/10.1016/j.kint.2017.04.025.
[51] Tortajada A, Yébenes H, Abarrategui-Garrido C, Anter J, García-Fernández JM, Martínez-Barricarte R, et al. C3 glomerulopathy–associated *CFHR1* mutation alters FHR oligomerization and complement regulation. J Clin Invest 2013;123:2434–46. https://doi.org/10.1172/JCI68280.
[52] Malik TH, Lavin PJ, Goicoechea de Jorge E, Vernon KA, Rose KL, Patel MP, et al. A hybrid CFHR3-1 gene causes familial C3 glomerulopathy. J Am Soc Nephrol 2012;23:1155–60. https://doi.org/10.1681/ASN.2012020166.
[53] Márquez-Tirado B, Gutiérrez-Tenorio J, Tortajada A, Lucientes Continente L, Caravaca-Fontán F, Malik TH, et al. Factor H-related protein 1 drives disease susceptibility and prognosis in C3 glomerulopathy. J Am Soc Nephrol 2022;33:1137–53. https://doi.org/10.1681/ASN.2021101318.
[54] Martínez-Barricarte R, Heurich M, Valdes-Cañedo F, Vazquez-Martul E, Torreira E, Montes T, et al. Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. J Clin Invest 2010;120:3702–12. https://doi.org/10.1172/JCI43343.
[55] Martínez-Barricarte R, Heurich M, Valdes-Cañedo F, Vazquez-Martul E, Torreira E, Montes T, et al. Human C3 mutation reveals a mechanism of dense deposit disease pathogenesis and provides insights into complement activation and regulation. 2010. https://doi.org/10.1172/JCI43343.
[56] Noris M, Remuzzi G. Glomerular diseases dependent on complement activation, including atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis, and C3 glomerulopathy: Core curriculum 2015. Am J Kidney Dis 2015;66:359–75. https://doi.org/10.1053/j.ajkd.2015.03.040.
[57] Dragon-Durey M-A, Frémeaux-Bacchi V, Loirat C, Blouin J, Niaudet P, Deschenes G, et al. Heterozygous and homozygous factor H deficiencies associated with hemolytic uremic syndrome or membranoproliferative glomerulonephritis: report and genetic analysis of 16 cases. J Am Soc Nephrol 2004;15:787. https://doi.org/10.1097/01.ASN.0000115702.28859.A7.
[58] Licht C, Heinen S, Józsi M, Löschmann I, Saunders RE, Perkins SJ, et al. Deletion of Lys224 in regulatory domain 4 of factor H reveals a novel pathomechanism for dense deposit disease (MPGN II). Kidney Int 2006;70:42–50. https://doi.org/10.1038/sj.ki.5000269.
[59] Wong L, Moran S, Lavin PJ, Dorman AM, Conlon PJ. Kidney transplant outcomes in familial C3 glomerulopathy. Clin Kidney J 2016;9:403–7. https://doi.org/10.1093/ckj/sfw020.
[60] Alasfar S, Carter-Monroe N, Rosenberg AZ, Montgomery RA, Alachkar N. Membranoproliferative glomerulonephritis recurrence after kidney transplantation: using the new classification. BMC Nephrol 2016;17:7. https://doi.org/10.1186/s12882-015-0219-x.
[61] Zand L, Lorenz EC, Cosio FG, Fervenza FC, Nasr SH, Gandhi MJ, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. J Am Soc Nephrol 2014;25:1110. https://doi.org/10.1681/ASN.2013070715.
[62] Le Quintrec M, Rabant M, Marinozzi C, Kamar N, Buchler M, Mousson C, et al. Uncontrolled pathways activation after renal transplantation and C5B9 deposits on graft predict graft outcome in adult renal transplant with C3 glomerulopathy. Transpl Int 2013;26. WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030–5774, NJ USA. (p. 9–9).
[63] Andresdottir MB, Assmann KJ, Hoitsma AJ, Koene RA, Wetzels JF. Renal transplantation in patients with dense deposit disease: morphological characteristics of recurrent disease and clinical outcome. Nephrol Dial Transplant 1999;14:1723–31. https://doi.org/10.1093/ndt/14.7.1723.
[64] Droz D, Nabarra B, Noel LH, Leibowitch J, Crosnier J. Recurrence of dense deposits in transplanted kidneys: I. Sequential survey of the lesions. Kidney Int 1979;15:386–95. https://doi.org/10.1038/ki.1979.50.
[65] Caravaca-Fontán F, Lucientes L, Serra N, Cavero T, Rodado R, Ramos N, et al. C3 glomerulopathy associated with monoclonal gammopathy: impact of chronic histologic lesions and beneficial effects of clone-targeted therapies. Nephrol Dial Transplant 2022;37:2128–37. https://doi.org/10.1093/ndt/gfab302.

[66] Bomback AS, Smith RJ, Barile GR, Zhang Y, Heher EC, Herlitz L, et al. Eculizumab for dense deposit disease and C3 glomerulonephritis. Clin J Am Soc Nephrol 2012; 7:748–56. https://doi.org/10.2215/CJN.12901211.
[67] Lebreton C, Bacchetta J, Dijoud F, Bessenay L, Fremeaux-Bacchi V, Sellier-Leclerc AL. C3 glomerulopathy and eculizumab: a report on four paediatric cases. Pediatr Nephrol 2017;32:1023–8. https://doi.org/10.1007/s00467-017-3619-2.
[68] Sahin H, Gok Oguz E, Akoglu H, Atilgan G, Ulusal Okyay G, Karaveli Gursoy G, et al. Successful treatment of posttransplant recurrent complement C3 glomerulopathy with Eculizumab. Iran J Kidney Dis 2018;12:315–8.
[69] Gurkan S, Fyfe B, Weiss L, Xiao X, Zhang Y, Smith RJ. Eculizumab and recurrent C3 glomerulonephritis. Pediatr Nephrol 2013;28:1975–81. https://doi.org/10.1007/s00467-013-2503-y.
[70] Gonzalez Suarez ML, Thongprayoon C, Hansrivijit P, Kovvuru K, Kanduri SR, Aeddula NR, et al. Treatment of C3 glomerulopathy in adult kidney transplant recipients: a systematic review. Med Sci (Basel) 2020;8:44. https://doi.org/10.3390/medsci8040044.
[71] Kurtz KA, Schlueter AJ. Management of membranoproliferative glomerulonephritis type II with plasmapheresis. J Clin Apher 2002;17:135–7. https://doi.org/10.1002/jca.10026.
[72] Rabasco C, Cavero T, Román E, Rojas-Rivera J, Olea T, Espinosa M, et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney Int 2015; 88:1153–60. https://doi.org/10.1038/ki.2015.227.
[73] Wong E, Nester C, Cavero T, Karras A, Le Quintrec M, Lightstone L, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy. Kidney Int Rep 2023; 8:2754–64. https://doi.org/10.1016/j.ekir.2023.09.017.
[74] Bomback AS, Kavanagh D, Vivarelli M, Meier M, Wang Y, Webb NJA, et al. Alternative complement pathway inhibition with Iptacopan for the treatment of C3 glomerulopathy-study design of the APPEAR-C3G trial. Kidney Int Rep 2022;7: 2150–9. https://doi.org/10.1016/j.ekir.2022.07.004.
[75] Wiles JA, Galvan MD, Podos SD, Geffner M, Huang M. Discovery and development of the oral complement factor D inhibitor danicopan (ACH-4471). Curr Med Chem 2020;27:4165–80. https://doi.org/10.2174/0929867326666191001130342.
[76] Nester C, Appel GB, Bomback AS, Bouman KP, Cook HT, Daina E, et al. Clinical outcomes of patients with C3G or IC-MPGN treated with the factor D inhibitor Danicopan: final results from two phase 2 studies. Am J Nephrol 2022;53:687–700. https://doi.org/10.1159/000527167.
[77] Nester C, Nast C, Appel G, Barratt J, Fervenza F, Fremeaux-Bacchi V, et al. POS-045 evaluating BCX9930, an oral factor D inhibitor for treatment of complement-mediated kidney disease: a proof-of-concept study (RENEW). Kidney Int Reports 2022;7:S457–8. https://doi.org/10.1016/j.ekir.2022.04.067.
[78] Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609. https://doi.org/10.1056/NEJMoa2023386.
[79] Bomback A, Herlitz LC, Yue H, Kedia PP, Schall TJ, Bekker P. POS-112 effect of avacopan, a selective C5A receptor inhibitor, on complement 3 glomerulopathy histologic index of disease chronicity. Kidney Int Reports 2022;7:S47–8. https://doi.org/10.1016/j.ekir.2022.01.124.
[80] ChemoCentryx. A randomized, Double blind, placebo controlled phase 2 study to evaluate the safety and efficacy of Avacopan (CCX168) in patients with C3 Glomerulopathy. clinicaltrials.gov; 2023.
[81] de Castro C, Grossi F, Weitz IC, Maciejewski J, Sharma V, Roman E, et al. C3 inhibition with pegcetacoplan in subjects with paroxysmal nocturnal hemoglobinuria treated with eculizumab. Am J Hematol 2020;95:1334–43. https://doi.org/10.1002/ajh.25960.
[82] Dixon B, Greenbaum LA, Huang L, Rajan S, Ke C, Zhang Y, et al. Clinical safety and efficacy of Pegcetacoplan in a phase 2 study of patients with C3 Glomerulopathy and other complement-mediated glomerular diseases. Kidney Int Reports 2023;0. https://doi.org/10.1016/j.ekir.2023.08.033.
[83] ChemoCentryx. A randomized, Double blind, placebo controlled phase 2 study to evaluate the safety and efficacy of Avacopan (CCX168) in patients with C3 glomerulopathy. clinicaltrials.gov; 2023.
[84] Apellis Pharmaceuticals, Inc. An open-label, randomized, controlled, phase 2 study to evaluate the safety and efficacy of Pegcetacoplan in the treatment of post-transplant recurrence of C3G or IC-MPGN. clinicaltrials.gov; 2022.
[85] Lafayette RA, Rovin BH, Reich HN, Tumlin JA, Floege J, Barratt J. Safety, tolerability and efficacy of narsoplimab, a novel MASP-2 inhibitor for the treatment of IgA nephropathy. Kidney Int Reports 2020;5:2032–41. https://doi.org/10.1016/j.ekir.2020.08.003.
[86] Omeros Corporation. A phase 2 study to evaluate the safety and effect on proteinuria of OMS721 in subjects with IgA nephropathy, lupus nephritis, membranous nephropathy, or C3 glomerulopathy including dense deposit disease. clinicaltrials.gov; 2020.
[87] Avasare RS, Canetta PA, Bomback AS, Marasa M, Caliskan Y, Ozluk Y, et al. Mycophenolate Mofetil in combination with steroids for treatment of C3 glomerulopathy. Clin J Am Soc Nephrol 2018;13:406–13. https://doi.org/10.2215/CJN.09080817.
[88] Caravaca-Fontán F, Díaz-Encarnación MM, Lucientes L, Cavero T, Cabello V, Ariceta G, et al. Mycophenolate Mofetil in C3 glomerulopathy and pathogenic drivers of the disease. Clin J Am Soc Nephrol 2020;15:1287–98. https://doi.org/10.2215/CJN.15241219.
[89] Kumar A, Nada R, Ramachandran R, Rawat A, Tiewsoh K, Das R, et al. Outcome of C3 glomerulopathy patients: largest single-Centre experience from South Asia. J Nephrol 2020;33:539–50. https://doi.org/10.1007/s40620-019-00672-5.
[90] Le Quintrec M, Lapeyraque A-L, Lionet A, Sellier-Leclerc A-L, Delmas Y, Baudouin V, et al. Patterns of clinical response to Eculizumab in patients with C3 glomerulopathy. Am J Kidney Dis 2018;72:84–92. https://doi.org/10.1053/j.ajkd.2017.11.019.
[91] Gonzalez Suarez ML, Thongprayoon C, Hansrivijit P, Kovvuru K, Kanduri SR, Aeddula NR, et al. Treatment of C3 glomerulopathy in adult kidney transplant recipients: a systematic review. Med Sci (Basel) 2020;8:44. https://doi.org/10.3390/medsci8040044.
[92] Welte T, Arnold F, Kappes J, Seidl M, Häffner K, Bergmann C, et al. Treating C3 glomerulopathy with eculizumab. BMC Nephrol 2018;19:7. https://doi.org/10.1186/s12882-017-0802-4.
[93] Kim JS, Foster KW, Westphal SG. Eculizumab in post-transplant C3 glomerulonephritis caused by a C3 mutation. Clin Nephrol 2020;93:51–6. https://doi.org/10.5414/CN109890.
[94] Garg N, Zhang Y, Nicholson-Weller A, Khankin EV, Borsa NG, Meyer NC, et al. C3 glomerulonephritis secondary to mutations in factors H and I: rapid recurrence in deceased donor kidney transplant effectively treated with eculizumab. Nephrol Dial Transplant 2018;33:2260–5. https://doi.org/10.1093/ndt/gfx369.
[95] Norville K, Stephen J, Mead-Harvey C, Corey R, Votruba C. Evaluation of Eculizumab use in renal transplant recipients. Prog Transplant 2023;33:162–7. https://doi.org/10.1177/15269248231164163.