The role of complement in kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Uncontrolled complement activation can cause or contribute to glomerular injury in multiple kidney diseases. Although complement activation plays a causal role in atypical hemolytic uremic syndrome and C3 glomerulopathy, over the past decade, a rapidly accumulating body of evidence has shown a role for complement activation in multiple other kidney diseases, including diabetic nephropathy and several glomerulonephritides. The number of available complement inhibitor therapies has also increased during the same period. In 2022, Kidney Diseases: Improving Global Outcomes (KDIGO) convened a Controversies Conference, "The Role of Complement in Kidney Disease," to address the expanding role of complement dysregulation in the pathophysiology, diagnosis, and management of various glomerular diseases, diabetic nephropathy, and other forms of hemolytic uremic syndrome. Conference participants reviewed the evidence for complement playing a primary causal or secondary role in progression for several disease states and considered how evidence of complement involvement might inform management. Participating patients with various complement-mediated diseases and caregivers described concerns related to life planning, implications surrounding genetic testing, and the need for inclusive implementation of effective novel therapies into clinical practice. The value of biomarkers in monitoring disease course and the role of the glomerular microenvironment in complement response were examined, and key gaps in knowledge and research priorities were identified.

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In 2015, Kidney Diseases: Improving Global Outcomes (KDIGO) convened a controversies conference on 2 prototypical complement-mediated kidney diseases: atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy

(C3G).[1] Since that time, evidence has emerged for a role of complement in the cause or progression of a broader range of kidney diseases, including diabetic nephropathy and a number of glomerulonephritides, with contributions of complement dysfunction ranging from primary causal to secondary driver of progression (Figure 1). The kidney appears to be a prime target of complement dysregulation (Figure 2), as systemic genetic defects in complement regulatory proteins may underlie isolated nephropathies, and multiple forms of kidney disease engage all pathways of the complement system.[2] The unique susceptibility of the kidney to complement-mediated injury may be due to several factors, including high glomerular blood hydrostatic pressure and filtration of plasma in glomerular capillaries, which together lead to high concentrations of complement proteins in close proximity to the glomerular basement membrane. In addition, the presence of fenestrae in glomerular endothelial cells may increase access of large plasma proteins to the glomerular basement membrane. Finally, the glomerular basement membrane does not express intrinsic complement regulators, which are present on endothelial cells.[2]

In 2022, KDIGO convened a second controversies conference to discuss the varied and expanding role of complement dysregulation in kidney disease. This timing was pertinent, as complement inhibitor therapies for kidney disease have expanded from eculizumab and its longer-acting derivative ravulizumab (C5 inhibitors used in aHUS) to avacopan (a C5a receptor blocker used in antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV]) and a number of new therapeutic agents, some of which are in clinical use for other indications (Table 1, Figure 3, and Supplementary Table S1).[3–13]

At the conference, for each disease considered, participants reviewed the evidence indicating whether complement plays a primary or a secondary role in pathogenesis and progression. Participants also critically examined the value of biomarkers of complement activity in monitoring disease course, whether specific drivers (i.e., genetic or acquired) dysregulate complement activity, and the potential impact/role of the glomerular microenvironment in contributing to the complement response. How current evidence informs management in terms of serological or genetic evaluations or approaches to complement inhibition was described. In addition, patients and caregivers described their experiences and concerns as related to diagnosis, prognosis, and management (Table 2).

The conference provided an opportunity to revisit the current literature on aHUS and C3G to assess whether the guidance outlined in the 2015 conference report requires updating. For primary diseases (C3G, immune complex membranoproliferative glomerulonephritis [IC-MPGN], and complement-mediated forms of HUS), the focus was on new information impacting management since the 2015 meeting. For all diseases, areas of consensus (Supplementary Table S2) and the most clinically relevant knowledge gaps and major priorities for research were identified (Table 3).[14,15]

Conference plenary presentations are available on the KDIGO website, https://kdigo.org/conferences/controversies-conference-on-complement-in-ckd/.

DIABETIC NEPHROPATHY AND FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Diabetic kidney disease

Although current experimental data do not support complement activation as a primary etiology in diabetic kidney disease (aka diabetic nephropathy), several lines of evidence indicate that it plays a contributory role in disease progression.[16,17] Activation of the complement cascade has been described in multiple animal models of diabetic nephropathy.[18,19] Less severe diabetic nephropathy is seen in mice homozygous for the targeted deletion of the C5a[20] or C3aR[21] genes or with pharmacologic inhibitors of complement.[21] A limitation of these studies is that mouse models poorly recapitulate human diabetic nephropathy, especially its late stages. Early candidate gene studies have indicated that pathogenic genetic variants in mannan-binding lectin genes are associated with disease progression.[22,23] In addition, summary data-based Mendelian analysis suggests a causal role for complement in diabetic chronic kidney disease.[24] Consistent with these findings, experimental evidence indicates that hyperglycemia may cause complement activation through enhanced mannan-binding lectin activity and that glycation impairs complement regulation.[25] In patients with diabetic kidney disease, biopsies have shown complement deposits focally in glomeruli, and analyses of kidney gene expression have identified complement gene activation.[26] It remains unclear whether complement is activated by the diabetic milieu or how age, sex at birth, obesity, and infections impact the complement response in diabetic nephropathy and its potential role in endothelial cell damage.

FSGS

In animal models, there is evidence that complement is activated and plays a role in the progression of FSGS.[27,28] However, animal models do not recapitulate genetic or permeability factor–induced human FSGS. In humans, evidence of complement activation is indicated by biomarker data: plasma C3 levels correlate with disease outcome; kidney biopsies stain positive for complement activation products (mostly in areas of sclerosis); and urine has higher levels of complement activation byproducts.[29] Transcriptional profiling in collapsing FSGS shows hallmarks of inflammation and this may be the form of FSGS in which complement activity is most robust.[30] However, complement gene mutations have not been identified as causative factors in FSGS.[31] It is noteworthy that complement is activated by infection, and infection is often associated with collapsing FSGS.

Clinical implications for management of diabetic kidney disease and FSGS

Evidence supports complement activation in diabetic kidney disease based on studies analyzing urine, plasma, and kidney

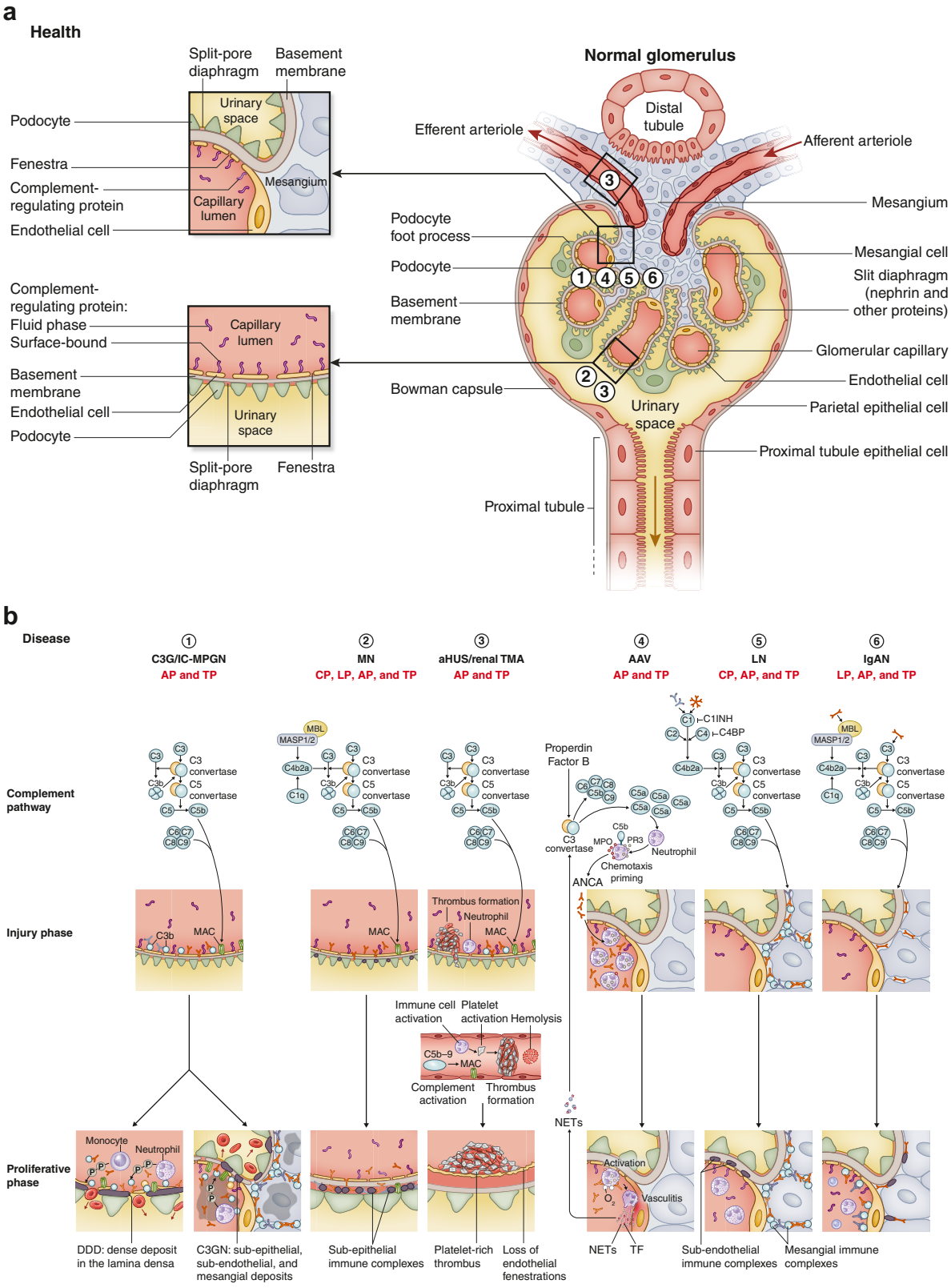

Figure 1 | Role of complement in various kidney diseases. Uncontrolled complement activation can cause or contribute to glomerular injury in multiple kidney diseases. (**a**) The renal glomerulus is a unique capillary bed. The lining glomerular endothelial cells (GECs) differ from most endothelial cells in that they are extraordinarily flattened and densely perforated by transcellular fenestrae, which constitute 30%–50% of their surface area. In addition, because the glomerulus lies between 2 arterioles—an upstream afferent arteriole and a downstream efferent arteriole—hydrostatic pressure is high. These properties contribute, at least in part, to the high permeability of the glomerular capillary wall to water and small solutes, but also to the vulnerability of the glomerulus to complement-mediated (continued)

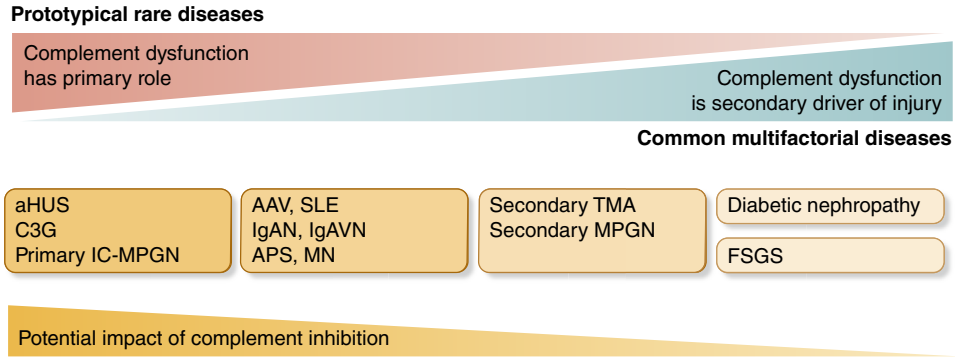

Figure 2 | Glomerular pathologies caused by complement dysregulation. Consensus viewpoint comparing rare but prototypical complement-mediated diseases such as atypical hemolytic uremic syndrome (aHUS) and complement component 3 glomerulopathy (C3G) with more complex multifactorial diseases in which complement activation may play a secondary role in contributing to disease burden. The role of complement in multifactorial disease requires validation through clinical trials and studies of complement biomarkers. AAV, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; APS, antiphospholipid antibody syndrome; FSGS, focal segmental glomerulosclerosis; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; IgAVN, IgA-associated vasculitis with nephritis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy.

biopsies both in patients and animal models.[32] Kidney biopsies are often obtained from patients with atypical presentations, making reference values difficult to determine. In FSGS and in diabetic nephropathy, the data are limited and can be confounded by phenotypic variation (infection, glycemia, etc.). Future studies should examine complement marker correlation with disease activity and progression, but at present, there is insufficient evidence to enrich trial enrollment based on complement biomarkers. It was generally viewed that complement inhibition is more likely to slow rather than prevent disease progression and that the overall weight of risks to benefits may be more favorable for complement inhibition in FSGS, where there is faster progression and fewer treatment options, than in minimal change disease. For complement-based therapeutic interventions in FSGS, at present, trial enrollment should focus on clinical criteria and target patients with rapidly progressing disease who have failed standard therapy and have no other therapeutic option.

It is not known whether complement inhibition is protective in diabetic nephropathy.[33] Given its prevalence, there is a large unmet need for novel therapeutics, especially for patients who do not respond to current treatments. Meeting participants came to the same conclusion regarding FSGS.

In both conditions, innovative trial designs (such as basket and platform trials) may be useful to evaluate potential benefits in patients showing activation of complement.

IgA NEPHROPATHY AND IgA-ASSOCIATED VASCULITIS WITH NEPHRITIS

Current data suggest that complement activation is equally important in the pathogenesis of IgA nephropathy (IgAN) and IgA-associated vasculitis with nephritis (IgAVN).[34–40] In most cases of IgAN/IgAVN, complement activation is driven by lectin[41–46] and/or alternative pathway activation,[46–50] as demonstrated through extensive evidence from studies of serum, kidney tissue, urine, and genetics in IgAN and kidney, gut, and skin biopsy studies in IgAVN. In both conditions, complement activation due to mesangial IgA immune complex deposition is an important cause of glomerular injury.[36,38,42,43,50] In IgAV, complement activation also appears to be important in the development of skin and gut lesions.[39,40,46] However, the precise relationship between the extent of complement activation and the risk of kidney injury and disease progression in both IgAN and IgAVN requires further validation. Racial or ethnic differences may

Figure 1 | (continued) damage and injury. (**b**) The complement cascade is constitutively active due to C3 tick-over. Activating complement components cannot distinguish self from nonself, with health relying on regulators of complement activation (RCA) proteins to prevent the occurrence of complement-mediated damage. GECs express decay-accelerating factor, membrane cofactor protein, and cluster of differentiation 59 (CD59); however, complement regulation over the fenestrae is dependent on fluid-phase RCA proteins such as factor H, factor I, C4b binding protein (C4BP), and C1 inhibitor. For each of 6 glomerular diseases (complement component 3 glomerulopathy [C3G]/immune-complex membranoproliferative glomerulonephritis [IC-MPGN], membranous nephropathy [MN], atypical hemolytic uremic syndrome [aHUS], antineutrophil cytoplasmic antibody [ANCA]–associated vasculitis [AAV], lupus nephritis [LN], and IgA nephropathy [IgAN]), the principal complement pathway is shown, activation of which leads to injury, segueing into a proliferative phase of glomerular damage. If scarring has not occurred, many of these glomerular changes are predicted to be reversible. As a growing number of therapeutic agents targeting different parts of the complement cascade become available, understanding how complement activation contributes to these diseases will be paramount if we are to judiciously use these new drugs to improve patient outcomes. AP, alternative pathway; C1INH, C1 esterase inhibitor; CP, classical pathway; DDD, dense deposit disease; IgAVN, IgA-associated vasculitis with nephritis; LP, lectin pathway; MAC, membrane attack complex; MASP, mannan-binding lectin (MBL)–associated serine protease; MPO, myeloperoxidase; NET, neutrophil extracellular traps; PR3, proteinase 3; TF, tissue factor; TMA, thrombotic microangiopathy; TP, terminal pathway.

Table 1 | Complement inhibitors in clinical development[a] for kidney diseases

Target of inhibition	Drug	Inhibitor type	Mechanism	Route	Clinical trials
C1	ANX009	Antibody	Inhibits C1q substrate interactions	SC	NCT05780515 (lupus nephritis, phase 1, recruiting)
C3, C3b	Pegcetacoplan	Peptides conjugated to polyethylene glycol	Binds C3 and C3b and prevents interaction and activity of the C3 and C5 convertases of the classical, lectin, and alternative pathways	SC twice weekly	NCT05148299 (post-BMT TMA, phase 2, recruiting) NCT04572854 (post-transplant recurrence C3G or IC-MPGN, phase 2, active not recruiting) NCT03453619 (C3G) (basket in glomerulopathies, phase 2, completed)[4] NCT05067127 (C3G or IC-MPGN, phase 3, active not recruiting) NCT05809531 (C3G or IC-MPGN, phase 3 open-label extension of a previous study, recruiting)
C3	AMY101	Small peptide	Binds C3 and blocks its binding to and cleavage by C3 convertases into C3a and C3b	IV	NCT03316521 (phase 1 healthy male volunteers, completed)
C3	ARO-C3	Small, interfering RNA	Inhibits C3 synthesis in the liver	SC	NCT05083364 (phase 1/2a dose-escalating: healthy volunteers, adult patients with C3G and IgAN, recruiting)
C3b, C5	KP104	Antibody plus factor H regulatory domain	Blocks the alternative and terminal pathways	IV	NCT05517980 (IgAN and C3G phase 2, not yet recruiting) NCT05504187 (lupus nephritis phase 2, not yet recruiting)
C5	Cemdisiran	Small, interfering RNA	Inhibits C5 synthesis in the liver	SC	NCT03841448 (IgAN, phase 2, completed)[5]
C5	Crovalimab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV, then SC	NCT04958265 (aHUS, phase 3, recruiting, children between 28 days and 17 years of age) NCT04861259 (aHUS, phase 3, recruiting)
C5	Eculizumab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV	NCT03518203 (HUS post-BMT with multiple organ dysfunction syndrome, phase 2, completed) NCT01029587 (CAPS to enable kidney transplant, phase 2, completed) NCT05702996 (HUS secondary to gemcitabine, phase 2, not yet recruiting) NCT05726916 (HUS secondary to hypertensive emergency, phase 2, not yet recruiting) NCT02205541 (STEC-HUS, phase 3, completed)[6] NCT05876351 (aHUS in China, phase 3, recruiting)
C5	Gefurulimab (ALXN1720)	Bispecific minibody	Binds C5, inhibiting its cleavage into C5a and C5b. It also binds to albumin, which increases its half-life	SC	NCT05314231 (proteinuria, phase 1B, completed)
C5	Ravulizumab	Antibody	Prevents cleavage of C5 by the C5 convertase	IV, SC	NCT04564339 (IgAN and LN, phase 2, recruiting) NCT04743804 (trigger-associated TMA, phase 2, terminated) NCT04543591 (adult and adolescent post-BMT HUS, phase 3, recruiting) NCT04557735 (pediatric post-BMT HUS, phase 3, recruiting)

(*Continued on following page*)

Table 1 | (Continued) **Complement inhibitors in clinical development[a] for kidney diseases**

Target of inhibition	Drug	Inhibitor type	Mechanism	Route	Clinical trials
C5	Nomacopan or coversin (rVA576)	Small protein	Inhibits terminal complement activation by tightly binding to C5 and preventing C5a release and C5b-9 formation, and inhibits leukotriene B4 by capturing the fatty acid within the body of the nomacopan protein	SC	NCT04784455 (pediatric post-BMT HUS, phase 3, recruiting)
C5a	Vilobelimab (IFX-1)	Antibody	Selectively inhibits C5a activity leaving the MAC intact	IV	NCT03712345 (GPA and MPA, phase 2, terminated) NCT03895801 (GPA and MPA, phase 2, completed)
C5aR1	Avacopan	Small molecule	Blocks the binding of the anaphylatoxin C5a with the C5aR1 receptor	Oral twice daily	NCT02464891 (aHUS on dialysis, phase 2, terminated) NCT03301467 (C3G, phase 2, completed) NCT02384317 (IgAN, phase 2, completed)[7] NCT02994927 (AAV, phase 3, completed)[8] NCT01363388 (AAV, phase 2, completed) NCT02222155 (AAV, phase 2, completed)
Factor B	IONIS-FB-LRx	Antisense oligonucleotide	Inhibits liver synthesis of factor B	SC	NCT04014335 (IgAN, phase 2, active not recruiting, ASN poster SA-PO926)[8a] NCT05797610 (IgAN, phase 3 recruiting)
Factor B	Iptacopan (LNP023)	Small molecule	Prevents activity of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT04889430 (aHUS, phase 3, recruiting) NCT03832114 (C3G, phase 2, adults with native or transplanted kidney,[9] extension NCT03955445) NCT04817618 (C3G, phase 3, adults and adolescents >12 years, recruiting, for adults interim results reported) NCT05755386 (IC-MPGN, phase 3, adults and adolescents >12 years, recruiting) NCT03373461 (IgAN, phase 2, completed)[10] NCT04578834 (IgAN, phase 3, recruitment completed, interim results reported) NCT04154787 (MN, phase 2, terminated) NCT05268289 (LN, phase 2, recruiting)
Factor Bb	NM8074	Monoclonal antibody	By binding Bb, it is able to inhibit both C3 and C5 convertases and the MAC formation	IV	NCT06226662 (AAV, phase 2, not yet recruiting) NCT05647811 (C3G, phase 1b/2a, not yet recruiting) NCT05684159 (aHUS, phase 2, not yet recruiting)
Factor D	BCX10013	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway more efficiently than BCX9930	Oral once daily	NCT06100900 (PNH, phase 1, dose escalation)

Factor D	Danicopan (ALXN2040, ACH-4471)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral twice daily	NCT03124368 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03369236 (C3G or IC-MPGN, phase 2, completed)[11,12] NCT03459443 (C3G or IC-MPGN, phase 2, terminated)
Factor D	Vemircopan (ALXN2050, ACH-0145228)	Small molecule	Prevents formation of C3 and C5 convertases of the alternative pathway	Oral	NCT05097989 (IgAN or LN, phase 2, recruiting)
MASP-2	CM338	Monoclonal antibody	Blocks initiation of the lectin pathway	SC	NCT05775042 (IgAN, phase 2, recruiting)
MASP-2	Narsoplimab (OMS721)	Antibody	Blocks initiation of the lectin pathway	IV	NCT05855083 (pediatric post-BMT HUS, phase 2, recruiting) NCT03205995 (aHUS, phase 3, status unknown) NCT02682407 (C3G, IgAN, LN, MN, phase 2, status unknown) NCT03608033 (IgAN, phase 3, terminated)
MASP-3	OMS906	Antibody	Blocks initiation of the lectin pathway	IV	NCT06209736 (C3G, IC-MPGN, phase 2, not yet recruiting)
Renin[b]	Aliskiren	Small molecule	Blocks renin-mediated C3 cleavage	Oral	NCT04183101 (C3G, phase 2, recruiting)

AAV, antineutrophil cytoplasmic antibody–associated vasculitis; aHUS, atypical hemolytic uremic syndrome; BMT, bone marrow transplant; C3G, complement component 3 glomerulopathy; CAPS, catastrophic antiphospholipid syndrome; GPA, granulomatosis with polyangiitis; HUS, hemolytic uremic syndrome; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; IV, intravenous; LN, lupus nephritis; MAC, membrane attack complex (C5b-9); MASP, mannan-binding lectin-associated serine peptidase; MN, membranous nephropathy; MPA, microscopic polyangiitis; PNH, paroxysmal nocturnal hematuria; SC, subcutaneous; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy.

[a]As of March 1, 2024. For eculizumab, completed and published studies are not listed. For all agents, only studies evaluating the diseases covered in this paper are listed, and withdrawn studies are not listed. Studies on generic/biosimilar agents or in phase 4 are also not listed. The studies enroll adults only unless specified.

[b]Recent data do not support a role for renin in the cleavage of C3 and suggest that the use of aliskiren as a renin inhibitor to decrease complement activity and C3 convertase formation is misguided.[13]

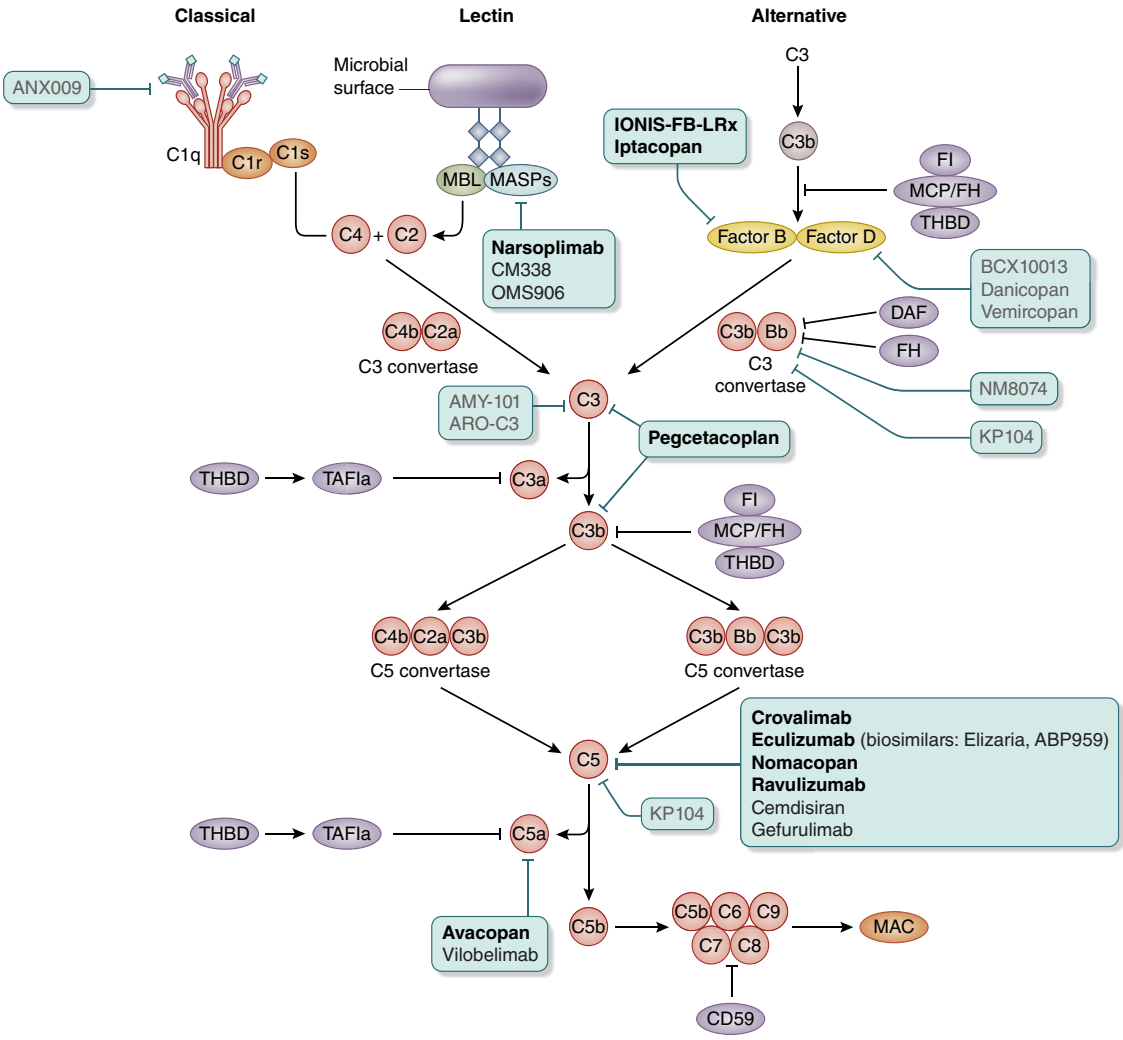

Figure 3 | Therapeutic inhibitors of complement activity. In the near future, multiple drugs that target the complement system will be available. It is highly likely that drug effect will vary depending on the underlying disease process and patient-specific factors such as the presence of genetic variants in complement genes or autoantibodies to different complement components, which will make precision medicine a possibility. Agents in bold have reached phase 3 or later in development. CD59, complement defense 59; DAF, decay-accelerating factor; FB, factor B; FH, factor H; FI, factor I; MAC, membrane attack complex; MASP, mannan-binding lectin–associated serine peptidase; MBL, mannan-binding lectin; MCP, membrane cofactor protein; TAFIa, activated thrombin activatable fibrinolysis inhibitor; THBD, thrombomodulin gene.

play a role, as C1q mesangial deposition has been shown to predict worse outcomes of IgAN only in the Asian population.[51,52]

Single-center, nonvalidated studies suggest an association in IgAN between worsening outcomes and increased complement activation markers in the kidneys, urine, and blood. These studies need to be independently validated, and biomarkers need to be evaluated to determine whether they could improve the prognostic precision of the International IgAN Risk Prediction Tool.[53,54]

Clinical implications

In IgAN and IgAVN, there are currently no validated complement-associated biomarkers (kidney biopsy stains, plasma or urinary biomarkers, and genotypes) that inform prognosis, treatment selection, or monitoring of treatment response.[55]

There is a significant unmet need to evaluate the role of complement therapies in IgAVN,[56,57] recurrent IgAN/IgAVN post-transplant,[58] and pediatric IgAN/IgAVN. In IgAN, current data show an antiproteinuric effect of complement blockade, supporting further evaluation of complement therapies targeting the lectin, alternative, and terminal complement pathways.[5,7,10,59–64] The use of complement inhibition may be particularly effective in children, who tend to have a more florid inflammatory component and less sclerotic damage compared with adults. To date, phase 2 and phase 3 clinical trials of complement therapies in IgAN (<200 patients) have suggested a reduction in proteinuria and have not demonstrated significant adverse events (Supplementary Table S1), including, in

Table 2 | Patient and caregiver concerns, unmet needs, and perspectives on genetic testing and repeat biopsies

Concerns
• Kidney diseases for which the role of complement dysregulation is pivotal often have no known effective treatment options, leading to kidney failure and risk of recurrence after kidney transplant
• Kidney diseases involving complement overactivation can have a profound impact on the daily lives of patients and caregivers, limiting participation in important or meaningful activities
• For young patients, the lack of natural history data leads to uncertainty regarding course and impact of disease, which can influence decisions on career and family planning
• Evidence on the correct management of many complement-mediated nephropathies is limited in quantity and quality, and awareness of innovative therapies (either in clinical trials or marketed) is often insufficient
• Approved agents are not universally available due to limited affordability
• Lack of awareness of complement-mediated diseases among health care professionals delays diagnosis and hinders optimal management
• Because complement blocking therapies increase the risk of infection, their long-term use is potentially concerning
Unmet needs
• A more widespread understanding of and expertise in treating complement-mediated kidney diseases among nephrologists worldwide
• Natural history and biomarker studies in rare conditions
• Awareness of existing studies and potential for enrollment among patients and health care providers
• Trial designs that increase likelihood of receiving active treatment either through ratios other than 1:1 active:placebo or through open-label extension
• Programs with early access to treatment in the adolescent/pediatric population once safety has been established
• Availability of innovative treatments judged more likely to be effective than existing options as first-line therapy in aggressive forms of disease
• Consideration for adopting serial treatment strategies given the heterogeneity of disease course and treatment response within some complement-mediated diseases
Genetic testing and screening
• Opinions and preferences regarding genetic screening and testing are highly variable among patients ◦ Some individuals want to know as much as possible about their disease, especially if early diagnosis can lead to better outcomes ◦ Others do not, especially if the knowledge is not actionable
• Whether and how genetic findings could impact insurance or transplant candidacy
• Accurate information about and understanding of variant-attributable risk of disease are paramount ◦ Precluding a living-related transplant or undergoing embryo selection because of an allele that is unlikely to cause disease is undesirable
• Appropriate and well-informed genetic counseling is crucial, as parents can experience significant psychological burden if they are told that they transmitted a deleterious genetic variant to their child
Repeat biopsy in the setting of a clinical trial
• In general, patients are reluctant to undergo repeat biopsies, particularly in the setting of atypical hemolytic uremic syndrome, where it may be riskier and where other reliable parameters of response to treatment (e.g., platelet count, lactate dehydrogenase, and serum creatinine) are well established
• However, particularly in glomerular diseases with less well-established efficacy endpoints and a more gradual disease progression, patients and caregivers recognize the need for histologic proof of a therapeutic agent affecting disease progression and may be motivated to collaborate in developing, through data from repeated biopsies, noninvasive diagnostic approaches (e.g., novel imaging technologies, improved diagnostic biomarkers, and liquid biopsy approaches)

particular, infections with encapsulated bacteria (where vaccination and/or prophylactic antibiotics may be considered for alternative and terminal pathway inhibitors).[5,7,10,63,64]

MEMBRANOUS NEPHROPATHY

Primary membranous nephropathy (MN) is driven by the production of autoantibodies and *in situ* formation of immune complexes, followed by complement activation.[65] In experimental animal models of MN, complement activation after immune complex deposition is essential for the development of podocyte injury and proteinuria, although its role after immune complexes are cleared is not known.[66–69] In primary MN, activating pathways other than the classical have been considered dominant, as C1q is typically absent or minimal.[70] The presence of C3, factor B (FB), and properdin by immunostaining on the kidney biopsy supports a role for the alternative pathway.[71] C3 (and C4 when measured) is nearly always found in conjunction with IgG in the subepithelial deposits by immunostaining.[72,73] In addition to human biopsy data, recent experimental data implicate C3a and podocyte C3aR and C5aR in primary MN.[13,74,75] In terms of the lectin pathway, mannan-binding lectin is found in the typical fine granular capillary wall deposit pattern on primary MN biopsies.[76] *In vitro*, human IgG4 anti–phospholipase A2 receptor lacking terminal N-linked galactose can bind mannan-binding lectin and activate the lectin pathway to cause podocyte injury.[74]

Most primary MN biopsies exhibit strong IgG4 and C3 staining by immunofluorescence, with minimal C1q,

Table 3 | Key questions and research needs regarding complement involvement in kidney disease (top priorities are highlighted in bold)

Condition	Important knowledge gaps and key questions	Potential research and translation strategies
Diabetic nephropathy	• The role of hyperglycemia in complement activation • The relationship between complement activation products and disease severity/outcomes • Outcome data on complement therapies in patients with diabetic nephropathy or FSGS	• Basket or platform clinical studies in diabetic nephropathy and FSGS for patients who rapidly progress despite maximal guideline therapy ◦ With comprehensive specimen banking • Focused analysis of complement pathway genes and disease
FSGS	• Better characterization of disease heterogeneity and subgroups • The relationship between complement-related biomarkers and disease progression	• Mining of existing comprehensive-omics studies of tissue samples, transcriptome, epigenome, proteome, metabolome, "complementome" (complement-related-omics)
Lupus	• Whether the measurement of complement activation products in plasma, tissue, and urine can inform therapy	• **Define the role of eculizumab in lupus-associated TMA and in class V LN** • **Clarify the contribution of the lectin complement pathway to lupus pathogenesis** • **Develop urinary biomarkers of remission of glomerular inflammation**
APS	• Clinical tools for complement activation assessment	• **Trial of patients treated with C5 inhibition for vascular and obstetric forms of APS** • **Consider using long-term complement blocking therapies (C5 inhibition) for patients with high risk of thrombotic recurrence such as triple-positive patients (patients with 2 positive serum IgG aPL antibodies and 1 positive functional plasma lupus anticoagulant test result), who are at increased risk for thrombosis despite good anticoagulation** • **Trials of short-term therapy for high-risk situations such as vascular injury**
AAV	• Whether complement biomarkers can be used to: ◦ Identify patients likely to benefit from therapy ◦ Identify nonresponders ◦ Guide dose and duration of treatment • The role of complement-directed therapy in severe kidney disease, ANCA-negative pauci-immune GN, extrarenal manifestations, and granulomatous airway disease • The optimum duration of therapy and role in maintenance therapy (alone or in combination with other agents) • The role of C5aR in induction of autoimmunity[14] • Whether C5aR2 inhibition or deletion exacerbates disease in animal models; clinical studies ongoing (InflaRx: NCT03712345) • The relative risks and benefits of targeting other complement components (no effect of C5b-9 inhibition in animal models[15]) • Whether C5aR1 blockade or other complement-directed therapies attenuate thrombotic or cardiovascular risk in AAV	• **Use clinical trial data and biosamples to evaluate kidney histopathology and longitudinal complement biomarkers in predicting treatment response, in particular plasma C5a levels in patients treated with avacopan** • **Post-authorization surveillance studies of long-term safety, relapse risk, and kidney disease progression** • **RCT and observational outcome studies (with biomarker analysis) evaluating specific disease manifestations when eGFR is <15 ml/min per 1.73 m^2**
IgAN, IgAVN	• Whether the role or contribution of complement is the same in: ◦ adults and children ◦ people of various ethnicity or ancestry ◦ glomeruli and tubulointerstitium ◦ throughout the lifetime of disease	
MN	• Identify the best complement biomarker to assess ongoing complement activation in MN • Whether there is an adjunctive role for complement inhibition in addition to B-cell depletion therapies	• **Identify noninvasive (plasma, urine) complement biomarkers of ongoing complement activation within the glomerulus** • **Elucidate the dominant mechanisms of complement-mediated podocyte and other kidney cell injury (e.g., tubular cell) during the natural history of the disease, including following the disappearance of circulating autoantibodies** • **Evaluate the optimal time to institute complement therapy in the natural history of MN and in relation to the presence/level of circulating autoantibodies**

Table 3 | (Continued)

Condition	Important knowledge gaps and key questions	Potential research and translation strategies
		• **Explore whether there are autoantibodies to complement regulators that exacerbate complement-mediated injury in the kidney in some or all patients with MN** • Measure the impact of complement inhibition on autoantibody levels and vice versa in primary MN
Complement-mediated forms of HUS	• The terminology and spectrum of entities that should be considered as complement-mediated kidney TMA • **Whether there is a benefit of C5 inhibition in HUS distinct from primary complement-mediated kidney TMA/HUS** • **A reliable and easily implemented diagnostic test for atypical HUS** • **Assess the role of inhibitors targeting the alternative C3 convertase in the treatment of complement-mediated HUS** • The role of noncomplement mechanisms of endothelial cell injury in complement-mediated TMA • The relevance of high-titer anti–factor H autoantibodies in patients with no clinical signs of TMA • The role of complement inhibition in STEC-HUS	• Assess the exact implication of complement (potentially as a second hit) in secondary TMAs • Identify biomarkers with validated negative and/or positive predictive value for diagnosis, treatment monitoring, and/or assessment of relapse after treatment discontinuation • Design and conduct prospective clinical trials with complement inhibitors in secondary kidney TMA • Standardize anti–factor H antibody tests • Assess the long-term outcome of repeated recurrences of atypical HUS • Identify additional predictive factors of relapse after discontinuation of treatment
IC-MPGN and C3G	• Histopathological classification: does the distinction between C3G and IC-MPGN make pathophysiological sense, given that the underlying causes are identical in primary forms? • Better characterization of disease heterogeneity and subgroups • The role of C3NeFs in disease causation • The role of immunosuppression in C3G, especially in comparison with complement inhibition • Standardized nomenclature for rare non-Mendelian genetic variants • The utility of identifying anti-C3b, anti-FB, and anti-FH autoantibodies for diagnosis and treatment	• **Use an (adaptive) platform clinical trial to assess efficacy and safety of new complement inhibitors** • **Explore strategies to identify groups of patients with homogeneous etiology** • **Simplify and standardize C3NeF and C5NeF assays** • Explore the prognostic significance of clinical, histologic, and biomarker data to predict outcome and to use as surrogate endpoints • Conduct functional assays to assess the effect of potentially damaging genetic variants • Quantify disease risk effects of genetic variants/C3NeFs/other autoantibodies

AAV, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis; aPL, antiphospholipid; APS, antiphospholipid antibody syndrome; C3G, complement component 3 glomerulopathy; C5aR, C5a receptor; C5b-9, membrane attack complex; eGFR, estimated glomerular filtration rate; FB, factor B; FH, factor H; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IgAN, IgA nephropathy; IgAVN, IgA-associated vasculitis with nephritis; LN, lupus nephritis; MN, membranous nephropathy; NeF, nephritic factor; RCT, randomized controlled trial; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy.

suggesting similar pathways of complement activation in the various disease subtypes (although 1 subtype of primary MN associated with autoantibodies to protocadherin-7 appears to exhibit minimal C3 staining[77]). When evidence of classical pathway activation is present on biopsy (significant C1q, often with a predominance of non-IgG4 subclasses of IgG), a secondary etiology should be considered (e.g., systemic autoimmune disease, infection, malignancy, or exposures).[78,79] However, a study has very recently shown that, while C1q is indeed minimal on routine immunofluorescence of MN biopsy tissue, it can become readily detectable when formalin-fixed tissue undergoes antigen retrieval, unmasking C1q.[80] This finding, suggesting that classical pathway activation may be more common in MN than previously assumed, needs further study.

Clinical implications

Current evidence clearly implicates the alternative, lectin, and perhaps also classical pathways of complement in driving primary MN, but no complement biomarkers have been validated. Phase II clinical trials are evaluating complement C3, alternative pathway, and lectin pathway inhibition in MN (see Table 1). In primary MN, targeting the lectin and alternative pathways may be appropriate, whereas the inhibition of the classical pathway may be useful in managing secondary forms of MN. A recent observation of recurring primary MN in a patient receiving eculizumab for complement factor I–deficient aHUS suggests that targeting the terminal pathway may not have significant effectiveness.[81]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

In SLE, multiple effector mechanisms cause glomerular inflammation. Based on animal model data, immune complexes mediate glomerular inflammation through Fc receptor engagement and activation of the classical and terminal pathways, although it is the alternative pathway that drives much of the kidney damage.[82] Complement activation is also associated with extrarenal manifestations.[83] Paradoxically, congenital complement deficiencies, mainly of C1q and C4, may lead to the development of SLE.[84] Explaining this association in terms of abnormalities in the classical pathway is problematic, as C3 deficiency does not predispose

to SLE. However, C1q does modulate the mitochondrial metabolism of CD8+ T cells, thereby blunting the response to self-antigens. This link between C1q and CD8+ T-cell metabolism may explain how C1q protects against lupus and has implications for the role of viral infections in the perpetuation of autoimmunity.[85] Low circulating complement levels (C3 and C4) due to extensive complement activation[83] are associated with disease activity and are included in common disease activity scores.[86] In addition, plasma complement split products and cell-bound complement activation products, namely, erythrocyte-bound C4d and B cell–bound C4d, are being investigated as promising biomarkers of disease activity and of specific manifestations of SLE.[87]

Clinical implications

Low circulating C3 and C4 levels predict response to belimumab,[88,89] and their early normalization has been associated with renal response in trial settings, for example, the Aspreva Lupus Management Study.[90] Measuring anti-C1q antibody titers is valuable in the diagnosis of hypocomplementemic urticarial vasculitis syndrome.[91] There are case reports of using eculizumab in lupus nephritis[92] and in thrombotic microangiopathy (TMA) secondary to lupus.[93] Complicating the interpretation of these case reports, however, is a common polymorphism in C5, Val802Ile (rs17611; 9-121006922-C-T [GRCh38]), that makes C5 Val802 more sensitive to cleavage by neutrophil elastase and other proteases typically not implicated in complement activity.[94] The result is the generation of functional C5a-like fragments that drive inflammation.[95] Importantly, this off-target cleavage of C5 by elastase is not inhibited by eculizumab.[95] A clinical trial of ravulizumab (a monoclonal anti-C5 antibody) is ongoing (NCT04564339).

There are many reports assessing complement activation fragments as clinical biomarkers in SLE.[87,96,97] However, these assays are not routinely available and require careful sample handling to avoid spurious results due to *ex vivo* complement activation. It is also not clear what extra value they would add to widely available serological markers of disease activity (double-stranded DNA antibody titer, C3 and C4 levels). Some complement assays may have clinical utility when using complement inhibitors. For example, the optimal use of eculizumab/ravulizumab may be aided by the ability to determine if full inhibition of C5 activation in plasma has been achieved (e.g., through C5 activation assays) and whether there is evidence of C5 inhibition in the kidney biopsy (e.g., by staining for C5b-9 and quantifying inflammatory cells). Meeting participants had reservations about C3 inhibition in SLE due to the role of C3 in the physiological removal of immune complexes and about inhibition of the classical pathway due to the strong association between complete deficiency of classical pathway proteins and lupus-like syndromes. Adverse interactions between complement inhibitors and existing standard-of-care treatment for lupus, including B-cell depletion with anti-CD20 antibodies, would not be expected.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

Complement is implicated in the pathogenesis of the 3 forms of primary APS (vascular, obstetric, and catastrophic).[98,99] Deposition of complement has been reported in vessel walls,[100,101] and there is evidence of classical pathway activation in primary APS, which occurs even in quiescent APS (i.e., far from the thrombotic event).[102–104] There is no clear evidence of a relationship between plasma complement and vascular manifestations. However, one small study showed that persistently high plasma C5a and sC5b-9 levels during quiescent APS are associated with higher risk of vascular recurrence and may identify patients who might benefit from complement inhibition.[105] Notably, in obstetric APS, a multicenter registry showed that low preconception C3 and C4 levels were associated with adverse pregnancy outcomes,[106] and another multicenter study showed that increased Bb and sC5b-9 levels in early pregnancy strongly predicted adverse pregnancy outcomes.[107] Eculizumab has been used in catastrophic APS, with reports of improvement in some cases.[108] The evidence of efficacy is difficult to evaluate as eculizumab is used with concomitant therapies, such as intravenous immunoglobulin, plasma exchange, or cyclophosphamide. Eculizumab has also been used to prevent rethrombosis after surgery in APS.[100]

Clinical implications

In catastrophic APS, the use of complement inhibitors may be a suitable therapeutic option, and eculizumab is listed as a treatment option in European Alliance of Associations for Rheumatology guideline recommendations.[109] Complement blockade will increase infection risk, and because infections are considered to trigger vascular events in APS, antibiotic prophylaxis may be prudent.[110] Clinical trials of anticomplement therapy in the 3 forms of APS are highly challenging and would need an innovative design to achieve robust conclusions. There is no evidence that complement inhibition would interfere with the mechanism of action of anticoagulant therapies, which are the mainstay of APS management.

ANCA-ASSOCIATED VASCULITIS

Previously described *in vitro*, *in vivo*, and clinical evidence implicate complement activation in the development of AAV and AAV-glomerulonephritis.[15,111] In summary, there is evidence of alternative and terminal pathway activation in AAV with glomerular staining for FB, properdin, membrane attack complex, and C3d[112] and elevated plasma levels of C3a, C5a, and Bb in active disease.[113] In a mouse model of anti-myeloperoxidase–associated glomerulonephritis, either FB or C5 deficiency prevented disease, whereas C4 deficiency had no discernable effect.[114] These outcomes indicate that the alternative and terminal pathways, but not the classical and lectin pathways, are required for disease induction. Further studies in a mouse model of anti-myeloperoxidase–associated AAV showed that, while glomerulonephritis was prevented by either C5a receptor deficiency or blockade of a humanized C5a receptor with avacopan, C6 deficiency had no effect.[15] This result indicates that the production of C5a and its

interaction with the C5a receptor and not the membrane attack complex is driving the glomerulonephritis. *In vitro* studies have shown that activation of primed (i.e., tumor necrosis factor-α treated) neutrophils with ANCA (either myeloperoxidase or proteinase 3) resulted in C5a generation.[115] C5a, in turn, primed neutrophils for subsequent ANCA-induced activation in a C5a receptor–dependent manner. Taken in aggregate, these data provided the rationale for investigating the efficacy of C5a-C5a receptor blockade in AAV.

Clinical implications

Clinical trial data support the use of avacopan (C5aR1 blockade) as a steroid-sparing therapy in AAV/AAV-glomerulonephritis (granulomatosis with polyangiitis and microscopic polyangiitis; Supplementary Table S1).[8,116,117] Treatment is well tolerated and enables glucocorticoid withdrawal, a major benefit to patients. Some evidence suggests that avacopan treatment improves recovery of estimated glomerular filtration rate (eGFR) and albuminuria level, although further confirmation is required. It is also unclear if blockade of C5aR1 (or other complement-directed therapy) attenuates thrombotic or cardiovascular risk. Key considerations are the optimum duration of therapy and its role in maintenance (alone or in combination with other agents), as well as the role of C5aR in induction of autoimmunity.[14] Presently, avacopan is used in combination with a rituximab or cyclophosphamide regimen for treating adult patients with severe disease, and studies are needed to determine optimal patient groups and disease stages. Clinical studies of C5a blockade using an anti-C5a antibody (vilobelimab) are in progress (InflaRx: NCT03712345; Table 1). The utility of complement biomarkers to predict response to treatment or guide dose or duration of treatment is unclear. Also unclear is the role of complement-directed therapy in severe kidney disease, ANCA-negative pauci-immune GN, extrarenal manifestations, and granulomatous airway disease.

TMAs, COMPLEMENT-MEDIATED FORMS OF HUS

Terminology

The current terminology of atypical, primary, and secondary HUS needs updating because it is confusing and does not reflect pathogenesis. The National Kidney Foundation has recently reviewed the spectrum of conditions associated with TMA and proposed a diagnostic approach that should ideally reflect the underlying pathogenic mechanisms, the role of complement and other potential triggers, and responsiveness to complement blockade.[117a] Novel terminologies should not negatively impact access to or reimbursement for complement inhibitors.

Complement involvement and associated pathogenicity

Current evidence strongly supports alternative and terminal pathway dysregulation driving most forms of aHUS. Beyond complement dysregulation, many other causes, including deficiencies in diacylglycerol kinase-ε (DGKe), cobalamin-C deficiency, interferon β administration, and vascular endothelial growth factor inhibition, have mechanistic roles in driving a kidney TMA phenotype. TMAs mediated by DGKe and MMACHC (methylmalonic aciduria [cobalamin deficiency] cblC type, with homocystinuria) are nonresponsive to C5 inhibition.[118] It is not known whether interferon-β and vascular endothelial growth factor inhibition–mediated TMAs respond to C5 inhibition.

Biomarkers (complement levels and functional assays; Supplementary Table S3), detection of anti–factor H (FH) autoantibodies, and complement genetics may help distinguish transient versus permanent complement activation/dysregulation in specific settings. Complement activation may be self-resolving. Constitutive AP dysregulation is not synonymous with permanent activation requiring continuous treatment. Complement activation may be a TMA-causing event, an amplifying factor, or a by-product. It is unclear if this distinction will be helpful for TMA/HUS reclassification. However, it may be helpful for the long-term management of patients, particularly in determining the duration of complement inhibition.

Biomarkers

The report from the 2015 Controversies Conference highlighted the need of specific biomarkers that could help diagnose and monitor complement-mediated forms of HUS (TMA).[1] To date, there is no universally available diagnostic biomarker for aHUS. Clinical diagnosis relies on the exclusion of other conditions. However, an autoimmune form of complement-mediated TMA can be identified in the acute phase by the presence of anticomplement FH autoantibodies.[119] Importantly, complement biomarkers are helpful in the identification of the etiological factor involved (Supplementary Table S3).

To date, no biomarker with the ability to identify complement AP dysregulation in the setting of HUS has been validated for clinical use in patient management and selection of candidates for C5 blockade at disease onset. A normal blood complement profile does not exclude a complement-mediated HUS. However, biomarkers/tests are helpful to monitor complement inhibition and relapse risk (e.g., complement total blood test [CH50], free C5, sC5b-9, anti-FH autoantibodies). In routine practice, only CH50 and eculizumab trough levels are used to assess the degree of terminal complement blockade. Newly developed assays, such as *ex vivo* cell-based tests (human dermal microvascular endothelial cells-1 assay and modified Ham test), have been proposed to diagnose and monitor complement-mediated forms of TMA.[120–122] These assays require further validation before implementation in the clinic. Moreover, a pressing issue remains obtaining uniform and comparable dosing of anti-FH autoantibodies, which currently is difficult to harmonize and reproduce between different laboratories.

Genetics

Genetics and autoantibody screening in patients with suspected complement-mediated HUS are listed in Supplementary Table S4. Complement genetic findings (common and rare variants, copy number variations, etc.) should be interpreted by a laboratory with expertise in complement-related diseases. The term variant should be used instead of mutation, with identified variants classified as pathogenic/likely pathogenic, of uncertain significance, or benign/likely benign (Supplementary Table S5). Atypical HUS has a variable (low) penetrance, and rare variants in complement genes are only predisposing factors for the disease.[123,124] The risk of developing disease increases with the number of genetic risk factors and is modulated by the *CFH* (complement factor H) and *MCP* (membrane cofactor protein) risk haplotypes.[125]

Genetic analysis can stratify the risk for aHUS relapse/recurrence after treatment discontinuation and kidney transplantation (Supplementary Figure S1).[126–129] In the 2015 Conference report,[1] related kidney donors were to be considered only if donors were free of any causative genetic (or acquired) factors identified in the recipient. The absence of pathogenic complement gene variants in the index case and the potential kidney donor is not a contraindication to kidney donation. In addition, donor *CFH* or *MCP* aHUS risk haplotypes are not contraindications to donation.[1] Healthy carriers of complement pathogenic variants are at risk of developing aHUS after kidney donation.[130] Genetic analysis can stratify the risk of disease development in such donors.

C5 polymorphisms may explain resistance to inhibition with eculizumab and ravulizumab, but these are very rare and mainly restricted to Asian populations.[131] The detection of anti-FH autoantibodies impacts the initial management of aHUS (combination of plasma exchange and/or complement inhibitor and/or immunosuppressive drugs). The evolution of anti-FH autoantibodies can stratify the risk of disease relapse/recurrence after treatment discontinuation or kidney transplantation. The management of patients with a persistently high titer of anti-FH autoantibodies and no clinical manifestations of TMA remains controversial.

Treatment

Currently available. C5 inhibition, when available, is the gold standard treatment for complement-mediated forms of aHUS.[132] Timing of therapy with the prompt use of C5 blockade is crucial for short- and long-term outcomes; however, establishing the diagnosis remains challenging, and treatment should be started without waiting for results of genetic screening. In countries where access to complement inhibitors is lacking, prompt prescription of plasma exchange should be considered. In most centers, anti-C5 drugs are used as prophylaxis in patients at high risk of recurrence after kidney transplantation. However, alternative strategies can be considered, including living donation in combination with a protocol to reduce endothelial injury[133] or combined liver-kidney transplant. Of note, pregnancy/postpartum-HUS, which is a diagnosis of exclusion, is deemed to be within the spectrum of complement-mediated kidney TMA, and as such, it should be treated with C5 blockade.

Emerging. For the acute and/or remission phase, various C5 inhibitors are available or in development, including antibodies, small, interfering RNA, and short- and long-acting drugs with multiple modes of administration. Targeting the alternative pathway at the level of C3 activation/FB/factor D inhibition is a potential alternative (Table 1; Figure 3). Overall, due to the disease severity, the use of any emerging agents should be primarily limited to maintenance of remission until their noninferiority to eculizumab is clearly established in the acute phase. Existing data (Supplementary Table S1) demonstrate the efficacy of ravulizumab at onset and in the maintenance phase, particularly in children[134]; in adults, results have been less clear, possibly because the populations studied may have included patients who did not have primary aHUS.[135] However, in the acute phase, before a diagnosis of complement-mediated aHUS is established, the use of long-acting complement blockade (ie, ravulizumab and crovalimab) raises concern.

Discontinuation of therapy. Once kidney function has improved and stabilized, discontinuation should be considered in patients without pathogenic variants in complement genes. The risk of relapse after discontinuation in these patients is very low, <5%.[136–138] Discontinuation in patients with pathogenic complement gene variants and those with persistently high-titer anti-FH autoantibodies should be determined on a case-by-case basis, in a shared-decision process. Extreme caution in stopping is warranted in patients with chronic kidney disease stages G3b–G5 and in kidney transplant recipients. Discontinuation requires close monitoring (monthly blood tests and weekly urinary dipsticks) and early treatment restart in the event of relapse. In patients requiring long-term C5 inhibition, regimens can be individualized if optimal complement blockade is maintained (CH50 <10%). The utility of drug trough level measurement is debatable.

C5 inhibition is ineffective in patients with *DGKe* variants or cyanocobalamin C deficiency in the absence of complement variants. There is also no proof that complement inhibition is beneficial in moderate or severe forms of Shiga toxin-producing *Escherichia coli*–associated (STEC)–HUS,[139] although some *in vitro* and *ex/in vivo* data document complement activated in STEC-HUS. Some case reports have claimed improvement of severe STEC-HUS after C5 blockade; however, it should be noted that STEC-HUS is a self-limiting condition in most cases. The ECULISHU trial (Eculizumab in STEC-HUS; ClinicalTrials.gov NCT02205541), a randomized controlled study in which 100 pediatric patients were assigned 1:1 to eculizumab or placebo, failed to show a benefit of eculizumab in the acute phase[6] (see Supplementary Table S1). Moreover, concerns regarding hepatic toxicity of eculizumab in STEC-HUS have been raised.[140,141] Results of the ECUSTEC

(Eculizumab in STEC; EudraCT 2016-000997-39) randomized trial are anticipated.

Complement inhibition in other forms of HUS. Enrichment of complement pathogenic variants in other forms of TMA has not been proven. Retrospective data have yielded discrepant results regarding the benefit from short-term C5 blockade.[142,143] Prospective controlled trials are in progress. After hematopoietic stem cell transplant, TMA is difficult to diagnose given the multiple potential causes of low platelet count, acute kidney injury, or anemia/hemolysis. Similarly, a differential diagnosis of *de novo* HUS post-kidney transplantation is difficult. In the absence of an alternative cause, including antibody-mediated rejection, treatment with a C5 blocker is to be started and re-evaluated based on complement genetic results and clinical response. In other forms of secondary TMA, there is no definite proof of benefit from C5 inhibition.

C3 GLOMERULOPATHY AND IMMUNE-COMPLEX MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Histology

C3G. C3G typically appears as a membranoproliferative pattern, although mesangial, endocapillary proliferative, crescentic, and sclerosing patterns may be present with light microscopy. With immunofluorescence microscopy, C3 is dominant and C1q is typically negative.

IC-MPGN. IC-MPGN is characterized by the deposition of immune complexes containing both polyclonal immunoglobulins and complement. This lesion classically results from chronic antigenemia with or without circulating immune complexes and is usually due to infections or autoimmunity.[144] IC-MPGN can be identical to C3G with light microscopy; however, on immunofluorescence, C3 staining is co-present with IgG and with C1q, IgA, and IgM at varying intensities. Identifying the driving antigen can be challenging and requires a thorough clinical history with review of antecedent exposures and comorbidities (mainly infection).[145,146] In adults, infections, autoimmune disease, and monoclonal immunoglobulin are responsible for most cases of IC-MPGN.[147]

True primary immunoglobulin-associated MPGN is rare in adults. It is more prevalent in children and often associated with genetic and/or serologic evidence of dysregulation of the alternative pathway.[148,149] IC-MPGN may evolve to C3G, and in such cases, an infection is the most frequent disease trigger.

Genetic testing

The genetics of C3G and IC-MPGN are complex and, in the opinion of most participants, should be evaluated in all patients with paraprotein-negative C3G and primary IC-MPGN. Studies suggest that rare variants (minor allele frequency <0.1%), most frequently in *CFH*, *CFI*, *C3*, or *CFB*, will be found in approximately 20% of patients, often with a corresponding quantitative complement protein deficiency.[148–150] The presence of a rare variant is associated with poor kidney survival.[148]

Familial C3G is rare and has been linked to (i) dominantly inherited gain-of-function genomic rearrangements that generate *CFH-related* (*CFHR*) fusion genes with duplication of the N-terminal dimerization domains such as classic CFHR5 nephropathy (endemic in Cyprus; *CFHR*5/5), although other examples include *CFHR2/5*, *CFHR3/1*, *CFHR5/2*, and *CFHR1* fusions[151–155]; (ii) dominantly inherited *C3* gain-of-function variants in single families such as c.2768_2773delACGGTG, p.(Asp923_Gly924del); c.2327T>C, p.(Ile756Thr); and c.2390A>T, p.(Asp797Val), which lie in a mutational hotspot area[156,157]; and (iii) recessively inherited biallelic *CFH* variants, which have been described with dense deposit disease and C3G glomerulonephritis presenting early in life.[158,159] Genetic counseling for these families is complex and nuanced, and segregation analysis must include comprehensive genetic and complement biomarker testing. Risk for disease cannot be determined by only following allele segregation as illustrated by single truncating/missense variants in genes such as *CFB*, *CFH*, and *C3*, in which the observed phenotype is dependent on the underlying genetic complement background and the circulating levels of complement proteins.[160] This complexity means not only that penetrance is highly variable but also that the observed phenotype can be C3G/IC-MPGN, aHUS, or another related disease, significantly complicating variant interpretation and genotype-phenotype association studies.

Identifying non-monogenic genetic risk factors for C3G and IC-MPGN. Common variants in *HLA* (human leukocyte antigen), *C3*, *CFH*, and *CD46* (MCP) alter risk of C3G and IC-MPGN but have only modest effects (odds ratio: 1.4–2.5).[161–163] This effect is not clinically actionable if the individual carries no other genetic variants; however, if a pathogenic variant is present, common variants that modify risk may impact penetrance and inform genetic counseling in these families.[164,165] International collaborations are recommended to study the genetics of C3G, with controls for variant ascertainment and ancestry, complemented with robust functional characterization of identified variants.

Serologic testing

Nephritic factors (NeFs) are present in 40%–80% of patients and constitute a heterogeneous group of autoantibodies that stabilize either or both C3 convertase and C5 convertase complexes. They are distinct from anti-FB and anti-C3 autoantibodies in that NeFs bind convertases but not the native proteins from which convertases are derived. The most specific and sensitive assays quantitate NeF activity by complement-driven hemolysis of sheep erythrocytes (Supplementary Table S6).

The presence of NeFs is typically associated with a reduction in circulating C3 and an increase in complement activation products. High C3NeF/C5NeF activity correlates

with low C3 levels (C3NeF and C5NeF) and high sC5b-9 levels (C5NeF). C3NeF is more prevalent in dense deposit disease, and C5NeF is more prevalent in C3G glomerulonephritis and IC-MPGN.[166,167] Detection of NeFs indicates an autoimmune process, can define the site of complement dysregulation, and may suggest responsiveness to treatments inhibiting the complement cascade at different levels. C4NeFs are occasionally identified in C3G and IC-MPGN, have a similar effect as C5NeF,[166a,167,168] and are believed to activate the convertases of the classical and lectin pathways (C4b2a and C4b2aC3b).

NeF screening should be accompanied by complement biomarker profiling to determine the degree of co-occurring complement dysregulation (Supplementary Table S6). The role of cluster analysis in revealing the impact of C3NeFs and C5NeFs on diagnosis and clarifying disease etiology is promising but needs validation.[167,169,170] Testing for anti-FB autoantibodies is useful, as transient high titers of these antibodies have been associated with post-infectious glomerulonephritis.[171]

No commercial NeF assays are available, and testing is performed in specialized laboratories. Many of these laboratories work actively with the International Union of Immunological Societies Committee for the Standardization and Quality Assessment of Complement Measurements to cross-validate complement assays and ensure rigor and reproducibility in testing results. Common reference lab protocols need to be validated and disseminated for serologic testing of autoantibodies to FH, NeFs, and individual complement components and their breakdown products. Correlation of complement measurements with clinical outcomes is important to allow the assessment of drug efficacy in the future.[166,167]

Monoclonal gammopathies

All adults over age 50 years presenting with C3G/IC-MPGN should be screened for monoclonal gammopathy.[144,171a] The chance of a monoclonal band being incidental to C3G is small in those <50 years of age (in clinical experience, the youngest case of monoclonal gammopathy–C3G has been a 17-year-old). To improve kidney outcomes, when a paraprotein is identified, treatment should be directed at the underlying hematological disease.[172] Anecdotally, a short course of eculizumab used in combination with hematological treatment has shown favorable results in patients with monoclonal gammopathy–driven C3G. Trial data would be needed to assess whether complement inhibition with or without clone-directed therapy is better than treatment of hematological disease alone.

Treatment

The natural histories of C3G and IC-MPGN are incompletely understood, making it difficult to define the prognostic value of early parameters of disease. There is evidence, however, that biopsy features, proteinuria, and kidney function are important prognostic markers. In addition, circulating complement biomarkers in plasma may be of prognostic significance because most cases show complement activation in fluid phase.[173]

In C3G, the frequency and functional effect of NeFs as well as the presence of variants in complement genes associated with deposition of C3 in the glomerulus strongly implicate activation of the alternative pathway of complement as playing a central, early role in disease pathophysiology. For autoimmune (C3NeF)-driven C3G, therapies targeting the autoantibody have not proven effective, suggesting that even small amounts of NeF may be sufficient to drive disease and that complete elimination is unachievable with currently available immunosuppressive strategies. Therapy targeting the alternative pathway is an attractive approach in this disease and may address a significant unmet medical need.

Specific supportive therapies are beneficial. For mild cases (e.g., proteinuria <1 g/d with no tendency to increase in adults, <0.5 g/d in children, stable eGFR), general renoprotective therapies (renin-angiotensin-aldosterone system blockade as the initial antiproteinuric and antihypertensive measure) and low-sodium diet should be advised. In a retrospective observational study, the use of renin-angiotensin-aldosterone system blockers was associated with better kidney survival.[174] It has been reported that renin is able to cleave C3,[175] but this claim has been refuted and should not inform treatment.[13] Evidence for using sodium-glucose cotransporter 2 inhibitors is lacking, but data from other glomerular diseases suggest a possible benefit, especially in adults with C3G/IC-MPGN and chronic kidney disease.

For patients with proteinuria 1–2 g/d (children >0.5 g/d) despite receiving optimized supportive therapy, treatment with mycophenolate mofetil or mycophenolic acid analogs (combined with corticosteroids) is considered reasonable, especially with albuminuria increases over time and severe activity lesions in kidney biopsy.[176–184] Although the mechanism of action is not known, mycophenolate mofetil likely decreases glomerular inflammation rather than inhibiting C3NeF activity. As baseline proteinuria increases, the probability of an effect with mycophenolate mofetil decreases. Relapse after discontinuation of treatment is frequent, although less likely with longer treatments.[180] In retrospective observational studies, mycophenolate mofetil has shown a greater capacity to induce remissions than other immunosuppressive regimens, although remarkable discrepancies have been reported between series. Some benefit from the use of calcineurin inhibitors has also been reported.[178–184] Currently, oral immunosuppressive agents are the mainstay of treatment for more severe forms of C3G and IC-MPGN given the lack of proven alternatives.

Terminal complement inhibition/plasma therapy. Case reports and case series suggest that crescentic, rapidly progressive disease or the presence of TMA lesions (occasionally but not always with high circulating sC5b-9 levels) is most likely to be responsive to eculizumab.[185] A very rapid, substantial, and sustained improvement has been reported

with eculizumab in some patients with these severe presentations; however, access to eculizumab is very limited in most countries. In addition, the rarity and speed of kidney function loss in these patients mean they are poorly represented in clinical trials, so case series data are unlikely to be forthcoming soon. The efficacy of eculizumab in slowly progressive forms of C3G seems limited.[185–187] Short-term benefits of plasma infusion or plasma exchange for refractory cases with an FH deficiency have been demonstrated,[188] but evidence of long-term benefit is lacking. Plasma-based treatment can be very arduous, and sensitization is a risk.

Complement alternative pathway inhibition might offer benefit to patients in whom clinical, biochemical, or histologic features suggest high risk of poor outcomes, such as those with high activity score, low chronicity index, proteinuria, nephrotic syndrome, or eGFR decline. Phase 2 and preliminary phase 3 study results with avacopan (a C5aR antagonist),[189] iptacopan (an FB inhibitor),[190] and pegcetacoplan (a C3 inhibitor)[191] indicate important short-term proteinuria reduction and stabilization of kidney function (Supplementary Table S1). Mechanistic data on the effect of these treatments in disease situations are lacking. Making trial biomarker data public would be beneficial for tailoring trial designs.

The evidence supporting complement inhibition is more limited in IC-MPGN.[192] Some cases of IC-MPGN behave similarly to C3G, and some patients switch from IC-MPGN to C3G. Consistent with this observation, there is overlap in common genetic variant risk factors and some serological markers. If underlying infectious, autoimmune, or monoclonal disease is ruled out, it is reasonable to treat IC-MPGN similarly to C3G. However, data on IC-MPGN patients treated with complement inhibitors are sparse (the EAGLE trial [Eculizumab in Primary MPGN] did include patients with IC-MPGN),[187] though recent trials will provide results soon (see Table 1). To retrospectively analyze the effects of different treatments, large cohorts with well-defined diagnostic criteria are needed, as well as inclusion of IC-MPGN cases in prospective studies with new complement inhibitors.

Endpoints. Proposed endpoints to assess treatment efficacy are a decrease in proteinuria and stabilization or improvement of eGFR.[1,2,193,194] Long-term natural history data are needed to determine how to define successful control of proteinuria.[195] Given the young age of disease onset, some patients may need kidney function for 80-plus years from disease onset. Histology, eGFR, eGFR slope, kidney failure, edema, nephrotic syndrome, and hematuria remission are factors to consider. Complement biomarkers (C3 levels, C3NeF activity, and biomarkers of alternative pathway activation) may be helpful in monitoring the effectiveness of complement inhibition, but better data are required to correlate systemic complement activity with clinical outcomes. Patients in attendance expressed the view that repeat biopsies are not necessarily unacceptable for participation in trials.

With the exception of data suggesting benefit of terminal pathway blockade in select cases,[187] there are currently insufficient data to tailor the selection of a specific complement inhibitor based on serological, genetic, and biomarker workup of patients with C3G and IC-MPGN.

CONCLUSIONS AND FUTURE DIRECTIONS

Numerous lines of evidence show that activation or dysregulation of complement plays some role in the pathogenesis of a growing array of kidney diseases. Although in aHUS and C3G/IC-MPGN alternative pathway dysregulation appears to be the main driver of disease, in other conditions, complement may play a more nuanced role, for example, perpetuating glomerular injury after immune complex deposition, as in MN, or contributing to chronic damage, as in diabetic kidney disease or FSGS. As a growing number of therapeutic agents targeting different parts of the complement cascade become available, understanding how and when to use them requires a vast improvement in our capacity to pinpoint the relevant complement pathway or protein involved in each patient and characterize its role (central or marginal) and its phase (acute or chronic). Table 2 highlights the concerns and needs of the patient population that should be honored and addressed. Supplementary Table S2 summarizes the group consensus on where we are for all the kidney diseases described based on currently available research, whereas Table 3 explicitly defines research priorities likely to improve our understanding of complement dysregulation in kidney diseases and to improve patient care. Crucially, biomarker studies are needed to identify disease-specific panels of biomarkers that can facilitate the diagnosis, treatment monitoring, and/or assessment of different glomerular diseases.

Given that these kidney diseases are mostly rare and heterogeneous, significant progress can be made only through concerted, multinational efforts to identify biomarkers of complement activation/dysregulation, standardize their measurement, and promote their global implementation. The clinical trials aimed at evaluating complement inhibitors in kidney diseases need to prospectively collect serum, whole blood, urine, and kidney biopsy tissue to validate existing and future diagnostic and prognostic tools. Dissemination of data on complement biomarkers in the tissue, plasma, and urine should be required in these studies. The limited biomarker data already available are listed in Supplementary Table S3. All relevant stakeholders (patient and caregiver associations, medical societies, national and international health authorities, and pharmaceutical companies) need to synergize to promote registries, biobanks, data sharing, and open access to trial results to allow our understanding and our resources to evolve to the point where we can fingerprint individual patients and offer them early, accurate diagnosis and safe, effective, and affordable treatment.

APPENDIX

Additional Conference Participants

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Supplementary material is available online at www.kidney-international.org.

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