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Balancing efficacy and safety of complement inhibitors

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ABSTRACT

Complement inhibitors have been approved for several immune-mediated diseases and they are considered the next paradigm-shifting approach in the treatment of glomerulonephritis. The hierarchical organization of the complement system offers numerous molecular targets for therapeutic intervention. However, complement is an integral element of host defense and therefore complement inhibition can be associated with serious infectious complications. Here we give a closer look to the hierarchical complement system and how interfering with proximal versus distal or selective versus unselective molecular targets could determine efficacy and safety. Furthermore, we propose to consider the type of disease, immunological activity, and patient immunocompetence when stratifying patients, e.g., proximal/unselective targets for highly active and potentially fatal diseases while distal and selective targets may suit more chronic disease conditions with low or moderate disease activity requiring persistent complement blockade in patients with concomitant immunodeficiency. Certainly, there exists substantial promise for anti-complement therapeutics. However, balancing efficacy and safety will be key to establish powerful treatment effects with minimal adverse events, especially when complement blockade is continued over longer periods of time in chronic disorders.

1. Introduction

Complement is a crucial element of the innate immune system during homeostasis functions as well as during host defense. Complement factors not only enhance the antimicrobial action of antibodies but also interact with the coagulation system [1,2]. Imbalances in the complement system can trigger unnecessary sterile thromboinflammation. The kidney is particularly susceptible to complement-mediated sterile inflammation, including immune-mediated kidney diseases, thrombotic microangiopathies (TMA), vasculitis, and progressive kidney fibrosis [3,4].

The first clinically available C5 inhibitor, eculizumab, approved for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), has promoted the development of other complement inhibitors [5–7]. Avacopan, an oral C5a receptor (C5aR) antagonist, controls antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) along with clinically relevant steroid-sparing effects [8]. Other indications for which the FDA approved complement therapeutics are listed in Table 1. Furthermore, these and numerous next-generation complement inhibitors are currently being explored in clinical trials for kidney and various diseases, ranging from acute inflammatory conditions to chronic disorders (Table 2).

Nevertheless, novel (and costly) drugs must undergo a thorough risk and benefit assessment. To customize complement-targeting therapies, we address this aspect by reviewing the multiple complement effector functions in the context of host defense and pathological conditions, how these functions are modulated by distinct targets of complement inhibitors, and patient-related factors that influence the personalized risk-benefit assessment.

2. The hierarchical nature of the complement system

The complement system comprises over 50 plasma and membrane-bound proteins that participate in both innate and adaptive immunity to maintain homeostasis (Fig. 1) [9]. Fluid-phase complement factors function as opsonins by binding to pathogens, dead cells, cell debris, and other particles, in addition to their role in chemotaxis as anaphylatoxins. Complement binding acts as “find-me” and “eat-me” signals, facilitating clearance of the particle by phagocytes. At endothelial surfaces, membrane-bound complement components form split products that drive endothelial activation and recruit/activate immune cells, enhancing host defense and sterile inflammation. The formation of the

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membrane attack complex (MAC) can directly induce lysis of pathogens for host defense but also rupture of blood cells in some hemolytic anemias, or result in tissue necrosis, i.e., sterile necroinflammation.

The activation of C3 convertase is a pivotal step in the complement cascade and can be facilitated in three different ways: the classical pathway, the lectin pathway, and the alternative pathway [10]. *Classical pathway* activation relies on the formation of antibody-antigen immune complexes. Recognition and binding of immune complexes to C1q lead to C1r and C1s subunit activation, culminating in C4 and C2 activation and subsequent C3 convertase formation (C4b2b). *Lectin pathway* activation depends on mannose-binding lectin (MBL) binding to microbial carbohydrate structures, involving MBL-associated serine proteases (MASP). MASP cleaves and activates C4 and C2, leading to C3 convertase C4b2b formation. In the fluid phase, the *Alternative pathway* maintains homeostasis via the gradual and spontaneous hydrolysis of C3, forming C3(H_2O). C3(H_2O) binds to factor B (FB) to form the C3 proconvertase, then factor D (FD) cleaves the Ba fragment to form the fluid-phase mature convertase, C3(H_2O)Bb. This convertase cleaves additional C3 to generate C3a and C3b. Furthermore, the binding of C3b to FB, followed by the cleavage of the Ba fragment, promotes the generation of the surface-phase C3 convertase, C3bBb. This further amplifies C3b levels through self-amplification. Enhanced surface density of C3b, produced by these C3 convertases, promotes the formation of C5 convertases (C4b2a3b and C3bBb3b) that cleave C5 into C5a and C5b. C5b leads to the assembly of MAC (C5b-9) on target cell surfaces, inducing direct cell injury.

The cleavage products of C3 and C5 possess multiple effector functions in host defense. C3b acts as an opsonin, promoting phagocytic clearance. Furthermore, C3b and its degradation product iC3b facilitates immune cell adhesion via complement receptor 1 (CR1: CD35), phagocytosis via the integrin receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18), and modulating adaptive immune responses via CR2 (CD21). C3a modulates immune cell functions through C3a receptor (C3aR) signaling [11]. C5a, a potent anaphylatoxin, exhibits diverse effector functions, including chemotaxis, the activation of immune and endothelial cells, priming neutrophils for extracellular trap formation, and intricate interactions with the coagulation system though C5aR (CD88) activation [12,13]. Notably, C4a, derived from the cleavage of C4, elicits inflammatory immune responses and is thus indicated as the third anaphylatoxin [14,15]. Nevertheless, as long as a functional C4a receptor has not been identified, the role of C4a as an anaphylatoxin remains debated [16].

The complement system, especially the alternative pathway, is tightly controlled by several regulator proteins [17]. Factor H (FH) acts as a key negative regulator, competing with FB for C3b binding and accelerating C3bBb decay. Moreover, in conjunction with factor I, FH facilitates the proteolytic inactivation of C3b. In contrast, properdin, functioning as a positive regulator, plays a major role in the formation, stabilization, and activity of C5 convertase of the alternative pathway.

3. Balancing benefits and risks: the drug target

The hierarchical organization of the complement system may imply that a proximal and unselective inhibition may elicit more efficacy but also impair host defense, while a more distal or more selective inhibition of the complement cascade will have less adverse effects on host defense but might be not as efficacious in blocking inflammation. So far, the theory, but what is the evidence?

Proximal (C3) inhibition of the entire complement cascade should be most efficacious to suppress inflammatory disorders. Indeed, C3-deficient mice are literally protected from inflammatory disease models including AAV [18] and membranous nephropathy (MN) [19] (Table 3). Notably, a recent phase 3 trial compared the efficacy of the C3 inhibitor pegcetacoplan to the C5 inhibitor eculizumab in patients with hemolysis due to PNH. C3 blockade was more potent in improving hemoglobin levels and the need for blood transfusions [20]. Trial data indicated similar infectious adverse events (pegcetacoplan vs eculizumab: 29 % vs 26%) during a 16-week time frame, a duration too short for a reliable safety assessment. Indeed, the duration of persistent C3 inhibition may be much longer in chronic disorders with foreseen exposure to pegcetacoplan such as C3 glomerulopathy (C3G) and IgA nephropathy (IgAN) (Table 2). Standard-of-care with other immunosuppressive drugs may increase the risk for infectious complications. Furthermore, considering that adaptive immunity is incompletely developed during early childhood, and young patients rely more on innate immunity [21], in young children, the risk for infectious complications could be higher with proximal complement inhibition compared to adolescents and adults. Even those without immunodeficiency should undergo thorough evaluation for latent infections and possibly prophylactic measures when considering C3 inhibitors that elicit persistent C3 blockade.

Distal (C5) inhibition of the terminal complement cascade

Table 1
FDA approved complement inhibitors.

Target	Drug name	Type	Route	Intervals	Indication (approval)
C1r, C1s, MASPs	C1 esterase inhibitor (Cinryze)	Purified protein	IV	Every 3–4 days	Hereditary angioedema (2008)
C1r, C1s, MASPs	C1 esterase inhibitor (Berinert)	Purified protein	IV	Acute attacks	Hereditary angioedema (2009)
C1r, C1s, MASPs	C1 esterase inhibitor (Ruconest)	Recombinant protein	IV	Acute attacks	Hereditary angioedema (2014)
C1s	Sutimlimab	mAb	IV	2 weeks weekly then every 2 weeks	Cold agglutinin disease (2022)
FB	Iptacopan	Small molecule	PO	2 times daily	Paroxysmal nocturnal hemoglobinuria (2023)
C3	Pegcetacoplan	Peptide	SC	2 times weekly	Paroxysmal nocturnal hemoglobinuria (2021)
C3	Pegcetacoplan injection	Peptide	Intravitreal injection	Every 25–60 days	Geographic atrophy (2023)
C5	Eculizumab	mAb	IV	5 weeks weekly then every 2 weeks	Paroxysmal nocturnal hemoglobinuria (2007), Atypical hemolytic uremic syndrome (2011), Myasthenia gravis (2017), Neuromyelitis optica spectrum disorder (2019)
C5	Ravulizumab	mAb	IV	2 weeks for 2 doses then every 8 weeks	Paroxysmal nocturnal hemoglobinuria (2018), Atypical hemolytic uremic syndrome (2019), Myasthenia gravis (2022)
C5	Avacincaptad pegol	RNA aptamer	Intravitreal injection	Once monthly	Geographic atrophy (2023)
C5	Pozelimab	mAb	IV/SC	Once weekly	CD55-deficient protein-losing enteropathy (2023)
C5	Zilucopan	Peptide	SC	Once daily	Myasthenia gravis (2023)
C5aR	Avacopan	Small molecule	PO	2 times daily	Antineutrophil cytoplasmic antibody-associated vasculitis (2021)

C5aR: C5a receptor, FB: factor B, MASP: mannose-binding lectin-associated serine protease.

Table 2
Complement inhibitors in clinical trials for kidney diseases.

Disease	Target	Drug name	Type	Route	Phase	Trial Code	Status
aHUS	C5	Eculizumab	mAb	IV	2	NCT00844844	Completed
					2	NCT00844545	Completed
					2	NCT00844428	Completed
					2	NCT00838513	Completed
					2	NCT01757431	Completed
					2	NCT01194973	Completed
					2	NCT01193348	Completed
					4	NCT02574403	Completed
					4	NCT04859608	Recruiting
					3	NCT05876351	Not yet recruiting
	C5	Ravulizumab	mAb	IV	3	NCT02949128	Completed
					3	NCT03131219	Completed
	C5	Crovalimab	mAb	IV	3	NCT04861259	Recruiting
					3	NCT04958265	Recruiting
	FB	Iptacopan	Small molecule	PO	3	NCT04889430	Recruiting
					3	NCT05795140	Not yet recruiting
					3	NCT05935215	Not yet recruiting
	Bb	NM8074	mAb	IV	2	NCT05684159	Not yet recruiting
	MASP-2	Narsoplimab	mAb	IV	3	NCT03205995	Unknown
TMA	C5	Eculizumab	mAb	IV	2	NCT01410916	Completed
					3	NCT02205541	Completed
					2	NCT03518203	Completed
					3	NCT05726916	Not yet recruiting
					3	NCT05702996	Not yet recruiting
	C5	Ravulizumab	mAb	IV	3	NCT04557735	Recruiting
					3	NCT04543591	Recruiting
					3	NCT04743804	Terminated
	C5	Nomacopan	Recombinant protein	SC/IV	3	NCT04784455	Recruiting
	C3	Pegcetacoplan	Synthetic peptide	SC	2	NCT05148299	Recruiting
	MASP-2	Narsoplimab	mAb	IV	2	NCT02222545	Completed
					2	NCT05855083	Recruiting
AAV	C5	Eculizumab	mAb	IV	2	NCT01275287	Withdrawn
	C5aR	Avacopan	Small molecule	PO	2	NCT01363388	Completed
					2	NCT02222155	Completed
					3	NCT02994927	Completed
	C5a	Vilobelimab	mAb	IV	2	NCT03712345	Terminated
					2	NCT03895801	Completed
C3G	C5	Eculizumab	mAb	IV	1	NCT01221181	Completed
	C5aR	Avacopan	Small molecule	PO	2	NCT03301467	Completed
	C3	Pegcetacoplan	Synthetic peptide	SC	2	NCT03453619	Active
	FB	Iptacopan	Small molecule	PO	2	NCT03832114	Completed
					3	NCT04817618	Recruiting
					3	NCT03955445	Recruiting
	Bb	NM8074	mAb	IV	2	NCT05647811	Not yet recruiting
	FD	Danicopan	Small molecule	PO	2	NCT03369236	Completed
	FD	Pelecopan	Small molecule	PO	2	NCT05162066	Terminated
	MASP-2	Narsoplimab	mAb	IV	2	NCT02682407	Unknown
IC-MPGN, C3G	C5	Eculizumab	mAb	IV	2	NCT02093533	Completed
	C3	Pegcetacoplan	Synthetic peptide	SC	3	NCT05067127	Recruiting
					3	NCT05809531	Not yet recruiting
	FD	Danicopan	Small molecule	PO	2	NCT03124368	Completed
					2	NCT03459443	Terminated
	MASP-3	OMS906	mAb	IV	2	NCT06209736	Not yet recruiting
LN	C5	Ravulizumab	mAb	IV	2	NCT04564339	Recruiting
	C3	Pegcetacoplan	Synthetic peptide	SC	2	NCT03453619	Active
	FB	Iptacopan	Small molecule	PO	2	NCT05268289	Not yet recruiting
	FD	Vemircopan	Small molecule	PO	2	NCT05097989	Recruiting
	MASP-2	Narsoplimab	mAb	IV	2	NCT02682407	Unknown
IgAN	C5	Ravulizumab	mAb	IV	2	NCT04564339	Recruiting
	C5	Cemdisiran	RNAi	SC	2	NCT03841448	Active
	C5aR	Avacopan	Small molecule	PO	2	NCT02384317	Completed
	C3	Pegcetacoplan	Synthetic peptide	SC	2	NCT03453619	Active
	FB	Iptacopan	Small molecule	PO	2	NCT03373461	Completed
					3	NCT04578834	Recruiting
					3	NCT04557462	Recruiting
	FB	IONIS-FB-LRx	Antisense oligonucleotide	SC	2	NCT04014335	Recruiting
	FB	RO7434656	Antisense oligonucleotide	SC	3	NCT05797610	Recruiting
	FD	Vemircopan	Small molecule	PO	2	NCT05097989	Recruiting
	FD	Pelecopan	Small molecule	PO	2	NCT05162066	Terminated
	MASP-2	Narsoplimab	mAb	IV	2	NCT02682407	Unknown
					3	NCT03608033	Unknown
MN	C3	Pegcetacoplan	Synthetic peptide	SC	2	NCT03453619	Active
	FB	Iptacopan	Small molecule	PO	2	NCT04154787	Terminated
	FD	Pelecopan	Small molecule	PO	2	NCT05162066	Terminated
	MASP-2	Narsoplimab	mAb	IV	2	NCT02682407	Unknown

including the MAC is an established strategy to protect host cells from excessive complement-mediated inflammation. Eculizumab and ravulizumab have shown efficacy and tolerability in patients with aHUS [66,67], as well as those with myasthenia gravis, wherein autoantibodies against acetylcholine receptors induce MAC formation, resulting in structural damage to the neuromuscular junction and impairment of signal transmission (Table 1) [68,69]. Murine models with C5 deficiency and inhibition further support the therapeutic potential of C5 targeting in various kidney diseases, including aHUS [22,23], lupus nephritis (LN) [45], and MN [63]. Currently, numerous clinical studies are testing the effect of eculizumab, ravulizumab, nomacopan, and cemdisiran (Table 2). Whether siRNA-based long-lasting C5 inhibitors such as cemdisiran are prone to more infectious complications compared to biological C5 inhibitors is currently unknown.

Theoretically, inhibiting C5 preserves C3-associated effector functions, e.g., C3b-mediated opsonization and immune cell activation, thereby reducing the risk of infectious complications compared to an upstream C3 blockade, which also abrogates C3b effects. However, C5 inhibition still compromises both C5a- and C5b-9-mediated host defense mechanisms. Indeed, eculizumab therapy is associated with Neisseria species infections, primarily cleared by MAC, ranging from 0.25 to 0.9 cases per hundred patient-years [70,71]. Meningococcal vaccination and antibiotic prophylaxis can minimize this risk, which could be avoided by selective inhibition of C5a/C5aR to preserve the capacity for terminal MAC formation.

Selective inhibition of C3 or C5 split products without affecting MAC formation: Targeting C3a/C3aR may suppress inflammatory disease mechanisms while preserving C3b- and C5b-9-mediated host defense. Nevertheless, the response to C3aR deficiency in animal models presents inconsistencies. C3aR ablation or inhibition reduced proteinuria and glomerular histopathology in IgAN mice [62] and MN rats [64], whereas C3aR deficiency accelerated kidney dysfunction and elevated autoantibody levels in lupus mice [53]. These paradoxical outcomes may relate to the diverse roles of C3a on immune cells, e.g., anti-inflammatory effects dominate during the acute phase, whereas pro-inflammatory aspects dominate the chronic phase [11]. Thus, targeting C3a/C3aR may offer therapeutic options depending on the disease context and its implicated immune cell subsets.

The C5aR inhibitor avacopan exhibited non-inferiority in achieving remission of AAV and superiority in patients sustaining remission to oral prednisolone concurrently receiving cyclophosphamide or rituximab [8]. For now, avacopan-treated patients did not encounter Neisseria infections, although safety data on avacopan are still limited. Animal studies reported the therapeutic potential of C5aR inhibitor also in C3G [30], LN [46,47], and IgAN [62]. Selective C5aR inhibition introduces a perspective for efficacious and safe complement inhibition in immune-mediated diseases, which could be acceptable for patients even with concomitant immunodeficiency due to chronic kidney disease (CKD) and/or other immunosuppressants.

Selective inhibition of the lectin or alternative pathway: Inhibiting complement components within the initial pathways is another strategy to interfere with the complement system more selectively. Plasma-derived or recombinant C1 inhibitors represent the established treatment for hereditary angioedema with C1 inhibitor deficiency/dysfunction resulting from genetic mutations encoding C1 inhibitor (Table 1). C1 inhibitor normally prevents uncontrolled activation of the complement system (C1r and C1s in the classical pathway, as well as MASP-1 and -2 in the lectin pathway) and kallikrein-bradykinin cascade [72,73]. Consequently, the supplementation of C1 inhibitor in patients with hereditary angioedema suppresses the overactivation of these cascades, thereby regulating vascular permeability and mitigating angioedema attacks. Notably, C1 inhibitors have been tested in patients with antibody-mediated rejection following kidney transplantation, where the overactivation of the classical pathway is considered to be involved in its pathogenesis [74,75].

Genetic deletion or inhibition of FB and FD, elements of the alternative pathway, improved murine models of C3G [41], AAV [25], LN [57–60], and MN [63,65]. Meanwhile, numerous clinical studies are testing the efficacy and safety of FB and FD inhibitors in complement-mediated kidney disorders (Table 2). MASP represents another upstream target to suppress the complement initiation process. First data of the MASP-2 inhibitor narsoplimab were recently reported from a phase 2 trial involving patients with hematopoietic stem-cell transplantation (HSCT)-associated TMA (HSCT-TMA). MASP-2 inhibition showed a favorable response without notable safety concerns [76], and ongoing clinical trials are currently testing narsoplimab also in other kidney diseases (Table 2). Nevertheless, the balance between efficacy and safety of these drugs in humans with and without immunodeficiencies remains unclear and likely depends on the disease context.

4. Balancing benefits and risks: treatment duration and dosing intervals

Conceptually, persistent complement blockade imposes higher risks than short term treatment. A prospective clinical trial revealed the potential for eculizumab discontinuation based on complement genetics in aHUS patients [77]. Elevated C5b-9 plasma levels upon eculizumab discontinuation corresponded with an increased susceptibility to aHUS relapse, indicating the feasibility of individualized treatment optimization through complement monitoring. Another study has demonstrated the potential of gradual spreading eculizumab treatment intervals, from once every two weeks to spans of three and then four weeks, under monitoring of disease activity and biomarkers in aHUS patients [78]. Obviously, less immunological activity requires less C5 inhibition. A phase 4 clinical trial is presently underway assessing the efficacy of personalized eculizumab infusion intervals based on monitoring (Table 2).

Given the potential for recurrent infections owing to compromised C3 functions, persistent C3 blockade seems risky, especially in chronic disorders. While such decisions will depend on disease pathogenesis associated with complement genetics, patient immunodeficient profile, and the results from forthcoming clinical investigations, limiting drug use to phases of high immunological activity will yield greater benefits and less infectious complications. Furthermore, the reduced risk associated with discontinuation or spaced administration may benefit from a complement biomarker-guided therapeutic approach also here.

5. Balancing benefits and risks: picking the right disease

Strategically, owing to their anti-inflammatory properties and their potential for infectious complications, complement inhibitors should be applied to the diseases characterized by severe and immunologically acute conditions, which are life-threatening or progressive toward organ failure. Conversely, for diseases with a chronic course, which although not immediately life-threatening but culminate in gradual organ failure, the decision of the optimal timing when to start and discontinue the complement inhibitors, and the optimal duration poses a challenge. Prolonged treatment, especially with proximal and unselective complement inhibitors, may come with the risk for infectious complications. Hence, for chronic diseases, more selective complement inhibitors such as C5a/C5aR or initial pathway components may have advantages. Together, choosing the right complement inhibitor may involve a series of considerations including disease pathogenesis, severity, immunological disease activity, therapeutic duration, patient age, and coexistent

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, aHUS: atypical hemolytic uremic syndrome, C3G: C3 glomerulopathy, C5aR: C5a receptor, FB: factor B, FD: factor D, IC-MPGN: immune complex-mediated membranoproliferative glomerulonephritis, IgAN: IgA nephropathy, LN: lupus nephritis, MASP: mannose-binding lectin-associated serine protease, MN: membranous nephropathy, TMA: thrombotic microangiopathy.

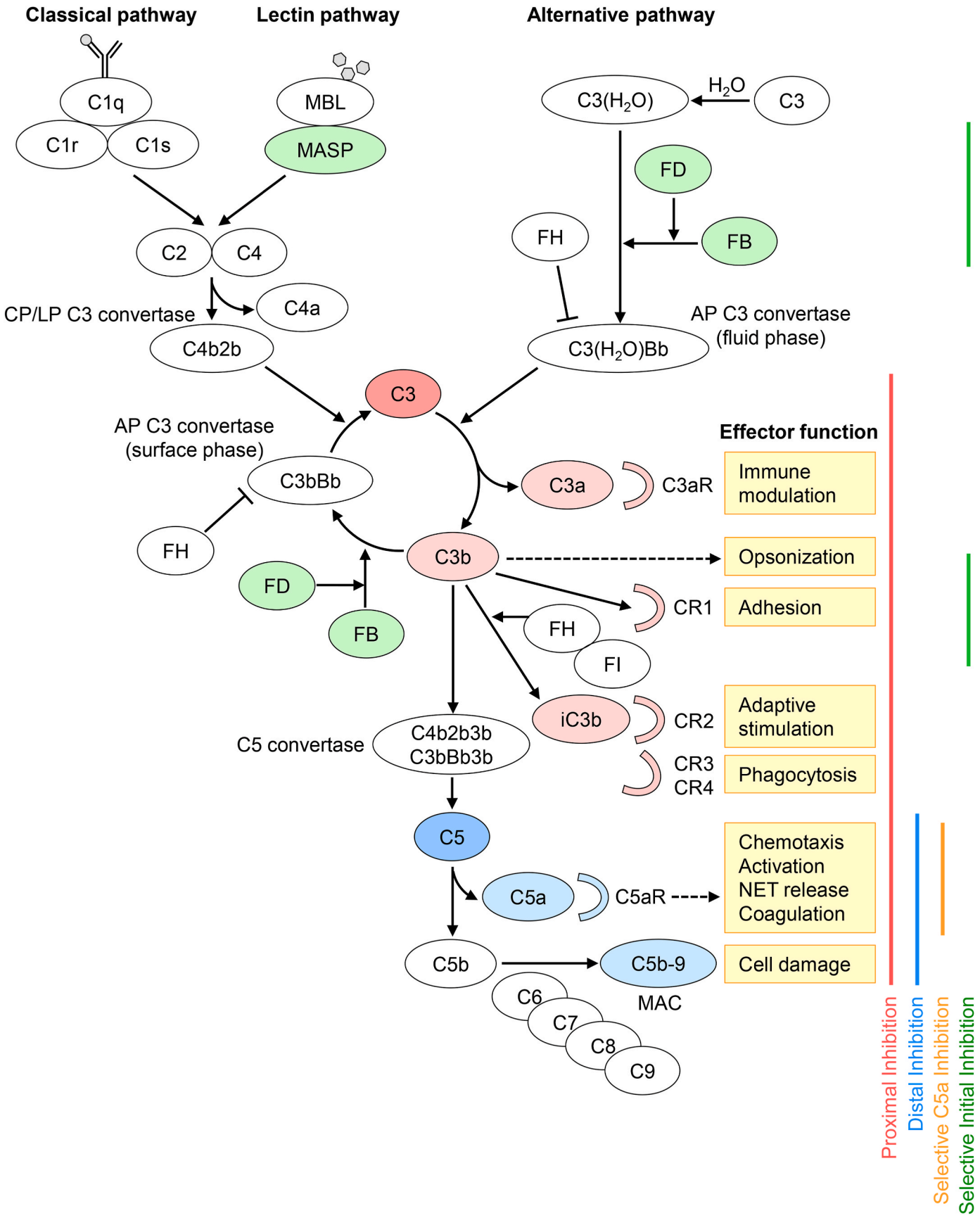

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Fig. 1. Modulation of complement effector functions through targeted complement inhibition
Complement system is originally activated by the classical, lectin, and alternative pathways for innate defense. The classical pathway is initiated by Immune complexes recognized by C1q followed by C1r and C1s subunit activation, while the lectin pathway is triggered by damage-associated molecular patterns or mannose-binding residues, mediated by the MBL/MASP complex. Both pathways converge to form the C3 convertase C4b2b. Additionally, the alternative pathway undergoes low-level activation through spontaneous hydrolysis of C3 (C3(H_2O)), generating the C3 convertase C3(H_2O)Bb. These C3 convertases cleave and activate C3 into C3a and C3b. Alongside Bb, a cleavage product of FB by FD, C3 convertase C3bBb is formed, initiating a self-amplifying loop by cleaving more C3. Enhanced surface density of C3b promotes the formation of C5 convertases (C4b2b3b and C3bBb3b), cleaving C5 into C5a and C5b. The latter leads to the assembly of MAC (C5b-9) on target cell surfaces, inducing direct cellular damage. C3a and C5a serve as potent anaphylatoxins, modulating immune cell phenotype, recruiting leukocytes, activating immune and endothelial cells, priming neutrophils for NET formation, and interacting with the coagulation system. C3b contributes to opsonization and, alongside its degradation product iC3b, facilitates immune cell adhesion (via CR1), phagocytosis (via CR3 and CR4), and modulate adaptive immune responses (via CR2). To prevent excessive complement activation and self-harm, complement regulators such as FH and FI tightly control the complement cascade. These regulators destabilize convertases to disrupt the amplification loop, and facilitate C3b degradation. Excessive complement activation adversely affects host cells and augments proinflammatory responses. Proximal inhibition at the level of C3 shut all the downstream effector functions. Distal inhibition of C5 suppresses both the functions of C5a and C5b-9 while preserving C3-associated functions. Selective inhibition of C5a regulates immune cell activities while preserving C3 and C5b-9-mediated host defense. Selective inhibition at the levels of FB, FD and MASP is directed towards the pathogenic initial pathways, partially dampening the downstream effector functions.
AP: alternative pathway, C3aR: C3a receptor, C5aR: C5a receptor, CP: classical pathway, CR: complement receptor, FB: factor B, FD: factor D, FH: factor H, FI: factor I, LP: lectin pathway, MAC: membrane attack complex, MASP: mannose-binding lectin-associated serine protease, MBL: mannose-binding lectin, NET: neutrophil extracellular trap.

primary or secondary immunodeficiencies.

5.1. Immunologically active/severe kidney disease

5.1.1. Atypical hemolytic uremic syndrome (aHUS)

aHUS is characterized by overactivation of the alternative complement pathway, resulting in microvascular immunothrombosis with subsequent thrombocytopenia, hemolytic anemia, and acute kidney injury [7,79–81]. The condition is equally prevalent in children and adults with a lower threshold for alternative pathway activation due to genetic or acquired factors [82,83]. A wide spectrum of environmental factors that trigger alternative pathway activity can serve as a second hit [82–84]. In 60% of aHUS patients, pathogenic variants are detectable including gain-of-function mutations in complement activators or loss-of-function mutations in complement regulators associated with the alternative pathway [7], i.e., autoinflammatory forms of aHUS. In approximately 6–10% of aHUS patients, autoantibodies inhibit complement regulator FH, i.e., autoimmune forms of aHUS [85].

Eculizumab and Ravulizumab are efficient in controlling aHUS activity, by suppressing C5 [66,67]. Notably, in aHUS mice, C5b-9 deficiency improved survival and TMA but did not prevent macrovascular thrombosis, whereas C5aR deficiency reduced macrovascular thrombosis but had no impact on survival and TMA. This suggests the distinct pathogenic roles of C5b-9 and C5a in aHUS, thus implying the potential effectiveness of C5 blockade for both [23].

20–30% of aHUS patients experience disease flares following the discontinuation of eculizumab [77,86]. Moreover, the treatment duration can be long which increases safety concerns. Currently, selective inhibitors targeting Bb (NM8074) and FB (iptacopan) are being tested in clinical trials with aHUS patients, also following switch from eculizumab to iptacopan (Table 2). The favorable outcomes and tolerability demonstrated in recent trials in PNH patients with iptacopan monotherapy [87] (NCT04558918) or add-on therapy to eculizumab [88] support these drugs as promising alternative approaches with more selective complement inhibitors, especially in patients requiring long-term treatment.

5.1.2. Hematopoietic stem-cell transplantation-associated thrombotic microangiopathy (HSCT-TMA)

HSCT-TMA, a form of secondary TMA, involves substantial endothelial injury due to the transplantation procedure and associated complications, such as immunosuppressants, graft-versus-host disease, and infections. It occurs frequently in approximately 10–20% of cases [9] and is associated with poor renal outcomes and high mortality rates [89]. HSCT-TMA involves complement activation through the lectin pathway [90], and MASP-2 inhibitor narsoplimab was effective and tolerable in a phase 2 clinical trial for HSCT-TMA [76]. Given the severe nature of this disease without available specific strategies [89], upcoming complement inhibitors have the potential to become primary therapy for TMA in this context.

5.1.3. Antineutrophil cytoplasmic antibody-associated vasculitis (AAV)

AAV is characterized by small vessel vasculitis, concomitant with the development of pathogenic autoantibodies ANCA [91]. C5a primes neutrophils via C5aR to facilitate ANCA-mediated neutrophil local retention and activation [92,93]. AAV predominantly affect individuals in the middle and older age and is frequently associated with CKD and a standard-of-care including immunosuppressants [94]. Both of these imply considerable secondary immunodeficiency and risk for infections, which would favor more highly selective complement inhibitors not further impairing host defense.

The C5aR antagonist avacopan is efficient and allows to almost complete avoidance of glucocorticoids [8]. Although optimal treatment duration should be determined in the future studies, this selective complement inhibition represents a pioneering achievement even applicable to immunologically active and severe disease, with the potential to extend its application to other diseases.

5.2. Chronic glomerulonephritis

5.2.1. C3 glomerulopathy (C3G)

C3G is a rare form of inflammatory glomerular disease characterized by glomerular C3 accumulation without concomitant immunoglobulin deposition [95]. C3G arises from the excessive activation of the alternative complement pathway [17,96], supported by evidence derived from animal experiments (Table 3). In approximately 25% of C3G patients, inborn errors of complement immunity contribute to overactivation of the alternative pathway, i.e., autoinflammatory C3G [97,98], while in autoimmune C3G [99], autoantibodies that target the C3 convertase stabilize and increase its half-life. As a third form, monoclonal paraproteins can act as an additional mechanism for activating the alternative pathway [100,101]. While each of these forms may require a different causal therapeutic approach, complement inhibitors may abrogate the key pathomechanism in all of them. Likely, this is clinically important because approximately 70% of children and 50% of adults with C3G still progress to kidney failure within 10 years [17].

Eculizumab is effective only in a subset of patients with C3G [102], potentially due to robust activation of upstream complement at the level of C3 convertase, and because chronic forms of C3G are not necessarily immunologically active [103]. Currently, inhibitors targeting upstream complement components are underway (Table 2). Of note, the FD inhibitor danicopan showed an insufficient pharmacokinetic and pharmacodynamic response in C3G patients [104]. Similarly, FD-deficient C3G mice are not protected and show persistent activation of the

Table 3
Complement involvement tested in animal models with kidney diseases.

Disease	Target	Model	Drug	Phenotype	Reference
aHUS	C5	$C5^{-/-}$.$FH^{-/-}$.FHΔ16-20 mouse	–	No disease development (normal renal function and histopathology). Reduced glomerular C3 and C9 deposition.	[22]
	C5	Nephrotoxic nephritis in $C5^{-/-}$.$FH^{-/-}$.FHΔ16-20 mouse	–	Reduced hematuria, proteinuria, glomerular neutrophils and thrombosis, glomerular C9 deposition.	[22]
	C5	$C5^{-/-}$.$FH^{R/R}$ (FH W1206R point mutation) mouse	–	Improved survival, kidney function, thrombocytopenia, renal TMA	[23]
	C5	$FH^{R/R}$ mouse	Anti-C5 mAb (BB5.1)	Improved survival, thrombocytopenia, renal TMA	[23]
	C5aR	$C5aR^{-/-}$.$FH^{R/R}$ mouse	–	Improved macrovascular thrombosis. No improvement of survival, kidney function, thrombocytopenia, renal TMA.	[23]
	C6	$C6^{-/-}$.$FH^{R/R}$ mouse	–	Improved survival, kidney function, renal TMA. No improvement of macrovascular thrombosis.	[23]
	C9	$C9^{-/-}$.$FH^{R/R}$ mouse	–	Improved survival, kidney function, renal TMA. No improvement of macrovascular thrombosis.	[23]
	Properdin	$Properdin^{-/-}$.$FH^{R/R}$ mouse	–	Improved survival, kidney function, thrombocytopenia, anemia. No development of micro- and macrovessel thrombosis.	[24]
	Properdin	$FH^{R/R}$ mouse	Anti-properdin mAb (14E1)	Improved survival, thrombocytopenia, anemia. Reduced micro- and macrovessel thrombosis.	[24]
AAV	C5	Transfer of anti-MPO Ab in $C5^{-/-}$ mouse	–	Reduced hematuria, proteinuria, glomerular crescents and necrosis.	[25]
	C5	Transfer of anti-MPO Ab in WT mouse	Anti-C5 mAb (BB5.1)	Reduced hematuria, proteinuria, glomerular crescents, necrosis and neutrophil influx.	[26]
	C5aR	BM transplant from C5aR−/− to MPO-immunized MPO−/− mouse	–	Reduced proteinuria, glomerular crescents, necrosis and neutrophil influx	[27]
	C5aR	Transfer of anti-MPO Ab in hC5aR knocked-in mouse	hC5aR antagonist (CCX168)	Reduced hematuria, proteinuria, glomerular crescents and necrosis.	[28]
	C6	Transfer of anti-MPO Ab in $C6^{-/-}$ mouse	–	No improvement in glomerular crescents.	[28]
	C3	Transfer of anti-MPO Ab in $C3^{-/-}$ mouse	–	Improved kidney function. Reduced hematuria and glomerular crescents.	[18]
	FB	Transfer of anti-MPO Ab in $FB^{-/-}$ mouse	–	Reduced hematuria, proteinuria, glomerular crescents and necrosis.	[25]
	Properdin	Transfer of anti-MPO Ab in $properdin^{-/-}$ mouse	–	No improvement in kidney function, hematuria, proteinuria, glomerular crescents.	[18]
	MASP-2	Transfer of anti-MPO Ab in MASP-$2^{-/-}$ mouse	–	Exacerbated kidney dysfunction, hematuria, glomerular crescents.	[18]
C3G	C5	$C5^{-/-}$.$FH^{-/-}$ mouse	–	Improved survival and kidney function. Reduced glomerular crescents and hypercellularity.	[29]
	C5	Nephrotoxic nephritis in $FH^{-/-}$ mouse	Anti-C5 mAb (BB5.1)	Reduced proteinuria and glomerular neutrophil infiltration.	[29]
	C5	$Properdin^{-/-}$.$FH^{m/m}$ mouse	Anti-C5 mAb (BB5.1)	Improved survival. Reduced proteinuria, glomerular crescents, glomerular C9 deposition, glomerular leukocyte infiltration.	[30]
	C5aR	Properdin inhibition in $C5aR^{-/-}$.$FH^{m/m}$ mouse	–	Improved survival. Reduced proteinuria, glomerular crescents, glomerular leukocyte infiltration.	[30]
	CRIg	$Properdin^{-/-}$.$FH^{m/m}$ mouse	CRIg-Fc	Improved survival and kidney function. Reduced glomerular crescents, hematuria, proteinuria, glomerular C3 deposition. Restored plasma C3 levels.	[31]
	CR1	$FH^{-/-}$ mouse	Soluble CR1	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[32]
	CR3 (Itgam)	$Itgam^{-/-}$.$FH^{-/-}$ mouse	–	Exacerbated mortality and glomerular inflammation.	[33]
	FH	$FH^{-/-}$ mouse	Purified mouse FH	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[34]
	FH	$FH^{-/-}$ mouse	Purified human FH	Reduced glomerular C3 deposition after 5 days of treatment. Generate anti-hFH Ab triggering IC glomerulonephritis with renal failure after 10 days.	[35]
	FH	$FH^{-/-}$ mouse	Mini-FH ($FH^{1\text{-}5\hat{}18\text{-}20}$)	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[36]
	FH	$FH^{-/-}$ mouse	CR2-FH	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[37]
	FH	$FH^{-/-}$ mouse	FHmoss	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[38]
	FH	$FH^{-/-}$ mouse	Homodimeric mini-FH ($FH^{1\text{-}5\hat{}18\text{-}20\hat{}R1\text{-}2}$)	Reduced glomerular C3 deposition. Restored plasma C3 levels.	[39]
	FH	Nephrotoxic nephritis in $FH^{-/-}$ mouse	IgG-$FH_{1\text{-}5}$	Reduced glomerular C3 deposition. Improved glomerular histopathology.	[40]
	FB	$FB^{-/-}$.$FH^{-/-}$ mouse	–	Improved kidney function and glomerular histopathology. Reduced glomerular C3 deposition. Restored plasma C3 levels.	[41]
	FD	$FD^{-/-}$.$FH^{-/-}$ mouse	–	Exacerbated mortality, proteinuria, kidney dysfunction, glomerular histopathology.	[42]
	Properdin	$Properdin^{-/-}$.$FH^{-/-}$ mouse	–	Exacerbated proteinuria, glomerular inflammation/histopathology and C3 deposition.	[43]
	Properdin	$Properdin^{-/-}$.$FH^{m/m}$ mouse	–	Exacerbated mortality, proteinuria, kidney dysfunction, glomerular histopathology and C3 deposition.	[44]
	Properdin	$FH^{m/m}$ mouse	Anti-properdin mAb (14E1)	Exacerbated mortality, proteinuria, glomerular histopathology and C3 deposition.	[44]
LN	C5	NZB/W F1 mouse	Anti-C5 mAb (BB5.1)	Improved survival. Reduced proteinuria, glomerular crescents, mesangial matrix volume.	[45]
	C5aR	$C5aR^{-/-}$ MRL/lpr mouse	–	Improved survival, kidney function. Reduced glomerular crescents, hypercellularity, IgG deposition, $CD4^+$ T cell infiltration.	[46]

(*continued on next page*)

Table 3 (*continued*)

Disease	Target	Model	Drug	Phenotype	Reference
	C5aR	MRL/lpr mouse	C5aR antagonist (cyclic hexapeptide)	Improved kidney function. Reduced proteinuria, kidney leukocyte infiltration.	[47]
	C3	$C3^{-/-}$ MRL/lpr mouse	–	Exacerbated proteinuria and glomerular IgG deposition.	[48]
	Crry	Crry-transgenic MRL/lpr mouse	–	Improved survival, kidney function. Reduced proteinuria.	[49]
	Crry	MRL/lpr mouse	Crry-Ig	Improved kidney function. Reduced proteinuria, glomerulosclerosis, glomerular Ig and C3 deposition.	[50]
	CRIg	MRL/lpr mouse	CRIg-Fc	Reduced proteinuria, glomerular C3 and IgG deposition. Improved glomerular histopathology. Restored serum C3 levels.	[51]
	CR2	MRL/lpr mouse	CR2-Crry	Improved survival, kidney function. Reduced proteinuria, glomerular crescents, hypercellularity, Ig and complement deposition, anti-dsDNA antibody levels.	[52]
	C3aR	$C3aR^{-/-}$ MRL/lpr mouse	–	Exacerbated kidney dysfunction, proteinuria, interstitial fibrosis, anti-dsDNA antibody levels.	[53]
	C3aR	MRL/lpr mouse	C3aR antagonist (SB290157)	Improved survival, kidney function. Reduced kidney leukocyte infiltration.	[54]
	FH	$FH^{-/-}$ MRL/lpr mouse	–	Exacerbated mortality, kidney dysfunction, proteinuria, glomerulonephritis.	[55]
	FH	MRL/lpr mouse	CR2-FH	Improved survival and glomerular histopathology. Reduced proteinuria, glomerular IgG/C3/C1q deposition, anti-dsDNA antibody levels.	[56]
	FB	$FB^{-/-}$ MRL/lpr mouse	–	Reduced proteinuria, glomerular IgG deposition. Improved glomerular histopathology.	[57]
	FB	NZB/W F1 mouse	FB antisense oligonucleotide	Improved survival. Reduced proteinuria, glomerular C3 deposition. Restored plasma C3 levels.	[58]
	FB	MRL/lpr mouse	FB antisense oligonucleotide	Improved kidney histopathology. Reduced glomerular C3 deposition. Restored plasma C3 levels.	[58]
	FB	MRL/lpr mouse	FB inhibitor (LNP023)	Improved kidney function, glomerular histopathology. Reduced glomerular C3 and Ig deposition.	[59]
	FD	$FD^{-/-}$ MRL/lpr mouse	–	Improved kidney function, glomerular histopathology. Reduced glomerular C3 deposition, autoantibody levels.	[60]
	MASP-1/3	MASP-$1/3^{-/-}$ MRL/lpr mouse	–	Reduced proteinuria, glomerular C3 deposition. Improved glomerular histopathology. Restored serum C3 levels.	[61]
IgAN	C5aR	Sendai virus infection-induced IgAN in C5aR−/− mouse	–	Reduced proteinuria, glomerular IgA and C3 deposition, mesangial proliferation and hypercellularity.	[62]
	C3aR	Sendai virus infection-induced IgAN in C3aR−/− mouse	–	Reduced proteinuria, glomerular IgA and C3 deposition, mesangial proliferation and hypercellularity.	[62]
MN	C5	α3NC1-immunized $C5^{-/-}$ mouse	–	Reduced proteinuria.	[63]
	C3	THSD7A-immunized $C3^{-/-}$ mouse	–	Reduced proteinuria, glomerular C3/FB/FH/C5b-9 deposition. Preserved slit diaphragm length.	[19]
	C3	THSD7A-immunized mouse	C3 siRNA	Reduced proteinuria, glomerular C3/C5b-9 deposition.	[19]
	C3aR	Passive Heymann nephritis rat	C3aR antagonist (SB290157, JR14a)	Improved glomerular histopathology. Reduced proteinuria, glomerular IgG deposition.	[64]
	FB	α3NC1-immunized $FB^{-/-}$ mouse	–	Reduced proteinuria.	[63]
	FB	Passive Heymann nephritis rat	FB inhibitor (LNP023)	Improved glomerular histopathology. Reduced proteinuria, glomerular C3 deposition.	[65]

AAV: antineutrophil cytoplasmic antibody-associated vasculitis, aHUS: atypical hemolytic uremic syndrome, BM: bone marrow, C3aR: C3a receptor, C3G: C3 glomerulopathy, C5aR: C5a receptor, CR: complement receptor, Crry: CR1-related gene/protein y, FB: factor B, FD: factor D, FH: factor H, IgAN: IgA nephropathy, LN: lupus nephritis, MASP: mannose-binding lectin-associated serine protease, MN: membranous nephropathy, MPO: myeloperoxidase, NC1: noncollagenous domain-1, THSD7A: thrombospondin type-1 domain containing protein 7A, TMA: thrombotic microangiopathy.

alternative pathway [42]. Nevertheless, case series demonstrated the greater response of eculizumab in patients with crescentic rapidly progressive C3G compared to those with chronic forms [105], implying that careful patient selection and prioritizing those with active disease could pave the way for the success of forthcoming complement inhibitors in the context of C3G.

5.2.2. *Lupus nephritis (LN)*

LN is a form of autoimmune glomerulonephritis, one of the most severe organ manifestations of systemic lupus erythematosus (SLE) [106,107]. Genetic deficiency of complement classical pathway components (e.g., C1q and C4), essential for the clearance of apoptotic and necrotic cells, is linked to SLE development by facilitating inappropriate immune response to autoantigens on dead cells [108–110]. Conversely, most SLE cases without deficiencies involve excessive complement activation, particularly within the alternative pathway, which is further supported by animal studies (Table 3) [111–113].

Eculizumab has shown efficacy in LN cases, particularly those with TMA [114]. Given the pathogenic involvement of the complement system in LN, and considering the results of animal experiments where C3 deficiency failed to protect lupus mice from disease progression [48], the proposition arises for a selective complement inhibition approach in the context of highly active LN forms, e.g., replacing glucocorticoids with alternative pathway inhibitors during the initial active phase.

5.2.3. *IgA nephropathy (IgAN)*

IgAN is the most prevalent autoimmune glomerulonephritis. Approximately 30–40% of patients eventually progress to kidney failure within 20–30 years [115]. The pathogenesis of IgAN involves the activation of the complement system, wherein glomerular and circulating complement components from the alternative, lectin, and terminal pathways have been observed [116–120]. The use of animal models for IgAN presents challenges, as small animals lack the dominant hypogalactosidated IgA antigen [119]. However, Sendai virus infection-induced IgAN mice with deficiencies in either C5aR or C3aR showed favorable kidney outcomes [62].

Ongoing trials with numerous complement inhibitors for IgAN are currently in progress (Table 2). Avacopan and narsoplimab demonstrated reductions in proteinuria in certain cases with biopsy-proven IgAN during phase 2 trials [121,122], whereas the phase 3 trial of narsoplimab (NCT03608033) failed to achieve statistically significance on the primary endpoint of proteinuria reduction for this indication. Of note, a patient with refractory IgAN treated with eculizumab developed an exacerbation of proteinuria and kidney function decline upon

discontinuation of eculizumab [123]. Beyond elucidating the role of complement activation and the dominant molecule in IgAN, which will be informed by forthcoming clinical trial findings, the treatment duration and selectivity for this heterogenous chronic disease should be discussed for future clinical application. Prolonged or unselective complement blockade, or its application in immunologically inactive IgAN patients, raises questions.

5.2.4. *Kidney fibrosis*

Complement activation also plays a role in the context of kidney interstitial fibrosis in experimental models. C5a stimulation caused kidney fibroblast proliferation and activation [124], as well as increased production of transforming growth factor-β_1 which was inhibited by C5aR antagonist [125]. Deficiency and inhibition of C5aR protected mice from kidney fibrosis following unilateral ureteral ligation (UUO) [125] and ischemia-reperfusion injury [124]. Furthermore, deficiency in C3 and C3aR improved kidney fibrosis in UUO mice [126,127]. Indeed, C5a/C5aR or C3a/C3aR inhibitors may elicit positive kidney outcomes also by preventing interstitial fibrosis.

Notably, recent discoveries recognize the intracellular complement system as a pivotal regulator of fundamental cellular metabolism across various cells and tissues, while its dysregulation contributes to various pathological conditions including kidney fibrosis [128,129]. Macrophage-specific C5 deficiency ameliorated kidney fibrosis induced by folic acid by modulating mitochondrial C5aR1 hyperactivation [130], implying that the intracellular complement components C5 and C5aR1 could be a novel therapeutic target for kidney fibrosis, potentially in combination with traditional extracellular complement.

6. Balancing benefits and risks: identifying the right patient subgroup

Identifying the suitable patient subgroup is an additional pivotal consideration particularly to reduce infectious risks of complement inhibitors. In addition to primary immunodeficiency, secondary immunodeficiency caused by multiple factors including chronic kidney disease, aging, and immunosuppressive drugs, increases susceptibility to infections and diminishes vaccine responses [131]. Consistently, proteinuric kidney disease patients treated with steroids show an elevated risk for severe infections [132–134]. Hence, in contrast to patients without immunodeficiency, for whom any complement inhibitors could be an option, selective complement inhibitors are theoretically desirable for patients with primary/secondary immunodeficiency to reduce infectious complications. In clinical trials enrolling older patients with AAV, with an approximate age of 60 years and concurrent kidney dysfunction (mean estimated glomerular filtration rate 40–50

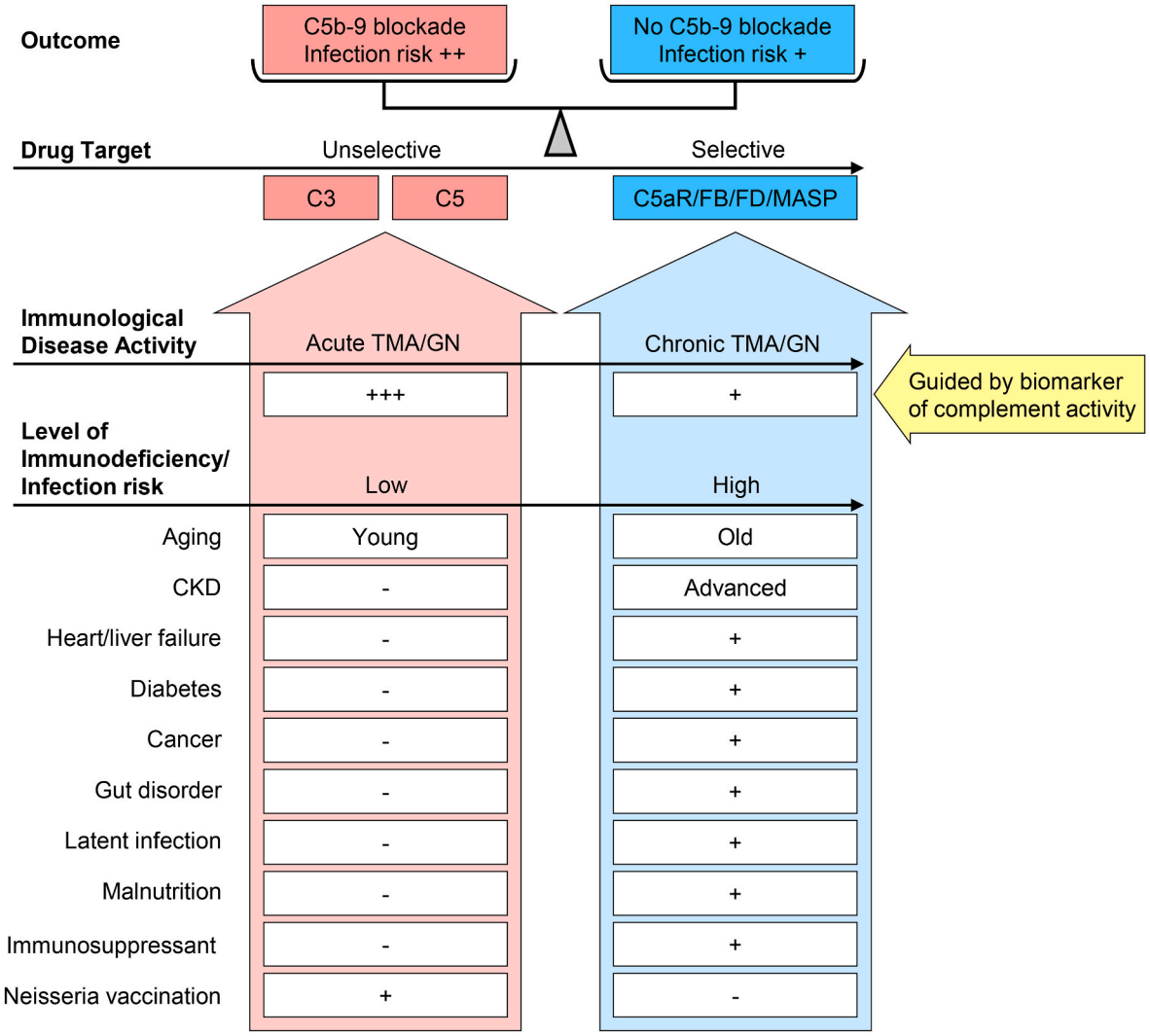

Fig. 2. The conceptual framework to identify targets of complement inhibitors based on disease activity and infectious risk factors
C5aR: C5a receptor, CKD: chronic kidney disease, FB: factor B, FD: factor D, GN: glomerulonephritis, MASP: mannose-binding lectin-associated serine protease, TMA: thrombotic microangiopathy.

mL/min/1.73 m^2), the administration of avacopan with immunosuppressants was tolerable [8,135], supporting the potential application of selective inhibitors even among those with immunodeficiency.

7. Conclusions

Based on the pathogenesis and immunological activity of the disease and infectious risk factors related to the patient immunodeficient profile, we propose a strategic framework to identify targets of complement inhibitors in Fig. 2. The most optimal application of complement inhibitors would be young patients without immunodeficiencies. C5 inhibition and in particular C3 inhibition may be highly efficacious in life-threatening acute forms such as aHUS or rapid-progressive glomerulonephritis. In contrast, for patients with immunodeficiencies, e.g., advanced age, CKD, concurrent administration of immunosuppressive agents, we should focus on selective complement inhibitors by targeting C5aR or initial pathway components to minimize infectious risks. Complement inhibitors can be further expanded to chronic diseases such as C3G, LN, and IgAN only when involving immunologically active conditions and when therapeutic alternatives are insufficient or toxic, wherein selective inhibitors during active phase should be the primary approach to avoid infections. Furthermore, complement biomarker-guided patient stratification becomes necessary to identify the patient subpopulation who benefit from these drugs and to optimize the therapeutic timing and duration, for maximizing their therapeutic impact while minimizing the risk of infections.

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CRediT authorship contribution statement

Kanako Watanabe-Kusunoki: Investigation, Writing – original draft. **Hans-Joachim Anders:** Conceptualization, Supervision, Writing – original draft.

Conflict of interest

HJA received consultancy fees from Novartis.

Data availability

No data was used for the research described in the article.

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