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REVIEW

Emerging immunotherapies for autoimmune kidney disease

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ABSTRACT

Autoimmunity is a leading cause of chronic kidney disease and loss of native and transplanted kidneys. Conventional immunosuppressive therapies can be effective but are non-specific, noncurative, and risk serious side effects such as life-threatening infection and cancer.

Novel therapies and targeted interventions are urgently needed. In this brief review we explore diverse strategies currently in development and under consideration to interrupt underlying disease mechanisms in immune-mediated renal injury. Because autoantibodies are prominent in diagnosis and pathogenesis in multiple human glomerulopathies, we highlight several promising therapies that interfere with functions of early mediators (IgG and complement) of the effector arm and with an epicenter (the germinal center) for induction of humoral immunity.

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Introduction

Immune-mediated injury to the glomerulus, the filtering unit of the kidney, is a leading cause of chronic kidney disease worldwide. In the U.S. glomerulonephritis (GN) ranks third behind diabetes and hypertension as a major cause of chronic kidney disease,[1] which nonetheless is thought to be a significant underestimation of the national burden of these diseases.[2,3] Wetmore et. al. used a large employer group health plan database to estimate a prevalence of 70 and 52 cases, respectively, per 100,000 persons, and an incidence of 20 and 10 cases, respectively, per 100,000 patient-years for primary GN and GN secondary to systemic immunologic disease between 2007–2011.[2] Estimated rates were an order of magnitude higher in a large Medicare cohort of average age 75 years, with a combined period prevalence rate of 1223.6 per 100,000 persons.[2] In patients who undergo transplantation due to renal failure, kidney allografts are also at significant risk for loss from a recurrent or de novo GN.[4]

Humoral autoimmunity is a hallmark of many GN, in which detection of autoantibodies in the circulation or kidney is key to diagnosis. Considerable evidence indicates that autoantibodies and autoreactive B cells underlie or contribute to disease pathogenesis. Kidney-targeted autoimmunity may arise as an organ-restricted disease, as in IgA nephropathy, membranous nephropathy, membranoproliferative GN, anti-glomerular basement membrane GN, and C3 glomerulopathy, or emerge as part of a systemic disorder. Up to 80% of patients with systemic lupus erythematosus (SLE) or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis develop autoimmune GN.[5,6] The causes of autoimmune GN remain unknown, although gene-environment interactions that lead to a breach in immune tolerance likely underlie most GN. Clinical presentation and prognosis can vary, even within a single diagnostic category; rapidly progressive GN or development of persistent heavy proteinuria and elevated serum creatinine generally carry a worse prognosis. Most GN are incurable and many currently have no specific treatment.

Available interventions manage inflammation and underlying autoimmunity in many patients and can be life-saving, but use of these drugs is fraught with complications and a substantial non-response rate.[7,8] Current regimens rely heavily on high doses of broadly immunosuppressive drugs, a small cadre of which are used for diverse diseases of varying pathogenesis. Systemic immunosuppression cripples healthy as well as pathogenic lymphocytes and risks severe complications due to a globally weakened immune system's inability to fight infection and cancer. Steroids can also precipitate disabling bone necrosis and diabetes. In diseases such as SLE and vasculitis relapses are common, occurring in approximately half of patients during long-term followup,[9-11] and disease control requires repeated exposure to high-dose immunosuppression with attendant cumulative toxicity. Novel targeted therapies are urgently needed. It is thus an optimistic time for patients and caregivers in that a wide range of mechanisms are being explored to dissect their role in disease pathogenesis and their potential for therapeutic intervention. In this focused review we selectively survey disease mechanisms and treatment strategies for immune-mediated nephropathies to sample the diverse approaches under consideration and highlight several promising emerging therapies. Because of the prominence of antibody- and complement-mediated injury in autoimmune glomerular diseases, we emphasize recent or novel interventions that interrupt early branch points in the effector (IgG and complement) and inductive (germinal centers) limbs of humoral immunity. This includes employing enzymes to glycoengineer IgG to confer anti-inflammatory properties or to degrade pathogenic IgG or IgA, using inhibitors to block production or activity of the potent

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pro-inflammatory complement component C5a, and deploying antagonists to interfere with B cell survival and activating factors or with IL-21, a key driver of germinal center B cell differentiation and IgG production (Table 1). These agents have shown efficacy in preclinical studies and several are currently in clinical trials or already approved in autoimmune kidney diseases.

Humoral autoimmunity in immune-mediated renal injury

Autoantibodies and B cells contribute to pathogenesis in multiple immune-mediated kidney diseases and modifying their production or activity is a major goal of therapy. Autoantibodies are capable of initiating cell or organ injury by multiple mechanisms, including activating potent inflammatory cascades by engaging IgG Fc receptors (FcgR) and components of the classical complement pathway; direct binding to antigen to trigger or neutralize target activity, as demonstrated for anti-thyroid-stimulating hormone receptor IgG in autoimmune thyroid diseases; and, labeling cells for in vivo degradation and removal, as described in autoimmune hemolytic anemia. Autoreactive B cells also have antibody-independent roles, including modulating immune responses via autoantigen presentation to T cells and cytokine secretion.[38-40] A common current approach to therapeutic intervention in immune-mediate renal diseases involves global reduction in antibody, B cell, and other cell mediator levels using plasmapheresis and immunosuppressive agents such as anti-CD20 monoclonal antibody (mAb) (rituximab), cyclophosphamide, or mycophenolic acid. These strategies are beneficial in some diseases and patients, but require invasive procedures and sophisticated technical support (pheresis) or several weeks to months of therapy for maximal effectiveness. In this regard, rituximab depletes CD20-positive B cells but not CD20-negative long lived plasma cells, a major source of circulating IgG. This restricted activity contributes to the substantial delay between rituximab infusion and decline in autoantibody levels observed in some patients. As described below, novel approaches are being developed to modify the production or function of pathogenic autoantibodies and lymphocytes.

Modulation of IgG glycosylation

Modification of IgG function by engineering changes in glycosylation of the IgG crystallizable fragment (Fc) is a promising approach to immunotherapy.[41] The Fc of IgG, comprised of the CH2 and CH3 domains of the heavy chain constant region, mediates its major effector functions.[42] IgG Fc CH2 domains contain binding sites for complement component C1q; these sites are exposed in antigen-bound IgG, allowing C1q recognition, formation of the C1 complex, and activation of the classical complement pathway. However, evidence that much of the IgG-mediated inflammation in autoimmunity is dependent on FcgR activity or alternative complement activation, not Fc-mediated C1q binding, has focused attention on FcgR-mediated functions.[43] The IgG Fc is recognized by leukocyte Fcgamma receptors (FcgR). Engagement by activating FcgR on monocytes or granulocytes can trigger an oxidative burst and release of proinflammatory cytokines and chemokines that initiate or amplify inflammatory responses, and mediate antibody-dependent cytotoxicity and antigen uptake. The binding and signaling of IgG – FcgR pairings is profoundly influenced by the presence and type of sugar moieties at asparagine (Asn)-297 in the Fc CH2 domain.[44] Galactose, fucose, N-acetylglucosamine (GlcNAc), and terminal sialic acid are variably added to the core GlcNAc/mannose glycan at this evolutionarily conserved N-linked glycosylation site, potentially generating over thirty IgG glycoforms with different functions.

The carbohydrate composition of Asn297 and resulting function of IgG can be modified in vivo and in vitro for therapeutic benefit. One approach leverages an immune evading tactic of bacterial pathogens. *Streptococcal pyogenes* secretes endoglycosidase S (EndoS), an IgG-specific glycoside hydrolase that catalyzes removal of the majority of sugar moieties from the N-glycan core on all subclasses of human IgG[45] and markedly decreases the capacity of most IgG to bind FcgR in vitro.[46,47] EndoS hydrolysis of mouse anti-collagen-II IgG or K/BxN mouse serum containing arthritogenic IgG1 prior to injection of the IgG into host mice attenuated development of joint inflammation in the recipients, without altering IgG autoantigen binding.[12,13] Recombinant EndoS administered directly to animals is well tolerated in vivo and has been shown to efficiently hydrolyze glycans of circulating IgG. In vivo EndoS is efficacious in multiple murine models of autoantibody-mediated disease, including lethal immune thrombocytopenia, lupus in the BXSB strain, and anti-myeloperoxidase (MPO) ANCA vasculitis – without altering autoantibody titers.[13-15] Potential limitations of EndoS therapy include retention of Fc effector functions in some deglycosylated IgG, as shown for the human IgG2 subclass,[47] and development of neutralizing anti-enzyme antibody responses. Repeated injections will likely be necessary due to ongoing in vivo repletion of serum IgG by plasma cells.

An alternative mechanism by which IgG can acquire anti-inflammatory properties is through attachment of terminal alpha2,6 sialic acid moieties to galactose residues on the core glycan.[16,48-50] The significance of IgG sialylation was initially explored during investigation of mechanisms underlying the anti-inflammatory properties of intravenous immunoglobulin (IVIG). It was proposed that the component of IVIG that mediates much of its anti-inflammatory activity is the minor fraction of IgG (typically 5–10% in healthy humans) that bears a fully sialylated Fc.[16,17] Kaneko and colleagues observed enhanced protection against inflammatory arthritis in the K/BxN serum transfer model using IVIG enriched for sialic acid and lack of efficacy using IVIG in which sialic acid was removed by neuramindase treatment.[16] Anthony et. al. subsequently engineered a recombinant sialylated IgG1 Fc that demonstrated potent anti-inflammatory activity in K/BxN arthritis.[17] Sialylation confers anti-inflammatory properties that are dependent on upregulation of inhibitory FcgRIIb on monocytes.[51-54] In some disease models efficacy also depends on binding of IgG to type II FcgRs, in particular mouse specific ICAM3-grabbing nonintegrin related 1 (SIGN-R1), an orthologue of human dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN, also known as CD209) expressed on myeloid regulatory cells,[18,19] reviewed in ref.[55,56] Type II FcgR binding is attributed to a conformational shift in the Fc domain of sialylated IgG that changes its FcgR specificity from type I FcgRs, such as activating

Table 1. Emerging therapies to block humoral immune effectors in autoimmune kidney disease.[a,b,c]

Category	Name of Product	Type of Product	Mechanism of Action	Advantages	Disadvantages	Preclinical Data	Reference	Current or Potential Use
Ig-targeted therapy: Modulation of IgG glycosylation	Endoglycosidase S (Endo S)	Bacterial enzyme	IgG-specific glycoside hydrolase; deglycosylates human IgG & blocks FcγR binding	Effective against all human IgG subclasses	Neutralizing Abs, Retained FcγR binding, Repeated injections	Protects in passive arthritis, ITP, BXSB lupus, AAV	12-15	Chemoenzymatic glyco-engineering of IgG
	Sialic acid-enriched IVIG, rIgG, IgG-Fc	Modified human IgG for infusion	Fc 2,6-sialylation confers anti-inflammatory properties (shifts binding to type II FcγR on myeloid regulatory cells; upregulates FcγRIIB)	Minimize lot-to-lot variation of IVIG; Use of rIgG removes risk of human pathogen transmission	In vitro sialylation is inefficient	Protects in K/BxN arthritis	16-19	In vitro IgG chemoenzy matic glyco-engineering
	ST6GAL1 & B4GALT1 fusion proteins	Soluble endogenous enzymes; attach β1,4-galactose & α2,6-sialic acid to IgG core glycans	Fc 2,6-sialylation confers anti-inflammatory properties (shifts binding to type II FcγR on myeloid regulatory cells; upregulates FcγRIIB)	In vivo specificity for tissue-bound IgG	Need source of local substrate delivery	Protects in K/BxN arthritis & NTN GN; sialylates IgG in joints & kidneys	20	Potential use in IC GN
Ig-targeted therapy: Ig degradation	IgG endopeptidase (IdeS, imlifidase)	Bacterial enzyme	Cleaves IgG to F(ab')2 and Fc, thus inactivating Fc-mediated functions	Rapid, isotype-specific; Acts on all 4 human IgG subclasses	Neutralizing Abs; Degradation of protective anti-microbial IgG	Protects mice from IgG-mediated arthritis & ITP	21,22	Phase 1/2 complete; In phase 2 trials in anti-GBM GN & pre- transplant sensitized patients
	IgA1 protease	Bacterial enzyme	Cleaves human IgA1 to Fc and Fd fragments	Spares other Ig isotypes & repertoires	Neutralizing Abs	Protects in passive IC & humanized KI/Tg models	23-25	Potential use in IgA nephropathy
Complement pathway blockade	Eculizumab	Humanized anti-C5 mAb	Prevents cleavage of human C5 to C5a & C5b	Potential broad applicability: C5 is common to all 3 C pathways	Risk invasive Neisseria; ongoing upstream C activity; inconvenient i.v. infusions	Protects in arthritis, BWF1 lupus, NTN GN, AAV[b]	26-29	Approved for PNH; In phase 2 trials in aHUS, MPGN; Potential use in C3G
	CCX168	Small molecule C5aR antagonist	Blocks action of C5a, a potent pro-inflammatory C component	Oral; Potential broad applicability: C5a is common to all 3 C pathways	Ongoing upstream C activity	Ameliorates anti-MPO vasculitis in humanized C5aR model	30	Phase 1/2 complete; Phase 3 trial in AAV & Phase 2 trial in C3G ongoing
	OMS721	Fully human anti-MASP 2 mAb	Inhibits MASP cleavage of C4 & C2 in lectin pathway	Does not interfere with Ig-dependent classical pathway	Unclear role of lectin pathway in most GN	Protects in GI & cerebral IRI [b]	31,32	Phase 1/2 complete; Phase 3 trials in IgAN & aHUS & Phase 2 trial in IgAN, LN, MN, & C3G ongoing
Inhibition of B cell maturation, survival & activation	Belimumab	Humanized anti-BAFF /BlyS mAb	Binds and inhibits active soluble BAFF	Spares anti-microbial memory B cells	Spares autoAb memory B cells	Protects in BWF1 and NZM2410 lupus [b]	33,34	FDA approved in lupus; Phase 2 in MN complete; Phase 3 trial in AAV ongoing
Germinal center blockade	NNC0114-0006	Anti-IL-21 mAb	IL21 inhibition, blocks signature Tfh cytokine that drives GC B cells & IgG production	Does not interfere with existing anti-microbial immunity	Multifunctional cytokine: blockade may have unexpected effects	Protects in MRL/lpr, BWF1, B6.Sle1.Yaa lupus [b]	35, 36,37	Phase 1 in RA complete; Phase 2 trial in type I DM ongoing

[a] Autoantibodies and complement are prominent proximal mediators of inflammation in multiple autoimmune kidney diseases, including but not limited to lupus nephritis (LN), ANCA vasculitis, IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis (GN), and autoantibody-mediated C3 glomerulopathies.

[b] Due to species-specificity of many receptor-ligand interactions, these preclinical studies used surrogate species-specific anti-rodent mAb or other reagents (eg., anti-C5, anti-MASP-2, BAFF-R-Ig, anti-IL-21, anti-IL-21R, IL-21R-Fc fusion protein).

[c] Abbreviations: AAV, ANCA-associated vasculitis; Abs, antibodies; aHUS, atypical hemolytic uremic syndrome; ANCA, anti-neutrophil cytoplasmic antibody; BAFF/BLyS, B cell activating factor/B lymphocyte stimulator; B4GALT1, beta-1,4-galactosyltransferase 1; C, complement; C3G, C3 glomerulopathy; DM, diabetes mellitus; FcgR, Fc gamma receptor; GBM, glomerular basement membrane; GC, germinal center; GN, glomerulonephritis; IC, immune complex; IRI, ischemia-reperfusion injury; ITP, idiopathic thrombocytopenic purpura; i.v., intravenous; IVIG, intravenous immunoglobulin; K/BxN, T cell receptor Tg and MHC Class II Ag7 mice; KI, knock-in; mAb, monoclonal Ab; MASP, mannan-binding lectin (MBL)-associated serine protease; MPGN, membranoproliferative GN; MPO, myeloperoxidase; NTN, nephrotoxic nephritis; PNH, paroxysmal nocturnal hemoglobinuria; RA, rheumatoid arthritis; rIgG, recombinant IgG; ST6GAL1, beta-galactoside alpha-2,6 sialyltransferase 1; Tg, transgenic.

FcgRIIa, IIIa, and IIIb and inhibitory FcgRIIb, to type II FcgRs such as SIGN-R1. These mechanisms are engaged in resolution of experimental GN: IVIG protects mice from nephrotoxic serum nephritis, a nephritis induced by administration of heterologous anti-glomerular basement membrane (anti-GBM) antiserum, only when FcgRIIb expression is intact.[53]

High doses of IVIG, preparations of which contain polyclonal IgG pooled from thousands of healthy donors, have been used successfully to manage a variety of autoimmune diseases with antibody-triggered inflammation. However, IVIG is subject to lot-to-lot variation and expensive to manufacture, in part due to the processing required to preclude infectious disease transmission.[57] Replacement of pooled donor IVIG with in vitro glycoengineered sialylated polyclonal or monoclonal IgG, Fc fragment multimers, or Fc-fusion proteins may provide a safer, cheaper, more efficacious option for therapy.[49,58,59] Efforts to optimize these reagents will likely be informed by ongoing parallel efforts to glycoengineer IgG for gain-of-function using glycosidase inhibitors as a therapy to enhance inflammation in control of infection and cancer.[41]

Technical challenges in efficiently generating sialylated IgG Fc in vitro remains a roadblock to this approach. An alternative to administering exogenous IVIG or its engineered biomimetic substitutes is therapeutic in vivo IgG sialylation. The addition of terminal alpha2,6 sialic acid to galactose residues on IgG N-glycans is catalyzed by the sialyltransferase ST6GAL1 in the trans-Golgi.[60] An enzymatically active soluble form of ST6GAL1 is also secreted by hepatocytes and capable of sialylating circulating IgG.[61] Pagan and colleagues capitalized on this pathway in engineering fusion proteins containing soluble forms of ST6GAL1 and B4GALT1, the enzyme that attaches beta1,4 galactose to IgG core glycans and thus provides the substrate for sialic acid addition. In mice with K/BxN serum-induced arthritis or nephrotoxic serum-induced GN, coadministration of the soluble enzymes selectively increased sialylation of endogenous IgG deposited in joints and kidneys, respectively, and protected mice from autoimmune inflammation to a degree comparable to that observed with administration of IVIG.[20] Specificity for tissue-deposited IgG was attributed to the local release of the enzyme substrates, galactose and sialic acid, by activated platelets recruited to the sites of inflammation. In vivo enzyme therapy was well tolerated, with little evidence of off-target sialylation effects and little change in sialylation of circulating IgG. Protection from K/BxN serum-induced inflammation required inhibitory FcgRIIB, STAT6, and either SIGN-R1 or transgenic human DC-SIGN,[20] suggesting that suppression pathways mirrored those engaged by IVIG. Notably, improvement in arthritis scores was also observed when enzymes were administered after disease induction,[20] suggesting the approach may be efficacious in established disease that better mimics the situation in the clinic. It remains to be determined if the approach is effective in the absence of local platelet activation, or if substrate can be delivered via an alternative source.

It is of note that multiple additional mechanisms have been described for IVIG actions. This includes functions attributed to the Fab regions of the polyclonal Ig and direct effects of IVIG on T cells to blunt pathogenic TH1 and TH2 responses and promote Treg expansion.[57,62-64] It is thus likely that efficacy of glycoengineered IgG in patients will vary depending on the balance of effector mechanisms engaged in an individual and disease.

Therapeutic IgG degradation

In addition to secretion of EndoS enzyme, *Streptococcus pyogenes* produces an endopeptidase, termed IdeS, with unique specificity for IgG.[65] IdeS cleaves IgG at the hinge region to generate F(ab')2 and Fc fragments.[21] This dissociates Ag binding from Fc-mediated effector functions, another mechanism for interfering with pathogenic IgG. Recombinant IdeS cleaves mouse IgG2a, but not mouse IgG2b, and when injected in vivo protects against joint inflammation mediated by transfer of arthritogenic IgG2a anti-collagen II autoantibodies and rescues mice from lethal IgG-mediated immune thrombocytopenic purpura.[21,22] Degradation of circulating IgG is rapid and isotype-specific, and IdeS in vivo is well tolerated. Whereas IdeS efficiently cleaves only a subset of rodent IgG subclasses, limiting its use in some preclinical models, IdeS efficiently cleaves all four human IgG subclasses. Its activity in a clinical setting was recently demonstrated in open-label phase 1–2 trials in which IdeS administered to highly HLA-sensitized patients rapidly abolished total and donor-specific anti-HLA IgG and permitted HLA-incompatible kidney transplantation.[66] IdeS thus presents a novel approach to eliminate undesired antibodies that is less invasive and does not require the specialized machinery and technical expertise of plasmapheresis and extracorporeal immunoadsorption. As with these interventions, IdeS will likely be particularly useful in acute disease to eliminate pre-formed pathogenic IgG while awaiting onset of action of anti-B cell therapies that limit antibody rebound. Off-target toxicity is limited due to IgG-restricted proteolytic specificity.

IgA1-specific cleavage in IgA nephropathy (IgAN)

Bacterial IgA proteases that cleave the hinge region of IgA have therapeutic potential in IgA-mediated disorders. IgA1 proteases with specificity for human IgA1 and not the IgA2 isoform are being developed as therapy for IgA nephropathy. This is the most common GN in the world and leads to end stage kidney disease in a substantial percentage of patients; there is currently no cure or specific treatment. Hallmarks of the disease include circulating aberrantly glycosylated IgA1, development of IgG autoantibodies that target the abnormal IgA1, and deposition of predominantly aberrant IgA1 as well as some IgG in the renal mesangium. Early attempts to study pathogenesis and develop and test therapies using mouse models were frustrated by the absence of an IgA1 isoform in mice, which produce a single IgA that resembles human IgA2. Humanized models have now been developed and recent studies support efficacy of IgA1 protease therapy. Lamm and colleagues used an IgA nephropathy model generated by passive infusion of soluble human IgA1/anti-IgA immune complexes to demonstrate a decrease in glomerular IgA1 deposits after administration of recombinant *Haemophilis influenzae* IgA1 protease.[23] Lechner and colleagues tested efficacy of the *H. influenzae* IgA1 protease in a novel dual

humanized alpha1-KI-CD89Tg mouse, which expresses human IgA1 and IgA1 receptor CD89 and spontaneously develops IgAN at a young age. IgA1 protease rapidly and markedly decreased serum IgA1 levels and glomerular IgA1 deposition, and repeated administration ameliorated renal inflammation and hematuria, although it did not alter proteinuria.[24] Expression of CD89 and other putative mediators was also blunted by IgA1 protease therapy, suggesting that some benefit may derive from secondary effects of enzyme administration.[24] Bacterial IgA1 proteases can degrade aberrantly glycosylated human IgA1 in serum, immune complexes, and kidney sections from patients with IgAN,[25] suggesting potential benefit in human disease. IgA1 protease, like other bacterial proteases, is highly immunogenic, a property that will limit its utility if neutralizing antibodies are induced. The duration and impact of accompanying loss of normal IgA1-mediated immunity will require further investigation.

Eculizumab to block activation of complement C5 in renal disease

Complement deposition contributes to tissue injury in kidney diseases linked to abnormal activation of innate or adaptive immunity. Complement is activated by three pathways that converge at activation of C5: the classical pathway, triggered by binding of C1q to the Fc region of antigen-bound IgG; the mannose binding lectin pathway; and, the alternative pathway. Activation triggers cleavage of complement components in a cascade of enzymatic reactions that generates various proinflammatory fragments, including anaphylatoxins C3a and C5a, and triggers formation of the C5b-9 membrane attack complex (MAC). These mediators and the leukocytes that they recruit protect the host by repelling invading microbes, assisting in removal of cell debris or immune complexes, and coordinating activation of adaptive immune responses that engage B cells and T cells. Excess complement activation and damage to autologous tissues is prevented by a system of fluid-phase and cell- or tissue-bound complement regulators, including soluble complement factor H (CFH), factor I, and cell membrane-associated cofactor protein (MCP, or CD46).[67] These proteins are particularly critical in controlling the alternative pathway, which is normally constitutively active due to low level spontaneous conversion of C3 to C3b. When complement is aberrantly or excessively activated in the circulation or in tissues including the kidneys due to defective complement regulation or autoantibody deposition, downstream mediators can overwhelm local complement regulatory capacity and contribute to cell injury or death, unrestrained inflammation, tissue destruction, proteinuria, and irreversible kidney injury.

Uncontrolled C3 activation due to genetic or acquired defects that compromise the alternative complement pathway can lead to one of two distinct and rare clinical syndromes: C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS). The fundamental defect in both disorders is dysregulation of the alternative pathway, reviewed in ref.[68] The causes for dysregulation are heterogeneous. Gene mutations and copy number variations that compromise the function of complement regulatory proteins have been described for CFH, CFH-related (CFHR) proteins 1–5, factor I, and MCP, as have gain-of-function mutations in C3. A prominent subset of patients produce C3 nephritic factors, autoantibodies that bind a neoepitope and stabilize the C3 convertase C3bBb. Anti-factor B or anti-C3b Ig that stabilize C3bBb and antibodies that bind and neutralize complement regulatory protein CFH or factor I are also reported.[69-71]

C3 glomerulopathy encompasses several complement-mediated kidney diseases, typically presenting as either C3 glomerulonephitis (C3GN) or dense deposit disease (DDD), a distinction determined in part by characteristic patterns of injury on electron microscopic exam of renal tissue.[72-75] C3 nephritic factor autoantibodies are detected in approximately 50% and 80% of patients with C3GN and DDD, respectively.[70,76] C3 glomerulopathy is characterized serologically by low serum C3 levels and clinically by chronic progressive renal failure, with half of patients reaching end stage kidney disease by 10–15 years. Kidney biopsy shows a membranoproliferative GN pattern of injury on light microscopy and prominent glomerular C3 deposition in the absence of significant antibody deposits on immunofluorescence staining. Disease recurs in kidney allografts of approximately half of transplanted patients.

Atypical HUS is a rare acute life-threatening systemic illness marked by severe renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. Individuals at risk include those with mutations in the genes encoding complement or its regulatory components or with autoantibodies against these components, similar to C3 glomerulopathy, as well as rare cases associated with variants in genes encoding two noncomplement thrombosis-related proteins, diacylglycerol kinase epsilon and thrombomodulin.[77] Genetic causes underlie approximately 60% of cases of aHUS.[77,78] In susceptible patients infection, vaccination, pregnancy, and other conditions can provoke alternative pathway activation and C5b-9 deposition on microvascular endothelial surfaces, precipitating aHUS. The clinical consequences are thrombosis, platelet activation and consumption, intravascular hemolysis, organ ischemia, and renal failure. The factors that determine the phenotypic expression (C3 glomerulopathy versus aHUS) of uncontrolled alternative pathway activation are as yet unclear, although differential activation of complement in the fluid phase versus at the endothelial cell surface has been proposed.[75] A recent analysis of rare genetic variants in over 3,500 patients with C3 glomerulopathy or aHUS revealed a different distribution of variants between the two diseases, indicating distinct genotype-phenotype associations and suggesting differences in molecular basis.[71]

The development of therapies that target complement component C5 and prevent its activation has dramatically improved clinical outcomes for patients with aHUS. Eculizumab, the first available complement-blocking therapy, is a humanized anti-C5 mAb that binds human C5 with high affinity and prevents its cleavage, blocking generation of proinflammatory, prothrombotic C5a and subsequent assembly of the terminal C5b-9 complex. Eculizumab was bioengineered to minimize immunogenicity and remove IgG effector functions.[79] Safety and efficacy of eculizumab were established in randomized controlled trials of patients with paroxysmal nocturnal hemoglobinuria, a genetic disorder that results in uncontrolled complement activation and chronic hemolysis

due to deficiency of membrane-associated complement regulatory proteins CD55 and CD59.[80] Subsequent case reports and phase 2 clinical trials demonstrated efficacy of eculizumab in aHUS.[81-84] Eculizumab is life saving in aHUS patients unresponsive to or intolerant of replacement therapy using plasma infusion or exchange and can prevent progression of renal disease. Eculizumab therapy also permits successful renal transplantation in patients who do progress to end stage kidney failure. Major limitations are the inconvenience of twice-monthly intravenous infusions and the high cost of therapy; liver transplant remains an accessible alternative to cure disease for patients with a genetic deficiency of a complement factor synthesized in the liver.[77] Prolonged or life-long maintenance therapy is often needed, because aHUS relapse rates approach 30% after therapy cessation, and the rate of organ failure after relapse is approximately 5%.[85] Efficacy is limited in some patients, including those with certain C5 mutations or with disease due to variants in non-complement thrombosis-related genes.[86,87] Development of neutralizing antibodies is rare with this humanized mAb.[85] Safety of eculizumab is partly due to preservation of function of the proximal complement pathways, such that C3b-mediated microorganism opsonization and immune complex clearance are unaffected. However, patients are at risk for infection with encapsulated bacteria, particularly Neisseria meningitidis for which protection depends on terminal complement pathway activity, and patients should be vaccinated prior to initiating eculizumab therapy.

Eculizumab has efficacy in a subset of patients with C3 glomerulopathies, although with less predictable results than in patients with aHUS, based on available case reports, a small open label trial, and registry survey.[88-90] This subset demonstrates improved or stabilized renal function and decreased proteinuria, although some experience relapses after discontinuation of therapy. Limited efficacy suggests a role for ongoing upstream complement activity despite terminal C5 blockade. Due to the heterogeneity of clinical presentation, complexity of pathogenesis, and spectrum of potential complement abnormalities, individualized interventions may be needed for optimal outcomes in in C3 glomerulopathy. Ideally choice of therapy will capitalize on novel complement-targeted therapies as they become available and will be guided by genetic and immunochemical analysis to determine the molecular profile of a given patient's defective complement cascade.

Because eculizumab acts downstream of C3 activation, it has therapeutic potential in diseases dependent on each of the three complement pathways. Efficacy of eculizumab in autoantibody-mediated disorders other than paroxysmal nocturnal hemoglobinuria and C3 glomerulopathies is suggested by animal studies. Although direct testing of eculizumab in non-humanized preclinical models is precluded because of its highly species-restricted activity against human C5, the surrogate murine anti-C5 mAb BB5.1 is well-tolerated in mice, inhibits terminal complement activation in vivo, and ameliorates experimental autoimmune diseases. Anti-C5 mAb prevented joint inflammation and improved established disease in a type II collagen-induced model of rheumatoid arthritis,[26] improved renal disease and survival in (NZBxNZW)F1 murine lupus,[27] protected CFH-deficient mice from superimposed nephrotoxic serum-induced exudative GN,[28] and alleviated nephritis in an IgG transfer model of anti-MPO ANCA vasculitis.[29]

In humans complement activation also contributes to kidney injury in allograft rejection and multiple GN, in which classical, alternative, and lectin pathways are variably implicated. Eculizumab has been used successfully to prevent or manage antibody-mediated rejection in high risk renal transplantation, including highly HLA-sensitized patients and recipients of ABO-incompatible living donor kidneys,[91-94] and is under study in chronic antibody-mediated injury.[95] In GN there is evidence that different pathways dominate in different diseases, often with more than one pathway active in a given disorder.[96] An open label phase 2 trial is currently assessing eculizumab efficacy and safety in 10 patients with primary MPGN with persistent proteinuria (ClinicalTrials.gov NCT02093533). Eculizumab has been used anecdotally to treat patients with lupus or antiphospholipid syndrome presenting with thrombotic microangiopathy or refractory nephritis.[97,98] An early unpublished clinical trial of eculizumab in 117 patients with membranous nephropathy showed no difference in proteinuria over 16 weeks compared to placebo; however, since eculizumab was underdosed and methods are now available to monitor C5b-9 and autoantibody levels, there is interest in revisiting eculizumab therapy in this disorder.[99,100]

Alternative complement inhibitors

A second complement-inhibiting drug, plasma-derived or recombinant human C1 esterase inhibitor (C1-INH), is approved for patients with hereditary angioedema, a disorder associated with low levels of C1-INH.[101] C1-INH is a multifunctional serine protease inhibitor that blocks function of C1q-associated serine proteases C1s and C1r in the classic pathway, thus preventing activation of C4 and C2 and generation of the C3 convertase. C1-INH also inhibits serine proteases MASP-1 and MASP-2 in the lectin pathway and has additional noncomplement-related activities that may contribute anti-inflammatory potency.[102] Classical pathway activation may be critical in antibody-mediated transplant rejection, in which allograft deposition of C4 fragment C4d is prominent. A placebo-controlled phase I/II trial assessing administration of plasma-derived human C1-INH in HLA-sensitized renal transplant recipients demonstrated safety and evidence of in vivo complement inhibition[103] and additional clinical trials are ongoing.

Tissue damage due to activation of the alternative pathway in ANCA-associated vasculitis (AAV) appears to center on C5a interactions with the C5a receptor (C5aR, CD88). In AAV, anti-MPO or anti-proteinase3 autoantibodies bind target antigen on the surface of primed neutrophils to initiate inflammatory cascades that damage vascular endothelium. In the kidneys this leads to an aggressive crescentic GN that can rapidly lead to renal failure. In situ activation of the complement alternative pathway is implicated; C5a and alternative complement cleavage product Bb are detected in patients' biopsy specimens as well as urine and correlate with disease severity.[104,105] Ig, C1q, and C3 deposits are generally absent (hence the term "pauci-immune" nephritis), whereas lectin and classical pathway components MBL and C4d are variably identified.[104,106]

Pathogenesis of GN in the anti-MPO ANCA mouse model was shown to be dependent on alternative pathway activation and C5a/C5aR interactions, as demonstrated by amelioration of disease in mice deficient in factor B or C5aR but not in C4 or C6.[30,107,108] The C5a/C5aR amplification loop is also active during human neutrophil activation and priming by ANCA.[107,108]

C5a is the most potent chemotactic factor generated by complement activation, and is responsible for recruiting neutrophils, monocytes, and macrophages via the C5aR.[109] CCX168, an oral small molecule inhibitor of human C5aR, reduced anti-MPO-induced nephritis in mice in which the murine C5aR was genetically replaced with human C5aR.[30] Two recent phase II clinical trials, C5aR inhibitor on Leukocytes Exploratory ANCA-associated Renal vasculitis (CLEAR) and Clinical ANCA vasculitis Safety and efficacy Study of Inhibitor of C5aR (CLASSIC), using CCX168 (avacopan) in ANCA-associated vasculitis are now completed. The results found CCX168 to be safe and effective when replacing high dose steroids in a conventional therapeutic regimen.[110,111] A phase 3 trial (ADVOCATE, ClinicalTrials.gov Identifier: NCT02994927) is currently enrolling patients. CCX168 is also being evaluated in IgAN.

The lectin pathway may contribute to pathogenesis in multiple renal disorders.[112] Lectin pathway activation is initiated by binding of circulating mannose binding lectin (MBL), ficolins, and collectins to carbohydrates on bacteria, yeast, and other microbes. Binding prompts MBL-associated serine proteases (MASP)-1, −2, and/or −3 to cleave C4 or directly cleave C3.[113,114] Lectin pathway components, particularly MBL, have been detected in biopsies of patients with lupus nephritis, MPGN, membranous nephropathy, anti-GBM GN, and IgAN.[115-117] Glomerular deposition of lectin components was associated with more severe histologic injury in IgAN.[118] The mechanism of lectin pathway activation is unclear; however, certain isoforms of IgG bearing exposed N-acetylglucosamine residues and polymeric and N-linked degalactosylated IgA can bind and activate MBL.[119-121] In a phase 2 trial, 12 weeks of therapy with MASP inhibitor OMS721, an anti-MASP-2 mAb, resulted in over 70% reduction in proteinuria in patients with IgA nephropathy;[122] a phase 3 clinical trial is planned. OMS721 is also being evaluated in a phase 3 trial for aHUS.

A variety of novel complement inhibitors are in preclinical studies or under development, with approximately 20 candidate drugs in clinical trials for various indications.[123-125] The complexity of the complement system, comprising over 40 proteins, offers multiple potential targets. Short-term administration of human plasma-derived CFH normalized serum C3 levels and reversed renal C3 deposition in CFH-deficient mice that spontaneously develop C3 glomerulopathy, though long-term therapy was not feasible due to induction of anti-CFH antibody.[126] Various CFH-derived recombinant fusion proteins have also shown efficacy in the CFH-knockout model.[127] CFH/properdin double-deficient mice develop a rapidly progressive and fatal C3 glomerulopathy that is ameliorated with a fusion protein, CRIg-Fc, that interferes with function of C3b.[128] Soluble complement receptor 1 (CR1, CD35) restored complement regulation and serum C3 levels in CFH-deficient mice bearing transgenic human CR1.[129] Small molecule antagonists of protease factor D, a serine protease highly specific for factor B and the rate-limiting enzyme of the alternative pathway, efficiently blocked activation of this pathway in vitro and in factor D-humanized mice.[130] CFH-deficient mice humanized for relevant complement components will continue be useful to test novel therapies in the context of chronic C3 activation and within the limits of cross-species compatibilities.

Immunoadsorption

Extracorporal immunoadsorption over cartridges coated with Ig or IgG-adsorbing ligands can rapidly remove pathogenic IgG and immune complexes and is useful in managing acute severe Ig-mediated disease, as reviewed in ref.[131] Immunoadsorption has primarily been used as rescue therapy for refractory severe disease, relapsing disease, or when cyclophosphamide or other agents are not tolerated or contraindicated, particularly in SLE and anti-phospholipid syndrome. Immunoadsorption has also been applied to manage kidney disease in small numbers of patients with AAV, anti-GBM GN, and membranous nephropathy. Among ten patients with anti-GBM GN, immunoadsorption rapidly and effectively removed anti-GBM IgG, with unusually high rates of renal survival including reversal of dialysis dependency.[132] This approach is more specific than plasmapheresis, which depletes other plasma components such as coagulation factors. Conversely, removal of non-Ig pathogenic circulating immune mediators or replacement of protective factors may contribute to the therapeutic actions of plasma exchange and is not replicated in immunoadsorption. Both therapies are used in concert with B-cell targeted immunosuppression to control ongoing autoantibody production. Antigen-specific immunoadsorption that does not deplete protective IgG could prove safer and is feasible when pathogenic epitopes are well characterized and can be readily expressed in vitro, as recently described for pemphigus vulgaris.[133]

Additional therapies to interrupt the effector limb in immune nephritis

During the course of autoimmune kidney injury, a large number of effector cells of the adaptive and innate immune system and effector molecules are engaged in inflammation, cell injury and death, tissue repair, and fibrosis. Many of these are engaged downstream of activation of IgG effector mechanisms, complement activation, and endothelial injury. Autoreactive T cells are also recruited to the kidney, where they can directly injure tubular and other renal cells and release cytokines and mediators; the role of T cells in experimental anti-GBM and anti-MPO ANCA GN was recently reviewed in ref.[134] Therapy aimed at these mediators may be crucial to control and reverse established disease. A plethora of interventions using different strategies and drugs are in clinical use, clinical trials, or preclinical development that target cytokines, chemokines, Toll-like receptors, FcRs, transcription factors, macrophages, monocytes, platelets, T cells, fibroblasts and other mediators of

organ injury. Therapies that act on molecules or cells such as glomerular podocytes specific to kidney biology may impart organ specificity. Several murine models, such as anti-GBM GN and anti-MPO ANCA GN that rely on passive administration of autoantibodies, are available for examining therapeutic modulation of effector stages in established disease. Although beyond the scope of this focused survey the reader is referred to the many excellent recent reviews on these topics.

Targeting disease induction and immune tolerance

Control of the proximal limb of autoimmune responses prior to activation of the broad cascade of downstream mediators is a major goal of therapy. This is critical to block ongoing autoimmune responses and to manage disease in patients with persistent disease, relapses, flairs, or recurrent disease after kidney transplantation, in which repeat courses of induction immunosuppressive therapy lead to high cumulative doses and risk of serious side effects. Similar to efforts to intervene with effector mechanisms, enormous effort has been devoted to develop strategies and drugs to block or reverse activation of autoreactive cells and production of autoantibodies, as reviewed in ref.[135] Enzymes and factors that control gene expression, proximal signaling molecules such as Bruton's tyrosine kinase, cytokines, and cell receptors that regulate immune cell activation and interactions are attractive targets, as is expansion of inhibitory immune cell populations such as regulatory T cells (Treg). Some candidate signaling molecules control cells in both inductive and effector disease pathways. There has been a recent renewed appreciation for the role metabolic pathways play in governing immune cells and growing evidence that inhibition of glycolysis and other paths can have therapeutic benefit in autoimmunity, reviewed in ref.[136]

The holy grail for intervention in autoimmune disease is induction of antigen-specific tolerance to cure disease. GBM and immunogenic peptides can restore tolerance and reduce disease severity in a rat model of induced anti-GBM GN.[137,138] In a recent series of elegant experiments Ooi and colleagues identified antigen-specific T cells in patients with anti-GBM GN and exploited transgenic mice expressing HLA class II disease susceptibility genes to demonstrate the role for peptide-specific Treg in controlling nephritis.[139] Expansion of regulatory T cells is a promising therapeutic approach in autoimmunity. Efforts to develop antigen-specific therapies for other kidney-specific autoimmune diseases are hampered by the paucity of spontaneous autoimmune disease models or reproducible models of autoantigen-induced nephritis with which to measure autoimmune cell activation and fate.[140] Murine lupus strains have proven invaluable for investigating regulation in systemic autoimmunity, although study of antigen-specific intervention is complicated somewhat by the large number of different autoantibodies produced in SLE.[141]

Blocking B cells, plasma cells, and germinal centers

For many years cyclophosphamide was a cornerstone for management for severe manifestations in SLE, AAV, anti-GBM GN, and other autoimmune nephritides, due in part to its ability to cripple B cells and plasmablasts. More recently mycophenolic acid and anti-CD20 mAb (rituximab) were added to the standard anti-B cell armamentarium. One limitation of anti-CD20 therapy has been its inability to eliminate CD20-negative bone marrow-resident long-lived plasma cells that are the major source of circulating IgG. New biologics that interfere with humoral autoimmunity by blocking B cell and plasma cell survival factors B cell activating factor (BAFF or BLys) and/or a proliferation inducing ligand (APRIL) offer an alternative approach to humoral immunity blockade, are being tested for clinical use in a variety of disorders, including AAV and membranous nephropathy, and have been approved in active SLE, as reviewed in ref.[142,143] Proteasome inhibitors such as bortezomib are toxic to plasma cells; however, a limitation to their use for decreasing unwanted antibody levels was suggested in a transplant model in which bortezomib failed to control levels of circulating alloantibodies despite plasma cell depletion.[144] This outcome was attributed to a compensatory germinal center response.

The germinal center (GC) is the major microanatomic site specialized to support antigen-specific humoral responses and production of high affinity IgG, reviewed in ref.[145] GC components are thus attractive targets for therapeutically intervening in IgG-mediated diseases and blocking ongoing immune responses. GC develop in secondary lymphoid organs (spleen and lymph nodes) after antigen activation of B cells and T cells triggers differentiation to CXCR5+ICOS+PD-1+CD4+T follicular B helper cells (Tfh) and GC B cells. In autoimmunity GC and Tfh/B cell couplets are also detected ectopically in inflamed tissues, including the kidney interstitium, and serve as a site for in situ antigen-driven B cell selection.[146-149] Available evidence suggests that GC, Tfh/B cell interactions, and Tfh expansion contribute to production of pathogenic autoantibodies in human autoimmune disease.[150,151]

The interaction of CD4+ Tfh with GC B cells promotes IgG isotype class switch, somatic hypermutation, affinity maturation, and memory B cell and plasma cell differentiation that yield high affinity IgG. A variety of cytokines, chemokines, or receptors are engaged in Tfh/B cell crosstalk and are potential targets for uncoupling the interaction. Reagents that neutralize ICOS, CD40, CXCL13, CXCL10, CTLA-4, IL6-R, IL-21 and IL-21R are in clinical trials for autoimmune diseases or malignancies or in preclinical development.[152] A hallmark mediator of GC reactions is IL-21, a Tfh-derived cytokine produced in high quantities and that drives GC B cell differentiation and IgG production.[153,154] Administration of IL-21R-Fc fusion protein, anti-IL-21 mAb, or anti-IL-21-receptor mAb to block IL-21 activity successfully attenuated IgG autoantibody production and nephritis in murine lupus across multiple strains, including MRL/lpr, B6.Sle1.Yaa, and (NZBxNZW)F1.[35-37] A more subtle therapeutic effect was observed in BXSB.Yaa lupus,[155] a strain in which cell-selective deletion of the IL-21 receptor revealed a complex role for IL-21 in disease regulation.[156] Neutralizing anti-IL-21 mAb delayed onset of experimental autoimmune diabetes, and when used in combination with a glucagon-like peptide-1 agonist reversed severe hyperglycemia.[157] A similar regimen using an anti-IL-21 mAb is currently in clinical trials in type 1 diabetes (ClinicalTrials.gov: NCT02443155). Collectively

the results suggest that IL-21 or GC blockade may be beneficial in subsets of patients with autoimmune disease in which the balance of IL-21 activity favors pathogenic IgG autoantibody production. It is of note that IL–21 is a multifunctional cytokine that may also engage in non-GC interactions.

Expert opinion

Harnessing or blocking IgG and complement is an attractive approach to interrupt disease and inflammation in autoimmune kidney diseases with a prominent humoral component. These proximal effectors are pathogenic in many human GN, are active during ongoing autoimmune responses at presentation and in persistently active or relapsed disease, and lie upstream of multiple inflammatory pathways. Particularly promising are advances in glycoengineering that now permit in vitro modification of polyclonal or monoclonal human IgG to enrich for isoforms that confer anti-inflammatory properties when administered i.v., an enzyme (IdeS) produced by a human microbial pathogen that has been channeled to degrade IgG in vivo, and a small molecule inhibitor of the potent pro-inflammatory complement C5a receptor that appears safe in early clinical trials. Understanding of germinal center biology and Tfh/B cell interactions is rapidly advancing and is likely to identify new therapeutic targets at the hub for activation of humoral and cellular adaptive immunity. Strategies that restore immune tolerance by exploiting regulatory cells, cytokines, or self tolerogens may be the best hope for durable remissions.

Conclusion

A broad array of novel interventions are under investigation for treatment of autoimmune kidney diseases. A major goal is increased specificity over traditional therapies, achieved by targeting dominant disease mechanisms and mediators and permitting efficacy without disabling side effects. Many promising drugs that control various aspects of the immune inductive and effector limbs have been developed and are in preclinical or early clinical stages. Development of humanized preclinical models that permit in vivo evaluation of new agents in the context of human immune mediators and cells has proven invaluable in bridging bench and clinic; increasing the types and availability of such models remains a priority. Models of passively-induced glomerulonephritis remain useful for examining therapies targeted at effector pathways in established disease. Models of spontaneous autoimmunity are needed to test curative therapies aimed at inducing immune tolerance, for which there is urgent need for the subset of patients with relapsing or recurrent disease. Novel technologies or approaches, such as the use of combined proteomic and deep sequencing analyses to sequence patients' circulating pathogenic autoantibodies, will advance the field. Ongoing research that increases our understanding of the origins, pathogenic epitopes, mechanisms and mediators of nephritogenic autoimmunity will accelerate discovery and permit application of personalized approaches.

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No potential conflicts of interest were disclosed.

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