Anti–Glomerular Basement Membrane Disease: Recent Updates

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Anti–glomerular basement membrane disease is a small-vessel vasculitis involving the kidneys (∼90%) and the lungs (∼60%). Antibodies against the glomerular basement membrane are directly pathogenic in anti–glomerular basement membrane disease; however, recent research has highlighted the critical role of T cells. Novel autoantigens within the glomerular basement membrane are also now recognized. Atypical forms of the disease are reported along with preceding triggers, such as immune checkpoint inhibitors, immunomodulatory drugs, and vaccines. Kidney outcomes in anti–glomerular basement membrane disease remain poor despite significant improvement in patient survival in the last 2 to 3 decades. Treatment typically relies on combined plasmapheresis with intensive immunosuppression. Dialysis dependency at presentation is a dominant predictor of kidney outcome. Histologically, a low (<10%) percentage of normal glomeruli, 100% crescents, together with dialysis dependency at presentation, is associated with poor kidney outcomes. In such cases, an individualized approach weighing the risks and benefits of treatment is recommended. There is a need for better ways to stop the toxic inflammatory activity associated with this disease. In this narrative review, we discuss recent updates on the pathogenesis and management of anti–glomerular basement membrane disease relevant to patients of all ages.

Key Words: Anti-GBM disease, Outcome, Pathogenesis, Predictors, Treatment

Anti–glomerular basement membrane (anti-GBM) disease is a type of small-vessel vasculitis caused by pathogenic autoantibodies directly targeting the glomerular and alveolar capillaries.[1] The anti-GBM antibodies react against specific epitopes in the type IV collagen in the glomerular basement membrane (GBM) and alveolar basement membrane. It is a rare glomerular disease and comprises <1% of all causes of end-stage kidney disease,[2] yet it is an important cause (10-15%) of crescentic glomerulonephritis (GN).[3] Anti-GBM disease can be isolated to the kidneys (anti-GBM GN) or involve both the lungs and the kidneys (pulmonary-renal syndrome, also known as Goodpasture disease). About 90% of all patients will have kidney involvement; of which, 20-40% will have isolated kidney involvement. Less commonly, 10% of all patients will have isolated lung involvement.[4] The limited evidence base suggests that children and adults run a similar disease course.[5] While there has been significant progress in improving patient survival due to advances in intensive care, rapid immunosuppression, and the use of plasmapheresis, overall kidney survival remains poor. This narrative review highlights recent updates in the understanding and management of anti-GBM disease that are relevant to patients of all ages.

Epidemiology and Disease Triggers

The incidence of anti-GBM disease is about 1-1.64 per million population per year.[6] The disease has a double peak in age incidence, one in the second-third decade and one in the sixth-seventh decade. In children, 0.4% of all causes of CKD are reported to be due to anti-GBM disease.[7] the theory of seasonal variation. In a nationwide analysis of anti-GBM disease in Ireland over 11 years (2003 to 2014), clusters of cases were associated with influenza outbreaks during the winter.[6] Clustering of cases was also noted during the recent severe acute respiratory distress syndrome coronavirus 2 pandemic.[8] Inhaled hydrocarbon exposure and smoking are other well-reported triggers for anti-GBM disease.[9] The exact pathogenic role of these triggers is not fully understood.

Pathogenesis

The GBM comprises type IV collagen, laminin, proteoglycans like heparan sulfate, fibronectin, entactin, and other glycoproteins (Fig 1). Anti-GBM disease is caused by the direct binding of antibodies to in-situ antigens ordinarily present in the kidneys and lungs. Type IV collagen

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monomer is a triple helix of 3 helical alpha chains. The C terminus of each alpha chain contains a noncollagenous domain (NC1), which is crucial for the assembly of triple helical monomers into a basement membrane structure. The antigen is the NC1 domain of the triple helix monomer, which is hidden from the host immune system due to a structural conformation. The conformational epitopes EA (residues 17-31), and EB (residues 127-141), respectively, of the alpha3(IV)NC1 domain of type IV collagen are bound explicitly by anti-GBM antibodies. The severity of the disease seems to be directly linked to the level of anti-GBM antibodies.[10] A novel autoantigen, laminin-521, was identified recently in one-third of patients with anti-GBM disease in a retrospective cohort study from China.[11] More anti-GBM disease patients with lung hemorrhage had anti-laminin-521 antibodies than those without lung hemorrhage. Autoantibodies to entactin were also attributed to causing anti-GBM disease with a peculiar granular IgG deposition along the GBM in a minority of patients.[12] Peroxidasin is an enzyme of the heme peroxidase family, critical for maintaining the quaternary structure of type IV collagen hexamer. It forms sulfilimine cross-links between methionine and hydroxylysine residues of NC1 domains. McCall et al.[13] showed the presence of anti-peroxidasin antibodies in ~50% of patients with Goodpasture syndrome. In vitro, these antibodies inhibited hydrobromic acid formation. Due to structural similarity, these cross-reacted to anti-myeloperoxidase (MPO) antibodies and might have caused false assumptions of double positive anti-GBM disease and MPO-ANCA associated vasculitis (AAV) in some patients. Some patients with MPO-AAV have concurrent specific anti-peroxidasin antibodies that do not cross-react with MPO and are hypothesized to reflect active disease in MPO-AAV. Similarly, anti-peridoxasin antibodies are thought to be associated with a severe vascular injury in Goodpasture syndrome. Until further research shows the exact pathogenic characteristics of these antibodies, anti-peroxidasin antibodies represent novel antibodies in developing anti-GBM disease.[14]

Despite low-affinity natural anti-GBM antibodies in healthy adults,[15] only specific individuals are at risk of manifesting the disease. Genetic predisposition, such as HLA-DRB1 alleles DRB1*1501 and DRB1*0401 is associated with presenting anti-GBM antigen peptides to T cells. The presence of interstitial inflammation comprises mainly of CD4+ T-cells in most human kidney biopsies, the induction of anti-GBM nephritis in animals on exposure to the T cell epitope of Goodpasture antigen[16,17] and the presence of class-switched high-affinity IgG autoantibodies (which depend on T-cells)[18] give insight into the important role of T-cells in anti-GBM disease. Glomerular fibrin deposition in anti-GBM disease is hypothesized to be due to T-cell mediated macrophage expression of human tissue factor.[19] Moreover, T-regulatory cell development depends on HLA[20] as the epitope presentation by HLA-DR:15 prevents the formation of T-regulatory cells, which can trigger disease in genetically predisposed individuals (HLA-DR:15:01).

CLINICAL SUMMARY

- Anti–glomerular basement membrane disease is an important cause of crescentic glomerulonephritis that develops from autoantibodies directed to the glomerular basement membrane and a recently recognized key role of T cells.
- Dialysis dependency at presentation and a low percentage of normal glomeruli (<10%) and/or 100% glomeruli with crescents predict worse kidney outcomes irrespective of treatment.
- There is an unmet need for better and targeted therapies for improving kidney outcomes of anti–glomerular basement membrane disease.

Clinical Presentation

In patients of all ages, the extent of kidney and lung involvement dictates the clinical severity at presentation. Severe kidney injury in the manner of rapidly progressive glomerulonephritis (RPGN) is the most common presenting feature, and dialysis dependence at presentation is frequently described in observational cohort data (55-85%).[21] An international retrospective study of 123 patients suggested that the rates of dialysis dependency at presentation may have fallen over time, as 32% of patients were dialysis dependent at the time of presentation after 2007, compared to >55-70% between 1986 and 2006.[22] With regard to urine features, microscopic hematuria is almost universally present, whereas gross hematuria is seen in <25% of patients. Clinical symptoms from pulmonary hemorrhage, such as hemoptysis, cough, dyspnea, and anemia, are observed in 25-30% of patients, primarily young males and those with a smoking history or inhaled hydrocarbon exposure.[1] In a cohort of 28 cases of pulmonary hemorrhage due to anti-GBM disease, hypoxemia was noted in 58%,[23] and ~50% of cases developed acute respiratory failure requiring intubation.[24] Other systemic involvement, such as arthritis, myalgia, and skin rash, is uncommon, and their presence should prompt concern for concurrent AAV (seen in 30% of patients). Cerebral vasculitis from anti-GBM disease is rare but described.[25]

A summary of atypical, dual antibody and drug-induced variants of anti-GBM disease are summarized in Table 1.

Diagnosis

Serology. An urgent serological test report can have treatment implications in cases with RPGN where prompt use of plasmapheresis and/or immunosuppressive therapy can be attempted. About 90% of patients with anti-GBM disease have circulating IgG anti-GBM autoantibodies when tested by commercial assays[1] using enzyme-linked immunosorbent assay or bead-based fluorescence assays with recombinant alpha 3(IV) antigen. These assays will generally not pick up other pathogenic anti-GBM Ig subtypes (IgA, IgM) or rarer antigenic targets, for example, alpha4 or 5 (IV)NC1. The biosensor

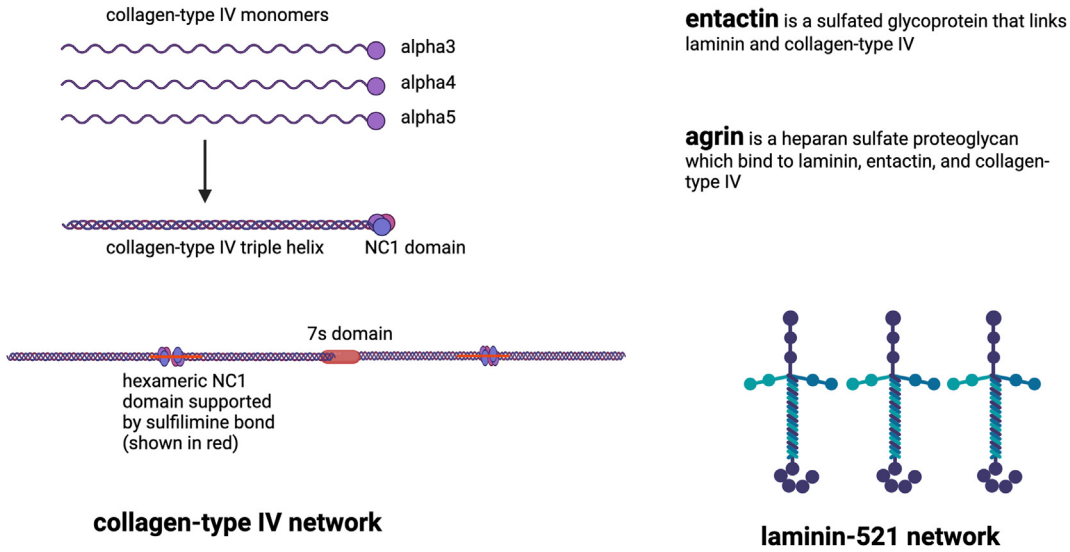

Figure 1. An illustration of the key components of glomerular basement membrane. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

system is a highly sensitive technique that can be applied in highly suspicious clinical cases with a negative result on conventional assays.[26] A newly developed chemiluminescence assay showed further promise with a sensitivity of 100%.[27]

Kidney Histology. In addition to autoantibody serology testing, confirmation with a kidney biopsy is preferred as this also provides prognostic information that may direct treatment choices, and it can diagnose atypical disease, especially in cases with negative serology. As with all invasive procedures, the risks and benefits must be evaluated, especially in critically unwell patients, as is typically seen in anti-GBM disease.

Light microscopy. Almost all (97%) patients with anti-GBM disease have crescents on the kidney histology, with 85% having crescentic (>50% glomeruli showing crescents) GN.[3] The mean crescent formation level (>75%) in anti-GBM disease is higher than in other causes of RPGN. In anti-GBM disease, crescents are typically widespread (Fig 2A). Other histological findings include fibrinoid necrosis in the glomerular tuft and rarely inflammatory cell infiltration in the capillary lumen. The absence of significant endocapillary hypercellularity and/or basement membrane thickening and uniform crescent morphology is distinctive of anti-GBM disease. Although fibrinoid necrosis precedes crescent formation and reflects a severe glomerular injury, the extent of fibrinoid necrosis does not predict anti-GBM disease prognosis.[28] Bowman's capsule break and periglomerular inflammation are not uncommon, including multinucleated giant cell formation. Interstitial fibrosis and tubular atrophy are usually proportional to the degree of crescent formation. However, artery or arteriole inflammation is not typical, and its presence suggests concomitant AAV. The Berden classification for AAV was used to classify kidney biopsies with anti-GBM disease.[22] Others have reported using histopathological activity and chronicity indices to score anti-GBM disease[28]; however, the indices did not reliably predict outcomes. The more recently reported renal risk score, extrapolated from the score used to stratify AAV patients,[29] includes (1) normal glomeruli percentage (N0: normal>10%, N1: normal 10%-25%, N2: normal <10%) and (2) and interstitial fibrosis/tubular atrophy (T0: none, mild to moderate, T1: moderate to severe) together with eGFR at presentation can predict kidney survival but not patient survival.[21]

Direct immunofluorescence. Linear polyclonal IgG staining in the GBM is the prototypical manifestation[1] (Fig 2B). Complement (C3) deposition is often seen in a patchy or diffuse pattern. IgG1 is the dominant immunoglobulin subclass with codominant IgG3 or IgG4 subclass deposition. IgG4-associated anti-GBM disease is rare and typically associated with milder kidney involvement. Immunoglobulins other than IgG, such as IgA and IgM, can also cause anti-GBM disease.

Differential diagnosis of linear IgG deposition. Linear IgG deposition along the GBM can be seen in diabetic nephropathy, monoclonal immunoglobulin deposition disease, and fibrillary glomerulonephritis.[30] Weak IgG1 dominant linear staining of the GBM with more intense or equal albumin staining is characteristic of diabetic nephropathy. Although not typical, pseudo-linear IgG deposition can be seen in fibrillary glomerulonephritis. Both monoclonal immunoglobulin deposition disease and fibrillary glomerulonephritis can be differentiated from anti-GBM disease by electron microscopy.

Electron microscopy. GBM breaks are appreciated better on electron microscopy. Fibrin tactoid formation, indicating cross-linked fibrin from activation of the coagulation system after GBM injury, can be seen as electron-dense structures; however, immune-complex type electron-dense deposits are typically lacking in anti-GBM disease.

Table 1. Atypical, Dual Antibody and Drug-Induced Variants of Anti-GBM Disease

Atypical anti-GBM disease[30,56]	~5-10% of all Cases of anti-GBM disease have absent circulating anti-GBM antibodies Mild clinical and/or histopathological presentation Management: § Exclude cases of IgG4-, IgA-, and IgM-mediated anti-GBM disease using modified assays § Thorough evaluation for atypical IgG antibodies using highly sensitive assays and modified assays targeting newer epitopes/antigens
Dual anti-GBM antibody and anti-MPO antibody positive disease[21,22,37,53]	~20-40% of all cases of anti-GBM disease Older age and more systemic manifestations than classic anti-GBM disease Relapse commoner than classic disease Outcomes similar to classic disease Management: § Initial phase is similar to classic anti-GBM disease; § Maintenance immunosuppression to prevent relapse akin to AAV
Drug-induced anti-GBM disease[57–68]	1. Anti-CD52 monoclonal antibody **(alemtuzumab)** is associated with the classic anti-GBM disease after 9-10 months of administration in genetically susceptible patients 2. TNF-alpha antagonists (**etanercept, adalimumab**) are associated with classic anti-GBM disease. The exact pathogenesis is unclear as TNF-alpha blockers are known to prevent/resolve anti-GBM GN in animal models. 3. Immune checkpoint inhibitors: Anti-programmed death-1 (**nivolumab, pembrolizumab**), CTLA4 antagonist (**tremelimumab**), kinase inhibitors (**dabrafenib, trametinib**) are associated with classic and atypical forms of anti-GBM disease 4. SARS-CoV-2 vaccines: Among all other de novo primary GNs reported, anti-GBM disease is rare after this vaccine. All types of SARS-CoV-2 vaccines such as **mRNA**, **Pfizer-BioNtech**, and **AstraZeneca** are associated with classic anti-GBM disease Management: Drug withdrawal + treatment similar to classic anti-GBM disease

Abbreviations: GBM, glomerular basement membrane; GN, glomerulonephritis; Ig, immunoglobulin; MPO, myeloperoxidase; TNF, tumor necrosis factor.

Lung Histology. Light microscopy of lung tissue in anti-GBM disease is characterized by non-specific inflammation in the alveolar septa (pulmonary capillaritis) and hemosiderin-laden macrophages. Immunofluorescence shows linear IgG deposition along the alveolar septa and helps differentiate the disease from idiopathic pulmonary hemosiderosis.[31,32] Transbronchial (lung) biopsy can be performed in suspected cases of anti-GBM disease with predominant lung involvement who are clinically stable. In reality, the diagnosis is usually based on clinical presentation and serology. Hemoptysis, falling hemoglobin, serial chest X-rays showing fleeting pulmonary infiltrates, and sequential bronchoalveolar lavage showing increasing blood are pointers for pulmonary hemorrhage.[33]

Treatment

One of the biggest challenges with this disease is the difficulty in identifying it early. The standard treatment comprises intense, rapid immunosuppression using plasmapheresis, corticosteroids, and cyclophosphamide (CYC).[34,35] Plasmapheresis is performed using a centrifugal bowl or plasma filter method with high plasma volume (50-60 mL/kg/session to a maximum of 4 L) exchanged daily until anti-GBM antibodies are undetectable or at least for 14 days. Plasmapheresis resulted in quicker disappearance of circulating anti-GBM antibodies and better serum creatinine at follow-up than placebo in a small, randomized trial comprising 17 patients.[36] Corticosteroids remain a key part of first-line treatment. Some centers use intravenous methylprednisolone pulses (500-1000 mg daily for 3 days) at the outset, followed by oral prednisone. Oral prednisone at 1 mg/kg body weight per day (up to a maximum of 60 mg/day) is used for 4-8 weeks, followed by a slow tapering over 6-9 months, depending on clinical course. In combination with corticosteroids, CYC is also considered a first-line treatment. Oral CYC (2-3 mg/kg body weight per day for 2-3 months) is used by most centers; however, some prefer using intravenous CYC derived from the European vasculitis study group (EUVAS) regimen for AAV. Intravenous CYC should be administered after plasmapheresis, to take into account removal of parent compound and metabolites during the procedure. The combination of plasmapheresis with immunosuppressive agents (CYC and steroids) was better than immunosuppressive agents alone in improving 1-year kidney survival (~30% vs ~10%) in a Chinese cohort.[37] Prophylactic treatments like co-trimoxazole (in case of intolerance, dapsone, or monthly pentamidine), anti-fungal (nystatin or fluconazole) proton pump inhibitor or H2 antagonist, and use of calcium/vitamin D supplements are practiced widely.[38] Rituximab, as an adjunct to

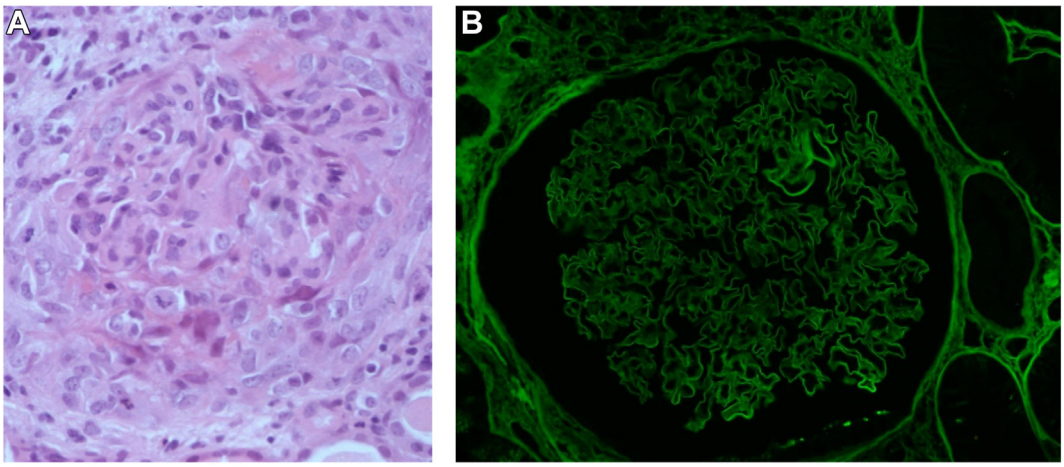

Figure 2. Kidney pathology in anti-GBM disease A). High power light microscopy image of kidney biopsy from a patient with anti-GBM disease showing a single glomerulus with crescentic change and compression of the glomerular tuft (hematoxylin and eosin stain, magnification ×400), B). Direct immunofluorescence of a single glomerulus showing linear IgG staining of the glomerular capillary loops (magnification ×400). Abbreviation: GBM, glomerular basement membrane. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

first-line therapy with corticosteroids and CYC, has effectively controlled pulmonary hemorrhage in patients with anti-GBM disease[39] in a small case series of 5 patients. In another retrospective study of 8 patients, rituximab led to the maintenance of serological and clinical remission in 8 and 7 patients, respectively.[40] The most common use of rituximab in anti-GBM disease has been in the context of contraindications to CYC or refractory disease with satisfactory effectiveness.[41] Immunoadsorption therapy was tested in a small study with 10 patients, and it was noninferior to plasmapheresis.[42]

Kidney transplantation is the best choice of kidney replacement therapy in patients developing end-stage kidney disease (ESKD) from anti-GBM disease, as recurrence of the disease is rare in the absence of circulating antibodies (<3%). Circulating anti-GBM autoantibodies significantly increases the risk of relapse after kidney transplantation[43]; therefore, a minimum of 6 seronegative months is taken as a prerequisite for kidney transplantation. Rituximab has been anecdotally used in treating circulating anti-GBM antibody titers in ESKD patients before transplantation.[1] Long-term patient and graft survival is reported to be similar to IgA nephropathy outcomes.[44] *De novo* anti-GBM disease can present as RPGN in patients with X-linked Alport Syndrome after kidney transplantation.[45] Patients with X-linked Alport syndrome with COL4A5 mutation are believed to be naïve to type IV collagen alpha5 chain and, therefore, are at risk of developing antibodies to this region after transplantation of a normal kidney that possesses the type IV collagen alpha5 chain.

Investigational Treatments. Imlifidase (IgG degrading enzyme of *Streptococcus pyogenes*) cleaves IgG into F(ab) and Fc fragments within hours.[46] Successful treatment of experimental glomerulonephritis with IdeS and EndoS,[47] IgG-degrading streptococcal enzymes, led to using IdeS in patients with anti-GBM disease. In a case series comprising 3 patients with refractory anti-GBM disease, IdeS treatment led to the quick disappearance of circulating anti-GBM antibody titer; however, kidney function was not resolved.[48] Nevertheless, in a recently published phase IIA one-arm study of 15 patients with severe disease and eGFR <15 mL/min/1.73m2, 10 were dialysis independent 6 months after IdeS treatment, 5 of whom were previously on dialysis.[49] Circulating anti-GBM antibodies were reduced within six hours after IdeS infusion. A phase III randomized trial, GOOD-IDES-02 (https://www.clinicaltrials.gov/ct2/show/NCT05679401), comparing standard of care treatment (corticosteroids, CYC, and plasma exchange) vs imlifidase in combination with standard of care treatment has started enrolling patients across multiple centers in the United States, the United Kingdom, and the European Union. Enrollment is expected to be completed in the next 3 years and a pediatric subgroup has been planned.

Targeting specific inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-1, migration inhibitory factor, and use of anti-inflammatory cytokines such as interleukin-4 and interleukin-11 have resulted in the prevention of anti-GBM GN in animal models[50] (Fig 3). Novel treatments, including modulation of the pathogenic epitope or HLA, lead to attenuated kidney injury in animal models.[51] T-cell epitope-derived peptides, which are modified to modulate T-cell differentiation in response to antigenic exposure in anti-GBM disease, can attenuate kidney inflammation.

Disease Prognosis and Predictors of Outcome

A delay in diagnosis is likely to worsen kidney survival.[37] Most (~90%) patients achieve serological remission with standard treatment within 6 months of presentation. With the advent of intense immunosuppression, the 1-year mortality from anti-GBM disease has reduced to

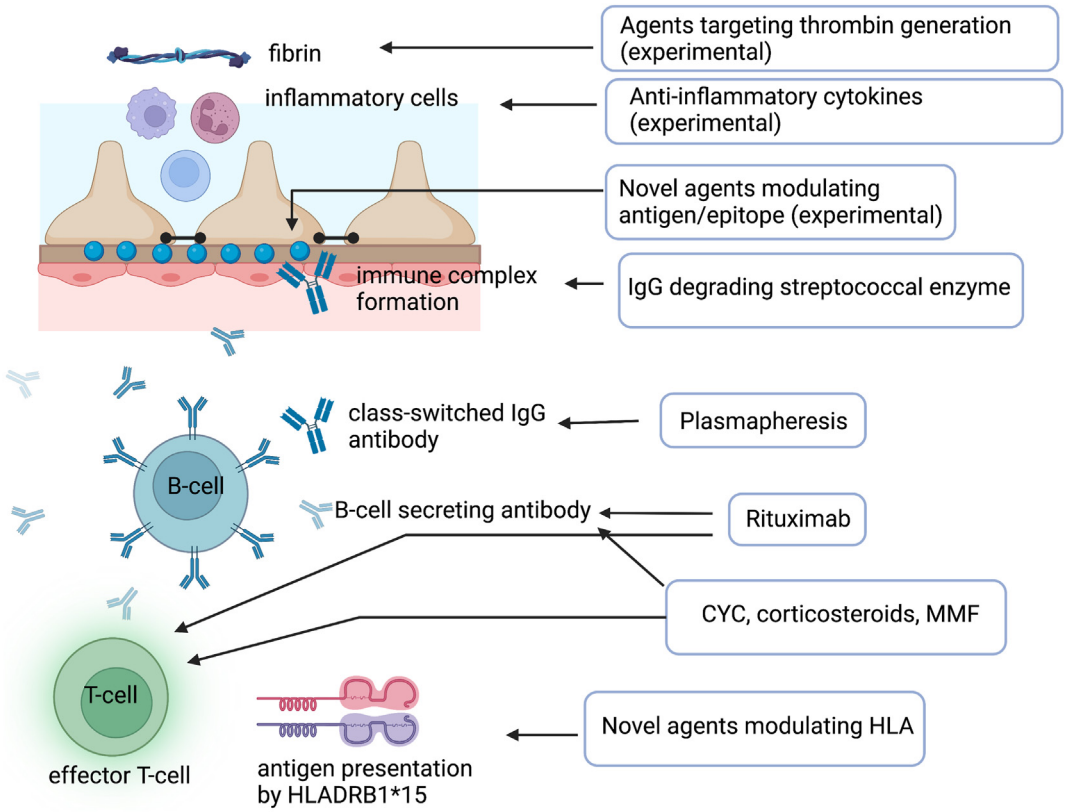

Figure 3. Pathogenesis and therapeutic targets in anti-GBM disease. Abbreviation: GBM, glomerular basement membrane. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

<40% (Table 2). Kidney survival at 1 year remains poor at 25-30% in most reports (Table 2). Patient survival once commenced on dialysis is similar to other ESKD causes.[2]

Histological Predictors of Disease Outcome. Most (>50%) patients have cellular crescent formation, the strongest histological predictor of kidney outcome.[52] Irrespective of staging, 100% crescents on biopsy with dialysis dependency were shown to be associated with nonrecovery of kidney function[22,34] (Table 2). One-quarter of patients with crescents >50% were reported to recover kidney function during follow-up after treatment in the study by Levy and colleagues[34] Another study from Spain showed crescents >50% to be a predictor of kidney failure on univariate analysis[53]; however, the predictive ability disappeared on multivariate analysis. None of the patients with 75% crescents recovered kidney function at 3 months in a cohort of patients from England.[28] Patients with >50% sclerosed glomeruli also typically present with dialysis-dependent kidney failure.[22] A more recent focus has been on the number of normal glomeruli as an indicator of outcomes. Daalen and colleagues,[22] in an international cohort, observed that kidney survival correlated with the percentage of normal glomeruli. Patients with 25% or more normal glomeruli had 5-year kidney survival of ~75% compared to <50% 5-year kidney survival in those with <25% normal glomeruli. In a recently reported multicenter study, Floyd and colleagues[21] tested the ability of renal risk score to predict outcomes of anti-GBM disease using 174 patients from 7 centers across Europe and the United States. The percentage of normal glomeruli was an independent predictor of ESKD, and among the 129 dialysis-dependent patients at presentation, 26% recovered kidney function. Patients with>25% normal glomeruli had the best kidney survival at 36 months, followed by those with 10-25% normal glomeruli. Patients with <10% normal glomeruli had poor kidney function recovery, suggesting that 10% is a useful threshold to identify the chance of potential kidney recovery. Nevertheless, 17% of dialysis-dependent patients with <10% normal glomeruli in this cohort still recovered sufficient kidney function to achieve dialysis independence during follow-up. Therefore, a threshold of 10% normal glomeruli should aid in decision-making, but it is not an absolute contraindication for avoiding treatment.

Interestingly, the extent of interstitial infiltrate, not Interstitial fibrosis and tubular atrophy, was an independent predictor of ESKD in the same study.[22] Similarly, Interstitial fibrosis and tubular atrophy did not independently predict kidney survival in the study by Floyd and colleagues.[21]

Clinical and Biochemical Predictors of Anti-GBM Disease. Several clinical and biochemical factors are associated with kidney survival (Table 2). In the seminal article by

Table 2. Kidney and Mortality Outcomes in Patients With Anti-GBM Disease With Any Identified Predictive Factors

Country, year	N	Predictors	1-y Kidney Survival	Predictors	1-y Patient Survival
USA, 1985[36]	17	(i). Serum creatinine (ii). Crescent percentage		_	_
UK, 2001[34]	71	(i). Dialysis dependence (ii). Serum creatinine >5.7 mg/dL (no dialysis)	8% 62%	Serum creatinine >5.7 mg/dL	65% 83%
China, 2011[37]	176	Serum creatinine	25%	(i). Serum anti-GBM antibody titer (ii). Presence of positive ANCA	72.7%
UK, 2015[28]	43	(i). Crescents 75% (ii). Oliguria	16%	Oliguria	88%
France, 2016[69]	122	Serum creatinine >5.7 mg/dL μmol/L	_	_	87%
International (Netherlands, UK, USA, New Zealand), 2018[22]	123	(i). Dialysis dependence (ii). Percentage of normal glomeruli (iii). Extent of interstitial infiltrate	25% (crescentic class)	_	~85% (crescentic class)
France, 2019[70]	119	_	_	(i). Age at onset (ii). Hypertension (iii). Dyslipidemia (iv). Need for mechanical ventilation (v). No PLEX	95%
India, 2021[71]	48	(i). Oliguria (ii). Serum creatinine (iii). Severe glomerulosclerosis (iv). IFTA	9.7%	(i). Age (ii). Serum creatinine (iii). Anti-GBM titers	40.4%
China, 2022[72]	448	(i). Serum creatinine (>6.07 mg/dL) (ii). Crescent percentage	37.5%	ANCA positivity	69.4%
Spain, 2022[53]	72	(i). Dialysis dependence (ii). Serum creatinine >4.7 mg/dL	13.5%	_	88%
International, 2023[21]	174	(i). Percentage of normal glomeruli (ii). Dialysis dependence	25% (high-risk group)	_	30.5% (3-year)

Abbreviation: GBM, glomerular basement membrane.

Levy and colleagues,[34] patients presenting with a serum creatinine of <5.7 mg/dL had 95% 1-year kidney survival; those with serum creatinine >5.7 mg/dL without dialysis requirement had 82% 1-year kidney survival. Strikingly, the 1-year kidney survival rate was reduced to 8% in patients requiring dialysis at presentation. Similar to previously mentioned studies, none of the patients requiring dialysis and with 100% crescents on kidney biopsy recovered kidney function at 1 year. Serum creatinine or eGFR at presentation did not accurately predict outcome in a recent international multicenter study.[21] Dialysis dependence at presentation has consistently been a stronger predictor of poor kidney survival.[22] Oligoanuria at presentation is also observed to predict the risk of long-term dialysis dependency.[28]

Decisions regarding Aggressive Treatment in an Individual Patient

Most patients receive prompt, aggressive immunosuppressive treatment at presentation. The Kidney Disease Improving Global Outcomes guideline recommends withholding immunosuppressive therapy and plasmapheresis in adults with advanced (potentially irreversible) kidney injury, defined as dialysis dependency with 100% crescents or >50% global glomerular sclerosis, without pulmonary hemorrhage.[35] In clinical practice, most clinicians would start plasmapheresis with or without immunosuppressive agents before the kidney biopsy results are available. Like any other clinical situation, withholding treatment in anti-GBM disease is based on weighing risks and benefits. Plasmapheresis is recommended in children and young patients with dialysis-dependent anti-GBM disease with or without pulmonary hemorrhage.[5,54] Risks of immunosuppression appear to be lesser in otherwise healthy young patients when compared to older adults. The conservative approach of withholding immunosuppression/plasmapheresis in kidney injury without pulmonary hemorrhage seems best suitable in (1) the medically frail with confounding comorbidities and (2). the presence of advanced, irreversible disease. Therefore, the decision to refrain from treatment should be cautiously guided by the individual patient's characteristics.

Targets to Improve Outcomes

Given the low incidence, it is impractical to employ screening tools for the early detection of anti-GBM disease. Given the rapidity of disease development, the silent nature of nephritis, and the lack of a prodrome, identifying patients at the early stages is challenging in anti-GBM disease. Therefore, all efforts to identify anti-GBM disease and prompt initiation of therapy should be made in cases of RPGN. For example, prompt return of anti-GBM antibody titers (ideally within a few hours) and a kidney biopsy performed and reported early are fundamental steps toward reaching a prompt diagnosis. International cohorts with biosampling would advance our understanding of the pathophysiology of anti-GBM disease, and large disease registries would monitor its disease course. There is an apparent unmet need for effective therapy in anti-GBM disease. Imlifidase is demonstrating significant promise in this field and it is under evaluation in patients of all ages. Targeting the reversal of kidney fibrosis (scarring) may be another potential option[55]; however, there is little evidence to demonstrate efficacy in advanced/chronic pathology to date.

CONCLUSION

Due to the rarity of this disease, the progress of evolving newer therapeutics for patient benefit is slow, and efforts to strive for early diagnosis and methods to risk stratify patients based on predictors of disease outcome may be realistic interventions in the short term to improve the existing management of anti-GBM disease. A better understanding of the pathogenesis of the disease is slowly emerging. Early clinical trials targeting the deposited IgG antibodies provide hope; future international collaborative efforts will bring much-needed improvements.

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