Review

Goodpasture syndrome and anti-glomerular basement membrane disease

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare life-threatening small-vessel vasculitis that typically affects the capillaries of kidneys and lungs, with most of patients developing rapidly progressive crescentic glomerulonephritis, and 40–60% concomitant alveolar haemorrhage. It is caused by the deposition in alveolar and glomerular basement membrane of circulating autoantibodies directed against antigens intrinsic to the basement membrane. The exact mechanism that induces the formation of autoantibodies is unknown, but probably environmental factors, infections or direct damage to kidneys and lungs may trigger the autoimmune response in genetically susceptible individuals. Initial therapy includes corticosteroids and cyclophosphamide to prevent autoantibodies production, and plasmapheresis to remove the circulating autoantibodies. Good renal outcomes may be achieved by a prompt treatment initiation. However, when patients present with severe renal failure requiring dialysis or with a high proportion of glomerular crescents at biopsy, renal outcomes are bad. Relapses are rare and when renal involvement is present, the suspect of concomitant diseases, such as ANCA-associated vasculitis and membranous nephropathy, should be raised. Imlifidase is showing promising results, which if confirmed will cause a paradigm shift in the treatment of this disease.

Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a rare life-threatening small-vessel vasculitis that affects pulmonary capillaries, glomerular capillaries or both, caused by the deposition in alveolar and glomerular basement membrane of circulating autoantibodies (1). Most patients present with alveolar haemorrhage and rapidly progressive crescentic glomerulonephritis that, if untreated, progresses quickly to end-stage kidney disease (ESKD) (2). The first description of this disease was made in 1958 by Stanton and Tange (3). They called it Goodpasture syndrome in honour of Doctor Ernest William Goodpasture, which first described a patient with haemoptysis and acute glomerulonephritis, both considered complications of an atypical infection (4). The term Goodpasture syndrome was thereafter used for several years to appoint pulmonary-renal involvement in the presence of anti-GBM antibodies. However, nowadays the preferred term is anti-GBM disease since afterwards also atypical forms of this disease have been described (5).

Epidemiology

Anti-GBM disease is a rare small-vessel vasculitis and it is the cause of 1–2% of acute glomerulonephritis and 10–15% of rapidly progressive crescentic glomerulonephritis (2). Among European and Asian populations, the incidence of anti-GBM disease is estimated to be between 0.5 and 1.8 cases per million population per year (2, 6-8). In United States, the prevalence of anti-GBM disease is 10 cases per million hospitalised patients (9). Anti-GBM disease has been described in White and Asian individuals, while it seems rarer in African individuals. Age distribution is bimodal, with a peak incidence in the third decade, when there is a slight male predominance, and in the six decade, when it affects mainly females (10-13). Patients younger than 30 years more frequently present with lung involvement, while patients older than 50 years are more likely to present with isolated renal involvement (14).

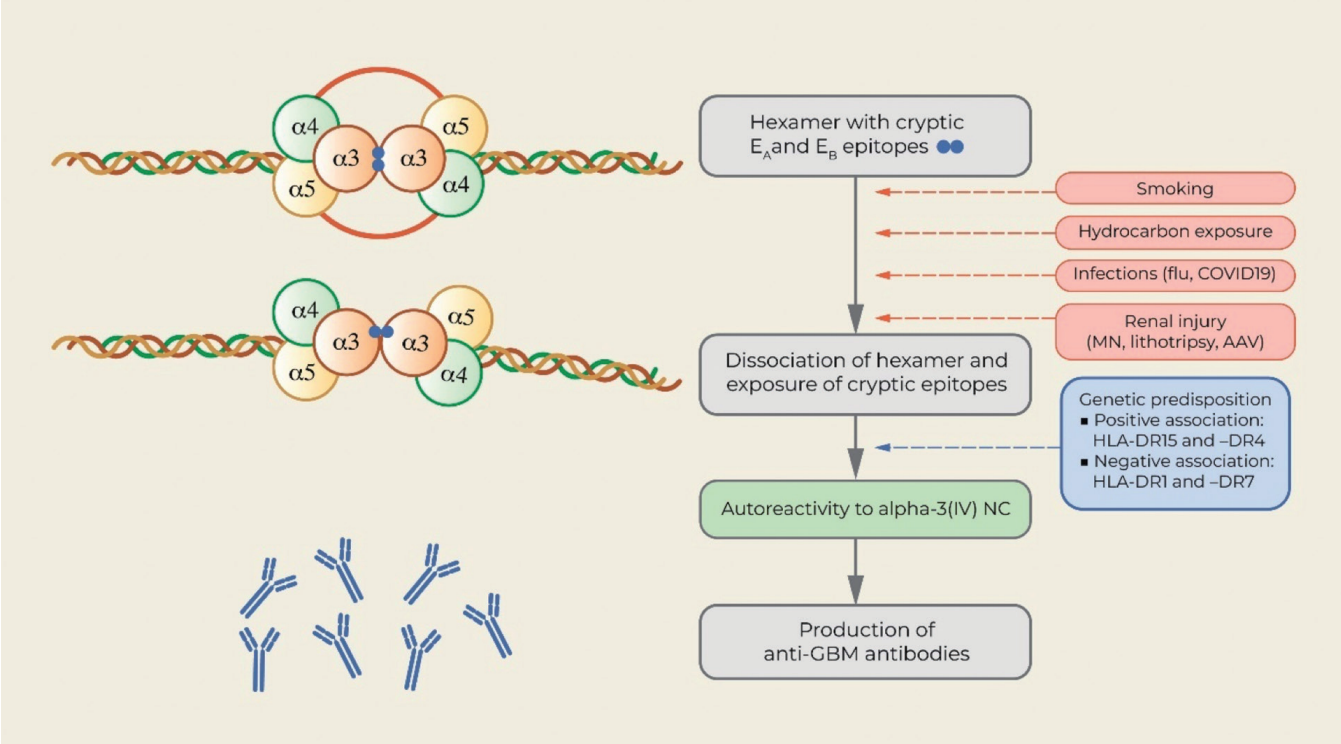

Fig. 1. Schematic representation of anti-GBM antibodies development.
E_A and E_B epitopes of α3 collagen chain are normally hidden inside the collagenous structure of the alveolar and glomerular basement membrane (GBM), which is held together by disulfide bonds across NC1 domains (red lines). Several environmental factors, such as smoking, hydrocarbon exposure, and infections, together with kidney injury, cause the disruption of hexamer structure and exposure of the hidden antigens. In patients with genetic predisposition this process may lead to the development of anti-GBM autoantibodies.
AAV: ANCA-associated vasculitis; alpha-3(IV) NC: noncollagenous (NC1) domain of the alpha-3 chain of type IV collagen; HLA: human leukocyte antigens; MN: membranous nephropathy.

Pathogenesis

Anti-GBM disease is an autoimmune disorder caused by circulating autoantibodies directed against an antigen intrinsic to GBM (Fig. 1). In the common form of anti-GBM disease, the autoantibody is a polyclonal immunoglobulin G (IgG), with IgG1 and IgG3 subclasses predominant, that target the epitopes E_A and E_B of the noncollagenous (NC1) domain of the alpha-3 chain of type IV collagen (alpha-3(IV) NC) (15–17). There are also rare cases in which IgG4 subclass and IgA (18, 19), or monoclonal immunoglobulins (20, 21), have been described. Anti-GBM antibodies may also target other alpha chains. A study demonstrated that antibodies that strongly bind to alpha-3(IV) NC may also recognise alpha-5(IV) and, to a lesser extent, alpha-4(IV) (22). Recently, autoantibodies directed against peroxidasin (23) and laminin-521 (LM521) (24) have been identified in patients with positive anti-GBM antibodies. Peroxidasin is an extracellular peroxidase that contributes to the formation of the sulfonimine cross-links in the NC1 domain (25), which may be disrupted by autoantibodies directed against peroxidasin, causing the exposure of cryptic epitopes (23). Laminin is a family of αβγ heterotrimeric glycoproteins that are abundant components of all basement membranes. LM521 is the major isoform in the mature GBM and is also abundant in alveolar basement membrane (ABM) (24). The role of antibodies against LM521 is still not completely known. The nephritogenicity of these antibodies has been demonstrated in animal models (26). In humans, a retrospective study found that antibodies against LM521 occur in about one third of anti-GBM disease patients and are significantly associated with lung involvement (24). Finally also anti-neutrophil cytoplasmic antibodies (ANCAs) have been described in up to 21-47% of patients with anti-GBM disease, with a predominance of antibodies directed against myeloperoxidase (anti-MPO Abs) compared to antibodies against proteinase-3 (anti-PR3 Abs) (14, 27). It has been demonstrated that ANCAs positivity precedes the appearance of anti-GBM antibodies, suggesting a possible role of ANCAs in exposing the cryptic epitopes (28).

Anti-GBM disease is frequently of unknown aetiology. There is increasing evidence that genetic susceptibility to anti-GBM disease is present, in particular in patients with HLA-DR15 and -DR4, while DR1 and DR7 seems to be protective (29). Immune dysregulation appears to predispose both the release of autoantibodies that unveil hidden cryptic epitopes and anti-GBM antibodies. Moreover, several triggers causing kidney or pulmonary injury, that favors the release of increased amounts of auto-antigen, have been described (13). Pulmonary infections (30), smoking (22), hydrocarbon solvent exposure and lung cancer have been identified as lung injury causes

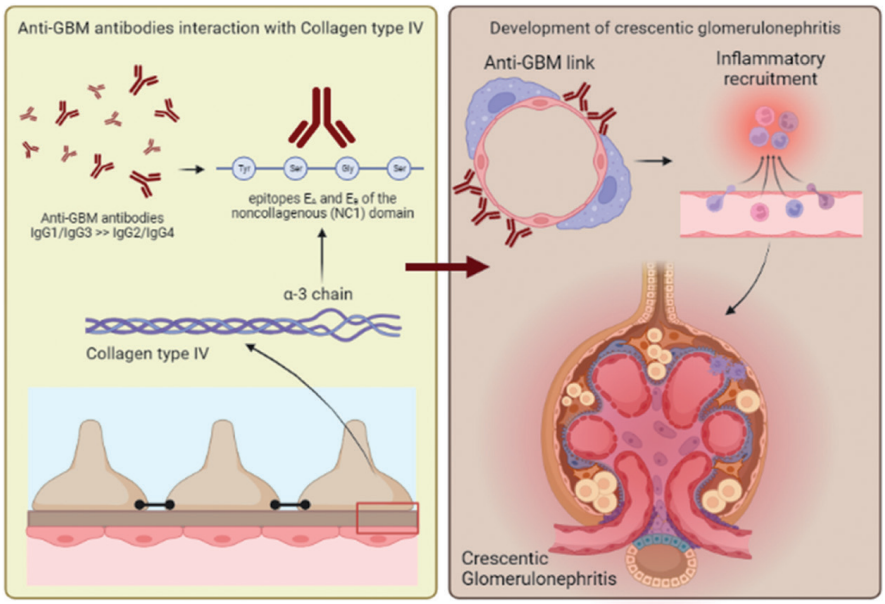

Fig. 2. Schematic representation of the pathogenesis of anti-GBM glomerulonephritis.
In the left panel antibodies (most frequently of the IgG1 and IgG3 subtype) are directed against the epitope EA and EB of the noncollagenous (NC1) domain of the alpha-3 chain of type IV collagen (alpha-3(IV) NC) of the glomerular basement membranes (GBM). This phenomenon leads to the recruitment of different inflammatory cells in the capillary loops of glomerular tuft (right panel), causing the disruption of GBM and capillary wall and extravasation of different cell types, with the formation of crescentic glomerulonephritis.

triggering anti-GBM disease development (22). Recently, a fivefold increase above the expected incidence was observed in North-West London during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, supporting the association between lung injury and anti-GBM disease development (31). Ureteral obstruction, membranous nephropathy, ANCA-associated glomerulonephritis and lithotripsy have been described as potential triggers of kidney injury (2, 22).

Experimental and clinical studies suggested that also autoreactive T cells may contribute to the development of anti-GBM disease. In addition to enhancing B cell function and antibody production, T cells may have a direct causative role in alveolar and glomerular injury (32). It has been demonstrated that T cells from patients with anti-GBM disease react against the alpha-3(IV) NC (33, 34). Moreover, the T cell immune response may be triggered by specific T cells epitopes of alpha-3(IV) NC, which are presented by the major histocompatibility complex (35, 36). This process was sufficient to determine acute glomerulonephritis (35). Finally, an important role may be played by regulatory T cells ($CD4^+$ $CD25^+$). These cells regulate the autoimmune response countering the effects of autoreactive T cells (37), in particular T-helper1 (Th1) and T-helper 17 (Th17), which play a role in crescent formation (38). In a murine model of anti-GBM disease, regulatory T cells ($CD4^+$ $CD25^+$) reduced the severity of glomerular lesions (39).

Anti-GBM antibody localisation in the basement membrane causes inflammation, activation of the complement system and release of reactive oxygen species. This inflammatory milieu causes the necrosis and the rupture of the GBM. The subsequent leakage of proteins in the Bowman space determines the activation and proliferation of parietal cells, which lose polarity. These events, together with lymphocyte and macrophage infiltration, cause the formation of cellular crescents (Fig. 2) (13, 40).

Pathology

The presence of crescents and the localisation of anti-GBM antibodies in the basement membrane are the two most important histological characteristics of anti-GBM disease. At light microscopy, focal or diffuse crescentic and/or necrotising glomerulonephritis is typical (Fig. 3). 95% of patients will have evidence of crescent formation on kidney biopsy, and that in 80% of patients more than half of glomeruli will be affected (41, 42). Together with this finding, various degrees of intracapillary proliferation or interstitial inflammation may be present. Intraglomerular inflammation can finally lead to Bowman capsule rupture, a potentially irreversible damage that can have prognostically unfavorable impact, as already demonstrated in other crescentic glomerulonephritis (43-45). In advanced stages, the inflammatory lesions may evolve to fibrous one, generating fibrous crescents, glomerulosclerosis, interstitial fibrosis, and/or tubular atrophy (13). At immunofluorescence, bright linear deposits of IgG1 and IgG3 (rarely IgG4 or IgA) and C3 are pathognomonic. Up to 1964, the diagnosis of anti-GBM disease was based on clinical data. After the advent of immunofluorescence, Scherr and Grossman described this typical linear IgG deposition in GBM, changing the history of this disease (46, 47). No electron-dense deposits are detected at electron microscopy, while signs of crescentic glomerulonephritis, such as GBM rupture and extracapillary localisation of fibrin and proliferating cells, may be observed. Lung biopsy is not routinely used in the diagnosis of anti-GBM disease. If performed, linear deposits of IgG along the ABM may be observed, even if immunofluorescence on lung tissue is often not informative (2).

In search of the anti-GBM antibody

The demonstration of circulating or deposited anti-GBM antibodies is necessary for the diagnosis. In routine diagnostics, the alpha-3(IV) NC is utilised as substrate by various immunoassay formats, most notably enzyme-linked immunoassay (ELISA) and indirect immunofluorescence tests, to detect anti-GBM antibodies. The detection of anti-GBM antibodies in serum using ELISA with the specificity of the antibody eventually confirmed by Western blot,

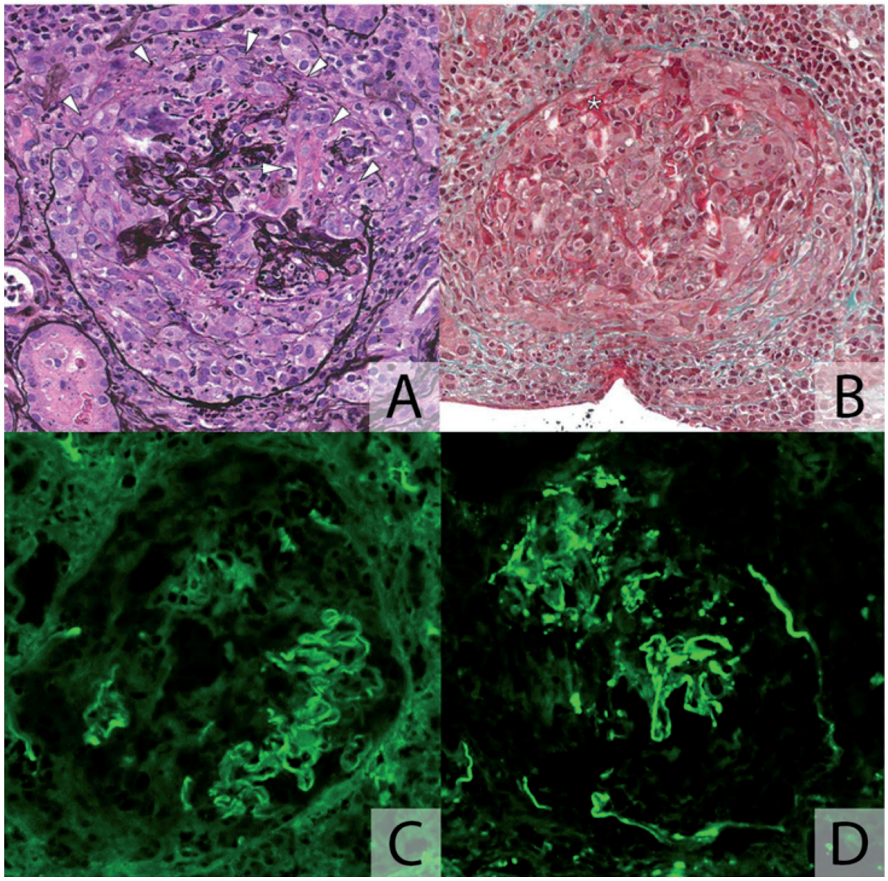

Fig. 3. Histological features of anti-GBM glomerulonephritis on renal biopsy.
A: Light microscopy shows the interruption of the GBM (white arrow) with deposition of fibrinoid necrosis and consequent extravasation of different cellular elements forming circumferential cellular crescents, finally leading to the disruption of Bowman capsule (white arrowhead, Jones Methenamine silver stain, x20).
B: Masson trichrome stain highlights fuchsinophilic areas corresponding to fibrinoid necrosis (white asterisk) in a glomerulus globally involved by cellular crescent and periglomerular inflammation.
C: Immunofluorescence demonstrates diffuse and global linear positivity of the capillary walls for IgG antisera (3+, x20) in areas still spared from the GBM break and cellular crescents formation.
D: This is almost invariably associated with the deposition of C3 with the same pattern (2-3+, x20), with focal extension to the Bowman capsule interrupted by the increase of intraglomerular inflammation.

is the preferred technique, while indirect immunofluorescence is rarely performed (48). The sensitivity of ELISA varies depending upon the commercial kit used, ranging from 63 to nearly 100 percent (49, 50). False negative results may occur, as in the case of low antibody titres (51) or in the presence of different immunoglobulins subclasses (as IgA or IgG4) and/or antibodies targeting antigens different from alpha-3(IV) NC (52). False-positive may result with commercial ELISA assays that do not use purified Goodpasture antigen (15, 50). Recently, chemiluminescence immunoassay (ChLIA) has been proposed as a promising alternative tool for accurate anti-GBM antibodies (IgG) assessment since it demonstrated sensitivity of 100% at a specificity of 98.6%. Moreover, it is a reliable and efficient fully automated process (52).

Clinical presentation and diagnosis

"Typical" anti-GBM disease

Up to 80–90% of patients present with features of rapidly progressive glomerulonephritis, characterised by active urinary sediment analysis, subnephrotic proteinuria and reduced urinary output. 40–60% of patients will have concurrent lung haemorrhage with haemoptysis and various degrees of dyspnoea. A small minority of patients may present with isolated pulmonary disease. In few cases, patients present with severe acute kidney injury requiring dialytic treatment (2). In the presence of rapid progressive glomerulonephritis, the diagnosis of anti-GBM disease is based on the detection of the anti-GBM antibodies either in serum or deposited in tissue, as described above. Although lung involvement is not always present, in the suspect of alveolar haemorrhage radiological examination and broncho-alveolar lavage are indicated. A characteristic feature of alveolar bleeding is the presence of haemosiderin-laden macrophages in the broncho-alveolar lavage (53). Haemoptysis is not always evident, therefore lung involvement should be suspected even in the absence of haemophtoe if severe anaemia is present (53).

"Atypical" anti-GBM disease

Unusual presentations of anti-GBM disease have been described since the discovery of this disease. Several cases and series of less severe renal involvement have been published (47, 54-57). It's still not clear whether these milder cases represent a less frequent phenotypic expression of a disease with a wide spectrum of severity or a distinct clinical sub-phenotype determined by a different pathogenesis (2). In a series of 20 patients with hematuria, proteinuria, mild kidney function impairment, and without pulmonary haemorrhage, kidney biopsy showed bright, linear IgG deposition along the GBM without features of crescentic glomerulonephritis. Monoclonality was commonly observed and anti-GBM antibodies were not detected with conventional assays (49). The authors hypothesised that differences in antigen specificity, Ig subclass, and/or ability to recruit inflammatory cells may account for the milder disease phenotype (57). This hypothesis is supported also by the findings of a Swedish series, in which four young females, who had severe lung disease but minimal kidney involvement, presented with IgG4 subclass anti-GBM antibodies, that were not detectable with conventional anti-GBM assays (19). The discrepancy between positive linear staining for IgG in kidney biopsy and negative anti-GBM antibodies may be explained by the fact that in "atypical" anti-GBM disease autoantibodies may be directed against epitopes different from the common epitopes present in commercial immunoassays (51).

Other variants

Double-positive anti-GBM and ANCA-associated disease

ANCA-associated vasculitis, in particular granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and anti-GBM disease have similar clinical manifestations, characterised by acute glomerulonephritis with or without pulmonary haemorrhage. In the approach to this clinical presentation, ANCA and anti-GBM antibodies are tested together and, in much higher frequency than expected by chance alone, they may both test positive. As described above, up to 10–50% of patients with anti-GBM disease also test positively for ANCA (usually anti-MPO Abs), and up to 10% of patients with ANCA positivity also have circulating anti-GBM antibodies (58, 59). The pathogenic mechanism of this association is still debated, but since low levels of ANCA may be detected years before the appearance of anti-GBM antibodies and clinical symptoms, it has been hypothesised that ANCA antibodies may induce glomerular inflammation that modify or expose usually sequestered disease epitopes in GBM, triggering anti-GBM antibodies formation (28). A recent study by Nishibata demonstrated that proteases released from neutrophils activated by ANCA can digest type IV collagen with subsequent unveiling of alpha-3(IV) NC (60). Another study demonstrated that up to 60% anti-GBM patients also have autoantibodies that target linear epitopes of MPO, *versus* 24% with autoantibodies that target intact MPO. The authors hypothesised that anti-MPO Abs targeting linear and conformational epitopes may arise sequentially, through a process of inter- and intra-molecular epitope spreading (61).

Patients with double positivity for anti-GBM and ANCA antibodies frequently experience the typical severe clinical presentation of anti-GBM disease, with acute glomerulonephritis and lung haemorrhage requiring aggressive immunosuppressive therapy and plasma exchange (27). Mortality and renal survival is similar to that of anti-GBM disease, while the multiorgan damage and the tendency to relapse during long-term follow-up are comparable to ANCA-associated vasculitis (27, 59, 62). The risk of ESKD is increased by the tendency to relapse, therefore prolonged maintenance immunosuppression and careful long-term follow-up is mandatory, unlike patients with just anti-GBM antibodies (63).

Anti-GBM disease associated with membranous nephropathy

There are several cases of anti-GBM disease associated with membranous nephropathy (MN) (64-68). As for the association with ANCA vasculitis, it has been postulated that the unveiling of hidden epitopes caused by one disease may be the trigger for the other disease occurrence. Consistently with this hypothesis, the onset of anti-GBM disease may precede, coincide with, or follow the diagnosis of MN. In one series of 8 patients with combined anti-GBM disease and MN, the antibody levels against the E_B conformational epitope of alpha-3(IV) NC were lower and serum antibodies against the phospholipase A2 receptor (PLA2R) were absent (66). In the same series patients had a lower serum creatinine level at diagnosis, lower proportion with oliguria/anuria, and better kidney survival at one year, compared to the typical anti-GBM disease (66). A rapid decline in kidney function in a patient with known MN should raise suspicion of the development of superimposed anti-GBM disease. These patients should be treated aggressively as for anti-GBM disease, while long-term treatment is uncertain (2).

Anti-GBM disease after kidney transplantation

A peculiar form of anti-GBM disease occurs in up to 5–10% of kidney transplants in patients with underlying Alport syndrome (69). Alport Syndrome is a hereditary disorder characterised by progressive kidney disease, hearing loss, and ocular abnormalities. This disorder is determined by mutations in any of the genes that encode the α3, α4, or α5 chains, causing an alteration of the normal type IV collagen network present in GBM (70). The mutated genes are COL4A3 and COL4A4 genes, located in chromosome 2, and COL4A5 gene, located in chromosome X. COL4A5 gene mutation is the most common, giving rise to typical X-linked Alport syndrome (70). In these patients, the immune system is accustomed to a defective form of α3, α4, or α5 chains. Therefore, the normal antigens contained in α3, α4, or α5 chains of the kidney allograft cause an alloimmune response with the development of anti-GBM antibodies (22). Also in the presence of anti-GBM antibodies, the development of overt glomerulonephritis is infrequent probably due to the effect of immunosuppression (71). However, when glomerulonephritis develops, an higher risk of graft loss is present (72) and repeated transplantation leads to more aggressive disease recurrence and rapid graft loss (73).

IgA-mediated anti-GBM disease

Few cases of anti-GBM disease mediated by circulating IgA anti-GBM antibodies have been described (18, 20, 74-83). In these cases, the antibody may not be recognised by standard ELISA and Western blotting techniques. In most of these cases rapidly progressive glomerulonephritis was present, while pulmonary involvement was found in 40% of cases. At kidney biopsy, the immunofluorescence showed linear staining for IgA. The prognosis of IgA-mediated anti-GBM disease was poor compared with typical anti-GBM disease, with high mortality related to pulmonary involvement and poor renal survival (50% of patients progressed to ESKD) (18, 20, 74–83). The pathophysiology of this disorder is still unknown, but the heterogeneity of the autoantigen and the peculiar clinical presentation and prognosis suggest that this IgA-related condition should be considered a different disease.

Anti-GBM disease and thrombotic thrombocytopenic purpura

Very few cases of anti-GBM disease with concomitant thrombotic thrombocytopenic purpura (TTP) have been described (84-87). TTP is a thrombotic microangiopathy caused by severely reduced activity of ADAMTS13, a von Willebrand factor-cleaving protease, that leads to small-vessel platelet-rich thrombi, thrombocytopenia, and mi-

croangiopathic haemolytic anaemia (88). This disease is frequently caused by the presence of anti-ADAMTS13 antibodies (88). Patients with anti-GBM and associated TTP presented with acute glomerulonephritis and lung haemorrhage, together with the symptoms of TTP (84-87). It is not known if this association is casual, or a common pathogenic mechanism is present. It has been hypothesised that the immunological mechanism associated with the presence of anti-GBM antibodies is also responsible for the production of anti-ADAMTS13 antibodies (87), but stronger evidences are required.

Anti-GBM disease after alemtuzumab treatment

Alemtuzumab is a humanised monoclonal antibody directed against the cell surface antigen CD52. It is used for the treatment of relapsing multiple sclerosis (89). Few cases of anti-GBM disease during the lymphocytes' repopulation phase have been described (90-92). The marked autoreactivity of the lymphocytes' repopulation phase may be responsible for the anti-GBM antibodies development. This hypothesis is supported by the fact that no cases of anti-GBM disease have been reported when alemtuzumab was used together with strong immunosuppression, as in the case of kidney transplant.

Anti-GBM disease and pregnancy

De novo anti-GBM disease in pregnancy is rare and just few cases have been described (93–99). Most patients presented after the first trimester with acute kidney injury, haematuria, proteinuria and anaemia (98). When haemodialysis was required antepartum, renal recovery with haemodialysis discontinuation was unlikely. Most of the cases described in the literature ended in live births. However, anti-GBM antibodies may cross the placenta causing pulmonary renal syndrome in the fetus with subsequent spontaneous abortion or stillbirth (98).

Anti-GBM antibodies in systemic lupus erythematosus

The presence of anti-GBM antibodies in systemic lupus erythematosus (SLE) is debated. Some reports on young Asian patients described the presence of anti-GBM antibodies in patients with SLE and rapidly progressive renal failure (100-104). In these patients, alveolar haemorrhage was significantly more frequent than in SLE patients without anti-GBM antibodies, and prognosis was worse (103). However, these findings were not confirmed on Caucasian patients (105). If this discrepancy is due to ethnic differences (106) or to the different specificity of the commercial anti GBM assays (49) is still not known.

Treatment

Standard treatment

Since the most frequent clinical presentation of anti-GBM disease is severe, a prompt and aggressive initial therapy is recommended (107). The therapy is based on plasmapheresis, which rapidly remove the pathogenic autoantibody, together with corticosteroids and cyclophosphamide, which inhibit autoantibody production and ameliorate inflammation (Table I) (2). This treatment was firstly described in 1976 by Lockwood *et al*. (108), and is still recommended by the KDIGO guidelines (109). These guidelines recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM glomerulonephritis, except in those who are treated with dialysis at presentation, have 100% crescents or more than 50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary haemorrhage (109).

The recommended treatment schedule includes prednisolone at the dosage of 1 mg/kg per day (maximum 60 mg) given orally. The dosage must be reduced weekly to 20 mg by 6 weeks, then gradually tapered until complete discontinuation at 6 months (110). Some authors suggest starting with 1 gram of methylprednisolone given daily for three days, but this indication is debated (2, 13, 14). Cyclophosphamide should be given orally since the equivalence of daily oral and pulsed intravenous cyclophosphamide has been demonstrated (111). The starting dosage is 2–3 mg/kg per day, to be adjusted in case of renal failure and older patients. The risk of cyclophosphamide toxicity is low since the treatment is usually continued for no longer than 2-3 months (109, 110).

The use of plasmapheresis is supported by the fact that allows a rapid reduction of antibodies titre (up to 60–65% every session) and is able to improve renal and patient survival compared to immunosuppression alone (14, 112, 113). Moreover, a small (n=17) randomised trial that compared the addition of plasma exchange to cyclophosphamide and steroids in anti-GBM disease confirmed the benefit of plasma exchange. In fact, in the plasma exchange group the fall of anti-GBM antibodies was rapid and renal outcomes were better (114).

Immunoadsorption is an alternative to plasmapheresis, although it may still be considered an investigational therapy. It is more efficient than plasma exchange for the removal of pathogenic autoantibody (up to 71–86% every session) and has the advantage to minimise allergic reactions (112, 115). The clinical outcomes of immunoadsorption are comparable to plasma exchange (115, 116).

Therapeutic alternatives

To date, there is insufficient evidence to support other immunosuppressive therapies. Few reports on successful treatment with mycophenolate mofetil and cyclosporine have been reported in literature (117-119). Interesting evidence is emerging with rituximab (RTX) and imliflidase. RTX is a chimeric mouse/human monoclonal antibody (mAb) with binding specificity to CD20 (120). The are several case reports on anti-GBM disease in which RTX has been used as either "add-on" to standard therapy or as a substitute for cyclophosphamide (121, 122). The usual dosage was 375 mg/m^2 (2 to 6 weekly doses) or 1000 mg (1 to 2 doses). RTX demonstrated a rapid reduction of anti-GBM antibodies, but without benefits on renal outcomes (122). Therefore, waiting for randomised trials, RTX should be reasonably used in patients that are refractory to standard treatment or with contraindications to cyclophosphamide. Imlifidase is an immunoglobulin G (IgG)-specific protease that cleaves human IgG into F(ab')2 and Fc fragments, causing a rapid decrease in anti-

Table I. Initial treatment of anti-GBM disease.

	Agent	Details	Considerations and warnings
Standard therapy	**Plasma exchange**	• Daily 4 L exchange for 5% human albumin solution • Continue until antibody levels are fully suppressed or for 14 d	• Add fresh human plasma (0.3-2.0 L) within 3 days of invasive procedure (*e.g.* kidney biopsy) or if alveolar haemorrhage is present. • Monitor platelet count, fibrinogen, haemoglobin and calcium
	Cyclophosphamide	• 2–3 mg/kg per day given orally for 2–3 months • 2 mg/kg if patients > 55 yr • Adjust for renal function: • -25% if GFR 45-59 mL/min • -40% if GFR 30-44 mL/min • -50% if GFR 15-29 mL/min • -60% if GFR <15 mL/min	• Monitor leukocyte count • Stop if leukocyte count falls to $<4 \times 10^9$/L and restart at reduced dose (75%) when recovered • No sufficient data to support IV cyclophosphamide • Other potential side effects (bladder and gonadal toxicity, tumor risk) are rare since the low cumulative dosage
	Corticosteroids	• Prednisolone 1 mg/kg per day (maximum 60 mg) given orally • Oral therapy may be preceded by pulse IV methylprednisolone (15-30 mg/kg [max 1000 mg] per day for 3 consecutive days) • Reduce gradually to 20 mg per day by 6 weeks • Gradually taper until complete discontinuation at 6–9 months	• Prednisolone is minimally removed by plasmapheresis, so should be administered after plasma exchange
Alternatives to cyclophosphamide	**Rituximab**	• 1 g for two doses	• Rituximab is removed by plasma exchange • Start rituximab after 7 days of corticosteroids and plasma exchange, and wait 48 hours after the infusion to restart plasma exchange
	Mycophenolate mofetil	• Start with 500 mg twice daily and titrate up as tolerated to a dose of 1000 mg twice daily	• Monitor for leukopenia and GI side effects
Investigational therapies	**Immunoadsorption**	• Performed as part of the plasmapheresis procedure	• Useful for patients allergic to blood products or with body weight >90 kg
	Imlifidase	• Add on therapy in severe and/or forms of anti-GBM disease	• Clinical utility of this approach remains to be determined

GBM: glomerular basement membrane; GFR: glomerular filtration rate; GI: gastro-intestinal; IV: intravenous.

body level and inhibiting antibody- and complement-dependent cytotoxicity (123). Imlifidase has been proposed as an alternative to plasmapheresis in refractory forms of anti-GBM disease. In an experimental model, imlifidase was able to reduce both circulating and deposited antibodies. In particular, it was able to remove the Fc portion of the antibodies attached to the GBM, preventing complement activation (124). Data on the use of imlifidase in clinical practice is limited. In a Swedish study, 3 patients affected by anti-GBM disease with acute glomerulonephritis requiring dialysis and without pulmonary involvement were treated with imlifidase. A rapid and complete clearance of antibodies was demonstrated. Unfortunately, no benefits on renal outcomes were observed and after 6 to 13 days a rebound of antibodies occurred (125). In an open-label phase 2a study on 15 patients with anti-GBM antibodies, the same rapid and complete clearance of anti-GBM antibodies after imlifidase infusion (in addition to standard therapy including plasma-echange) was observed. However, in this study also an improvement of renal outcomes was achieved, with 67% of patients being dialysis-independent at 6 months (126).

Outcome and prognosis

If the patients are promptly treated with the combination of plasma exchange, cyclophosphamide, and corticosteroids, the survival at 1 year is 80-90% and the efficacy of lung haemorrhage treatment is greater than 90% (12, 14). Renal survival is strictly related to the degree of kidney involvement at presentation. In patients with initial creatinine values less than 5.65 mg/dL, renal survival was 95% and 94% at 1 and 5 years, respectively. In those with creatinine greater than 5.65 mg/dL, but not requiring immediate dialysis, renal survival was 82% and 50 at 1 and 5 years, respectively. In patients requiring immediately dialysis, renal recovery occurred in only 8% at 1 year (121). Together with kidney function, also the proportion of glomeruli affected by crescents

correlated with renal survival (10, 14). Similar findings have been recently confirmed by Sanchez-Agesta *et al*. In a retrospective multicentre observational study including 72 patients with biopsy-proven anti-GBM disease, kidney survival was worse in patients with creatinine levels >4.7 mg/dL and in patients with more than 50% of crescents. Dialysis dependence at admission and creatinine levels >4.7 mg/dL remained independent significant predictors of ESKD in the multivariable analysis (127). Also another study demonstrated that renal survival may be accurately predicted using a model with need for renal replacement therapy and the proportion of normal glomeruli as predictors (128). Another indicator of poor renal outcome is complement component 3 (C3). Zhu *et al*. demonstrated that low C3 is correlated to a higher proportion of glomerular sclerosis progressing to kidney failure, highlighting also the role of complement activation in anti-GBM pathogenesis (129).

Without relapses, immunosuppressive therapy is rarely continued for more than 6 months, that is the time necessary for a correct corticosteroid decalage. In case of concomitant membranous nephropathy or ANCA-associate vasculitis, longer treatment is usually required (2).

In anti-GBM disease relapse is rare, occurring in <3% of patients (14), and is usually associated to ongoing exposure to pulmonary irritants such as cigarette smoke and hydrocarbons exposure (130, 131). There are no guidelines for the treatment of relapses, but discontinuation of environmental exposure is mandatory and the restart of therapy with corticosteroids and cytotoxic drugs is suggested (2). In the case of relapse with kidney involvement, concomitant diseases, as membranous nephropathy and ANCA-associated vasculitis, should be excluded. Therefore, renal biopsy may be of help in these cases.

Conclusions

Even though anti-GBM disease has been known for more than 60 years, aetiopathogenesis is still not completely understood, limiting the therapeutical approach. An effort to better understand the pathogenic mechanisms of anti-GBM disease must be done in order to pave the way for new therapies, which should ensure better outcomes and safer profile than the current standard treatment. If the promising results obtained with imlifidase are confirmed by the ongoing phase 3 trial (ClinicalTrials.gov Identifier: NCT05679401), a paradigm shift in the treatment of the disease will occur.

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