Anti-Glomerular Basement Membrane Antibodies

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ABSTRACT: Basement membranes form an anatomic barrier that contains connective tissue. They are composed of type IV collagen, laminin and proteoglycans. Anti-basement membrane antibodies bind to the non-collagen site of the α3 chain of type IV collagen. A group of renal diseases, pulmonary diseases and perhaps others affecting different organs have long been associated with the presence of antibodies directed against glomerular basement membrane (GBM), alveolar basement membrane and tubular basement membrane. Goodpasture disease has a frequency of 0.5 to 1 case by million/year, and is responsible for up to 20% of crescentic glomerulonephritis in renal biopsy. It has been associated with genetic and immune abnormalities and there are usually environmental triggers preceding clinical onset. Renal disease can occur isolated or in association with pulmonary hemorrhage. In general, renal disease has a rapid progression that determines severe compromise, with rare spontaneous resolution. The diagnosis of Goodpasture disease requires the presence of the anti-GBM antibody, either in circulation or in renal tissue. The prognosis of non-treated patients is poor. The standard of care is plasma exchange combined with prednisone and cyclophosphamide. Anti-GBM antibody levels must be monitored frequently until their disappearance, and then every 6 months to confirm sustained remission in the absence of clinical signs of recurrence. Prognosis of the disease is strongly associated with its initial presentation. Survival rates are related to the degree of renal compromise at onset of the disease. Recurrence of the disease post-transplantation is low.

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Basement membranes are extracellular structures that form an anatomic barrier containing connective tissue cells. They provide support for tissues and organs, as well as regulate important signals for differentiation and tissue maintenance. They are composed of specific molecules such as type IV collagen, laminin, proteoglycans and entactin, among others. Laminin and type IV collagen form a long and continuous net. Type IV collagen has autoaggregant properties and forms a stable and irreversible matrix over which other molecules of the basement membrane integrate. Each type IV collagen molecule consists of a long central domain of collagen, an N-terminal collagen domain (named 7s domain) and a non-collagen C-terminal domain (NC1 domain). Three subunits named alpha-chains (IV), more specifically α3, α4 and α5, are autoassembled to form a monomer. These monomers are joined by their NC1 domain by disulfide bridges forming fixed hexamers [1]. Recent studies have demonstrated that the α345 net is synthesized and deposited in the glomerular basement membrane exclusively by podocytes [2].

ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODIES

Anti-GBM antibodies (anti-GBM-Ab) are directed against the NC1 domain of the α3 chain of type IV collagen. They bind mainly to the aminoterminal region of the NC1 domain, and even if they can bind to other regions only the binding to this sector has been associated with the development of progressive renal disease [1]. Mutations in the *COL4A3* gene which codes the α3 chain (IV) NC1 [3] were not found at an experimental level or in clinical studies, suggesting that there are no relevant alterations in the amino acid sequence transcripted by this gene in the pathogenesis of the disease by anti-GBM. Two conformational epitopes, defined as E_A and E_B, have been confirmed for the anti-GBM-Ab [4]. Some authors [5] suggest that E_A and E_B are cryptic epitopes for B lymphocytes, protected by the quaternary structure of the hexamers created by bridges among monomers adjacent to NC1 chains. The dissociation of these NC1 chains exposes the pathogenic epitopes of the α3 and α5 chains, determining production of anti-GBM-Ab. The ultimate determining factor of exposure of these epitopes remains unknown, although it is believed to be the result of a combination of factors such as genetic susceptibility, post-transcription modifications, epitope extension and environmental factors [6]. The recognition of the epitope of type IV collagen by anti-GBM-Ab is the element that best correlates with the prognosis of the disease. In a review of 77 patients, whose anti-GBM-Abs recognized multiple epitopes of the α3 chain (IV), the titers of antibodies directed towards the N-terminal domain of NC1 were correlated to renal survival, while titers of antibodies

directed to other domains did not show any correlation to renal prognosis [7].

Anti-GBM-Abs have been found in low titers in healthy individuals [8]. Most of them recognize the same epitopes as the antibodies that participate in the anti-GBM disease [9]. The main difference between antibodies of healthy individuals and those of patients with anti-GBM disease is the restriction to Immunoglobulin (Ig) G2 and IgG4 subclasses in the former, and the predominant presence of IgG1 and IgG3 in the latter, which explains the belief that alteration in the distribution of subclasses of antibodies may be associated with the development and progression of anti-GBM disease [10]. Additionally, patients with preserved renal function have antibodies restricted to IgG4 subclass, in contrast to a predominance of IgG1 subclass in those with anti-GBM-Ab disease and renal function alteration [11]. The pathogenic role of the different subclasses of autoantibodies is related to the different ability that each has to activate complement and bind selectively to the Fc family of receptors, as shown recently in murine models of glomerulonephritis by anti-GBM-Abs [12].

Pedchenko et al. [13] demonstrated that the properties (specificity and affinity with NC1) of circulating antibodies are identical to those of antibodies deposited at the renal tissue level. Experimental models and clinical studies suggest that the presence of autoreactive T cells contributes to the development of the anti-GBM-Ab disease [14]. Isolated T cells in patients with this disorder react to the α3 chain of type IV collagen (the same molecule towards which anti-GBM-AB are directed), but not in control individuals [15]. Administration of anti-CD8 or anti-CD154 monoclonal antibodies has been effective at an experimental level in preventing and treating the formation of glomerular crescents [14,16]; in the same way, the presence of T regulatory cells (CD4+ CD25+) has reduced the severity of glomerular lesions in murine models of glomerulonephritis by anti-GBM [14]. These observations suggest that the presence of autoreactive T cells associated with the production of antibodies by B cells plays a direct role in the glomerular and alveolar lesion observed in this pathology. Nevertheless, the presence of autoreactive T cells has been demonstrated in healthy individuals in whom a mainly T cell response was directed towards peptides derived from the α3 chain (IV) [17].

The disease produced by glomerular basement membrane antibodies leads to high morbidity and mortality. Its diagnosis is based on the presence of autoantibodies and compatible clinical manifestations

Some genetic studies have demonstrated the existing relationship between anti-GBM-Ab disease and HLA-DRB1*1501 and DRB1*1502. Most of the reports (performed in Caucasian populations) found that the antigen DRB1*15 was present in 70–80% of the cases, compared to 20–30% among controls [18].

A group of diseases targeting kidneys, lungs and perhaps other organs has long been associated with the presence of antibodies directed against GBM, alveolar basement membrane and tubular basement membrane, and other basement membranes like those in choroid plexus [19]. Experiments by Lerner et al. [20] demonstrated the pathogenic role of anti-GBM-Abs. These authors observed that the administration in vivo of anti-GBM-Abs extracted from patients with Goodpasture disease (GD) and implanted in monkeys determined a similar disease pattern to GD. Anti-GBM-Abs extracted from renal tissue have identical specificity to those found in plasma, which explains the close correlation between plasma levels of anti-GBM and activity of GD [20]. The production of anti-GBM usually precedes the development of clinical manifestations by months [20].

CLINICAL MANIFESTATIONS

In 1919 Ernest Goodpasture reported the occurrence of rapidly progressive glomerulonephritis associated with pulmonary hemorrhage in an 18 year old patient with flu. The term Goodpasture disease or syndrome was first used in 1958 by Stanton and Tange [1] to describe the combination of pulmonary hemorrhage and glomerulonephritis. Even if this designation (GD) has been reserved for the clinical situation in which the presence of anti-GBM-Abs is associated with renal and pulmonary affliction, in many situations the term is used ambiguously to refer to anti-GBM-Ab carriers independently of whether they develop clinical manifestations associated with them or not [19].

GD has an estimated frequency of 0.5 to 1 case per million inhabitants/year according to a series published in New Zealand, Australia, the United Kingdom, the United States, China and Scandinavia [18]. It is responsible for 1%–5% of all cases of glomerulonephritis [21] and is the cause in 10–20% of patients with rapidly progressive glomerulonephritis with crescents on renal biopsy [22]. It occurs in all ethnic groups but is more frequent in European Caucasians. While all ages can be affected, there is a first incidence peak in the third decade of life and a second one in the sixth to seventh decade [23]. Alveolar hemorrhage is more frequent in young men, and isolated renal disease is more frequent in elderly patients without gender preference.

Environmental factors have been proposed as triggers for the disease. There are reports of an association between GD and exposure to hydrocarbons, treatment with extracorporeal lithotripsy, and ureteral obstruction, suggesting that antigens exposed by mechanical renal damage may launch the disease in susceptible individuals. Likewise, the impact of environmental factors on the development of alveolar hemorrhage is considerable. This is proven by the bond between smoking and alveolar hemorrhage, which is extremely rare in non-smokers [1].

Numerous diseases are associated with the presence of anti-GBM-Abs. However, the most consistent reported associations are with membranous nephropathy and vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA). Approximately 10% of patients with vasculitis associated with ANCA have anti-GBM-Abs, most of them exhibiting a perinuclear pattern (p-ANCA) and anti-myeloperoxidase antibodies [1]. In many cases the histologic manifestation is a pauci-immune glomerulonephritis with similar evolution and prognosis to ANCA-associated vasculitis. Multiple pathologies may manifest as rapidly progressive glomerulonephritis associated with pulmonary hemorrhage [1] [Table 1].

Historically, hemoptysis has been the most constant characteristic of the disease, present in over 70% of reported cases, and often precedes renal compromise by months or years [21]. It is possible that the lower prevalence of this manifestation responds to a reduction in smoking prevalence [1,21]. Usually, hemoptysis arises in the presence of respiratory infections. It may present as self-limited episodes or as a progression from mild hemoptysis to massive alveolar hemorrhage leading to death by respiratory failure. Alveolar hemorrhage is the leading cause of early death in anti-GBM disease [1,21].

Prognosis of the disease is strongly associated with its initial presentation. Survival rates are related to the degree of renal compromise at onset of the disease

Renal disease may occur in an isolated form or in association with pulmonary hemorrhage. In general, renal disease evolves fast, determining severe compromise with rare spontaneous resolution. Urinary sediment frequently reveals microscopic hematuria with red blood cell casts. When renal compromise progresses, macroscopic hematuria may be observed and lumbar pain may occur. Proteinuria is usually mild, but it may be intense in sub-acute cases. Frequently, the development of renal damage progresses to oliguria, constituting a predictor of poor prognosis. In this condition, volume overload, secondary infection and pulmonary hemorrhage with hypoxemia contribute to the development of renal failure [1,21]. Systemic vasculitis should be considered among the differential diagnoses since they may present as pulmonary-renal syndrome. Among these diagnoses, those associated with ANCA have the most clinical relevance, even more so since there is evidence that some patients develop both types of antibodies: anti-GBM-Abs and ANCA usually with anti-myeloperoxidase antibodies [24].

General symptoms usually include malaise, fatigue, mild fever and pallor, which frequently reflects a sideropenic anemia. Respiratory symptoms include shortness of breath and cough which can rapidly progress to hemoptysis [25].

Table 1. Entities presenting as rapidly progressive glomerulonephritis, renal failure and pulmonary hemorrhage [1]

Anti-glomerular basement membrane disease	
Systemic vasculitis	• Granulomatosus polyangiitis (Wegener's granulomatosis) • Microscopic polyangiitis • Systemic lupus erythematosus • Churg-Strauss syndrome*
Other vasculitis	• Rheumatoid vasculitis* • Behcet's syndrome* • Cryoglobulinemia • Pharmacologic: penicillamine, hydralazine
Other causes of renal failure and pulmonary hemorrhage	• Pulmonary edema with acute renal damage • Severe acute pneumopathy • Paraquat intoxication • Renal vein thrombosis with pulmonary embolism

*Very infrequent

DIAGNOSIS

Initially, anti-GBM-Abs detected by immunofluorescence were seen reacting against soluble non-collagen proteins in tissue samples of human GBM exposed to digestion by bacterial collagenases. Beginning in the 1970s these antibodies were detected by radioimmunoassays, using an immunologically purified sample of human GBM exposed to soluble collagenases [19]. The diagnosis of GD is based on detection of anti-GBM-Abs at a circulating level or in renal tissue. Detection is usually achieved by the enzyme-linked immunosorbent assay method, as well as by Western blot in specialized centers [19]. High antibody titers are often found in patients with progressive disease [26]. Recently, a case series demonstrated that negative test results for circulating anti-GBM antibodies do not rule out the possibility of anti-GBM disease and that IgG4 autoantibodies are a possible cause of false-negative test results. Whether this finding is more common in patients with the combination of severe lung disease and mild kidney disease remains to be determined [27]. Sensitivity varies according to the type of test, from 63 to 100% [26]. This variation in sensitivity highlights the value of renal biopsy when not contraindicated.

Antibodies may also be detected on renal biopsy. Characteristically, a linear stain of IgG is visualized with the frequent presence of C3 alongside the GBM. However, this stain pattern may also be visualized in other circumstances leading to false-positive results (anti-GBM disease, post-renal transplant Alport's syndrome, diabetes mellitus, severe nephrotic syndrome, systemic lupus erythematosus, renal allograft biopsy) [1,21]. Even if anti-GBM-Abs are mostly of the IgG type, the presence of IgA and IgM-type antibodies has been reported, determining the disease [28]. Renal biopsy is essential when suspecting renal compromise of the anti-GBM disease: aside from providing diagnostic confirmation, it has great value in determining renal prognosis. It is one situation in which renal biopsy is considered urgent for establishing treatment and prognosis. The histologic pattern initially shows mesangial expansion and

Table 2. Indications for treatment with plasma exchange combined with glucocorticoids and cyclophosphamide [22,33]

- Patients with glomerulonephritis associated with anti-GBM, except those who are dialysis-dependent from onset of the disease and those with crescents present in 100% of an adequate biopsy sample, in the absence of pulmonary hemorrhage
- Patients with alveolar hemorrhage, independent of the presence and/or severity of renal compromise
- Patients with severe renal compromise, including those with creatinine levels › 5–7 mg/dl, who do not require immediate replacement therapy
- Patients with less severe renal compromise (‹ 30–50% of crescents in renal biopsy): even if the most popular therapy is intravenous methylprednisolone followed by oral prednisone, many experts recommend combined therapy with plasma exchange together with glucocorticoids and cyclophosphamide
- Treatment must be initiated without delay while the diagnosis is being confirmed. If there is a high degree of diagnostic suspicion, treatment should begin with high doses of glucocorticoids and plasma exchange

hypercellularity, progressing usually to a focal and segmental glomerulonephritis with leukocyte infiltration accompanied by segmental necrosis with prominent cracks in the GBM. Afterwards, the glomerulus develops an extensive formation of crescents composed of epithelial wall cells and macrophages in association with destruction of GBM. A particular feature that differentiates this from other forms of glomerulonephritis with crescents is that these are usually found in the same evolutionary stage, emphasizing the explosive nature of the disease. Interstitial inflammation is often present, reflecting the binding of antibodies to the tubular basement membrane. While the disease progresses, the glomerulus exhibits a diffuse inflammation with segmental or global necrosis and extensive formation of crescents. Usually, deposits are not visualized on electron microscopy [1,21].

Patients suffering from glomerulonephritis with or without pulmonary hemorrhage may have granulomatosis with polyangiitis (Wegener) or microscopic polyangiitis, which is why the presence of anti-neutrophil cytoplasmic antibodies must be assessed in this population [29].

The association of anti-GBM-Abs with membranous nephropathy was first reported in 1974 [30]. However, little is known about the clinical and immunological features of patients with such a combination. Jia et al. [31] recently reported the clinical and immunological features of anti-GBM patients with membranous nephropathy. Eight patients with combined anti-GBM disease and membranous nephropathy were found to have significantly lower levels of serum creatinine, a significantly lower proportion of oliguria/anuria, and significantly better renal outcomes compared with 30 patients with classical anti-GBM disease. Antibody levels against the E_B conformational epitope of anti-α3(IV)NC1 were significantly lower in these patients, as were their levels of anti-α3 (IV)NC1 [31].

TREATMENT

The prognosis for non-treated patients is poor. Bolton and team [32], in their description of a series of 67 patients, reported that more than 90% died or required dialysis. In another series of 32 patients, 29 evolved to extreme renal failure, most of them in less than 6 months [21]. Prognosis improves after treatment and recovery is more likely if the renal disease is less severe [32].

The treatment of choice in anti-GBM disease is plasma exchange combined with prednisone and cyclophosphamide [22] [Table 2]. Plasma exchange is able to remove anti-GBM antibodies along with other inflammation mediators while immunomodulators lower antibody formation. A review of existing reports indicates that treatment with plasmapheresis and immunomodulatory drugs led to improvement in variables such as progression to end-stage renal disease and death in 40–45% of patients [22,33,34]. There has been only one controlled trial; this trial comprised 17 patients divided into two groups that received treatment with prednisone and cyclophosphamide alone or with plasma exchange [35]. In the group treated with plasma exchange, two of eight patients remained dialysis-dependent after treatment, while in the group treated only with immunomodulators six of nine patients remained dialysis-dependent. Even if the number of patients was low, the authors conclude that treatment with plasma exchange is superior to isolated immunosuppression. The basis for initiating treatment with plasma exchange is supported by an improvement in mortality and renal survival rates in this age of plasma exchange compared to historical series, as well as the biological plausibility of the benefit from fast removal of anti-GBM compared to slow reduction in isolated immunosuppressive therapy [36]. The initial prescription for plasma exchange usually includes a daily or alternating frequency of procedures with 4 L of exchange during 2 or 3 weeks [36]. In general, restoration is achieved with albumin except for those cases in which renal biopsy is required, where fresh plasma can be used to ensure that coagulation factors are potentially removed by plasma exchange [37]. Plasma exchange must be accompanied by administration of glucocorticoids (usually methylprednisolone 15–30 mg/kg with a maximum dose of 1000 mg daily during 3 days followed by prednisone 1 mg/kg/day with a maximum dose of 60–80 mg/day) and cyclophosphamide (with plans that include oral administration at doses of 2 mg/kg/day or intravenous administration) [35]. The length of the treatment is unknown. Usually, after the induction period with glucocorticoids and cyclophosphamide, treatment is maintained for at least 6 to 9 months with prednisone and azathioprine [33]. Most of the reported patients in lengthy series were treated successfully with plasma exchange for 2 or 3 weeks followed by cyclophosphamide and

The treatment of choice in anti-GBM disease is plasma exchange combined with prednisone and cyclophosphamide

glucocorticoids for the following 3 months and glucocorticoids alone for 6 to 9 months afterwards [33].

Anti-GBM antibody levels must be monitored weekly or twice weekly until negativity is reached and every 6 months thereafter in order to confirm sustained remission in the absence of clinical signs of recurrence. The presence of signs of recurrence along with positivity for anti-GBM antibodies is sufficient reason to justify a new cycle of plasma exchange. Sustained positivity of anti-GBM antibodies requires consideration of prolonging immunosuppressive therapy over time, usually with prednisone in decreasing doses and azathioprine in doses of 1–2 mg/kg/day. Renal recovery is unlikely in those dialysis-dependent patients [33]. In this context (and in the absence of pulmonary hemorrhage), the risks of treatment with plasma exchange may exceed the benefits. Patients who are dialysis-dependent may benefit from a short cycle of combined therapy with plasma exchange and immunosuppressive therapy.

Prognosis of the disease is strongly linked to its initial presentation [33]. Survival rates correlate with the degree of renal compromise at onset of the disease. Relapses are reported as infrequent [33] and more probable in the group of patients with positivity to ANCA [38]. Table 3 summarizes the key therapeutic recommendations.

Table 3. Therapeutic recommendations [33,35-37]

Plasma exchange

- Should be daily if possible, with exchange of 4 L and infusion of albumin. For patients with pulmonary hemorrhage or in those who recently underwent a renal biopsy infusion of fresh plasma is recommended
- Start with plasma exchange for 2–3 weeks to evaluate clinical parameters, and anti-GBM antibody titers thereafter. Treatment with plasma exchange should be maintained until pulmonary hemorrhage is resolved and/or until antibody titers have dwindled significantly or reached negativity
- For patients who develop a severe infection during the plasma exchange process intravenous immunoglobulin (100 to 400 mg/kg) should be administered together with antibiotic treatment.

Immunosuppression

To minimize antibody formation and recurrence of the disease, an initial course of 2–3 months of immunosuppressive treatment is recommended, with:

- Oral prednisone: 1 mg/kg/day with a maximum dose of 60–80 mg/day, eventually with intravenous methylprednisolone in a bolus of 15–30 mg/k/day (maximum 1000 mg) for 3 consecutive days. Oral prednisone dose may be decreased gradually after remission is induced (usually after 3 weeks), until reaching 20 mg/day. This dose should be maintained for at least 6 weeks with slow progressive dwindling until its withdrawal after 6 months
- Oral cyclophosphamide 2 mg/kg/day for 2–3 months
- Oral azathioprine 1 to 2 mg/kg/day together with prednisone, recommended for those patients who still show positivity to antibody after 4 months of treatment.

Prophylaxis

- *Pneumocystis girovesi:* given the toxicity of cyclophosphamide toxicity, prophylactic trimethoprim-sulfamethoxazole should be administered
- Gonadal toxicity: when treatment with cyclophosphamide is prolonged, prophylaxis to minimize gonadal toxicity should be initiated
- Oropharyngeal candidiasis: when treatment with prednisone is prolonged, local nystatin should be initiated
- Gastritis and gastrointestinal hemorrhage: when treatment with prednisone is prolonged, H2 receptor antagonist or a proton pump inhibitor should be initiated
- Bone demineralization: when treatment with prednisone is prolonged, calcium, vitamin D and eventually phosphonates should be given to reduce demineralization of the bone
- Tuberculosis: in patients with prolonged immunosuppressive therapy, prophylaxis with isoniazide may be indicated (consult local country's guidelines).

General recommendations: Smoking should be abandoned and occupational exposure to hydrocarbons should be avoided, since they increase the risk of recurrence

POST-TRANSPLANT RECURRENCE OF THE DISEASE

The incidence of the linear IgG stain in the transplanted kidney in recurrence may be close to 50%. The vast majority of patients, however, will remain asymptomatic [39]. The practice of waiting until clinical remission of the anti-GBM disease reaches at least 6 months and to wait until negativity of anti-GBM antibodies reaches at least 12 months prior to transplant may partially explain the low frequency of recidivism in the allograft [40]. In the same way, immunosuppressive therapy after transplantation may result in suppression of the antibody [40]. Given the low frequency of this complication, it is difficult to make recommendations for treatment. It seems reasonable to use the same therapeutic strategies mentioned for the disease in native kidneys.

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