Chapter 14: Anti-glomerular basement membrane antibody glomerulonephritis

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INTRODUCTION

This chapter makes treatment recommendations for GN mediated by antibodies against the GBM (i.e., anti-GBM GN) whether or not it is associated with pulmonary hemorrhage (Goodpasture's disease). The cost implications for global application of this guideline are addressed in Chapter 2.

14.1: Treatment of anti-GBM GN

14.1.1: We recommend initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Table 31) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (*1B*)

14.1.2: Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Table 31) while waiting for confirmation. (*Not Graded*)

14.1.3: We recommend no maintenance immunosuppressive therapy for anti-GBM GN. (*1D*)

14.1.4: Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (*Not Graded*)

BACKGROUND

Anti-GBM GN is generally a fulminant and rapidly progressive disease that is caused by autoantibodies to the noncollagenous domain of the α3 chain of type IV collagen. Anti-GBM GN is relatively rare, with an estimated annual incidence of 0.5-1 per million population. It can present as an isolated GN, or as a pulmonary-renal syndrome with severe lung hemorrhage. Prior to the introduction of intense immunosuppression for anti-GBM GN, patient survival was very poor. Although mortality has improved, kidney survival remains poor, possibly because of delays in making the diagnosis and initiating treatment. The strategy for treating anti-GBM GN is to remove the pathogenic autoantibodies from the circulation, and simultaneously prevent further autoantibody production and attenuate existing glomerular inflammation and injury.

RATIONALE

- Patient and kidney survival in untreated anti-GBM GN is poor.
- There is moderate-quality evidence that intense immunosuppression plus plasmapheresis improves patient and kidney survival; this evidence comes from one small RCT, one large, and several smaller retrospective series. All of these studies demonstrate good patient survival and moderate kidney survival, providing a compelling rationale to use immunosuppression and plasmapheresis.
- Many patients at presentation have severe kidney failure, and require dialysis. This is usually correlated with the number of glomeruli that show crescents on kidney biopsy. Despite intense immunosuppression, patients who are dialysis-dependent at the start of treatment and have 85–100% glomerular crescents do not recover kidney function, and generally will require long-term RRT.
- Because the progression of anti-GBM GN can be very rapid, and outcome is related to the severity at presentation, it is appropriate to start treatment immediately with high-dose corticosteroids. After the diagnosis is confirmed, cyclophosphamide and plasmapheresis must be started. Patients should be free of infection or receiving appropriate antimicrobial therapy.
- Patients with pulmonary hemorrhage as well as anti-GBM GN (Goodpasture's disease) should receive treatment with corticosteroids, cyclophosphamide, and plasmapheresis, even in the setting of severe kidney failure and extensive glomerular crescent formation. Without such therapy, Goodpasture's disease has a very high mortality. There is, however, no definite evidence that plasmapheresis is beneficial when there are only minor clinical signs of pulmonary hemorrhage.
- Because anti-GBM antibodies are pathogenic, it is prudent to wait until they are undetectable before considering a kidney transplant for those with ESRD.

As the pathogenesis of anti-GBM GN became clear, treatment regimens were designed to remove the circulating pathogenic antibody that caused the disease, suppress further synthesis of this pathogenic antibody, and attenuate the glomerular inflammatory response initiated by the anti-GBM antibody. The best summary of this approach is a large retrospective study of anti-GBM GN from the Hammersmith Hospital,[740] including 85 patients seen over 25 years. Seventy-one patients were treated with high-dose prednisone*

*Prednisone and prednisolone are interchangeable according to local practice, with equivalent dosing.

Table 31 | Therapy of anti-GBM GN

Corticosteroids	
Week	**Prednisone dose**
0–2	Methylprednisolone 500–1000 mg/d i.v. for 3 days, followed by prednisone, 1 mg/kg/d IBW (maximum 80 mg/d)
2–4	0.6 mg/kg/d
4–8	0.4 mg/kg/d
8–10	30 mg/d
10–11	25 mg/d
11–12	20 mg/d
12–13	17.5 mg/d
13–14	15 mg/d
14–15	12.5 mg/d
15–16	10 mg/d
16–	IBW <70 kg: 7.5 mg/d IBW ≥ 70 kg: 10 mg/d
Discontinue after 6 months	

Cyclophosphamide: 2 mg/kg/d orally for 3 months.
Plasmapheresis: One 4-liter exchange per day with 5% albumin. Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy. Plasmapheresis should be continued for 14 days or until anti-GBM antibodies are no longer detectable.
GBM, glomerular basement membrane; GN, glomerulonephritis; IBW, ideal body weight.
There is no evidence to support these dosing schedules, which are based on regimens associated with good outcome in observational studies.

(1 mg/kg/d) tapered over 6–9 months, oral cyclophosphamide for 2–3 months, and daily plasmapheresis for 14 days, or until the anti-GBM antibody was no longer detectable. The kidney outcome for this cohort was influenced by kidney function at presentation. Patients who had an initial SCr <5.7 mg/dl (<504 μmol/l) had a 1-year overall survival of 100% and a kidney survival of 95%, and at 5 years patient and kidney survival were both 94%. If the initial SCr was >5.7 mg/dl (>504 μmol/l) but dialysis was not required immediately, the patient and kidney survivals were 83% and 82% at 1 year, and 80% and 50% at 5 years, respectively. However, among patients who needed dialysis at presentation, patient and kidney survival were reduced to 65% and 8% at 1 year, and 44% and 13% at 5 years, respectively. Compared to nearly 100% mortality from pulmonary hemorrhage and kidney failure in historical series, this treatment strategy represented a significant improvement.

The role of plasmapheresis in addition to immunosuppression has been questioned, and was tested in a small RCT ($n=17$).[741] Although this study used prednisone and cyclophosphamide for immunosuppression, there were slight differences in dose and duration compared to the Hammersmith study. Most importantly, plasmapheresis was done every 3 days instead of daily and a mean of nine treatments was completed. All patients received prednisone and cyclophosphamide, and half were randomized to additional plasmapheresis. In those receiving plasmapheresis, anti-GBM antibodies disappeared about twice as fast as in the control group (all within 50 days, $P<0.05$). At the end of therapy, SCr in those receiving plasmapheresis was 4.1 ± 0.5 mg/dl (362 ± 44 μmol/l) compared to 9.2 ± 0.7 mg/dl (813 ± 62 μmol/l) in the controls ($P<0.05$); only two patients receiving plasmapheresis needed chronic dialysis vs. six in the controls. Although the two treatment groups were well-matched clinically at the beginning of the study, kidney biopsies showed a higher percentage of glomerular crescents in controls. Because of this difference in histology and the small study size, the evidence for better kidney outcome with plasmapheresis cannot be regarded as definitive.

Anti-GBM antibody titers should be regularly monitored.[742] Plasmapheresis may be stopped when the circulating antibody is no longer detectable, usually after 10–14 treatments. Corticosteroids have generally been continued for at least 6 months, and cyclophosphamide for 2–3 months. This immunosuppression must be sufficient both to prevent further antibody production, and to treat kidney inflammation.

About 20–30% of patients with anti-GBM disease will also have ANCA, usually with anti-MPO specificity, but the double-antibody–positive patients do not appear to have a different prognosis or disease course, according to most studies.[743–747]

The outcomes of the Hammersmith cohort[740] are representative of what can be expected with a uniform, aggressive approach to therapy as outlined. In other series of anti-GBM GN, not all necessarily using the same treatment regimens, and encompassing patients from the USA, Europe, China, and Japan, patient survival at 6–12 months was approximately 67–94%, and kidney survival was about 15–58%.[619,741,745,748,749]

The predictors of kidney survival in anti-GBM GN are SCr at presentation, the need for dialysis at presentation, and the percentage of glomerular crescents.[740,741,743] In two studies, patients with an initial SCr >5.7 mg/dl (>504 μmol/l) or 9.7 mg/dl (858 μmol/l) all became chronically dialysis-dependent despite aggressive treatment.[744,747] Two studies found that patients who required dialysis at presentation were never able to come off dialysis, despite aggressive treatment.[744,745] The most optimistic study observed that all patients with a combination of dialysis at presentation plus 100% crescents on kidney biopsy never recovered kidney function sufficiently to come off dialysis.[740] A survey of several studies shows dialysis dependence at diagnosis in a median of 55% (range 12–83%) of patients, 100% crescents on kidney biopsy in 20.5% (range 7–50%) of patients, and a median initial SCr of 6.9 mg/dl (610 μmol/l) (range 4.9–7.2 mg/dl [433–637 μmol/l]), underscoring the importance of early diagnosis and intervention.[740,741,744,745,747–750] These findings, along with the patient's general condition, will help in deciding how aggressive to be in treating the kidney manifestations of anti-GBM GN. However, in the presence of pulmonary hemorrhage, aggressive treatment should be undertaken, regardless of the kidney prognosis.[751]

In contrast to most other autoimmune kidney diseases, anti-GBM GN is not characterized by a frequently relapsing course; the autoantibodies seem to disappear spontaneously after 12–18 months.[752] Nonetheless, relapses of anti-GBM

GN have been reported in the literature, can manifest as recurrent clinical kidney disease or pulmonary hemorrhage, and are often associated with a reappearance of circulating anti-GBM antibodies.[752–755] It has been estimated that the mean time to recurrence is 4.3 years, with a range of 1–10 years, and that late recurrences may occur with a frequency of 2–14%.[748,752,754] Retreatment with intense immunosuppression and plasmapheresis is generally successful in re-inducing remission.[752]

There is very little information on the treatment of refractory anti-GBM GN. Some case reports have used MMF or rituximab, but no firm recommendation can be made.

There is very little evidence as to the timing of transplant after anti-GBM disease has caused ESRD. Most transplant centers require at least 6 months of undetectable anti-GBM antibody levels before kidney transplantation.[756,757] Recurrent anti-GBM disease in a kidney allograft is very unusual.[756,757]

RESEARCH RECOMMENDATIONS

- A study is needed to compare rituximab to cyclophosphamide, both combined with prednisone plus plasmapheresis for induction of remission.
- A study is needed to compare MMF plus prednisone plus plasmapheresis to standard treatment—cyclophosphamide plus prednisone plus plasmapheresis—for induction of remission.

DISCLAIMER