
In The Name Of
GOD

Anti-GBM disease Treatment

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Out Lines

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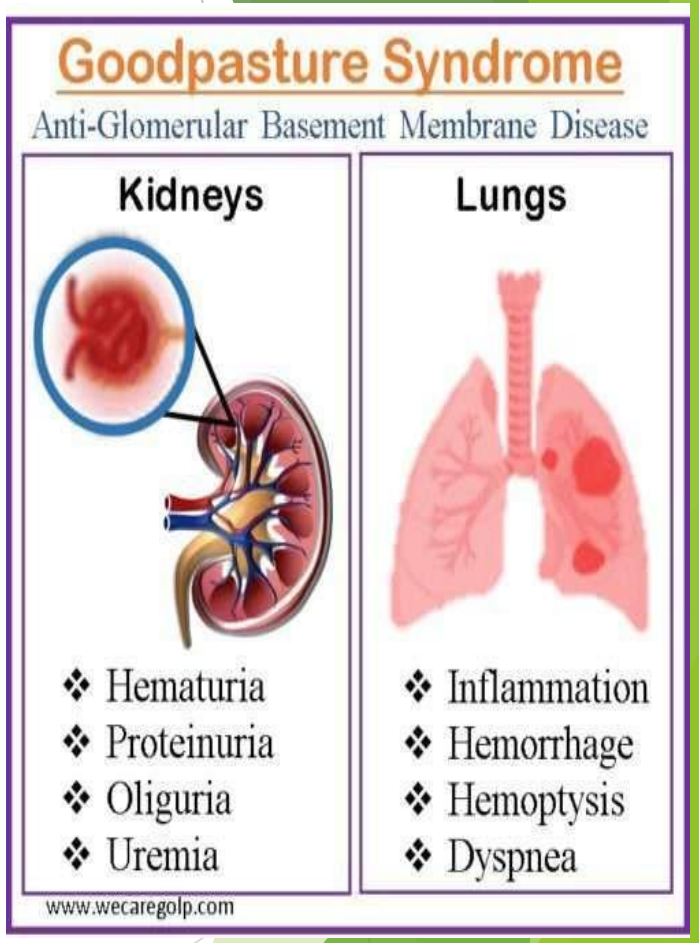
Anti-glomerular basement membrane (anti-GBM) disease

- A rare **small vessel vasculitis** that affects glomerular capillaries, pulmonary capillaries, or both.

- Most patients present with **rapidly progressive (crescentic) glomerulonephritis**, although some patients may present with relatively mild kidney impairment.

- In general, this disorder is **typically** associated with severe kidney injury that, **if untreated**, progresses quickly to end-stage kidney disease (ESKD).



IMPORTANCE OF EARLY INTERVENTION

- **Early diagnosis** and **intervention** are key determinants of the **response** to therapy and **long-term prognosis.**

- There is a **direct correlation** between the initial **plasma creatinine** concentration and the **percent of glomeruli with crescents**; in particular, crescents are usually present >75% of glomeruli when the plasma creatinine concentration is >5 mg/dL

- Avoidance of maintenance dialysis is uncommon in patients who require dialysis within 72 hours of presentation, particularly in those who have crescents involving all glomeruli

- A common clinical question is whether to start empiric therapy in patients with **suspected anti-GBM** disease before the diagnosis has been confirmed by serologic testing or kidney biopsy?

- Do not delay therapy in these patients and initiate therapy within 24 hours of a presumptive diagnosis.

- The results of diagnostic testing may take several days to become available, and delaying treatment may increase the patient's risk of developing irreversible kidney damage.

WHOM TO TREAT

- In most patients with anti-GBM disease recommend treatment with plasmapheresis combined with prednisone and cyclophosphamide.

- All patients with pulmonary hemorrhage (hemoptysis), independent of the **presence** and/or **severity** of kidney involvement.

- All patients with kidney involvement **who do not require immediate dialysis**

- Whether to treat patients who present **with dialysis-dependent kidney failure** without pulmonary hemorrhage is a more challenging decision.

- Some experts do not treat these patients, since there is a very low likelihood of kidney response, especially if the patient has 100 percent crescents on kidney biopsy

- Other experts consider a short trial (two to three weeks) **of plasmapheresis and immunosuppressive therapy**, particularly among the following patients:

- Patients with **very acute disease**, in whom irreversible injury is less predictable .

- **Younger patients** who are better able to **tolerate** aggressive immunosuppression.

- Patients whose biopsy shows **focal crescentic** glomerular damage associated with **acute tubular injury** .

- Patients with anti-GBM disease who have both antineutrophil cytoplasmic autoantibodies (ANCA) and clinical signs of a systemic vasculitis

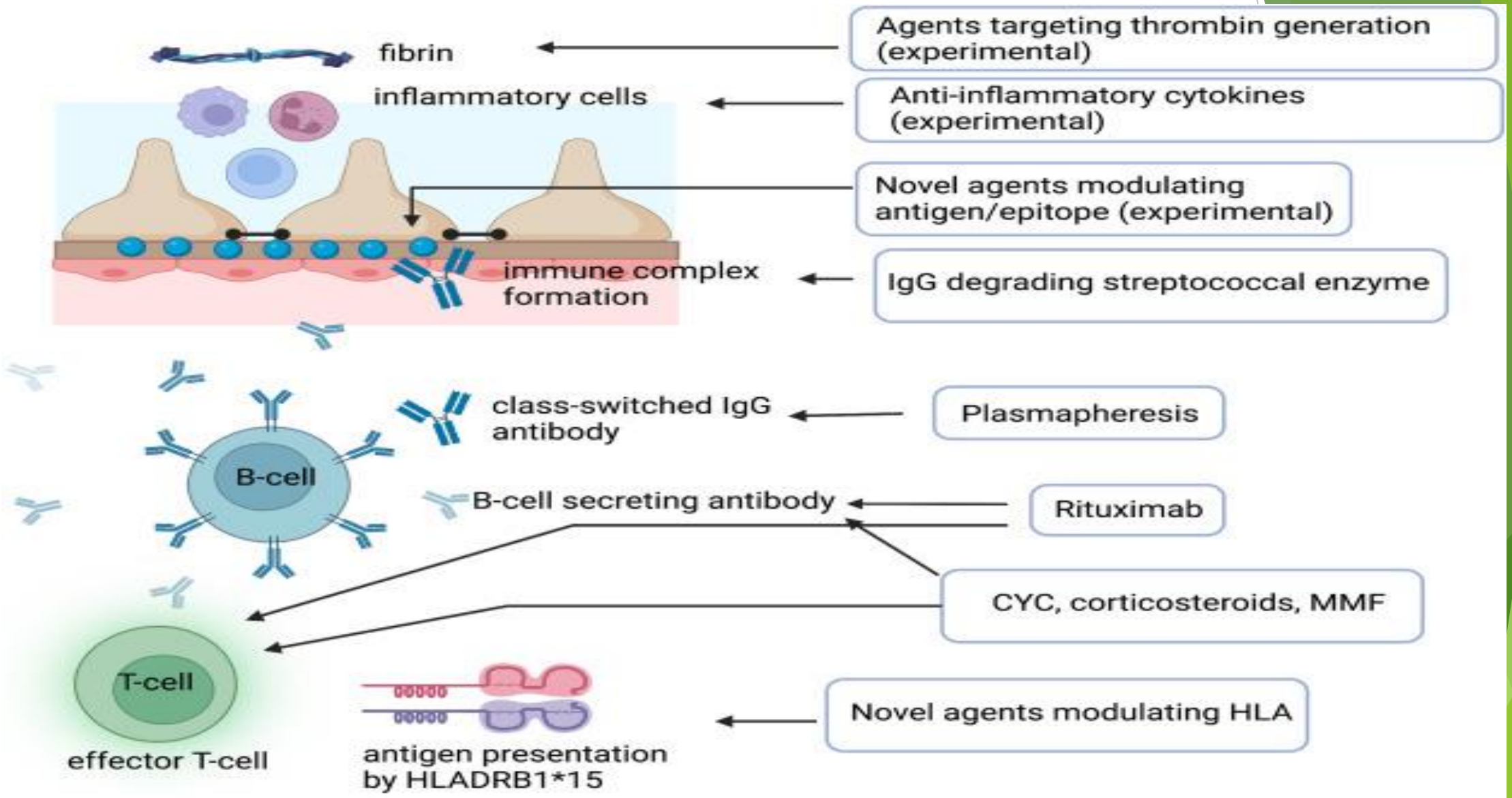
- In a retrospective analysis of 71 patients with anti-GBM disease who were treated with plasma exchange, prednisolone, and cyclophosphamide, patient and kidney survival varied with the **severity at presentation**:

- For patients with **creatinine < 5.7 mg/dL patient** and kidney survival were **100%** and 95 % at **one year** and 84% and 74 % at 90 months, respectively.

- For patients with a **creatinine >5.7 mg/dL** but who did not require immediate dialysis (within 72 hours of presentation**), patient** and kidney survival were **83%** and 82% at **one year** and 72 and 69 percent at last follow-up, respectively.

- In **immediate dialysis**, **patient** and kidney survival were **65%** and 8 % at **one year** and 36% and 5 % at last follow-up, respectively.

- All such patients who had **crescents in all glomeruli** on kidney biopsy required long-term maintenance dialysis


fibrin
inflammatory cells
immune complex formation
B-cell
T-cell
effector T-cell
antigen presentation by HLADRB1*15
Agents targeting thrombin generation (experimental)
Anti-inflammatory cytokines (experimental)
Novel agents modulating antigen/epitope (experimental)
IgG degrading streptococcal enzyme
class-switched IgG antibody
Plasmapheresis
B-cell secreting antibody
Rituximab
CYC, corticosteroids, MMF
Novel agents modulating HLA

INITIAL THERAPY

- Plasmapheresis plus immunosuppressive therapy: Plasmapheresis **removes** circulating anti-GBM **antibodies** and other **mediators of inflammation**, and the immunosuppressive agents minimize new antibody formation

- There are no large, randomized trials to support this approach, and most studies have been uncontrolled.

- In general, the available data suggest that approximately 30 to 45% of patients treated with plasmapheresis combined with immunosuppression will benefit by ESKD or death.

KDIGO 2021 Anti-GBM antibody glomerulonephritis

Recommendation 11.2.1: We recommend initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C).

- However, **recovery** is much more likely in patients who begin treatment before oligoanuria and is uncommon in patients who require dialysis or who have 100% crescents on biopsy

- The percent of crescents on initial kidney biopsy and entry plasma creatinine correlated better with outcome.
- **Regardless of therapy**, patients with less than 30% crescents and a plasma creatinine <3 mg/dL did well

- In observational studies, use of plasmapheresis has been associated with improved patient and kidney survival

- Despite the absence of definitive evidence of benefit, plasmapheresis is generally recommended for the treatment
- Two factors are considered by many experts to justify this recommendation:

- Improved morbidity and mortality in the era of plasmapheresis compared with historic rates

- Biological plausibility of greater amelioration of the consequences of disease with rapid removal of anti-GBM antibody, compared with a slower reduction in levels seen with immunosuppressive agents alone

Plasmapheresis regimen

- Initial plasmapheresis prescription is daily 4 liter exchanges for 2 to 3 weeks
- In general, **albumin** is given as the replacement fluid.
- If recent kidney biopsy or has pulmonary hemorrhage, one to two liters of FFP should be substituted for albumin at the end of the procedure

At the end of this 2-3 week regimen, the need for further plasmapheresis is determined by the **patient's clinical status** and **serum anti-GBM antibody titers**

- **Citrate-induced metabolic alkalosis** can be corrected by hemodialysis if needed

- If there is a severe infection in the setting of plasmapheresis, a single infusion of IVIG; 100 to 400 mg/kg can be given after a plasmapheresis session to partially replenish immunoglobulin levels

Immunosuppressive therapy

Glucocorticoids plus cyclophosphamide

Plasmapheresis must be accompanied by glucocorticoids and immunosuppressive agents, preferably cyclophosphamide.

Glucocorticoids

- Administer pulse intravenous (IV) methylprednisolone (15 to 30 mg/kg to a maximum dose of 1000 mg over 20 minutes) daily for 3 doses followed by daily oral prednisone (1 mg/kg per day to a maximum of 60 to 80 mg/day), which can be tapered once remission is induced.

- However, there is no evidence of benefit of pulse methylprednisolone over other glucocorticoid doses and schedules, and some clinicians treat with oral glucocorticoids without an IV pulse

Glucocorticoids

- On plasmapheresis days, we administer prednisone after plasmapheresis, although this agent is minimally removed by plasmapheresis

- Glucocorticoids are generally continued for up to six months.

Cyclophosphamide

- The initial cyclophosphamide dose is 2 mg/kg/d orally.
- Typically reduce the dose by 25% in **older adults** (age >60 years) and **frail** patients and adjust the dose appropriately for impaired kidney function
- On plasmapheresis days, administer cyclophosphamide after plasmapheresis.
- Continue cyclophosphamide for 3 months in most patients; if anti-GBM antibody levels are not substantially reduced by three months ,continue cyclophosphamide for up to a maximum of 6 months.

Cyclophosphamide

- In patients who cannot take oral medications, IV therapy may be used.
- The **optimal dosing** of **IV** cyclophosphamide is **uncertain**.
- Some centers use IV protocols similar to those used for the treatment of ANCA associated vasculitis or lupus nephritis; however, there is the use of these regimens in patients with anti-GBM disease

Maintenance therapy

- Most patients with remission do not require maintenance immunosuppressive therapy given the low rate of recurrence.
- An exception in double-positive for anti-GBM antibodies and ANCA.
- Such patients have a **higher risk of relapse of vasculitis** and should receive maintenance therapy similar to that used for ANCA-associated vasculitis.

Complications of treatment

- Cyclophosphamide (oral or IV) can be associated with Pneumocystic jirovecii (carinii) pneumonia, amenorrhea, alopecia, and bladder toxicity (hemorrhagic cystitis and bladder cancer).

- Complications with high doses of glucocorticoids include oropharyngeal fungal infections, gastritis (which can result in gastrointestinal bleeding in patients at increased risk), and bone loss.
- Both cyclophosphamide and glucocorticoids are associated with an increased risk of infection

Alternatives to cyclophosphamide

Rituximab

- Give 1 g for two doses.
- In daily plasmapheresis, the first of the two rituximab doses can be given after the initial seven consecutive days of plasmapheresis and glucocorticoids, since concurrent rituximab and plasmapheresis will result in removal of rituximab from the circulation.
- **After a 48-hour period** has elapsed, another seven days of plasmapheresis can be performed, after which the second of the two doses of rituximab is given.
- If the patient is receiving **alternate-day plasmapheresis**, rituximab should be given immediately after the exchange, which will permit time for binding of rituximab to B cells prior to the next plasmapheresis treatment.

Alternatives to cyclophosphamide

Mycophenolate mofetil

- Initial dose of 500 mg twice daily and titrate up as tolerated to a dose of 1000 mg twice daily.

- Monitor the white blood cell count for signs of leukopenia. Dose reduction is warranted in patients with leukopenia or significant gastrointestinal side effects.

Supportive measures for severe disease

- Patients presenting with life-threatening hemoptysis, for example, may require intubation and mechanical ventilation .
- Patients who develop severe kidney failure in spite of treatment may require initiation of dialysis.
- The indications for and timing of kidney replacement therapy are the same as those for other causes of kidney failure

Monitoring the response to therapy

Clinical status

- During the acute phase of the disease (first two to three weeks), monitor the serum Cr, a CBC, and urine output daily.
- In pulmonary hemorrhage, serial chest radiographs are reasonable to monitor for worsening alveolar hemorrhage.
- After discharge from the hospital, we typically schedule follow-up visits weekly for the first 2-4 weeks. If remain stable, the duration between follow-up visits can then be extended to every two to four weeks.

Monitoring the response to therapy

Anti-GBM antibody levels

- Monitor anti-GBM antibody levels weekly for the first six weeks **until they are undetectable on two consecutive occasions.**
- Then monitor anti-GBM antibody levels every other week for four weeks, and if they remain persistently undetectable, we monitor levels once monthly for six months.
- Check antibody levels if the patient experiences clinical signs suggestive of recurrence

- In patients receiving plasmapheresis combined with glucocorticoids and cyclophosphamide, disappearance of anti-GBM antibodies typically occurs **within four weeks of treatment**; the continued presence of antibodies beyond eight weeks is uncommon

- If antibody levels remain persistently elevated, the immunosuppressive regimen may require modification.

PATIENTS WITH RECURRENT DISEASE

- Relapses are uncommon (around 2 %)
- More common in patients who are also ANCA positive, in whom it is the vasculitis and not the anti-GBM disease that is reactivated
- Higher rate of recurrence in **smokers** or have exposure to **hydrocarbon** in their occupation
- Repeat a kidney biopsy to confirm the diagnosis and exclude concomitant pathologies such as ANCA-associated vasculitis and membranous nephropathy.

PATIENTS WITH RECURRENT DISEASE

- In confirmed cases of recurrent anti-GBM disease, treat with plasmapheresis combined with glucocorticoids and cyclophosphamide **using the same regimen as described above for initial therapy.**
- Rituximab or mycophenolate mofetil (MMF) may be considered as alternative therapies to cyclophosphamide in patients who develop recurrent disease or relapse while on cyclophosphamide or are unable to tolerate this drug

PATIENTS WITH PERSISTENT ANTI-GBM ANTIBODIES AFTER INITIAL THERAPY

- The optimal management of such patients is not known, and data are limited to case reports and small case series

- Not all patients with residual anti-GBM antibody titers will require a change in therapy, however, and treatment should be individualized based upon the patient's clinical picture.

clinical scenarios

- In persistent high antibody titer (defined as three times the upper limit of normal or higher) that is not decreasing in spite of therapy for at least 2-3weeks and who have evidence of ongoing disease activity (ie, ongoing pulmonary hemorrhage and/or active glomerulonephritis [persistent or new red blood cell casts in the urine and/or worsening kidney function]), some experts give **rituximab (1 g initially followed 14 days later by another 1 g dose).**

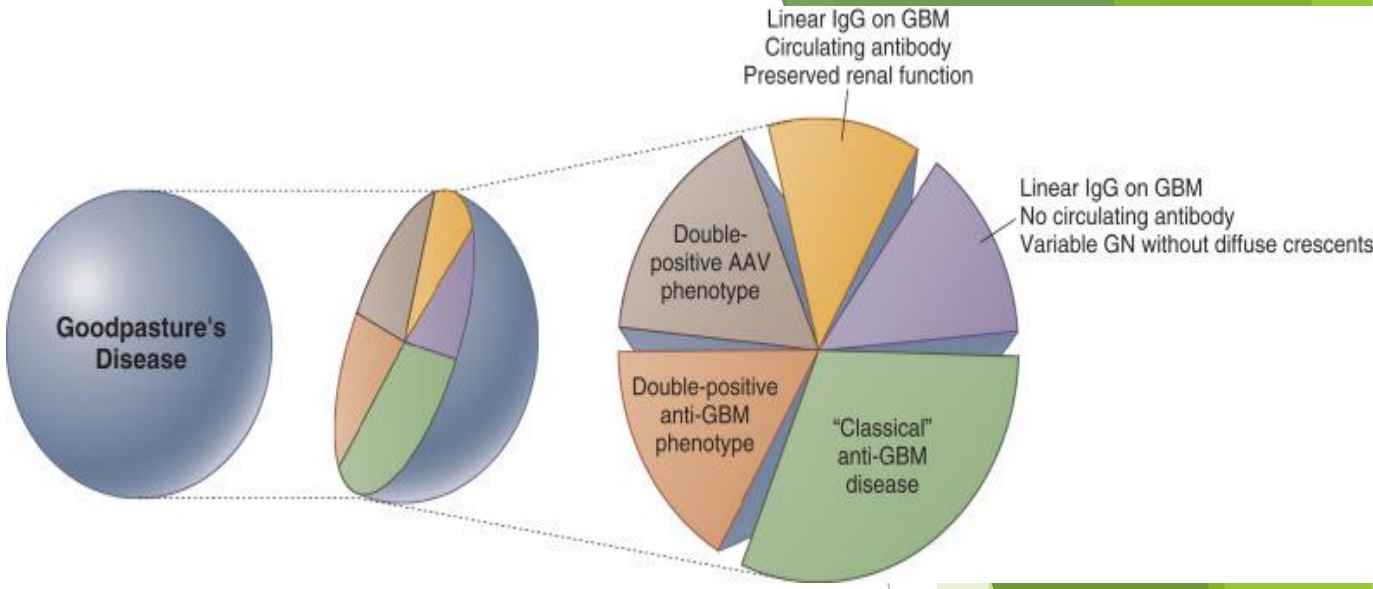
- The need for further daily plasmapheresis beyond four weeks should be reassessed, particularly in patients who have not yet recovered kidney function by one month of initial therapy and do not have pulmonary hemorrhage.

clinical scenarios

- In persistent high antibody titer who **are on dialysis**, have no pulmonary hemorrhage, and have a kidney biopsy showing a high percentage of crescents or glomerulosclerosis and interstitial fibrosis, **taper off treatment** and continue to monitor anti-GBM antibody levels.

- In persistent intermediate antibody titer (defined as 1-3 times the upper limit of normal) after 3-4 months of cyclophosphamide-based therapy who have recovered kidney function and are overall doing well, switch from cyclophosphamide to rituximab (1 g initially followed 14 days later by another 1 g dose).
- If rituximab is not available, switch to azathioprine (1 to 2 mg/kg per day) or mycophenolate mofetil (MMF; 1000 mg twice daily), continue treatment for 6-9 months.

SPECIAL POPULATIONS



- **Double-positive anti-GBM and ANCA-associated disease** should be managed initially as for anti-GBM disease since that is the more severe lesion.
- Double-positive patients will require maintenance immunosuppressive therapy for ANCA disease because of the tendency of vasculitis to relapse .

SPECIAL POPULATIONS

Because of reports that double-positive patients may be recover from dialysis than single-positive anti-GBM disease, treatment with plasmapheresis plus immunosuppressive therapy should be considered for those presenting with dialysis-requiring kidney failure

- **Anti-GBM disease associated with membranous nephropathy** treat such patients the same approach that used for patients with anti-GBM disease .

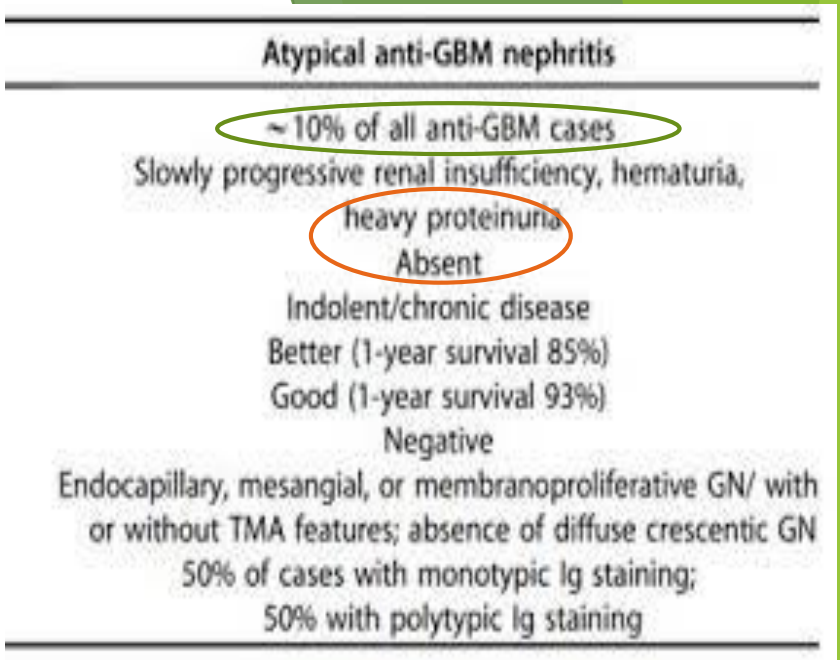
- Treatment response appears to be similar to of patients with anti-GBM disease without membranous nephropathy.

SPECIAL POPULATIONS

- Anti-GBM disease without detectable circulating anti-GBM antibodies

There are infrequent reports of patients with positive linear staining for immunoglobulin G (IgG) on kidney biopsy and negative anti-GBM antibodies

- known as "**atypical anti-GBM nephritis**," which is an **indolent form** of anti-GBM disease without pulmonary involvement
- Diffuse crescentic disease is uncommon in these patients.
- In such patients without significant crescentic glomerulonephritis, **do not administer treatment with immunosuppressive agents.**
- However, in rare patients who develop signs of progressive disease, we treat with glucocorticoids plus cyclophosphamide without plasmapheresis since there are no detectable circulating antibodies to remove with plasmapheresis.



Atypical anti-GBM nephritis
~10% of all anti-GBM cases
Slowly progressive renal insufficiency, hematuria, heavy proteinuria
Absent
Indolent/chronic disease
Better (1-year survival 85%)
Good (1-year survival 93%)
Negative
Endocapillary, mesangial, or membranoproliferative GN/ with or without TMA features; absence of diffuse crescentic GN
50% of cases with monotypic Ig staining; 50% with polytypic Ig staining

Recurrent anti-GBM disease after transplantation

Recurrence of anti-GBM disease after kidney transplantation is rare

In a multicenter retrospective cohort study of 53 patients with anti-GBM disease who underwent kidney transplantation from 1977 to 2015, recurrence occurred in a first kidney transplant in only one patient five years posttransplant in the context of cessation of immunosuppressive medications

INVESTIGATIONAL THERAPIES

- A number of investigational therapies have been proposed for the treatment of anti-GBM disease:

- Immunoadsorption
- Imlifidase

Immunoadsorption

- Immunoadsorption, performed **as part of the plasmapheresis** procedure, may be effective in some patients with anti-GBM disease, **even in** dialysis dependent patient.
- In one such individual, for example, the combined use of immunosuppression and immunoadsorption using a sepharose-coupled, sheep-antihuman IgG column for 25 cycles resulted in the recovery of kidney function, with a stable creatinine concentration of 2 mg/dL (177 micromol/L)
- Other small observational studies have also shown possible benefits of immunoadsorption

Immunoadsorption and Plasma Exchange are Comparable in ANCA or Anti-GBM Removal Kinetics

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

PROSPECTIVE

Nephrology ICUs (Multicenter)

ANCA Vasculitis and/or Anti-GBM Disease

January 2019 to August 2021

n=38

Difference in reduction rates of autoantibody titers over 7 sessions

PRIMARY OBJECTIVE

Immunoadsorption (IA)	Plasma Exchange (PEx)
n=16	n=22
100 mL/kg treated per session	60 mL/kg treated per session
-98%	-96%

p=0.39

The number of sessions needed to obtain undetectable auto-antibodies, or 50%, 75%, or 90% reductions did not differ between techniques

Greater reduction rates of auto-antibodies were observed when plasma was separated by filtration compared to centrifugation, with IA and PEx

IA was associated with a greater reduction in total IgG levels and allowed a better preservation of IgA and IgM levels than PEx

KI REPORTS
Kidney International Reports

Sallee M et al, 2024

Visual abstract by:
Edgar Lerma, MD, FISN
@edgarvlermamd

Conclusion Immunoadsorption and plasma exchange were comparable in ANCA or anti-GBM removal kinetics, despite a faster reduction of total IgG with IA.

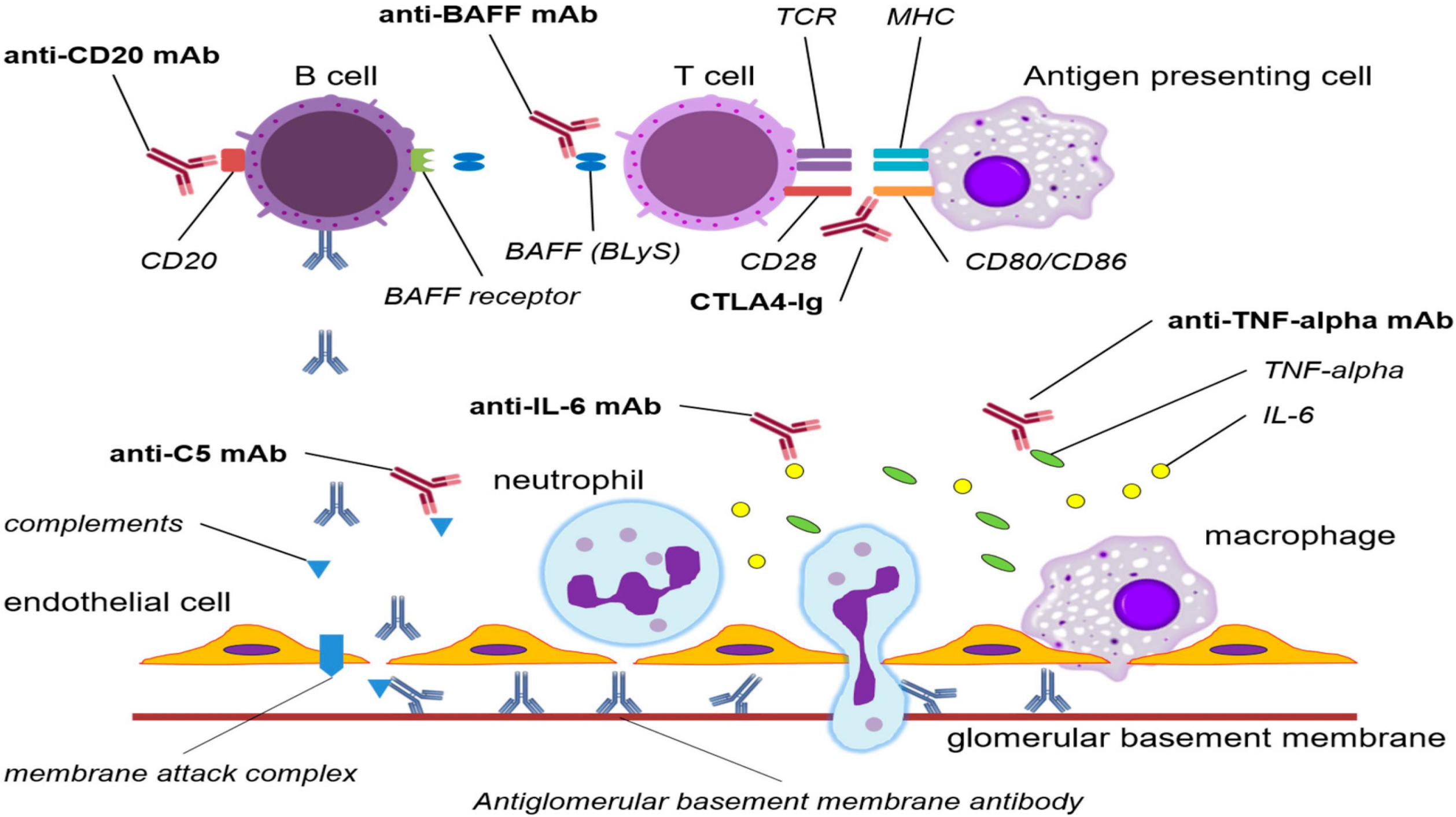
Imlifidase

- The IgG-degrading enzyme derived from Streptococcus pyogenes ,is a recombinant cysteine protease that cleaves all four subclasses of human IgG into F(ab')2 and Fc fragments, **inhibiting** complement-dependent and antibody-dependent **cellular cytotoxicity.**

- The efficacy and safety of this agent were evaluated in a phase 2a single-arm study of 15 patients with circulating anti-GBM antibodies and an eGFR <15 mL/min/1.73 m2 who received a single dose of imlifidase (0.25 mg/kg)

Imlifidase

- All patients also received standard therapy with cyclophosphamide and glucocorticoids; plasmapheresis was administered only if autoantibodies rebounded.
- At baseline, 10 patients were dialysis dependent and five had an eGFR between 7 and 14 mL/min/1.73 m2; six patients were also positive for antineutrophil cytoplasmic autoantibodies (ANCA).
- At six months, 10 of 15 patients (67 percent) were dialysis independent, which was a better outcome when compared with a historical control cohort (18 percent).
- Eight serious adverse events were reported (including one death), although none were assessed as probably or possibly related to therapy. Additional studies are required to confirm these findings


anti-CD20 mAb
B cell
anti-BAFF mAb
T cell
TCR
MHC
Antigen presenting cell
CD20
BAFF (BLyS)
BAFF receptor
CD28
CTLA4-Ig
CD80/CD86
anti-TNF-alpha mAb
TNF-alpha
anti-IL-6 mAb
IL-6
anti-C5 mAb
neutrophil
complements
macrophage
endothelial cell
glomerular basement membrane
membrane attack complex
Antiglomerular basement membrane antibody

The Immunobiological Agents for Treatment of Antiglomerular Basement Membrane Disease

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Abstract

Combination therapy with glucocorticoids, cyclophosphamide, and plasmapheresis is recommended as the standard treatment for anti-glomerular basement membrane (anti-GBM) disease, but the prognosis of this disease remains poor. Several immunobiological agents have been administered or are expected to be useful for anti-GBM disease in light of refractory disease or the standard treatments' tolerability. Many data regarding the use of biologic agents for anti-GBM disease have accumulated, verifying the effectiveness and potential of biologic agents as a new treatment option for anti-GBM disease. Tumor necrosis factor (TNF) inhibitors were shown to be useful in animal studies, but these agents have no clinical use and were even shown to induce anti-GBM disease in several cases. Although the efficacy of the TNF-receptor antagonist has been observed in animal models, there are no published case reports of its clinical use. There are also no published reports of animal or clinical studies of anti-B-cell-activating factor, which is a member of the TNF family of agents. Anti-interleukin (IL)-6 antibodies have been demonstrated to have no effect on or to exacerbate nephritis in animal models. Anti-C5 inhibitor was observed to be useful in a few anti-GBM disease cases. Among the several immunobiological agents, only rituximab has been demonstrated to be useful in refractory or poor-tolerance patients or small uncontrolled studies. Rituximab is usually used in combination with steroids and plasma exchange and is used primarily as an alternative to cyclophosphamide, but there is insufficient evidence regarding the efficacy of rituximab for anti-GBM disease, and thus, randomized controlled studies are required.

Kidney International Reports
Volume 6, Issue 10, October 2021, Pages 2713-2717

Nephrology Rounds

Eculizumab and Complement Activation in Anti–glomerular Basement Membrane Disease

Pravarut Nithagon [1], Frank Cortazar [2], Sujal I. Shah [3], Astrid Weins [3], Karen Laliberte [1], Anushya Jeyabalan [1], John Niles [1], Reza Zonozi [1]

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The use of terminal complement blockade with eculizumab, an anti-C5 monoclonal antibody, has the potential to be an effective novel therapy for anti-GBM disease. Its therapeutic role requires further investigation.

RESEARCH ARTICLE · Volume 91, Issue 7, P992-1006, July 2011 · Open Access

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Role of amino acid transporter LAT2 in the activation of mTORC1 pathway and the pathogenesis of crescentic glomerulonephritis

Ryota Kurayama [1] · Noriko Ito [1] · Yukino Nishibori [1] · ... · Hitoshi Endou [6] · Yoshikatstu Kanai [7] · Kunimasa Yan [1] ✉ ... Show more

RESULTS

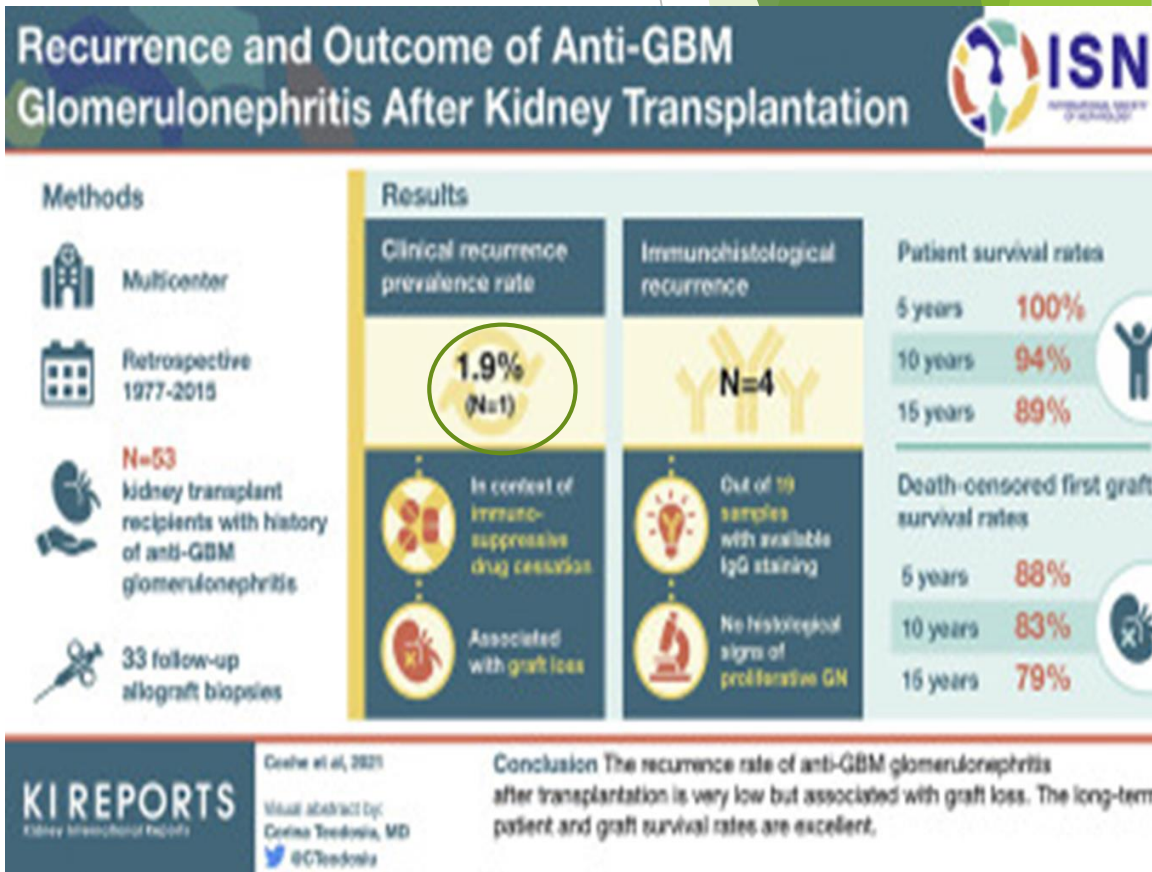
Activation of mTORC1 Pathway in CGN

Experiment 1 was investigated to determine whether mTORC1 pathway is involved in the pathogenesis of CGN. Rats were injected with anti-GBM antibody or saline (control) and the development of CGN was assessed by blood and urine examination and renal pathology followed for 7 days. Following the injection of antibody, the rats developed significant proteinuria on day 2 followed by heavy proteinuria and macrohematuria on day 5 and day 7, respectively (Figure 2). Although no significant change of serum creatinine level between CGN rats and control rats was observed, CGN rats obviously showed the lower level of serum albumin compared with that of control rats (Supplementary Table 2). Two serial sections from the kidney cortex were subjected to immunohistochemistry for p-S6RP, an activated form of downstream protein of the mTORC1 cascade, and PAS staining,

KIDNEY TRANSPLANTATION

- There are no data to guide the optimal timing of transplantation in this setting.

- Most transplant centers require at least six months of undetectable anti-GBM antibody levels before kidney transplantation.



Abstract

Plasma exchange

Daily 50 ml/kg (max. 4 L) exchange for 5% human albumin solution
(+ FFP 300-600 mL within 3 d of invasive procedure or in pt with alveolar hemorrhage)
Continue for 14 d or until Ab levels are fully suppressed
Monitor Ab levels regularly after cessation of treatment

Cyclophosphamide

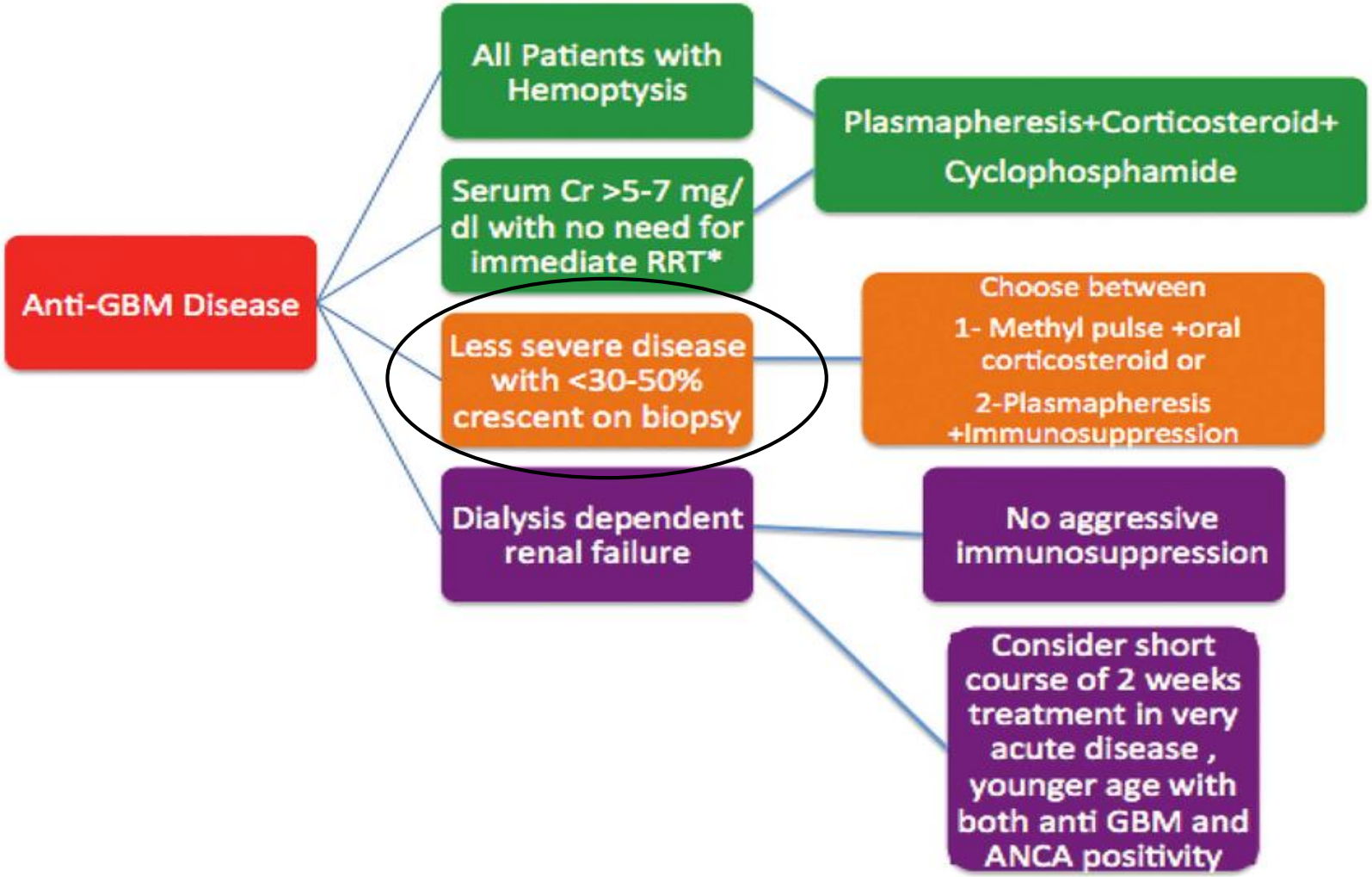
2-3 mg/kg/day given orally for 2-3 mo
(Reduce dose to 2 mg/kg in pts > 55 yr)

Corticosteroids

Prednisolone 1 mg/kg/day (max 60 mg) given orally
Reduce dose weekly to 20 mg/kg/day by 6 wks, then gradually taper until complete discontinuation at 6-9 mo

Monitor & Prophylactic treatment

- **Monitor:** CBC, Coagulogram, Renal function, Electrolyte, Ca, Anti-GBM Ab titer
- **Prophylaxis:** against infection (fungi, PCP, CMV), peptic ulcer


Anti-GBM Disease
All Patients with Hemoptysis
Serum Cr >5-7 mg/dl with no need for immediate RRT*
Plasmapheresis+Corticosteroid+ Cyclophosphamide
Less severe disease with <30-50% crescent on biopsy
Choose between
1- Methyl pulse +oral corticosteroid or
2-Plasmapheresis +Immunosuppression
Dialysis dependent renal failure
No aggressive immunosuppression
Consider short course of 2 weeks treatment in very acute disease , younger age with both anti GBM and ANCA positivity

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