EXTRACORPOREAL NEPHROLOGY GROUP [ECNG]

ANTI GBM ANTIBODY DISEASE

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INTRODUCTION

- **Incidence**: Approximately 1-2/1,000,000 (uncommon)
- 15% of all crescentic GN
- M=F
- Bimodal age of onset (3rd and 6th-7th decade)

- **2 major clinical presentations**:
  - Pulmonary renal syndrome
  - Rapidly progressive glomerulonephritis (Gen >50% crescents)
  - Hematuria is always present. Proteinuria is common

- **Predisposing factors:** **Medications, hydrocarbon use, cigarette smoking, genetic factors**

INTRODUCTION

- Anti GBM GN involves the kidney and Good Pasture syndrome refers to renal plus lung involvement [pulmonary hemorrhage].
- Target antigen : NCI [non collagenous – 1] domain of the alfa 3 chain of type 4 collagen. Newer antigens – Peroxidasin , Laminin 521 and Nidogen.
- Coexistence of anti –GBM Antibody and ANCA [MPO-ANCA] – double positive disease : needs long term follow up because of high relapse rate.
- Plasma exchange + high dose steroids + cyclophosphamide [or rituximab in selected cases].
- Poor prognosis : dialysis dependence at presentation , serum creatinine >6-7 and extensive crescents.
- Renal transplant - until anti – GBM antibodies remain negative for 6 months.
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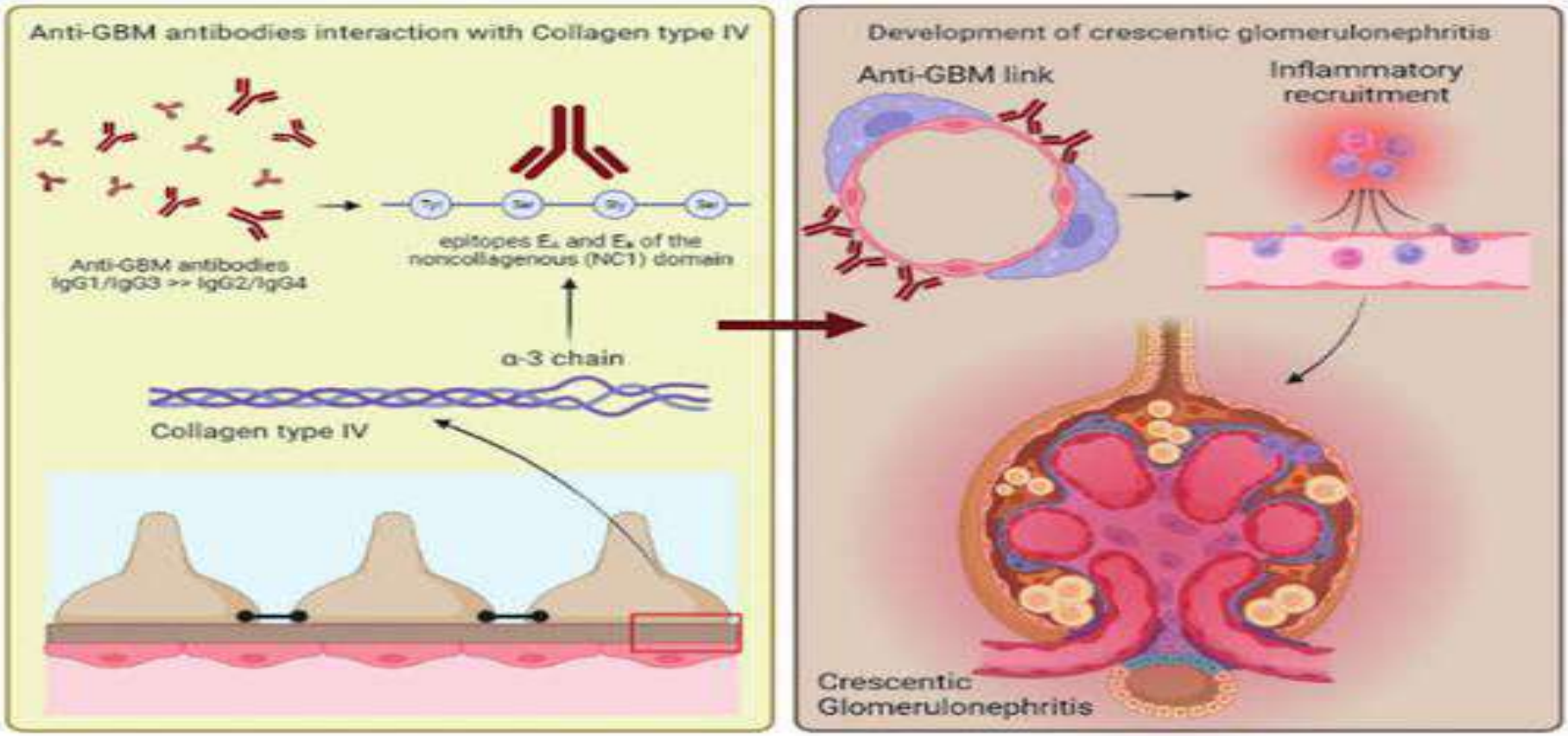
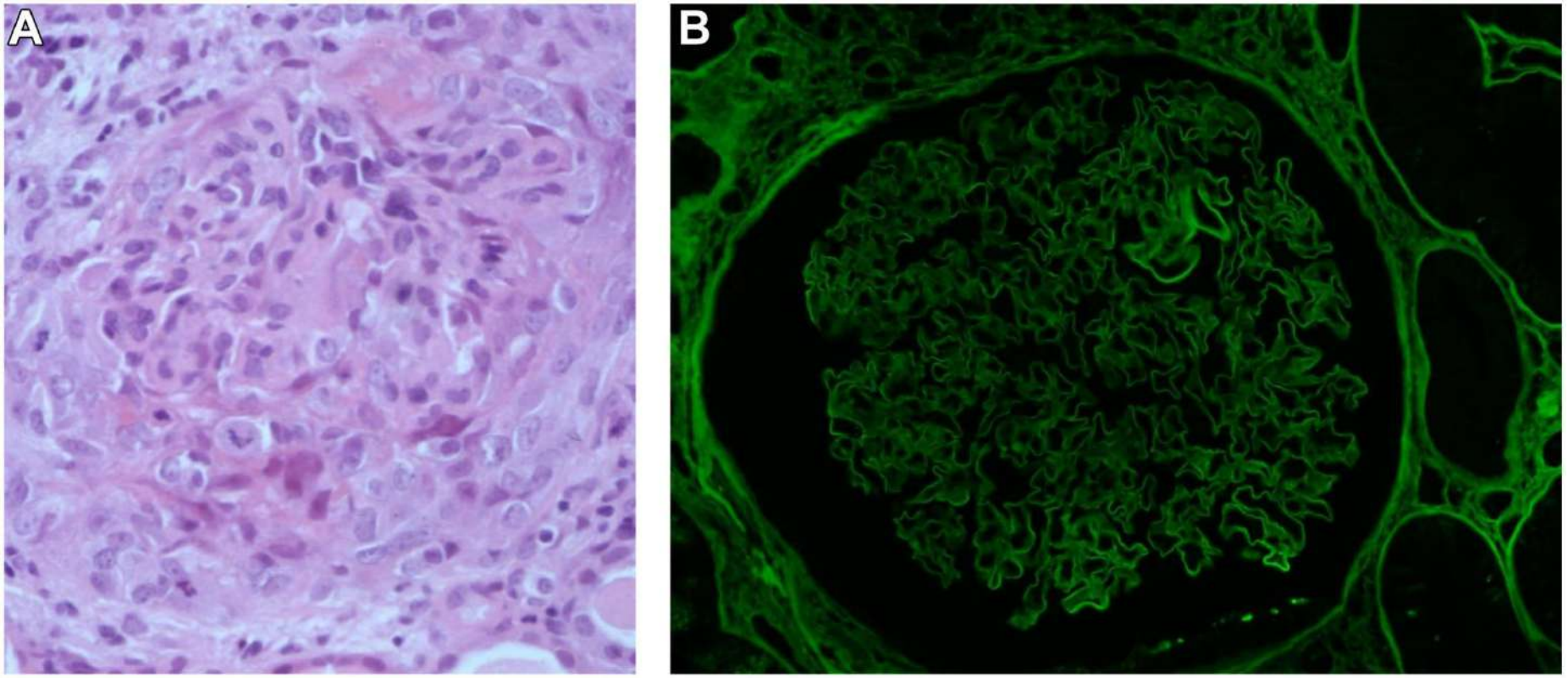
PATHOGENESIS



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**.

HISTOPATHOLOGY



Kidney pathology in anti-GBM disease A). High power light microscopy image of kidney biopsy from a patient with anti-GBM disease showing a single glomerulus with crescentic change and compression of the glomerular tuft (hematoxylin and eosin stain, magnification ×400), B). Direct immunofluorescence of a single glomerulus showing linear IgG staining of the glomerular capillary loops

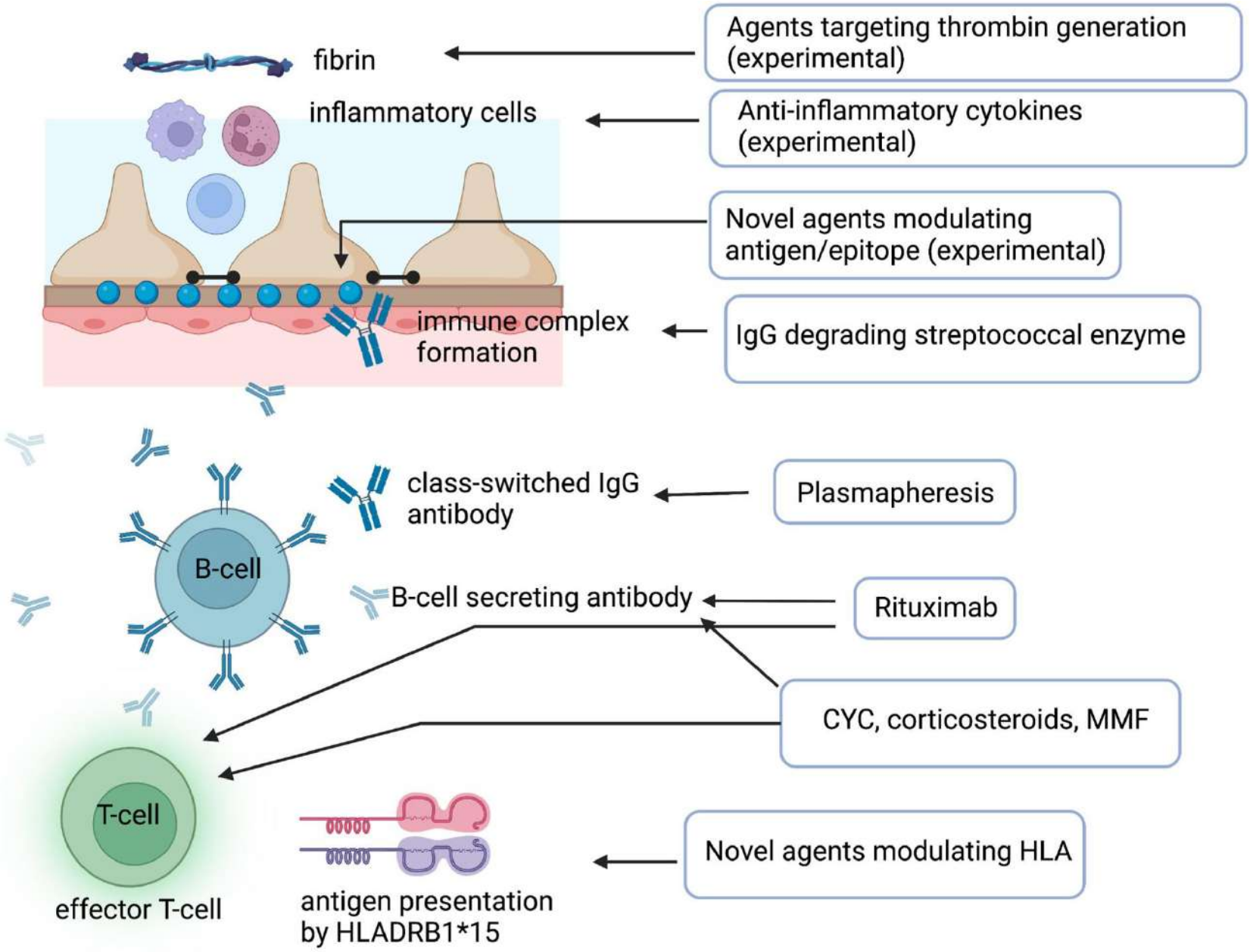
CRESCENTIC GN – D/D

	Anti GBM disease	Immune complex mediated GN	ANCA associated GN
Light microscopy:			
1. Age of crescents	monomorphic	Monomorphic/ pleomorphic	Pleomorphic
2. Necrotising lesions	++	+/-	+++
3. Periglomerular granulomas	++	+/-	+
4. Glomerular hypercellularity and GBM duplication	-	++	-
5. Vasculitis	-	-	+
Immunofluorescence:	Linear IgG	Immune complex deposits	<2+staining for Igs
Electron microscopy:		ectron dense deposits	No deposits

Atypical Anti GBM

	Typical Anti GBM	Atypical Anti GBM
Frequency	90%	10%
Clinical presentation	RPGN, hematuria, mild proteinuria	SPGN, hematuria, heavy proteinuria
Lung involvement	34-62%	Absent
Anti GBM Abs	Positive	Negative
Light microscopy	Diffuse crescentic GN	Endocapillary, mesangial or membranoproliferative +/-TMA Crescents <50%
Prognosis	Guarded	

PATHOGENESIS - THERAPUTIC TARGETS



Treatment (KDIGO 2020)

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar haemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer be detected; usually 14 days
Cyclophosphamide	• 2–3 mg /kg orally (reduce to 2 mg/kg in patients > 55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Corticosteroids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

Anti GBM post transplant

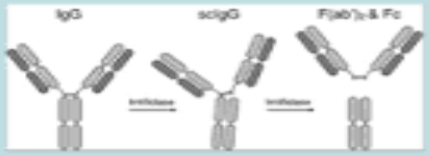
- Rarely recurs post transplant
- Occurs in 3-5% of patients with **Alport syndrome** post tx
- Due to alloantibodies against the GBM antigens that are lacking in Alport patients
- Clinical presentation is same as new onset disease, and serology is positive
- Epitope specificity in Alport patients is different from that of the autoantibodies in recurrent disease (α5NC1)
- Pts who lose a graft to anti GBM disease are at a higher risk of recurrence

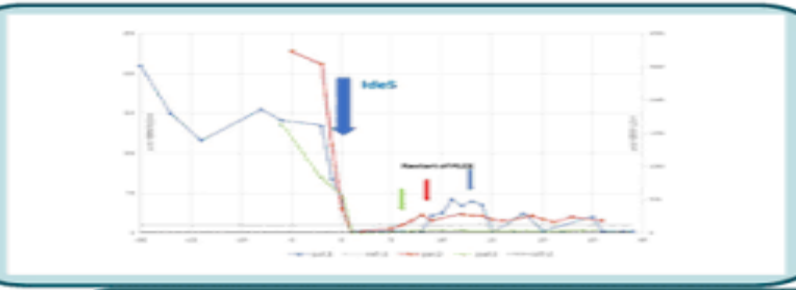
The IgG-degrading enzyme of *Streptococcus pyogenes* causes rapid clearance of anti-glomerular basement membrane antibodies in patients with refractory anti-glomerular basement membrane disease.

Anti-GBM disease → **Hypothesis** → **Anti-GBM levels before and after treatment**

- -anti-GBM IgG are central in the pathomechanism of Goodpasture disease
- -anti-GBM IgG removal via PLEX is standard of care
- -PLEX only removes approximately 1/3 of anti-GBM IgG per session

IdeS rapidly cleaves the anti-GBM antibodies





CONCLUSION:
IdeS treatment lead to rapid clearance of circulating and kidney bound anti-GBM antibodies

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Soveri et al, 2019

ERA ndt

Using imlifidase to elucidate the characteristics and importance of anti-GBM antibodies produced after start of treatment

Imlifidase treatment rapidly degrades all IgG and could elucidate how rapid removal of autoantibodies impacts clinical outcomes in anti-GBM disease

Methods

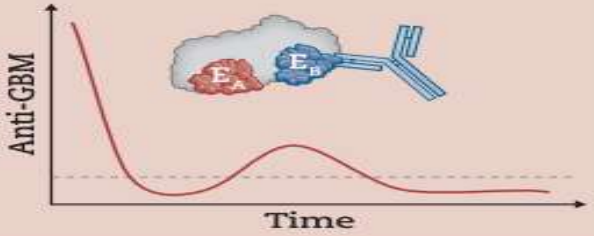
GOOD-IDES-01 trial:
n=15 anti-GBM disease
Treated with imlifidase

Serum anti-GBM E_A and E_B epitopes

Outcomes at 6 months:
- eGFR
- Need for dialysis

Results

Anti-GBM rebound occurred in 10/15 participants



Rebound was associated with ↓6 month eGFR

11 vs. 34
mL/min/1.73 m²
p = 0.055

Tyrberg, L. *et al.*
NDT (2023)
@NDTSocial

Rebound of anti-GBM antibodies, especially if directed towards the E_B epitope, was associated with poorer kidney outcomes. These findings provide rationale for using plasma exchange to curb rebound of anti-GBM antibodies.

Recurrence and Outcome of Anti-GBM Glomerulonephritis After Kidney Transplantation

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Methods

- Multicenter
- Retrospective 1977-2015
- N=53 kidney transplant recipients with history of anti-GBM glomerulonephritis
- 33 follow-up allograft biopsies

Results

Clinical recurrence prevalence rate

1.9% (N=1)

In context of immuno-suppressive drug cessation

Associated with graft loss

Immunohistological recurrence

N=4

Out of 19 samples with available IgG staining

No histological signs of proliferative GN

Patient survival rates

5 years	100%
10 years	94%
15 years	89%

Death-censored first graft survival rates

5 years	88%
10 years	83%
15 years	79%

KI REPORTS
Kidney International Reports

Coche et al, 2021

Visual abstract by:
Corina Teodosiu, MD
@CTeodosiu

Conclusion The recurrence rate of anti-GBM glomerulonephritis after transplantation is very low but associated with graft loss. The long-term patient and graft survival rates are excellent.

Efficacy and Safety of Rituximab in Anti-Glomerular Basement Membrane Disease

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Methods

- Review of individual patient-level data
- 67 patients with anti-GBM disease & at least one dose of rituximab
- 55% female (n = 37)
- 14 pediatric patients
- Median age 37 years (Min-max: 2 to 91)

Baseline Patient Characteristics

	Diffuse alveolar hemorrhage n (%)	Dialysis dependent n (%)	Cellular crescents median % (IQR)	Pulse Dose Steroids n (%)	Plasma Exchange n (%)	Cyclophosphamide n (%)	Rituximab doses median (IQR)	AE with Rituximab n (%)
Rituximab as 1st Line (n = 39)	16 (41)	23 (59)	93 (66 - 100)	32 (84)	32 (89)	8 (21)	2 (2 - 4)	10 (26)
9.5 months median follow-up time								
Rituximab as 2nd Line (n = 28)	8 (19)	9 (32)	35 (18 - 59)	24 (86)	26 (96)	28 (100)	4 (2 - 4)	1 (4)

Outcomes

EKSD-free survival*

46% vs 73% (p = 0.03)

Death

6 (15%) vs 0

* No difference in kidney survival between ANCA positive vs negative and Diffuse alveolar hemorrhage at presentation positive vs negative.

KI REPORTS
Kidney International Reports

Ivkovic V et al, 2025

Visual abstract by:
Arjunmohan Mohan, MBBS
𝕏 @Arjun_Mohan1

Conclusion Kidney survival was better when rituximab was used as a second line agent. Rituximab might be considered as second-line therapy in anti-GBM disease when further use of cyclophosphamide is contraindicated and potentially as first-line therapy in patients with mild disease or otherwise not suitable for initiation of cyclophosphamide.