C3 Glomerulopathy

The transplant

20th C3G Family Conference
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Objectives

- When is it time to transplant?
- What is the best regimen for the C3G patient now that AP blockers have been approved?
- What should recipients know about the transplant drugs they receive (risk of skin cancer, psychiatric side effects, etc.)
- How is recurrence after transplantation defined and why is that important?

Should patients with C3G be transplanted?

- Any patient who is expected to benefit from a kidney transplant should be considered a candidate for a transplant.
- Even patients who have had early transplant failure from C3G recurrence should consider a kidney transplant
- Risk of recurrent disease may be influenced by
  - Sex, age, ↑autoantibodies (C3Nef,C5Nef),↑complement activity (C3c,sMAC5b-9)
  - Not all recurrent disease leads to premature kidney loss
- Consequence of early kidney loss
  - early kidney failure from C3G probably predicts recurrent early loss.
  - Exposure to donor kidney leads to development of antibodies to HLA antigens.

<u>Sensitization (HLA antibodies) can make future transplants difficult.</u>

When should patients with C3G be transplanted?

- Ideally when the disease appears inactive
  - patient not requiring immunosuppressive therapy
  - Urine testing shows no red cells (blood) or casts
  - Signs of complement activation have resolved
    - Normal C3
    - undetectable C3 nephritic factor (if previously abnormal)
    - MORL assays: Normal CH50, Normal APFA, Normal hemolytic assay

- Adults with monoclonal Ig (MGRS) should first be treated for the plasma cell disease

How should C3G patients be transplanted?

- As with other transplants, a living donor is almost always preferable to a deceased donor transplant
- Immunosuppressive regimen should include standard therapy:
  - Induction antibody: Alemtuzumab (Campath®) or anti-thymocyte globulin (Thymoglobulin®) or basiliximab (Simulect®)
  - Maintenance:
    - Std: tacrolimus (Prograf®, Envarsus®), MMF/MPA (mycophenolate, Cellcept®, Myfortic®) +/- prednisone
    - Others: cyclosporin (Gengraf®), azathioprine (Imuran®), sirolimus (Rapamune®), everolimus (Zortress®), belatacept (Nulojix®)
- No data to support pre-operative use of eculizumab, iptacopan (FABHALTA) or pegcetacoplan (EMPAVELI)
- Transplant center should have a plan for monitoring for early transplant recurrence
  - Urine for blood (microscopic)
  - Urine protein or albumin

Side effects of transplant medications

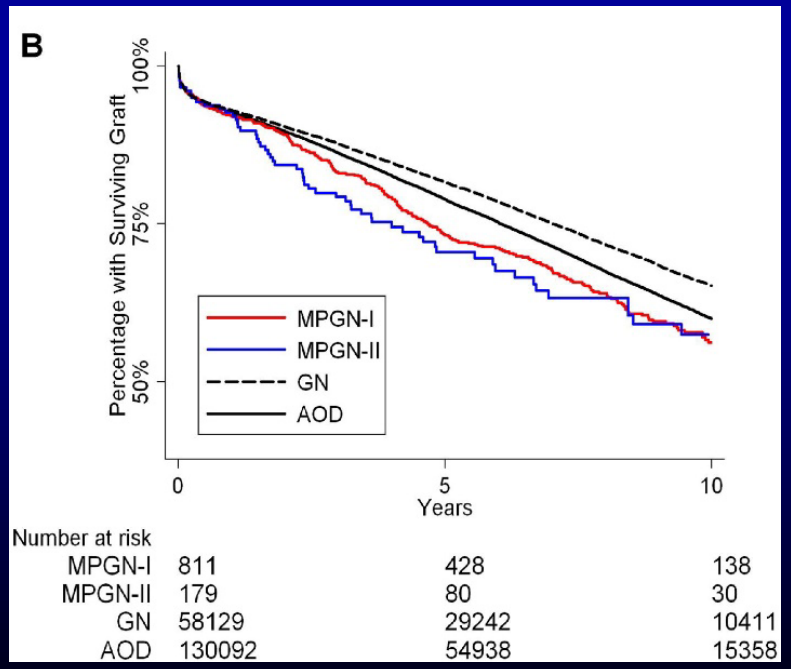
- Susceptibility to infections – mostly viral, fungal, parasitic
  - Common to transplant – CMV, EBV, BKV, pneumocystis, histoplasmosis
- Susceptibility to some cancers
  - Skin (squamous cell, basal cell, melanoma)
  - Other squamous cell cancers
  - Some lymphomas
  - Kaposi sarcoma
- Increased risk of diabetes (tacrolimus, prednisone)
- Increased risk of CKD (tacrolimus, cyclosporin)
- GI side effects: Nausea, diarrhea (mycophenolate)
- Low blood counts (mycophenolate, azathioprine)
- Hair loss/ excessive hair (tacrolimus, cyclosporin)
- Weight gain (prednisone)

Remember drug drug and drug-food interactions especially with tacrolimus, cyclosporin

Recurrent C3G after transplant

C3G (DDD)-recurrence I

- UNOS database (US transplant database – all comers)
  - Retrospective review (1987-2007) - 189,211 patients
  - 179 patients with MPGN II (DDD) – 0.1%: Median age 27 yr
  - Median kidney survival 11.1 yr (other GN 14.3 yr)
  - 10 year kidney survival 57.5% in MPGN II (other GN 65.2 yr)
  - Recurrent disease caused graft failure in 29.5% of patients



Kidney survival in MPGN II compared to other (death censored)

Angelo et al., American Journal of Kidney Diseases, 2011, 57: 291-299

C3G (C3GN) recurrence - II

- 21 patients at one institution with C3GN were transplanted
- Original disease diagnosed at a median age of 21 years
- 14 of 21 (66.7%) recurred after transplant; 6 of 8 had low C3 prior
- Median time to recurrence 28 months
- 3 of 14 had MGRS (Immunoglobulin or Ig excess from a process like myeloma)
- Kidney failure in 50% of those who developed recurrent disease
  - Median time 77 months
- Remaining 50% have functioning kidneys (median followup 73 months)

Zand et al., J Am Soc Nephrol. 2014, 25: 1110-1117

C3G recurrence - III

- 18 patients at one institution with C3G were transplanted (2016-2023)
- Median age at transplant 31 years, median follow-up 37 months
- 16 of 18 (89%) recurred after transplant
  - Increased mesangial or endothelial cells; C3 deposits, EM deposits
- Median time to recurrence 33 days (patients had protocol biopsies)
- 14 of 18 patient received no specific therapy for C3G
- No patient had a doubling of serum creatinine or failure of transplant
- At end of study eGFR 53; proteinuria 285 mg/day

Summary:

- Recurrence universal but impact on kidney function minimal over 3 years

Tarragon et al., C. J. Am Soc Nephrol. 2024, 19: 1005-1015

C3G – recurrence after transplant

- Recurrence very common if defined by C3 deposition
  - similar to IgA nephropathy
- But detectable C3 in biopsy may not always impact kidney function
- Clinically meaningful disease: 50% by 5 years
- Kidney failure in 50% by 7-15 years
  - (median kidney survival for DD kidneys is 12 years; LD kidneys 19 years)

Conclusion:

- Recurrence by biopsy probably universal
- But not all recurrence is clinically meaningful disease
- Outcomes likely to be better with treatments available

University of Iowa protocol for transplant in C3G

- We are willing to consider anyone with a history of C3G
- We evaluate for clinical activity +/- complement function testing – *Nester, Smith*
- We try to transplant when disease is inactive
- We monitor for disease after transplant
- We do not use complement blockers in anticipation of disease

Monitoring after transplant:

- We do not do protocol biopsies
- We look for blood, albumin, protein in the urine and if positive then biopsy
- Recurrence is more than just C3 deposition
- If clinically meaningful disease, then we consider iptacopan or pegcetacopan

Summary

- Kidney transplantation is the preferred option for any patient with end stage kidney disease including from C3G
- Although the risk of recurrent disease is high, it may not occur early or lead to early loss of kidney function
- New treatments for C3G after transplant are now available and its place will continue to be refined by ongoing clinical trials
- More transplant centers are now likely to accept patients with C3G

Questions

Iptacopan Reduces Proteinuria and Stabilizes Kidney Function in C3 Glomerulopathy

Carla M. Nester[1], Ute Eisenberger[2], Alexandre Karras[3], Moglie le Quintrec[4], Liz Lightstone[5,6], Manuel Praga[7], Giuseppe Remuzzi[8], Maria José Soler[9], Junhao Liu[10], Matthias Meier[11], Ronda Tawfik[10], Guido Junge[12], Andrea Biondani[12], Angelo J. Trapani[10], Nicholas J.A. Webb[11] and Edwin K.S. Wong[13,14]

Methods: This was a phase 2 extension study of 26 adult patients with native kidney (cohort A), or recurrent C3G (post kidney transplantation; cohort B) receiving open label iptacopan.

Results: At 12 months, patients in cohort A had a significant reduction in 24-hour urine protein-to-creatinine ratio (UPCR; 57%; $P < 0.0001$; confidence interval [CI]: 0.31–0.59), an improvement in estimated glomerular filtration rate (eGFR; 6.83 ml/min per 1.73 m^2; $P = 0.0174$; CI: 1.25–12.40), and an increase in serum C3 levels (geometric mean ratio to baseline: 3.53; $P < 0.0001$; CI: 3.01–4.15). In cohort B, most patients had normal urinary protein excretion at baseline (mean [range] 24-hour UPCR: 121 [9–445]), which was slightly lower by 12 months (21% reduction; CI: 0.48–1.31; $P = 0.3151$). In cohort B at 12 months, mean eGFR was at baseline values (mean change from baseline: −0.96 ml/min per 1.73 m^2; $P = 0.7335$; CI: −6.60 to 4.69). Cohort B patients had significantly higher serum C3 values at 12 months compared with baseline (ratio:1.96; CI: 1.70–2.27; $P < 0.0001$). In cohorts A + B combined, the median difference in C3 deposit score on renal biopsy from baseline was −7.00 (CI: −12.00 to 4.00;) at 9 to 12 months treatment with iptacopan.

Conclusion: These data provide a clinical rationale for further evaluation of long-term treatment of C3G with iptacopan.

Kidney Int Rep (2025) **10**, 432–446; https://doi.org/10.1016/j.ekir.2024.10.023

VALIANT: Phase 3 Trial of Pegcetacoplan for Patients With Native or Post-Transplant Recurrent C3G or Primary IC-MPGN

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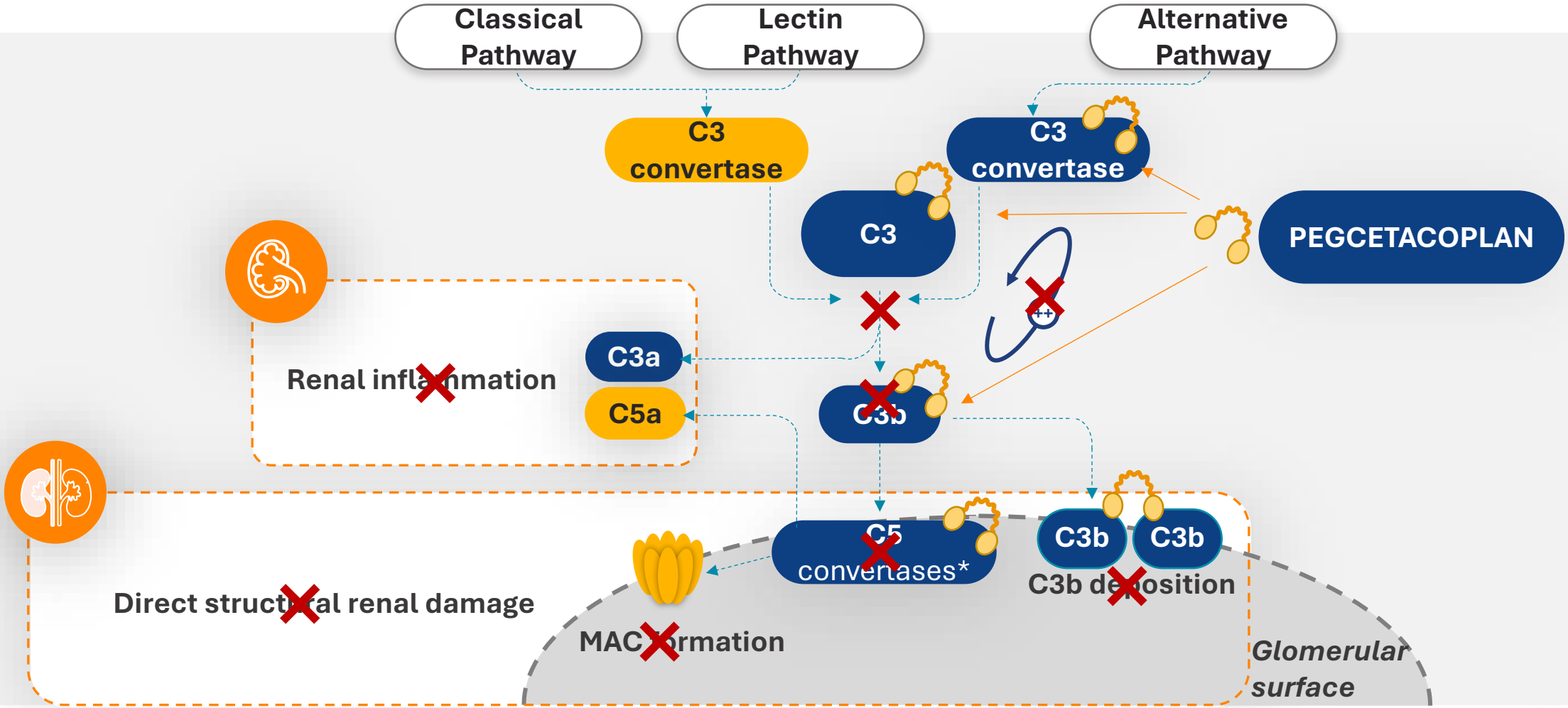
Pegcetacoplan, a Targeted C3 and C3b Inhibitor, Acts Centrally to Block Downstream Complement Activation in C3G and Primary IC-MPGN[1–7]



*C5 convertases: C4b2aC3b and C3bBbC3b. C3/5, complement 3/5; C3G, C3 glomerulopathy; IC-MPGN, immune complex membranoproliferative glomerulonephritis; MAC, membrane attack complex.

1. Smith RJH, et al. *Nat Rev Nephrol* 2019;15:129–43. **2.** Zipfel PF, et al. *Front Immunol* 2019;10:2166. **3.** Meuleman MS, et al. *Semin Immunol* 2022;60:1016342. **4.** Dixon BP, et al. *Kidney Int Rep* 2023;8:2284–93. **5.** EMPAVELI® (pegcetacoplan) US PI 2024. **6.** ASPAVELI Summary of Product Characteristics 2024. **7.** Lamers C, et al. *Nat Commun* 2022;13:5519.

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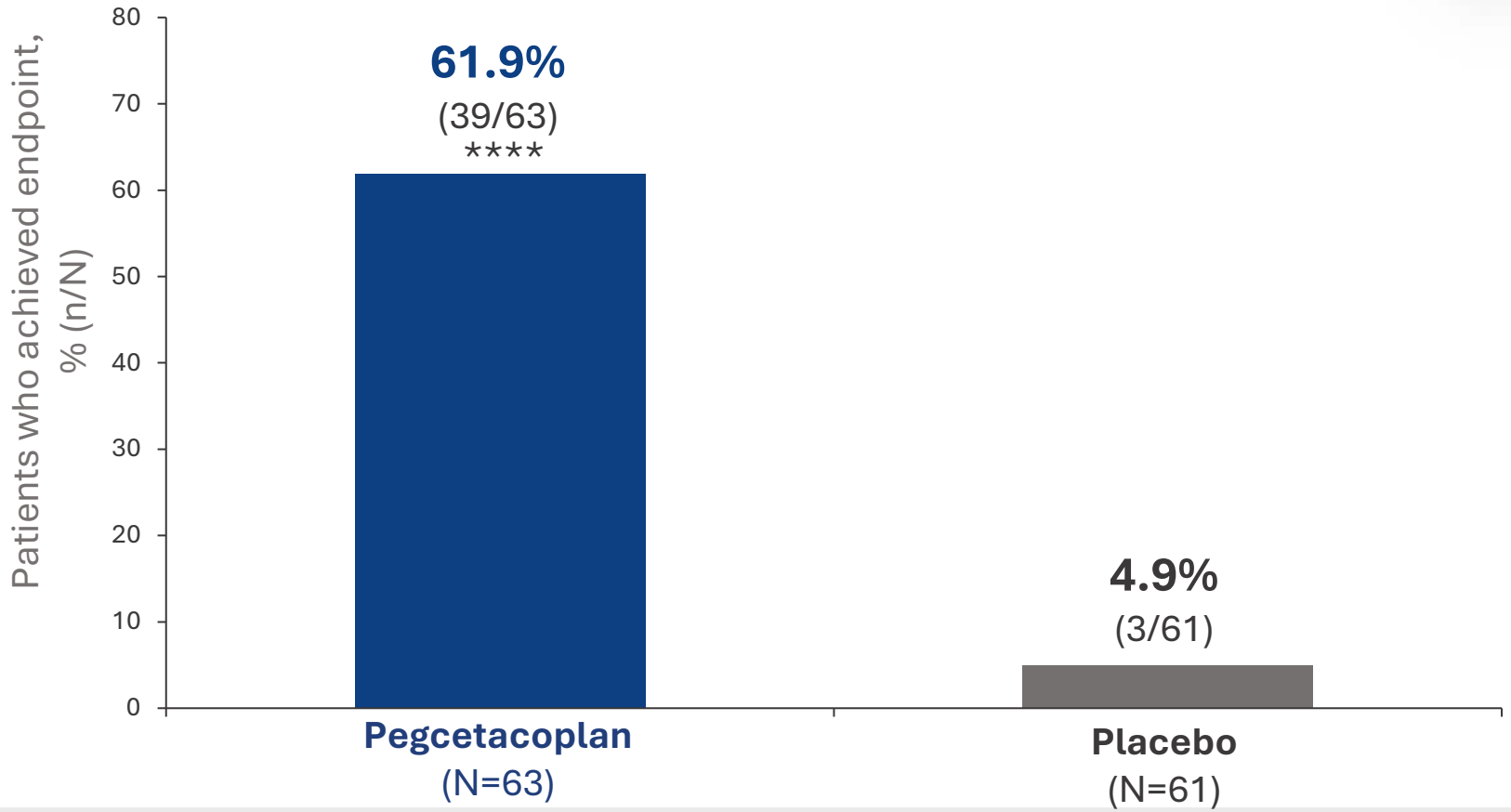
Significantly More Patients Achieved ≥50% Proteinuria Reduction With Pegcetacoplan vs Placebo

≥50% proteinuria reduction



Key secondary endpoint

Odds ratio
Pegcetacoplan vs placebo arms

32x

higher odds of achieving ≥50% proteinuria reduction

***P*<.0001**

****$P \leq .0001$. Intent-to-treat population (all randomized patients). 2-sided *P* values.

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