Long-Term Comparative Effectiveness of Rituximab vs. Calcineurin Inhibitors for the Treatment of Membranous Nephropathy

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Background

- Membranous nephropathy (MN) is an autoimmune glomerular disease that affects children and adults and is a common cause of nephrotic syndrome – yet no FDA-approved treatments for MN currently exist!
- Immunosuppressants (ISTs) are the cornerstone of MN treatment, but clinical trials evaluating their effectiveness are limited by small sample sizes and follow-up times less than 24 months
- No trials have evaluated the effectiveness of rituximab (RTX) and calcineurin inhibitors (CNIs), two common IST treatments for MN, head-to-head for long-term disease progression outcomes

Aim: generate high-quality evidence on the comparative effectiveness of RTX and CNIs for long-term MN outcomes using observational data

Methods

Study Sample and Data

- Cure Glomerulonephropathy (CureGN) is an ongoing prospective observational cohort study of children and adults with biopsy-proven MN among other glomerular diseases
- Individuals starting RTX or CNI at least 6 mos. after any previous non-steroid IST exposure were eligible **– allowing sequential re-entry** as participants could be eligible more than once

Statistical Analysis Framework

1. **Multiple Imputation (MI):** incomplete observations were multiply imputed and retained
2. **Propensity-Score Matching:** propensity scores estimated from a logistic GEE (to account for re-entry) were used in 1:1 optimal matching without replacement with exact matching on history of RTX and CNI use
3. **Analog to per-protocol analysis (PP):** individuals were artificially censored if they started a different non-steroid IST during follow-up and inverse-probability-of-censoring weights were applied
   - An **analog to intention-to-treat (ITT) analysis** based only on the initiated treatments was also considered
4. **Robust Survival Analyses**
   - **Hazard ratios (HRs)** with robust confidence intervals accounting for multilevel non-nested clustering (Austin and Cafri, Stat Med, 2020) were estimated and pooled from Cox proportional hazards models
   - **Restricted mean survival times (RMSTs)** with bootstrap confidence intervals were pooled over imputations (Schomaker and Heumann, *Stat Med*, 2018)
5. **Sensitivity Analyses** considered 3:1 matching with replacement, addressed varying treatment durations, and included regression adjustment for baseline covariates in addition to matching

Table 1. Primary **(bold)** and Secondary Outcome Definitions

Survival Outcome (Time to Event)	Definition
A. Complete Proteinuria Remission (CR)	UPCR[a] < 0.3 g/g
D. Complete or Partial Proteinuria Remission (CR or PR)	UPCR < 0.3 g/g OR 0.3 g/g ≤ UPCR ≤ 3.5 g/g with 50% reduction in UPCR
B. Relapse Following Complete Remission	UPCR > 1 g/g following complete remission
E. Relapse Following Complete or Partial Remission	UPCR > 1 g/g following complete remission OR UPCR > 3.5 g/g following partial remission
C. Composite Kidney Disease Progression (40%)	40% eGFR[b] decline, kidney replacement therapy, OR eGFR < 15
F. Composite Kidney Disease Progression (30%)	30% eGFR decline, kidney replacement therapy, OR eGFR < 15

[a]Urine protein-to-creatinine ratio (UPCR; g/g); [b]Estimated glomerular filtration rate (eGFR; mL/min/1.73m^2)

Results

Table 2. Pooled Participant Demographic and Clinical Characteristics After Matching

Characteristic[a]	RTX (N=137[e])	CNI (N=137)
Age (Years)	54.0 (41.5, 64.3)	50.2 (34.0, 62.0)
Female Sex	61 (44.5%)	54 (39.6%)
Race		
Black/African American	28 (20.5%)	23 (16.8%)
White/Caucasian	92 (67.3%)	94 (68.5%)
Other or Unknown[b]	17 (16.6%)	20 (14.7%)
eGFR[c]	69.1 (45.4, 94.4)	76.8 (49.3, 99.1)
UPCR[c]	5.2 (2.4, 8.3)	5.0 (1.8, 8.5)
PLA2R-Ab Level[c,d]	24.5 (2.0, 215.1)	23.6 (2.3, 206.8)

[a]Median (IQR), frequency (proportion) if categorical, obtained from pooling all individual matched dataset summaries using Rubin's rules; [b]Includes Asian, Native American, Multiracial, or Unknown; [c]Missingness (n for RTX, n for CNI): eGFR (18, 21); UPCR (37, 36); PLA2R (97, 92); [d]Anti-phospholipase A2 receptor antibody; [e]137 matches identified from 174 RTX and 155 CNI initiators

Figure 1. Pooled Kaplan-Meier Plots, 1:1 Per-Protocol Analyses

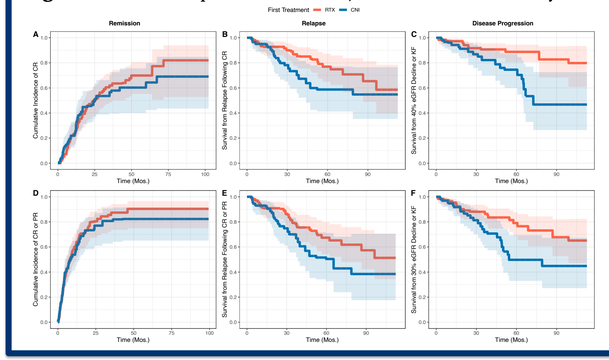
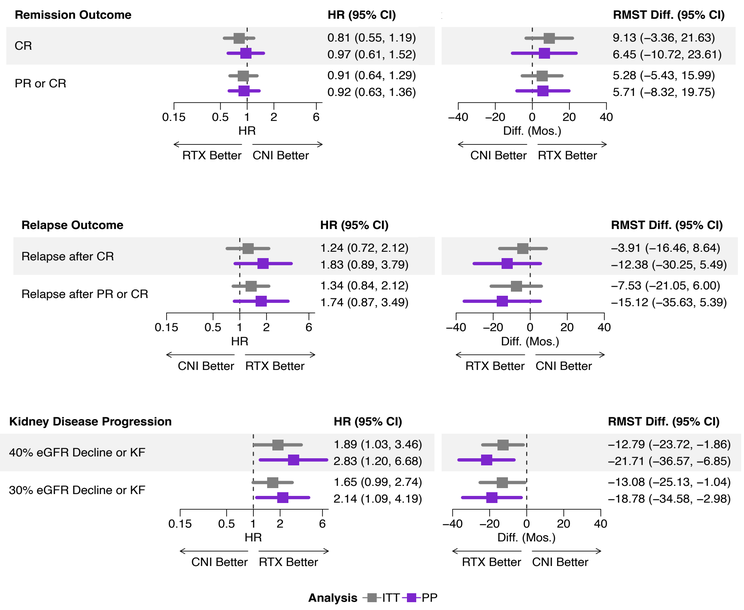


Figure 2. Forest Plot of HRs and RMSTs for 1:1 Matched Analysis



Outcome Notation: CR = Complete Proteinuria Remission (UPCR < 0.3 g/g); PR = Partial Proteinuria Remission (0.3 g/g < UPCR < 3.5 g/g with 50% reduction); KF= kidney failure (replacement therapy or eGFR<15);

Discussion

- In the 1:1 PP analyses, RTX was more effective for preserving eGFR than CNIs; while hazard ratios for proteinuria remission and relapse were imprecise, results suggested CNI initiators may have higher risks of relapse. Results for the 1:1 ITT analyses and both sets of supplemental 3:1 analyses were similar.
- We compared remission and relapse outcomes as in the MENTOR trial but extended the evaluation of these outcomes beyond 24 months and additionally considered long-term disease progression
  - Our inclusion criteria additionally reflected a broader, more pragmatic study population
- Long-term, head-to-head trials comparing treatments for MN and other glomerular diseases are generally infeasible, yet new treatments are emerging
- This study demonstrates how a matched design combined with sequential re-entry and multiple imputation can be applied to observational studies to generate high-quality evidence about comparative treatment effectiveness in MN and other rare disease contexts in the absence of clinical trials

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