Effects of Proteinuria Reduction on Delay of Kidney Failure in Patients With Immunoglobulin A Nephropathy

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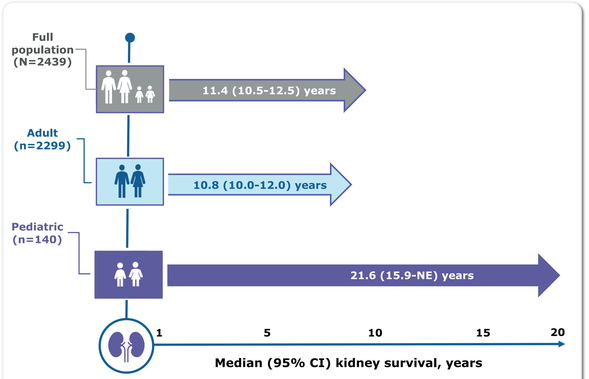
INTRODUCTION

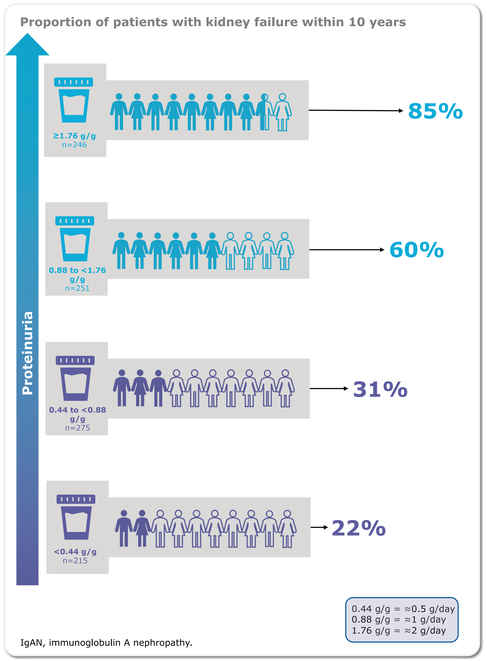
- Immunoglobulin A nephropathy (IgAN) is a rare, chronic, progressive inflammatory kidney disease[1]
  - IgAN results from the accumulation of IgA immune complexes within the glomerular mesangium, leading to inflammation and kidney damage[1]
- Proteinuria has been demonstrated to be a surrogate marker for disease progression and is predictive of long-term outcomes in patients with IgAN[2,3]
- Patients with IgAN have a high risk of progression to kidney failure in their lifetime[2]
  - In an analysis of 2439 patients with IgAN enrolled in the UK National Registry of Rare Kidney Diseases (RaDaR), median kidney survival time was 11.4 years (**Figure 1**)[2]
  - It was shown that most patients (>60%) with proteinuria of ≥0.88 g/g (≈1 g/day) are at high risk of progression to kidney failure within 10 years of diagnosis (**Figure 2**)[2]
- In this study, we estimated the delay to kidney failure or death associated with treatment effect reductions of proteinuria

Figure 1. Median (95% CI) Kidney Survival From Time of IgAN Diagnosis



IgAN, immunoglobulin A nephropathy; NE, not estimable.

Figure 2. Risk of Kidney Failure Within 10 Years of IgAN Diagnosis Based on Proteinuria Levels

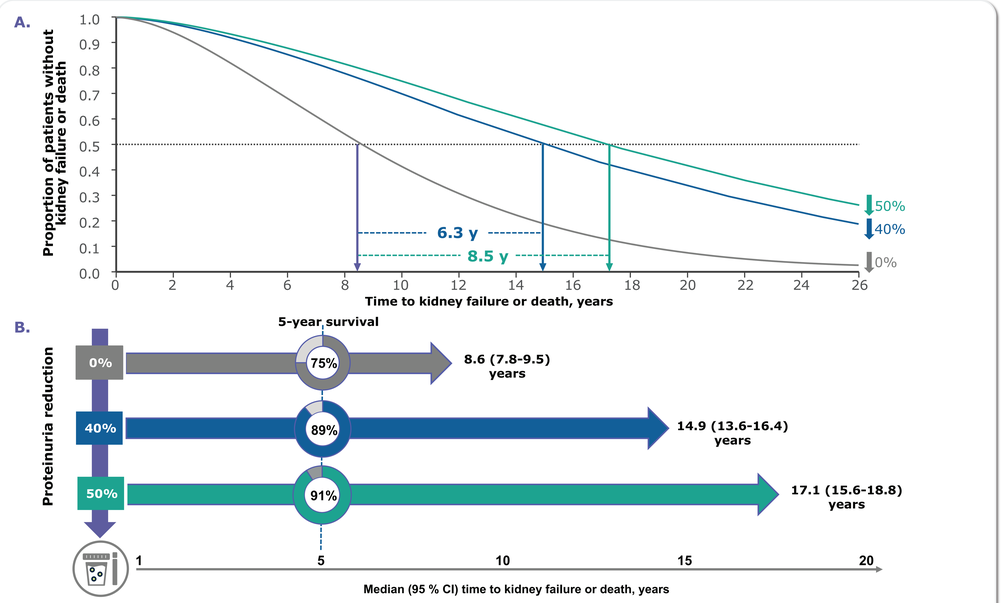


IgAN, immunoglobulin A nephropathy.

RESULTS

- Proteinuria reductions of 40% or 50% were estimated to extend the median time to kidney failure or death by 6.3 and 8.5 years, respectively (**Figure 4A**), and increase the 5-year kidney failure–free survival probability (**Figure 4B**)

Figure 4. Treatment Effect of 40% or 50% Reductions in Proteinuria in a Population Representative of a Phase 3 RCT



RaDaR IgAN cohort: phase 3 representative population (N=535; events=171); median (IQR) UPCR, 1.5 (1.1-2.2) g/g; mean (SD) eGFR, 61 (26) mL/min/1.73 m^2.
eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RaDaR, Registry of Rare Kidney Diseases; RCT, randomized clinical trial; UPCR, urine protein-to-creatinine ratio.

METHODS

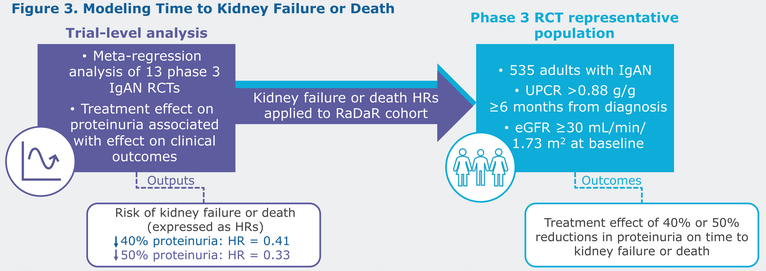
Step 1: Trial-Level Analysis

- Meta-regression trial-level analysis of 13 phase 3 IgAN randomized clinical trials (RCTs) was performed to predict treatment effects for risk of kidney failure or death (expressed as hazard ratios [HRs]) (**Figure 3**)

Step 2: Phase 3 RCT Representative Population

- Using HRs from the trial-level analysis for the 40% or 50% reductions in proteinuria at 9 months, the delay in time to kidney failure (defined as estimated glomerular filtration rate of <15 mL/min/1.73 m^2, initiation of dialysis, or transplant) or death in a subpopulation of the RaDaR IgAN cohort was estimated (**Figure 3**)
  - This subpopulation was selected to be representative of patients who would typically be included in a phase 3 RCT

Figure 3. Modeling Time to Kidney Failure or Death



eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgAN, immunoglobulin A nephropathy; RaDaR, Registry of Rare Kidney Diseases; RCT, randomized clinical trial; UPCR, urine protein-to-creatinine ratio.

OBJECTIVE

- To estimate the effect of a 40% or 50% reduction in proteinuria at 9 months on extending the time to kidney failure or death in an IgAN population representative of a typical phase 3 RCT

CONCLUSIONS

Patients with IgAN are at high risk of experiencing kidney failure, and delaying the time to kidney failure and the need for dialysis or a transplant is critical

This study demonstrated that achieving 40% or 50% reductions in proteinuria are associated with a substantially lower risk of kidney failure, delayed time to kidney failure or death, and improved kidney survival

Effective treatments that reduce proteinuria may lead to meaningful benefits and improved outcomes in patients with IgAN

DISCLOSURES

EC, LC, BH, and **CT** are employees and stockholders of Travere Therapeutics, Inc. **AM, KC,** and **DG** report consultancy fees from Travere Therapeutics, Inc. **JB** reports research funding and consultancy fees from Travere Therapeutics, Inc. **DP** reports no disclosures.

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RaDaR Registry of Rare Kidney Diseases

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