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

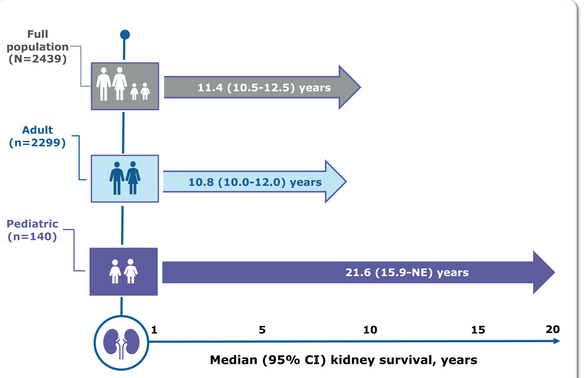
Elle Coe,[1] Alex Mercer,[2] Kevin Carroll,[3] Leah Conley,[1] Daniel Gale,[4] Bruce Hendry,[1] David Pitcher,[5] Crystal Traylor,[1] Jonathan Barratt[6]

[1]Travere Therapeutics, Inc., San Diego, CA, USA; [2]JAMCO Pharma Consulting, Stockholm, Sweden; [3]KJC Statistics Ireland Ltd, Dublin, Ireland; [4]Royal Free Hospital and University College London, London, UK; [5]UK Kidney Association, Filton, UK; [6]University of Leicester, Leicester, UK

INTRODUCTION

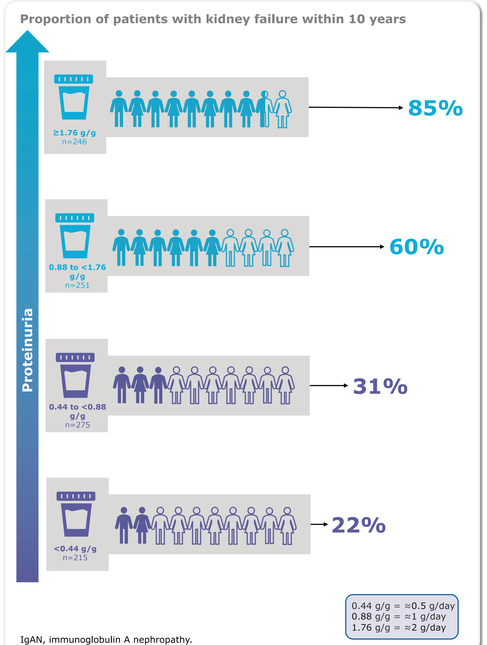
- Immunoglobulin A nephropathy (IgAN) is a rare, chronic, progressive inflammatory kidney disease[1]
  - IgAN results from the accumulation of IgA immune complexes within the glomerular mesangium, leading to inflammation and kidney damage[1]
- Proteinuria has been demonstrated to be a surrogate marker 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

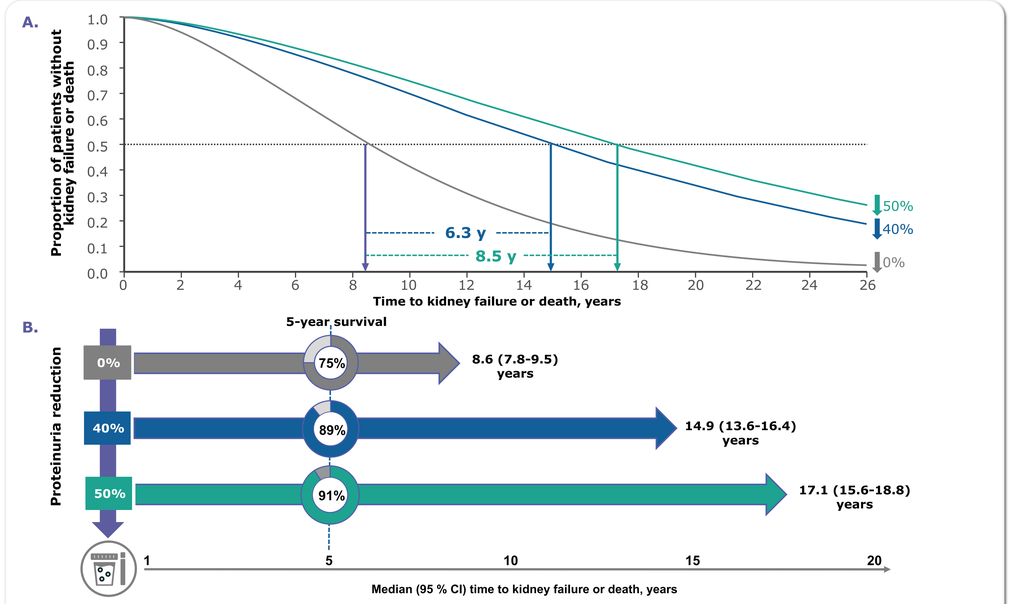


IgAN, immunoglobulin A nephropathy.

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.

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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1. Rajasekaran A, et al. *Am J Med Sci.* 2021;361(2):176-194. **2.** Pitcher D, et al. *Clin J Am Soc Nephrol.* 2023;18(6):727-738. **3.** Thompson A, et al. *Clin J Am Soc Nephrol*. 2019;14(3):469-481.

METHODS

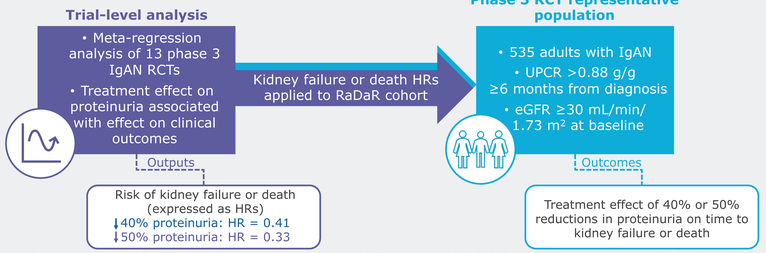
Step 1: Trial-Level Analysis

- 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

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Contact information: Elle Coe, elle.coe@travere.com

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