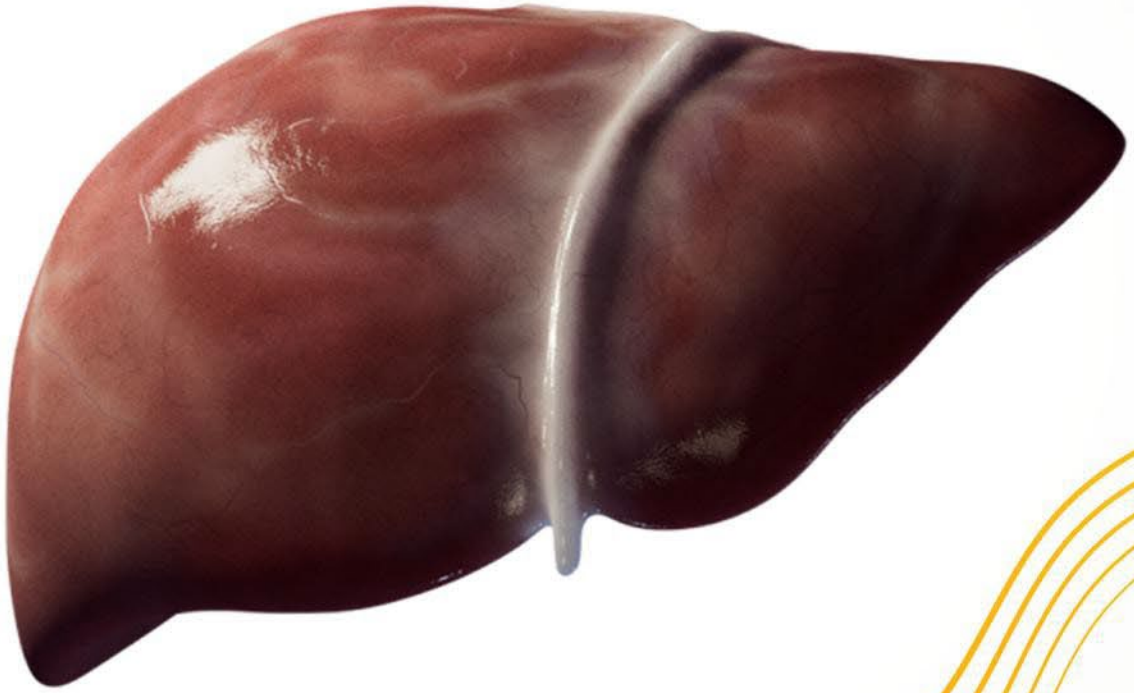
RLSE development: Brief experience from rare kidney disease*



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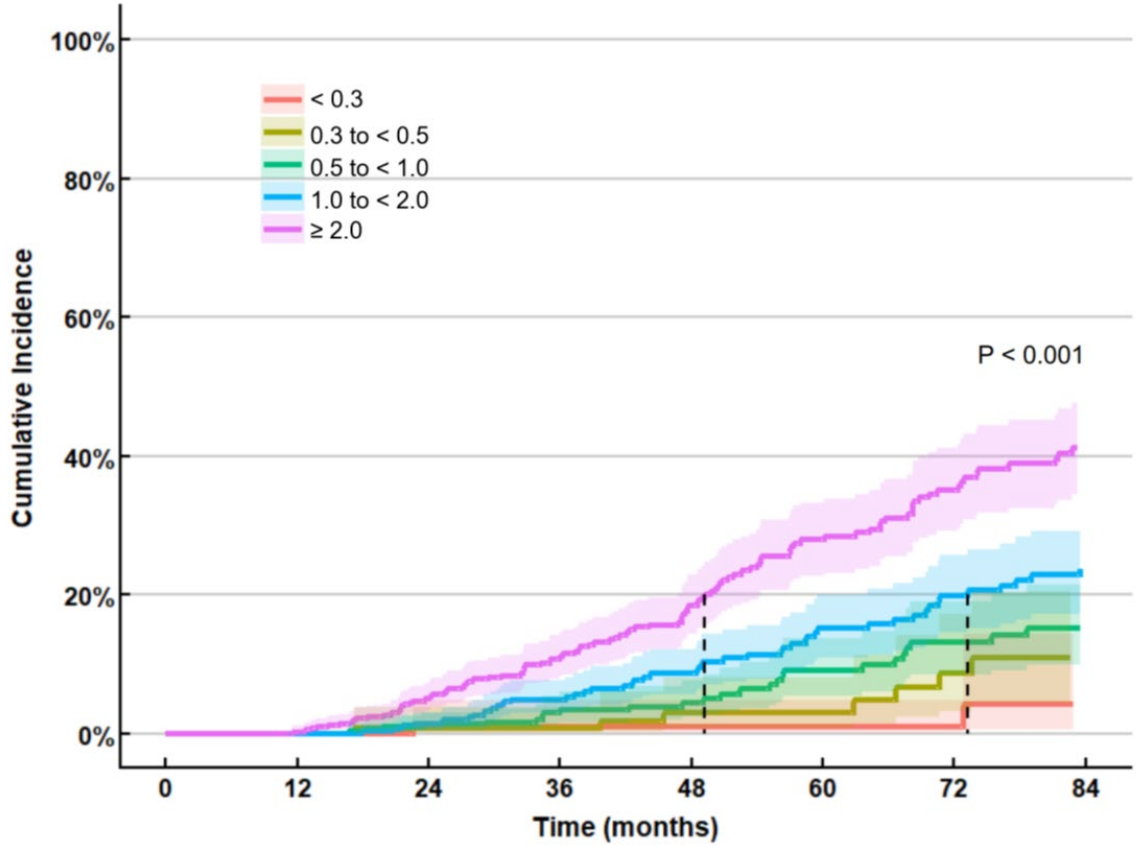
*For Educational Purposes Only upon request of Liver Forum

Proteinuria as a potential RLSE in IgA nephropathy

- IgA nephropathy is the most common cause of primary glomerular disease, but is relatively uncommon (US prevalence ~200k)
  - Diagnosis is confirmed by renal biopsy
  - Disease progression to end stage kidney disease is heterogeneous but may take decades
- Low prevalence and slow progression make clinical development of new treatments challenging
  - GFR already accepted as a surrogate
  - Large, long trials required to demonstrate clinical outcomes benefit
- Extensive assessment of potential RLSE identified urinary protein excretion as the highest potential
  - Substantial evidence link proteinuria to clinical outcomes
  - Used clinically as a marker of risk of disease progression

Lower baseline proteinuria correlates to improved kidney outcomes in IGAN



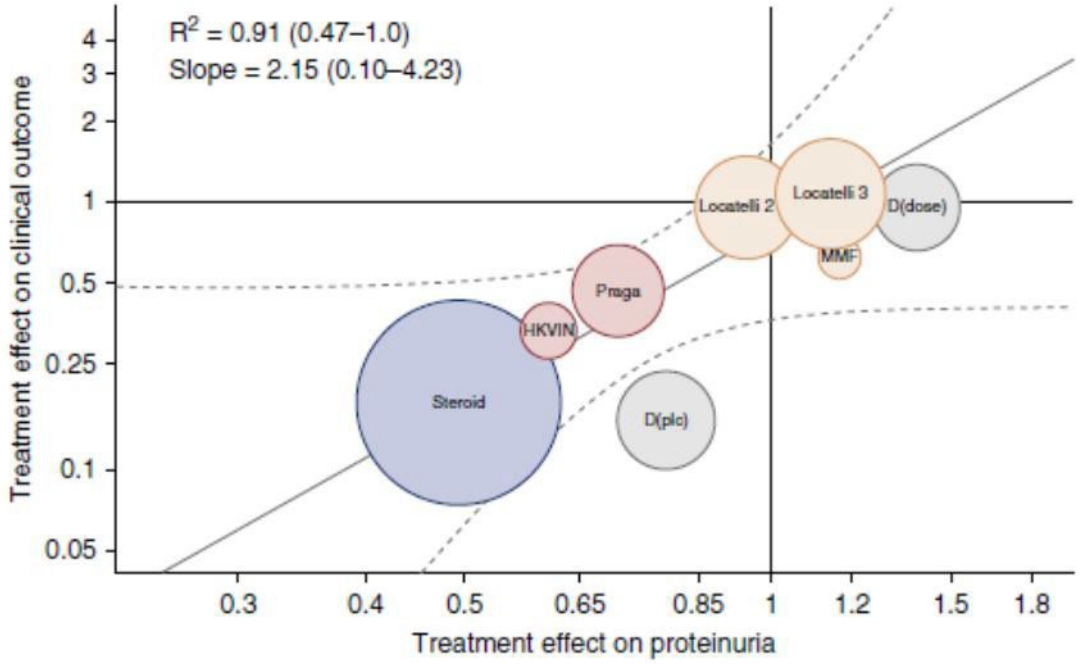
Kidney outcomes = doubling of sCr or ESKD

Tang, C et al. 2024 https://doi.org/10.1053/j.ajkd.2023.12.016

Adoption and implementation of proteinuria as an RLSE

- Multiple clinical trials analyzed to assess relationship between treatment effect on proteinuria and clinical outcomes
  - Data included diverse mechanisms of action (MMF, steroids, ACE inhibitors)
  - Established a framework for determining minimal clinically important difference
- Implementation of accelerated approval path has undergone evolution over time
  - Appropriate population characteristics and SoC
  - Standard length of follow up to assess RLSE
  - Additional data required to support AA
  - Agreement on confirmatory endpoint and path to full approval

Reduction of proteinuria correlates with improved clinical outcome



Kidney outcomes = doubling of sCr or ESKD

Thompson, A et al, 2019. doi: https:// doi.org/10.2215/CJN.08600718

Conclusions and learnings

- IGAN's heterogeneous, slow clinical progression, plus its relative rarity made drug development challenging pointing to the need for an RLSE
- Proteinuria is a strong predictor of disease progression in IGAN
- Reduction of proteinuria was shown in multiple clinical studies to correlate to a reduction in adverse clinical outcomes
  - Data from medicines with diverse MoAs was important for proteinuria to be recognized as a generally-applicable RLSE rather a therapeutic biomarker
- Adoption of proteinuria as an RLSE for IGAN stimulated drug development and is one reason for multiple new drug approvals

- Learnings:
  - Potential for accelerated approval is linked to the unmet medical need and feasibility of drug development
  - Establishing a disease marker that is clearly linked to disease progression is an important starting point
  - Exploration of target treatment effects should incorporate multiple MoAs (not all proteinuria reduction is beneficial)
  - Considering totality of data to be submitted for AA and for full approval should be part of evaluation of RLSE candidates