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Proteinuria combined with other relevant markers as a clinically meaningful surrogate endpoint for measuring disease progression and treatment response in patients with C3G and primary IC-MPGN: A Delphi consensus of European experts

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INTRODUCTION

C3 glomerulopathy (C3G) and primary (idiopathic) immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN) are rare, progressive kidney diseases that ultimately lead to kidney failure.[1] Real-world evidence supports early changes in proteinuria as a strong predictor of long-term outcomes.[2] Proteinuria is used as a primary endpoint in clinical studies due to its association with long-term kidney outcomes.[3] The **definition** of a **clinically meaningful change in proteinuria** has not yet been formally agreed upon for C3G and primary IC-MPGN.

AIM

To define proteinuria as a valuable endpoint and evaluate its use in combination with other markers to determine treatment efficacy in C3G and primary IC-MPGN.

METHODS

This European study used a modified Delphi technique to establish consensus over two survey rounds [4]. A steering group of six experts in the treatment of C3G and primary IC-MPGN attended a virtual meeting to discuss three domains.

After two review rounds, 31 statements were created and distributed in an online survey shared with nephrologists and kidney pathologists in France, Germany, Spain, Italy, and the UK. Survey respondents shared their level of agreement using a four-point Likert scale on each statement. The survey received 51 responses in round one and 50 in round two.

RESULTS

Three domains discussed:

A) **Importance of endpoints in assessing treatment efficacy for patients with C3G and primary IC-MPGN**

B) **Common endpoints currently used for the assessment of treatment in clinical trials**

C) **Proteinuria as a valuable and clinically meaningful endpoint**

29/31 statements achieved the **pre-set consensus threshold (≥75%)**. Respondents unanimously agreed that **monitoring proteinuria levels helps evaluate treatment response and predict long-term outcomes**, and that longitudinal measures of proteinuria along with other relevant endpoints (e.g. eGFR and glomerular C3), can be used to guide treatment decisions. The results suggest that a **≥50% reduction in proteinuria over six months** is representative of a **clinically meaningful change** in proteinuria.

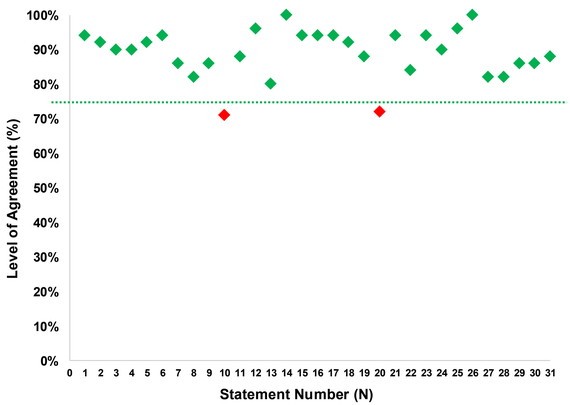

Figure 1: Agreement levels by statement. The pre-agreed threshold for consensus is depicted by the green line (75%).

Table 1: Final set of consensus statements with corresponding agreement values.

No:	Statement (S):	Agreement
Domain A: Importance of endpoints in assessing treatment efficacy for patients		
S1	Since kidney failure occurs late in the natural history of the disease, it is necessary to measure other surrogate endpoints in clinical trials, such as proteinuria, eGFR, and biomarkers that are associated with this outcome	94%
S2	Determining and measuring appropriate endpoints will contribute to a more accurate measurement of treatment efficacy	92%
S3	Determining and assessing appropriate endpoints will help HCPs make more precise treatment decisions	90%
Domain B: Common endpoints currently used for the assessment of treatment in clinical trials		
S4	eGFR is the most commonly used endpoint in clinical practice and clinical trials	90%
S5	eGFR is also one of the most common endpoints used to influence treatment decisions	92%
S6	Treatment should aim to stabilise or improve eGFR, with minimal decline over time, as a key indicator of treatment efficacy	94%
S7	eGFR can be influenced by non-disease factors, such as comorbidities and additional medications administered, making it a limited endpoint	86%
S8	eGFR is not sensitive enough to detect early loss of kidney function and can be influenced by non-disease factors, such as comorbidities and additional medications administered, which could be considered as limitations	82%
S9	Resolution of kidney C3 deposits is an important endpoint that demonstrates the treatment is targeting the root of the disease and may be considered alongside changes in eGFR and proteinuria in C3G and primary/ IC-MPGN	86%
S10	There is limited evidence that the reduction of C3 deposits in kidney biopsy is associated with better clinical outcomes, including improved kidney function and a lower risk of progression to chronic kidney disease in C3G and primary/ IC-MPGN	71%
S11	Evidence suggests that a reduction of C3 deposits in kidney biopsy is associated with better clinical outcomes, including improved kidney function and a lower risk of progression to chronic kidney disease in C3Gand primary/ IC-MPGN	88%
S12	Consideration of multiple endpoints provides more information about disease progression or treatment effects than considering individual endpoints in C3G and primary/ IC-MPGN	96%
S13	Repeat biopsies, used in addition to proteinuria and eGFR, may be helpful in informing future treatment decisions in specific patients, if feasible and appropriate	80%
Domain C: Proteinuria as a valuable and clinically meaningful endpoint		
S14	Monitoring proteinuria levels helps evaluate treatment response and predict long-term outcomes, as higher levels are often associated with the deterioration of kidney function and an increased risk of progression to kidney failure	100%
S15	Reducing proteinuria is a key therapeutic goal in managing patients with C3G and primary IC-MPGN	94%
S16	Proteinuria can be explained by a range of pathological features due to active, reversible glomerular lesions and chronic, irreversible changes	94%
S17	Proteinuria is a clinically meaningful endpoint and a useful indicator of disease progression, including kidney failure	94%
S18	There is strong evidence showing that proteinuria reduction is a clinically meaningful endpoint in many glomerular diseases	92%
S19	There is currently evidence from real world data supporting proteinuria as a surrogate marker for long-term kidney outcomes in patients with C3G and primary IC-MPGN	88%
S20	A minimum reduction of 30% in proteinuria over 6 months would be considered a clinically meaningful effect of treatment	72%
S21	A minimum reduction of 50% in proteinuria over 6 months would be considered a clinically meaningful effect of treatment	94%
S22	A minimum reduction of 50% in proteinuria over 12 months would be considered a clinically meaningful effect of treatment	84%
S23	Reduction in proteinuria, associated with stable/improved eGFR following treatment, indicates a clinically meaningful benefit	94%
S24	When reduction in proteinuria is achieved through the resolution of C3 deposits on kidney biopsy, it is an indication of a disease-transformative effect and, over time, will result in improved kidney survival compared to proteinuria reduction caused by hemodynamic changes	90%
S25	Reduction in proteinuria helps to preserve long-term kidney function and as a result is a goal of treatment	96%
S26	Longitudinal measures of proteinuria, along with other relevant endpoints (e.g. eGFR), can be used to guide treatment decisions	100%
S27	Reduction in proteinuria to <1g per day helps to preserve long-term kidney function, which is the long-term goal of treatment	82%
S28	Reduction in proteinuria to 0.5-1g per day helps to preserve long-term kidney function, which is the long-term goal of treatment	82%
S29	Reduction in proteinuria to <0.75g per day helps to preserve long-term kidney function, which is the long-term goal of treatment for patients who do not have chronic kidney damage	86%
S30	Reduction in proteinuria to <0.5g per day helps to preserve long-term kidney function, which is the long-term goal of treatment for patients who do not have chronic kidney damage	86%
S31	The absolute value of proteinuria must be taken into account when assessing the response to treatment	88%

CONCLUSIONS

Four expert-informed recommendations aimed at clearly defining clinically meaningful endpoints for evaluating treatment efficacy in patients with C3G and primary IC-MPGN were developed:

1. **Reduction in proteinuria helps to preserve long-term kidney function and as a result is a goal of treatment**
2. **Longitudinal measures of proteinuria, along with other relevant endpoints (e.g. eGFR, glomerular C3), can be used to guide treatment decisions**
3. **A minimum reduction in proteinuria of 50% over six months would be considered a meaningful effect of treatment**
4. **Reduction in proteinuria to <1 g per day helps to preserve long-term kidney function, which is the long-term goal of treatment**

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