Mapping The Path Across Glomerular Disease Barriers: Advancements in Personalised Therapies

What have recent advances in personalised therapies meant for the treatment of glomerular diseases, and how could these advances impact patient diagnosis?

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Glomerular diseases are a group of conditions that affect the glomeruli: the blood vessels in the kidneys that filter waste from the blood. Despite advancements in the diagnosis and treatment of glomerular diseases, they have remained challenging to manage given their complexity and rarity.

Historically, diagnostics have most often relied on a kidney biopsy, as there have been few biomarkers that carry sufficient specificity and sensitivity to meet the necessary attributes related to disease identification and activity.

The challenges in the conduction of clinical trials involving glomerular disease are due to several common barriers, including the complex nature of glomerular disease, which has led to inflated costs associated with recruiting and conducting clinical trials, the challenges involved in the development and manufacturing of medications and the provision of maintenance care to patients with existing therapies that offer only suboptimal efficacy.[1]

Consequently, the significant upfront production costs associated with studying glomerular disease – combined with the unclear timelines to profitability for investors – have deterred many potential start-ups from showing interest in the field. This is further compounded by the challenging nature of treating glomerulopathies, which present with wide-ranging heterogeneous features and varying degrees of multiorgan involvement. As a result, consistent treatment response outcomes can be difficult to achieve, thus posing a significant challenge to enrolment of subjects and sites alike.

In recent years, the clinical development landscape has witnessed significant changes, particularly in the study of glomerular disease with notable paradigm shifts that are helping to navigate and allow more efficient and advanced developments in novel and targeted therapies.

Increased efforts to share data from observational studies in patients with glomerular disease have led to collaboratively built registries that have enhanced our background knowledge of specific disease nuanced processes as potential aetiological pathways.

Biomarker discovery and development is enriched in the setting of new and diversified technologies and, in turn, leads to more clinical applications and subsequent therapies.

Such advancements have marked a significant shift in the way we approach glomerular disease treatments for patients with an aim toward more precision – to ultimately be based on their individual biology.

The Clinical Development Landscape

Improved access to appropriate medical care across the world has led to increased general life expectancies and, given the concern of a healthcare care shortage with ageing populations, there is increased awareness of

the need for improved efforts in preventative medicine. The prevalence of age-related comorbidities such as chronic kidney disease (CKD), which can progress to end-stage kidney disease (ESKD), continues to grow.

Biomarkers are being researched to combat these processes through earlier detection and improved sensitivity and specificity compared to current and ubiquitous markers, such as serum creatinine. Large collaborative efforts with shared data from longitudinal studies across populations have led to rapidly expanding genomic registries, which have in turn led to a much greater understanding of and practical application for diagnostic and therapeutic opportunities in population subgroups.

Biomarkers and targeted therapy within the backdrop of precision medicine are being increasingly emphasised to address the challenges associated with glomerular diseases. The continued identification of newer biomarkers as well as the improved understanding of existing ones with predictive and diagnostic attributes are key to enabling early intervention and personalised treatment plans. This has also led to the discovery of newer drug targets, paving the way for the development of novel therapies that specifically address the underlying pathophysiology of glomerular diseases. The NIH-sponsored Kidney Precision Medicine Project (KPMP) aims to redefine CKD and acute kidney injury (AKI) by integrating deep molecular phenotyping, biopsies and novel methods of molecular analysis (multiomics) in the hope of discovering specific drug targets. Consequently, it is thought that these discoveries will evolve the current classification of glomerulonephritis (GN), and likely eliminate the primary vs secondary dichotomy that is currently utilised.[2]

New approaches to study design, such as platform trials, have emerged to keep up with the latest developments in the field.

Platform trials allow for multiple interventions to be run simultaneously, with adaptive endpoints that can change over time based on emerging data. Patients are grouped based on their biomarkers, and treatments can be tailored to individual patients based on their needs.[3] CureGN, NEPTUNE and TRIDENT are examples of large platform studies in glomerular disease.

CureGN helps researchers understand glomerular diseases by enrolling patients and collecting data on disease characteristics and outcomes. NEPTUNE looks for biomarkers that can predict outcomes in patients with glomerular disease, while TRIDENT compares different treatments for IgA nephropathy in one trial. Platform trials can speed up drug development and enable the creation of more targeted therapies that address the specific cellular process pathways involved in glomerular disease, advancing precision medicine approaches efficiently.[4]

Operational Strategies for Glomerular Disease Studies

The incidence rates of primary GN range between 0.2-2.5 per 100,000 patients per year, which includes IgA nephropathy with an incidence of at least 0.25 per 100,000 patients per year in adults, making such conditions rare disorders according to the US Orphan Drug Act and EURORDIS-Rare Diseases Europe.[5] Long-term treatment and follow-up are required for the natural course of glomerular disease.

Barriers to recruitment include challenges related to trial design, patients' lack of awareness about clinical trials, burden due to the time and cost of travel to protocol appointments, interventions and the risk of side effects or mistrust of medical research. Slow recruitment results in extended study timelines, leading to increased resource use and costs. Realistic enrolment projections and adequately permissive eligibility criteria maintaining scientific validity play a significant role in ensuring timely enrolment. Prescreening is a time- and cost-effective method to accelerate patient recruitment by reviewing potential participants from site databases during study start-up.

As such, electronic healthcare records may be used to facilitate more efficient trial recruitment. For example, the European Rare Kidney Disease Reference Network (ERKNet) consolidates data from 45 paediatric and 12 specialised adult nephrology units from 21 countries and established the European Rare Kidney Disease Registry (ERKReg), a web-based registry for all patients with rare kidney diseases. In the UK, over 20,000 people are registered on the Renal Association's National Register of Rare Kidney Diseases (RADAR). The Glomerular Disease Study and Trial Consortium initiative created a multisite interconnected registry and biorepository platform for all forms of glomerular disorders allowing integrated clinical data collections. The registry data can further serve as a reference population for further collaborative research initiatives and provides the additional capacity to enrol patients for clinical trials.

Non-compliance with study treatments and assessments can lead to an underestimation of the treatment effects, and poor participant retention representative of a high drop-out rate may diminish the statistical power of the study. Similarly, incomplete outcome assessments during the follow-up period may potentially introduce bias – as such, whenever possible, all participants should continue to attend study visits even if the study treatment is discontinued or the study defined outcome is reached.

Strategies that may further minimise study burden and improve overall study compliance include the use of online platforms for trial-related tasks (eg, ICF, questionnaires) and remote visits as an alternative to in-person site

visits will give added flexibility for study participants so as not to disrupt work, family and social activities.

Measuring Safety, Efficacy and Evaluating Patient Outcomes

One of the key challenges in the evaluation of outcomes for treatments of glomerular disease is related to the natural course of the disease.

A sustained percentage decline in the glomerular filtration rate (GFR) as predictive of progression to kidney failure has been accepted as a surrogate endpoint for progression to ESKD by the International Society of Nephrology's International Consensus Meeting.[6] A sustained percent decline in GFR is defined as a relative decline from baseline in GFR of 40% or other thresholds (30%, 50% and 57%), depending on particular parameters.

However, extended large clinical trials are required to demonstrate any treatment effects if such endpoints are used. These significantly add to the challenge of utilising such parameters, as they are highly dependent on a number of attributes – including the disease being studied, comorbid illnesses and the mechanism of action of the study drug. A primary endpoint should be a slowing of kidney function loss, as measured by stabilisation or improvement in GFR or the slope of eGFR over a meaningful duration.

Podocytes are specialised cells found in the kidney's glomerulus that act as filtration barriers, but when injured lose their structural integrity, causing increased permeability of the glomerular barrier and protein to leak into the urine – both of which are hallmarks of glomerular disease and conditions like nephrotic syndrome – with the proteinuria continuing to further the cycle of injury. The degree of proteinuria in glomerular disease is commonly thought to be closely related to the progression of CKD, and its reduction is associated with improved outcomes. Change in proteinuria has been accepted as a surrogate endpoint to assess the effectiveness of therapies to slow the progression of CKD. The Kidney Health Initiative (KHI) IgAN workgroup has concluded that proteinuria reduction is a reasonable surrogate for a drug's effect on progression to ESKD and that it could be used as a basis for accelerated approval of new IgAN therapies.[7]

Studies are ongoing regarding the process of podocyte injury and novel uses of known therapies in ameliorating proteinuria. The ultrastructure of this barrier has become an important focus in the treatment of diseases affecting the kidney. Abatacept, a therapeutic agent utilised in the treatment of rheumatoid arthritis, has seen applications in reducing proteinuria in cases of treatment-resistant nephrotic syndrome. This treatment strategy relies on CTLA4-Ig, a natural ligand to CD80 expressed on injured podocytes, to reduce proteinuria and so similar research in this area may serve as a vital tool to expand treatment options for patients with kidney disorders.[8]

The immune complement cascade response and genetic susceptibility are currently the subjects of significant research as is the case in IgA nephropathy (IgAN). Studies have shown that Factor H, which is linked to the alternative complement pathway and present in mesangial immune deposits in European populations, can be activated by IgA1, leading to a faster progression of IgAN.

On the other hand, certain deletions in the factor H-related protein family (CFHR), such as CFHR1 and CFHR3 have been associated with a lower risk of IgAN progression.[9]

While the established standard of care treatment for IgAN has been renin-angiotensin-aldosterone system (RAAS) blockade (ie, RAAS inhibitors), recent trials have targeted a variety of pathways with subtle dysregulations in immune responses. Researchers in this field believe that IgAN is no longer a single disease, but rather a similar phenotypical endpoint.[10]

These findings demonstrate the importance of continuing research efforts in seeking to better understand IgAN and several other diverse diseases that can lead to discovering other links between genetics and inflammation. Most recently, a study suggested that further supports the fact that patients of African ancestry with kidney disease and proteinuria have a higher prevalence of APOL1 gene variants, which provide innate immunity against trypanosome infections but increase the risk for rapidly progressive proteinuric kidney disease.[10] In this study, patients with two APOL1 variants were treated with Inaxaplin, an APOL1 channel inhibitor, reducing urinary protein levels and demonstrating the potential for treating such genetic-mediated disease pathways.[11]

Key endpoints in renal disease trials are designed to detect treatment effects on disease progression and/or irreversible loss of kidney function; they may be confounded by other effects including background therapy affecting proteinuria and GFR.

Therefore, it is crucial to eliminate the impact of acute changes in eGFR and proteinuria that are likely to reflect haemodynamic rather than structural changes, and the persistence of any change in these endpoints must be confirmed after a washout or a stable treatment period appropriate to the agent's pharmacokinetic and pharmacodynamic profile.

As such, important collaborations gleaned from meetings such as the KDIGO Controversies Conference on Glomerular Diseases and programmes such as KPMP, which review disease pathogenesis, biomarkers and treatments to identify new therapeutic targets, serve to continually keep discussions on these important topics updated and recent.

Recent literature provides an overview of biomarkers that used together in specific contexts would aid early detection, monitoring progression, predicting treatment response and identifying patients at risk of adverse outcomes.[12] It categorises these biomarkers into five groups: renal function, inflammation, fibrosis, oxidative stress and kidney injury. Biomarkers for renal function included serum creatinine, blood urea nitrogen and estimated glomerular filtration rate (eGFR). Biomarkers for inflammation include C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha). Biomarkers for fibrosis include transforming growth factor-beta (TGF-beta) and matrix metalloproteinases (MMPs), while biomarkers for oxidative stress include reactive oxygen species (ROS) and malondialdehyde (MDA). Last, biomarkers for kidney injury include kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid-binding protein (L-FABP). Using these biomarkers could improve study efficiency and outcomes in the future, but further research is needed to optimise their clinical utility.

Furthermore, a combination of damage and functional biomarkers being used to improve early diagnostic accuracy and stratify high-risk groups for AKI, as relying solely on the rise of serum creatinine to detect AKI fails to identify early injuries and classify different AKI phenotypes.[13] Instead, combining biomarkers of tissue damage and kidney function with clinical information could lead to improved precision in predicting temporal and pathophysiologic characteristics of injury. They also highlight the recent validation of novel biomarkers for risk prediction and early diagnosis of AKI, like urinary tissue inhibitor, which offers prognostic information irrespective of renal function decline. These findings have important implications for the process of care and management of AKI, emphasising the need to incorporate multiple biomarkers when diagnosing AKI.

The FIDELIO study was conducted to investigate the efficacy of finerenone in slowing down the progression of fibrosis in patients with type 2 diabetes and chronic kidney disease accompanied by albuminuria. The study demonstrated that by targeting the mineralocorticoid receptor with Finerenone, renal fibrosis could be prevented or slowed down in diabetic nephropathy. The use of biomarkers played a crucial role in this study, where proteinuria biomarkers and mineralocorticoid receptor targeting resulted in a decrease in myofibroblast and collagen deposition. Additionally, renal inflammatory markers, such as PAI-1 and NKD2, were reduced as well.

A five-compartment model to understand the complex mechanisms involved in the development and progression of diabetic kidney disease (DKD), focusing specifically on inflammation as a key driver of disease has been suggested, including various biomarkers that have been studied in DKD, including markers of inflammation (such as TNF-α and IL-6), fibrosis (such as TGF-β and collagen) and oxidative stress (such as MDA and 8-OHdG).[14] They highlight inflammation as a crucial driving force in the pathogenesis of DKD and propose that targeting inflammation may offer promising results in treating this condition.

Equally important in personalised therapy trials is an emphasis on incorporating patient-reported outcomes (PRO), which are self-reported measurements that factor in improvements related to the quality of life (QOL) as a quantitative endpoint metric. For example, the FDA and NIH published Biomarkers, Endpoints, and Other Tools (BEST)

in 2016, which specifies several validated PRO instruments as markers for disease-specific outcomes in glomerular disease such as focal-segmental glomerulosclerosis (FSGS) PRO and ANCA-associated vasculitis (AAV) PRO. These tools give patients a major voice in clinical trials and assign greater importance to their experiences and perspective of improvement within their unique disease toward drug development and regulations.[15]

Conclusion

Glomerular diseases are complex and heterogeneous, which historically has limited the potential for cost and outcome-effective novel treatment strategies. However, recent advances have been able to provide the potential solutions needed to reduce healthcare costs, achieve more consistent treatment outcomes and ultimately improve the quality of life for those affected by ailment processes that were previously thought of as non-treatable. In summary, we are still very early in the number of exciting discoveries that have yet to yield themselves. However, the use of precision medicine and biomarkers as we currently know them, has created a template for mapping a course through what were previously thought to be obstacles. We can therefore continue to navigate the clinical development landscape of glomerular disease, allowing for faster and more accurate diagnoses, personalised treatment plans and improved overall patient outcomes.

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