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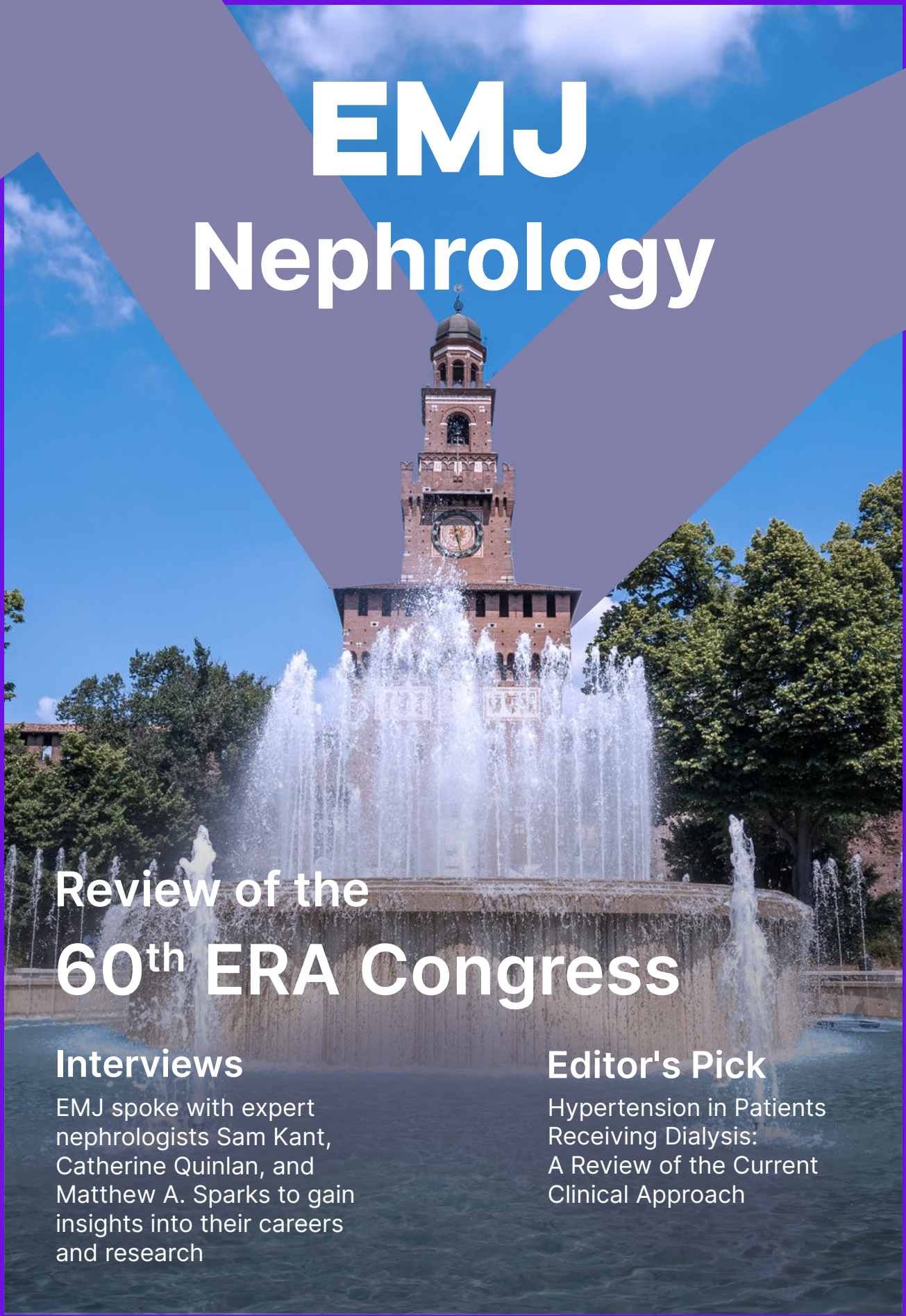

Review of the 60th ERA Congress

Interviews

EMJ spoke with expert nephrologists Sam Kant, Catherine Quinlan, and Matthew A. Sparks to gain insights into their careers and research

Editor's Pick

Hypertension in Patients Receiving Dialysis: A Review of the Current Clinical Approach

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

I am delighted to welcome you to the 2023 issue of *EMJ Nephrology*, covering highlights from the 60th European Renal Association (ERA) Congress, which this year took place in Milan, Italy. Among this year's highlights was a fascinating plenary lecture given by Adeera Levin, University of British Columbia, Vancouver, Canada, who discussed kidney health in the context of sex and gender.

In this issue we bring you the key highlights from the congress, including an insightful feature discussing current challenges in kidney donor selection. We have also handpicked some of the presented abstracts to provide an overview of the research trends from the congress, which included topics such as IgA nephropathy, underdiagnosis of acute kidney injury, and prediction of renal outcomes, to name a few.

We are proud to be featuring interviews with three experts who discuss renal transplant medicine, immunosuppression, hypertension, and kidney disease, among other topics. Among our featured articles you will find our Editor's pick, a review on hypertension in patients receiving dialysis, and an interesting study examining a potential correlation between haemodialysis tip and line placement, line length, and demographics, and repeatedly poor function due to fibrin sheath formation.

With the plethora of themes in nephrology, the topics covered in this issue span the whole range of the discipline and there is something for everyone here. I would like to close by thanking our Editorial Board, peer reviewers, contributors, and interviewees who have helped bring this great issue to fruition. I hope you enjoy reading it.

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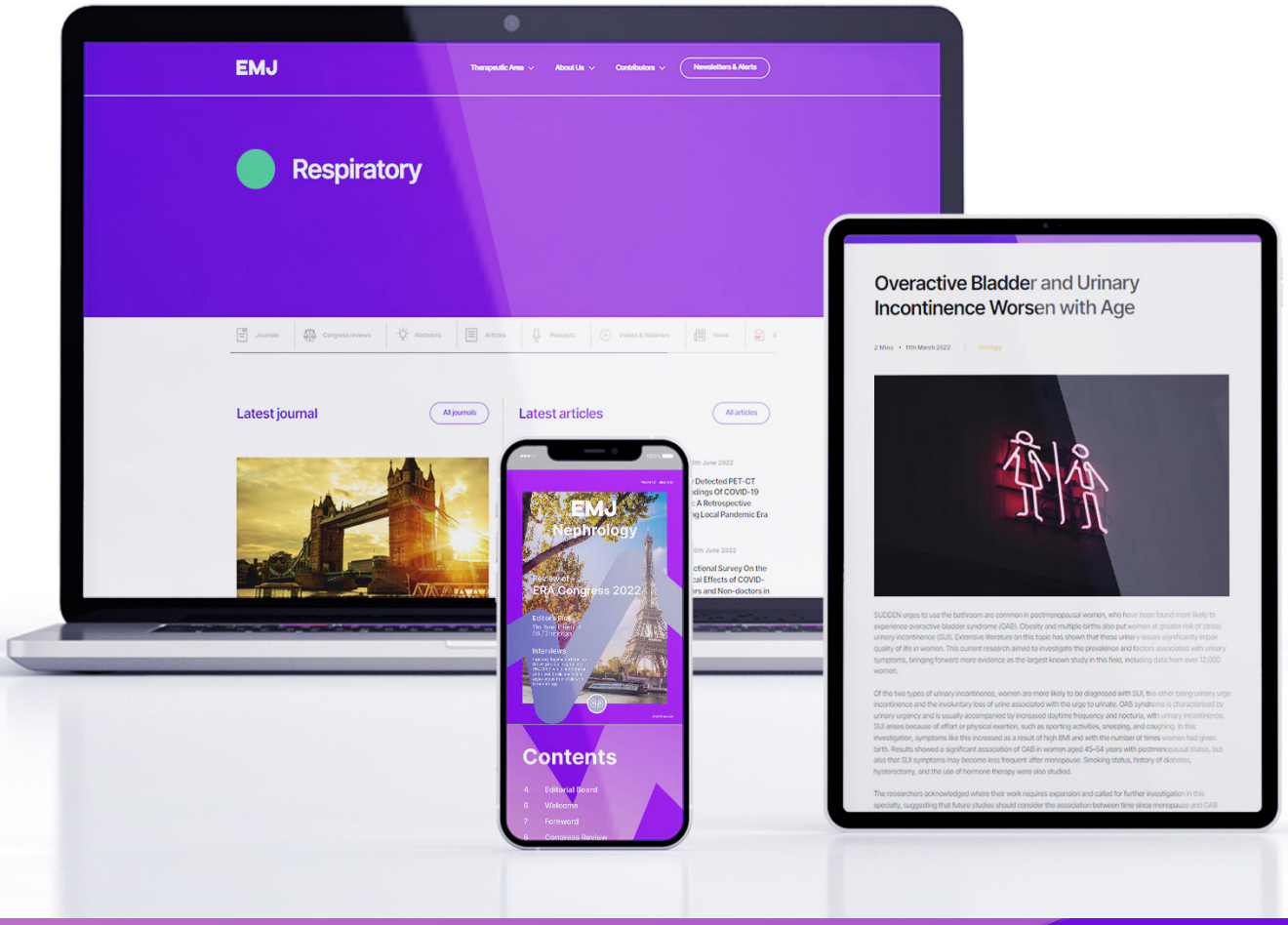

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Foreword

Dear Readers,

I am proud to welcome you to the latest issue of *EMJ Nephrology*. Here, you will find a selection of peer-reviewed articles, alongside a comprehensive review of the 60th European Renal Association (ERA) Congress 2023, which took place in person in Milan, Italy, between the 15th–18th June. The themes for this year's Congress were research and education, governance, and equality.

The Editor's Pick for this issue is a topical review article entitled 'Hypertension in Patients Receiving Dialysis: A Review of the Current Clinical Approach'. Given the complexity of the management and the impact of hypertension on morbidity and mortality in this patient cohort, a comprehensive understanding to optimise diagnosis and treatment is crucial to improving patient outcomes. This detailed review by Rowan et al. explores the up-to-date evidence surrounding diagnosing and managing hypertension in patients receiving dialysis.

Other featured articles include a review of the role of complement in glomerular diseases and the recent advances in targeting this pathway. Research characterising humoral and cellular immunity to severe acute respiratory syndrome coronavirus 2 in patients on maintenance dialysis following vaccination in a Portuguese cohort is also included.

You can also find engaging interviews with several experts in the field, covering topics that range from renal transplant and onconephrology to medical education.

For those who were unable to attend, our review of the ERA 2023 Congress includes coverage of late-breaking news on the CONVINCE trial, CONCORD study, Factor XIa inhibition in haemodialysis, and the impact of exercise during haemodialysis presented during the late-breaking clinical trials session, as well as research abstract highlights and topical features from key Congress sessions.

I would like to thank all of those who have contributed to the successful creation of this edition of *EMJ Nephrology*, including the Editorial Board, authors, and peer reviewers. Finally, I would like to thank you for your continued support. I hope that you enjoy this issue, and find it to be a valuable resource in your daily practice.

Angela Yee-Moon Wang
Editor-in-Chief, *EMJ Nephrology*

ERA 2023

Review of the 60th European Renal Association (ERA) Congress

Location:	Milan, Italy
Date:	15th–18th June 2023
Citation:	EMJ Nephrol. 2023;11[1]:10-16. DOI/10.33590/emjnephrol/10304934. https://doi.org/10.33590/emjnephrol/10304934.

CELEBRATING 60 years of congresses, the European Renal Association (ERA) held their 2023 congress in Milan, Italy, and virtually. Primarily known for its fashion show, Milan has also welcomed medical innovations, such as rifampicin, an antibiotic drug that has been used to treat tuberculosis, and witnessed the first procedure using haematopoietic stem cells as vectors for gene therapy in hereditary diseases.

In their joint pre-congress statement, ERA President, Christoph Wanner, and ERA Local President, Piergiorgio Messa, acknowledged the difficulties caused by the COVID-19 lockdown, which prevented ERA from holding the 2020 congress in Milan. "Now, after 3 years, we are very happy to be able to welcome all of you face-to-face in Milan," they stated.

In the opening ceremony, Messa hoped that attendees would enjoy the congress, as well as the various Milanese attractions, both new and old. Messa was then followed onto the stage by Ronald Gansevoort, Paper Selection Committee Chair, who reminded attendees that the ERA Congress is international, with more than 2,196 submitted abstracts from 86 countries.

This year's programme had been streamlined. Instead of the many categories and sub-categories that made up previous congress, this one consisted of seven main topic areas: dialysis; acute kidney disease and critical care nephrology; physiology, cell biology, and genetic diseases; chronic kidney disease; glomerular and tubule-interstitial diseases; kidney transplantation; and hypertension and diabetes. Gansevoort also noted that chronic kidney disease was the most popular topic, with 562 abstracts submitted.

Gansevoort went on to detail the new format of the focused oral sessions, where authors of the selected abstracts were to present their results orally, with a single slide and no paper poster. The presentations were presented in dedicated halls, and took a total of 4 minutes; 3 minutes for the presentation and 1 minute for questions. This change was due to the fact that the large halls would typically be empty of attendees, and oral presentations only would benefit the presenters.

Scientific Committee Chair, Francesca Mallamaci, noted the importance of including high profile female nephrologists in the Scientific Community. The current Scientific Committee has a good male–female balance, and every effort was made to include nephrologists from every European country, as well as non-European countries, with interests in different fields of nephrology.

"Gansevoort went on to detail the new format of the focused oral sessions."

This year's congress had three major themes: research, with a specific mission for education; governance; and equality, with each individual or group of people being given the same resources or opportunities.

A number of awards were presented this year, including the ERA Awards for Young Investigators, which are open to all ERA members aged 40 years and younger. These awards have been named after three well-known masters of nephrology. The Rosanna Gusmano Award is for young investigators in basic science; the Stanley Shaldon Award is for young investigators in translational science; and the Eberhard Ritz Award is for young investigators in clinical science.

The winners of the 2023 ERA Awards for Young Instigators included: Christoph Kuppe, Department of Nephrology, North Rhine-Westphalia Technical (RWTH) University of Aachen, Germany; Olivier Aubert, Department of Kidney Transplantation, Necker Hospital, Paris, France; Edouard Fu, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; and Stefanie Steiger, Division of Nephrology, Ludwig Maximilian University (LMU) Hospital of Munich, Germany.

"Now, after 3 years, we are very happy to be able to welcome all of you face-to-face in Milan."

Vladimir Tesar, Department of Nephrology, 1st Faculty of Medicine, Charles University of Prague, Czechia, was also awarded the ERA Award for Outstanding clinical contributions to the field, while Tobias B. Huber, Department of Medicine, University Medical Center Hamburg-Eppendorf, Germany, was given this award for their contributions to basic science in nephrology.

Next year's congress will be held in Stockholm, Sweden, between 23rd May–26th May. Until then, please enjoy highlights of the reviews presented at this year's congress.

Haemodiafiltration Reduces Mortality Risk Compared with Conventional Haemodialysis?

INSIGHTFUL findings from the prospective, multicentre, randomised controlled trial, CONVINCE, were presented during a late-breaking clinical trial session that took place at the ERA Congress 2023, in Milan, Italy, on Friday 16th June.

Building on evidence suggestive that haemodiafiltration (HDF) confers a survival advantage in patients with end-stage kidney disease compared to conventional haemodialysis (HD) at ≥23 L/session convection volumes, researchers looked to clarify this further.

Lead study investigator, Peter Blankestijn, Department of Nephrology and Hypertension, University Medical Center Utrecht, the Netherlands, reported the main outcomes from the CONVINCE trial. The trial aimed to identify whether HDF delivered consistently at high-dose confers mortality benefit when compared with high-flux conventional HD.

The trial included a total of 1,360 patients from 61 different centres in eight European countries. Patients were included if they were deemed likely to achieve 23 L convection volumes and could complete patient-reported outcome assessments. Baseline characteristics were similar across both groups, and median follow-up time was 30 months.

Rates of all-cause mortality were higher in those treated with high-flux HD (n=677) than those treated with high-dose HDF (n=683), at 21.9% and 17.3%, respectively. The hazard ratio for this was 0.77 (95% confidence interval: 0.65–0.93), which Blankestijn reported was highly statistically significant. Blankestijn further explained that although safety was not a specifically defined endpoint, no safety concerns were raised during the trial.

Blankestijn discussed conclusions from the study, highlighting that the findings show high-dose HDF (≥23 L convection volume per session) in post-dilution mode can be delivered over prolonged time periods, and confers a reduced risk of death when compared with standard high-flux HD.

In terms of limitations, patient selection limited generalisability as only those patients likely to achieve ≥23 L/session convection volume, and able to complete patient-reported outcome assessments, were included.

Blankestijn highlighted: "The CONVINCE study is a potential first step in identifying a new standard of care in chronic kidney disease. The advance of haemodiafiltration technology could change the way we treat specific patients living with chronic kidney disease." Looking towards the future, the team are looking to undertake a comprehensive analysis of the >10,000 sets of questionnaires to evaluate patient-reported outcomes, and hope to have the results later this year. ●

"The CONVINCE study is a potential first step in identifying a new standard of care in chronic kidney disease."

Exercise During Haemodialysis Improves Physical Function

Exercise may significantly improve physical function in patients with kidney failure on haemodialysis, compared with usual care, according to a study presented at the ERA Congress 2023. This group of patients are at risk of progressive physical deconditioning and multi-morbidity, which represents a high health economic burden. New data shows that this progressive cycle may be prevented through exercise intervention.

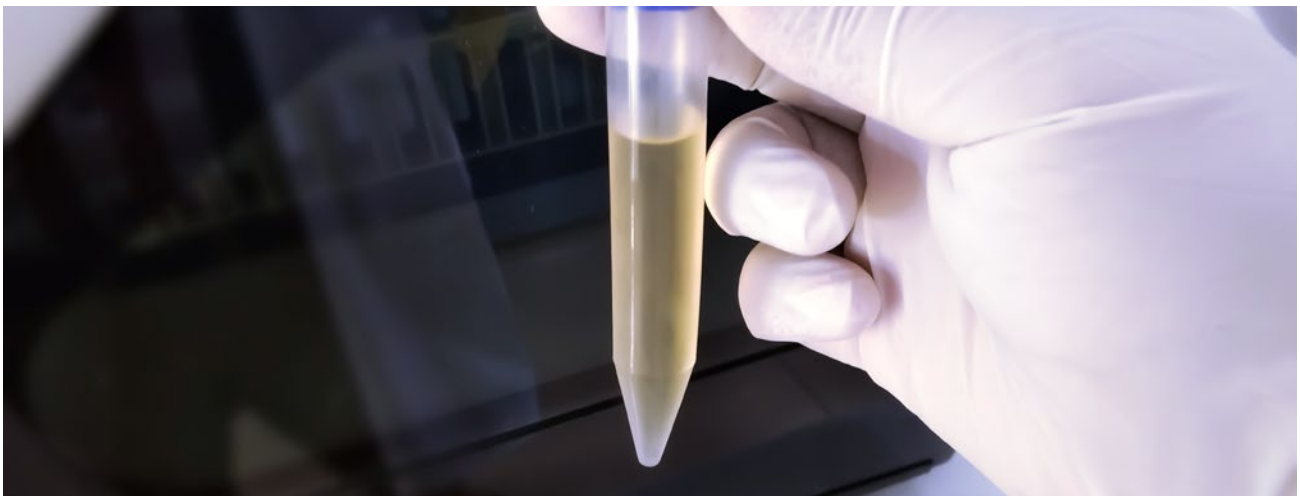
The multicentre, cluster randomised, controlled interventional trial assessed whether combined endurance and resistance training during haemodialysis led to improvements in physical function compared to usual care. Change in 60 second sit-to-stand test (STS60) between baseline and 12 months was the primary outcome. In total, 917 patients from 21 ambulatory dialysis centres were included in the study.

The team noted an improvement in STS60 repetitions from 16.2±7.6 to 19.2±9.1 in the exercise group, while the usual care group declined from 16.2±7.1 to 14.7±7.9 (95% confidence interval [CI]: 2.22–5.48; p<0.0001). Furthermore, the distance walked in 6 minutes (+37.5 m; 95% CI: 14.7–60.4; p=0.0013), as well as the timed up and go test (-1.1 s; 95% CI: -1.9–-0.3; p=0.0078) improved in the exercise group. Data further showed that those in the exercise group spent a median of 2 days in hospital annually, compared with 5 days in the usual care group. The vitality subscale and physical summary score were also found to improve in the exercise group; however, other subscales on the 36-item Short Form Survey (SF-36) quality of life instrument did not change.

The team concluded that physical function was significantly improved with 12 months of exercise in patients with kidney failure on haemodialysis, compared to usual care. ●

"Those in the exercise group spent a median of 2 days in hospital annually, compared with 5 days in the usual care group."

Reducing Urinary Albumin–Creatinine Ratio in Chronic Kidney Disease: A New Approach?



RESULTS from CONCORD, a multicentre, randomised, double-blind, placebo-controlled Phase II study were presented by Ronald Gansevoort, Division of Nephrology, University Medical Center, Groningen, the Netherlands, at the ERA Congress 2023, on Friday 16th June, in Milan, Italy.

The trial enrolled a total of 170 patients, and investigated the safety and efficacy of a soluble guanylate cyclase activator, runcaciguat. Soluble guanylate cyclase activators are a novel class of therapeutics that help dilate renal blood vessels, and therefore have the potential to enhance renal blood flow and slow chronic kidney disease (CKD) progression.

The inclusion criteria were: aged ≥45 years; had a diagnosis of chronic kidney disease with an estimated glomerular filtration rate of 25–60 mL/min/1.73m^2; a urine albumin–creatinine ratio (UACR) of 30–3,000 mg/g; established atherosclerotic cardiovascular and/heart failure (New York Heart Association Class I–II); stable antihypertensive treatment with maximum tolerated angiotensin-converting enzyme inhibitor /angiotensin II receptor antagonist treatment; and any of the following: ≥2-year history of Type 2 diabetes (T2D; ±stable dose of sodium-glucose co-transporter-2 inhibitor [SGLT2i] ≥3 months), and/or hypertension receiving medication for ≥5 years.

Patients were categorised into three strata: patients with CKD and T2D not treated with SGLT2i; patients with CKD and T2D treated with SGLT2i for ≥3 months; and patients with CKD without T2D. Reduction in UACR from baseline to the average of Days 22, 29, and 57, was the primary efficacy endpoint, according to a per-protocol analysis for Phase II trials.

In each stratum, patients were randomised on a 3:1 basis to receive either once daily runcaciguat or placebo. Following this, doses were up-titrated weekly over a 4-week period from 30 mg to 120 mg. In the subsequent maintenance phase, patients received the maximum tolerated dose for ≥4 weeks. This was followed by a safety follow-up period of 30 days.

The researchers found that patients with CKD who were on maximum tolerated dose of angiotensin-converting enzyme inhibitor/ angiotensin II receptor antagonist displayed significantly reduced UACR, irrespective of concomitant SGLT2i use, and that runcaciguat was well tolerated. ●

"Reduction in UACR from baseline to the average of Days 22, 29, and 57, was the primary efficacy endpoint."

Novel Disease-Modifying Treatment for IgA Nephropathy

A POTENTIAL disease-modifying treatment for patients with IgA nephropathy was explored in a presentation delivered by Richard Lafayette, Stanford University, California, USA, during a late-breaking clinical trial session at the ERA Congress 2023, on 17th June.

Lafayette presented results from the ORIGIN study, a Phase IIb, randomised, double-blind, placebo-controlled trial that sought to investigate the safety and efficacy of atacicept, a dual anti-BLyS/APRIL fusion protein.

A total of 116 patients with biopsy-proven IgA nephropathy; either a 24 hour urine protein of >0.75 g/day or a urine protein-creatinine ration of >0.75 g/g; an estimated glomerular filtration rate of ≥30 mL/min/1.73m^2; and optimised blockade of the renin-angiotensin system, were recruited to the trial. The trial involved randomisation to a 36-week course of subcutaneous self-administered atacicept (n=82) or placebo (n=34). Although three different doses of atacicept were evaluated for safety and efficacy, the presentation focused on the 150 mg atacicept dose option.

The primary and secondary efficacy endpoints of the study were 24-week and 36-week proteinuria, respectively. Lafayette explained that the study met both of these endpoints, with atacicept displaying reductions in proteinuria that were statistically and clinically significant.

Upon safety evaluation, a favourable safety profile was noted. Throughout the 36 weeks, there was a low rate of serious adverse events (2%), no increase in rated of infections compared to placebo, and no discontinuation or interruption of drug delivery due to hypogammaglobulinaemia.

Following on from the results of this Phase IIb study, the safety and efficacy of weekly atacicept 150 mg subcutaneous injection is now being investigated in a pivotal Phase III study. ●

"The primary and secondary efficacy endpoints of the study were 24-week and 36-week proteinuria, respectively."

Anticoagulation Using Factor XIa Inhibition in Patients Receiving Haemodialysis

CLINICAL trial results investigating the efficacy, safety, and optimal dose of osocimab, a factor XIa inhibitor, in patients with end-stage kidney disease (ESKD) on haemodialysis, were presented by Wolfgang Winkelmayer, Baylor College of Medicine, Houston, Texas, USA, during a late-breaking clinical trial session at the 60th ERA Congress on 16th June 2023.

Thromboembolic risk is greater in patients with ESKD on haemodialysis; however, there is currently a lack of safe and effective anticoagulants for these patients. Winkelmayer discussed CONVERT, a Phase IIb, double-blind, placebo-controlled, randomised trial which, after initial enrolment and application of exclusion criteria, involved 704 patients with ESKD receiving haemodialysis three times per week for ≥9 hours per week.

> **"Osocimab yielded rapid, dose-dependent, and sustained inhibition of factor XIa."**

The trial included three arms: lower-dose subcutaneous osocimab (loading dose of 105 mg followed by monthly doses of 52.5 mg; n=235); higher-dose subcutaneous osocimab (loading dose of 210 mg followed by monthly doses of 105 mg; n=234); or placebo (n=235). Patients were randomised on a 1:1:1 basis, and received treatment for up to 18 months.

Clinically relevant bleeding, a composite of major and clinically relevant non-major bleeding, was the primary trial outcome. Other outcomes evaluated were the extent of factor XIa inhibition; incidence of major adverse vascular events (composite of symptomatic venous thromboembolism, acute limb ischaemia, major limb amputation, non-fatal myocardial infarction or stroke, and vascular death); and extent of dialysis circuit clotting.

The researchers found that osocimab yielded rapid, dose-dependent, and sustained inhibition of factor XIa. In the lower-dose osocimab group, 16/232 (6.9%) experienced clinically relevant bleeding, compared with 11 out of 224 (4.9%) in the higher-dose osocimab group, and 18 out of 230 (7.8%) in the placebo group. The relative risk for moderate to complete dialysis circuit clotting at ≥1 visit was found to be significantly lower with osocimab than placebo and major adverse event rates were 3.0% in the placebo group, 2.7% in the higher-dose osocimab group, and 1.3% in the lower-dose osocimab group. For the future, further trials will be needed to determine if this novel therapeutic reduces thromboembolic risk in this patient cohort. ●

Deceased Donor Transplantation: Patient Selection, Ethics, and New Approaches

Authors: Darcy Richards, EMJ, London, UK

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RENAL transplantation was a hot topic at the 60th European Renal Association (ERA) Congress 2023, which took place both virtually and in-person in Milan, Italy, between 15th–18th June. One such session saw experts in transplant medicine, surgery, and transplant ethics deliver presentations on deceased donor kidney transplantation. Co-chaired by Marta Crespo, Hospital del Mar, Barcelona, Spain, and Christophe Mariat, University Hospital Saint-Étienne, Saint-Priest-en-Jarez, France, this symposium delivered invaluable insights into donor selection, transplant ethics, and approaches to improve graft viability and implementation.

INTRODUCTION

One of the main challenges faced by those working in solid organ transplantation and those on the waiting list to receive a transplant is the discrepancy between the number of donor organs needed and the number of organs available. Increasing the number of available donor organs is of key, and ongoing work is required to reduce donor organ discard rates, improve public confidence in organ donation, and enhance donor graft viability. This challenge will require multidisciplinary collaboration and ongoing clinical research.

DONOR AND RECIPIENT SELECTION

The transplantation process is complex, lengthy, and involves several stakeholders. Crespo poignantly stated: "The success of transplantation starts much before transplantation," highlighting that there are multiple factors that need to be considered and optimised even before the point of surgery is reached.

A key factor in this process is selecting the right donor for the right recipient. Piergiorgio Messa, Università degli Studi di Milano, Italy, eloquently discussed the challenges associated with donor-recipient matching. Whilst it is well-known that the best treatment for end-stage renal disease is renal transplantation, this is not always achievable. Messa commented: "The real problem, as we know, is that the number of patients on the waiting list is by far higher than the number of organs available each year." To highlight this point, Messa provided data from the USA, showing that approximately 80,000 patients with end-stage renal disease were registered on the renal transplant waiting list between 2010–2020, and <24,000 organs were available in that period. This 3:1 ratio of demand versus supply is similar in Europe.

Alongside this, poor utilisation of available organs is also a concern. Messa explained that data from the USA have stably shown that approximately 20% of the total number of kidneys recovered are not transplanted. Messa added that this is likely to be similar in Europe. Addressing this will be a key factor in closing the gap between the number organs needed and the number of organs available.

There is a need to balance equity and efficiency in renal transplant to ensure all patients have the same chance of receiving an organ, but also avoid organ misassignment or underutilisation.

This balance can be difficult to achieve in donor-recipient matching and organ allocation. For example, there are challenges around the projected recipient life expectancy and estimated donor organ longevity.

Another consideration for donor-recipient matching is donor quality. Historically, the expanded criteria donors and standard criteria donors have been used. However, Messa noted that this dichotomous system could risk an excess of discarded organs based on assumption of non-suitability. More recently, a continuous evaluation of both donor and recipient using the Kidney Donor Profile Index (KDPI) and estimated post-transplant survival score (EPTS) has been proposed. KDPI provides an estimate of how long a kidney is expected to function once transplanted, while EPTS estimates the length of time that a candidate is likely to benefit from a donor kidney. Both measures are scored on a scale of 0–100%, with lower scores indicating longer estimated transplant function and longevity of benefit, respectively. This provides a method to ensure that the donor organ goes to the ideal recipient.

However, this model is not without its limitations, as some components of the scores have greater weight than others, limiting the real predictive value of KDPI. Moreover, Messa discussed that the biggest limitation is that in real practice, users of the KDPI will have a threshold at which they judge a graft to be bad. Often, this threshold is a score of 85%, which can result in increased organ discard rates.

Messa stated that, presently, the main way to improve donor-recipient matching is to increase the number of organ donations. They discussed several ways in which this could be tackled, including increasing donation after cardiac death (DCD), living organ donation, reducing organ discard rates, and overcoming the opposition to organ donation.

"The number of patients on the waiting list is by far higher than the number of organs available each year."

IMPROVING GRAFT VIABILITY

In agreement with Messa, Gabriel Oniscu, CLINTEC, Karolinska Institutet, Stockholm, Sweden, also highlighted the increased demand, as well as demonstrable inequity, persistent wait list mortality, and poor utilisation of currently donated organs as key concerns for the transplant community.

Improving graft viability is a strategy to overcome the discrepancy in organ availability and patients on the waitlist. Oniscu explored several potential solutions for improving graft viability and implementation. One key strategy is the use of machine perfusion. Machine perfusion strategies can be employed at retrieval, preservation, or time of transplant, and can take place at normothermic, sub-normothermic, and hypothermic temperatures.

Messa discussed increasing DCD donors as a potential solution to increasing organ donations. Onsicu stated that there has already been an increase in DCD across Europe, and discussed that whilst outcomes have been good, warm and cold organ ischaemia remains a challenge. Onsicu further explained that to overcome this, circulation can be restored to the organ for some time before organ retrieval with an extracorporeal circuit, using normothermic regional perfusion to induce a scenario closer to that of donation after brainstem death. This scenario could enable a greater number of organs to be recovered from donors, contributing towards decreasing the gap between organs required and organs donated. To build on this further, Oniscu presented data from the UK which showed that graft failure halved, delayed graft function was lower, and there was a significant 1-year estimated glomerular filtration rate benefit in DCD with normothermic regional perfusion compared with DCD without normothermic regional perfusion. In this study, estimated glomerular filtration rate improved by 6.3 mL/min/1.73 m^2 at the end of the first year, translating to an additional 4 years of graft life free from dialysis. Other strategies discussed were donor hypothermia, which has been shown to be inferior to machine perfusion strategies, hypothermic oxygenated perfusion, and normothermic machine perfusion.

Oniscu further discussed the potential of sustainable organ perfusion services for donor organs, highlighting that implementation would be complex and require funding, education, and training. Additionally, they explored whether there could be role for developing purpose-built organ repair/reconditioning centres to help optimise utilisation of currently donated organs.

Oniscu also provided insight into potential future focuses, including functional and injury markers, functional MRI, near infrared spectroscopy, laser speckle imaging, anti-microRNA therapy, and nanoparticles for immunomodulation.

Although organ perfusion is now established in clinical practice, it remains unclear which strategy is best in different scenarios. Oniscu suggested that further work needs to be done to help unpick this, as there are benefits to each approach. Despite this, they concluded that rapid progress is being made towards understanding graft injury and identifying mitigating therapies.

ETHICAL CONSIDERATIONS

Not only does organ transplantation require meticulous consideration regarding donor-recipient matching and patient and organ optimisation, but considerable ethical input is also required. Mehmet Sukru Sever, İstanbul School of Medicine, Türkiye, explored donor, family, and allocation ethics, highlighting how these may conflict, and detailing the complexities of transplantation ethics.

Some of the key factors discussed were donation decision-making, the definition of death, and allocation criteria. Sever shared the definitions of circulatory death as when circulatory and respiratory functions have permanently ceased, and brain death as cessation of all functions of the entire brain. The latter is pivotal in legitimising organ removal from bodies in which circulatory and respiratory function is ongoing. There are three further sub-categories defining brain death: brainstem death, whole brain death, and higher brain death. Sever explained how these different definitions can cause public confusion, and discussed the need for uniformity in determining brain death globally.

The dead donor rule has been used deontologically to underline that the donor must be dead before organs are retrieved or that

retrieval should not cause death of the donor. Sever highlighted that whilst this helps maintain public trust, it can contradict autonomy, neglect utility, and misuse non-maleficence. They discussed how such academic controversies can have harmful impacts, such as a reduction in organ donation, and discussed how provision of simple, concise, and transparent information to the community would be more effective in preventing public misunderstandings.

As well as discussing the ethics and potential harms associated with directed and conditional donation, Sever also explored opt-in and opt-out strategies for organ donation. Sever spotlighted that Spain is the most successful country in terms of organ donation, and that whilst they adopt an opt-out strategy, they have reported that donation rates are not different to rates seen with an opt-in strategy.

Sever concluded by discussing the ethical considerations for organ allocation. They stated: "Developing ethically and legally approved organ allocation systems is a must," and explained that policies for reducing disparities should be balanced with utility, cost, and efficiency. Sever commented that "the optimal strategy for increasing organ donation should combine utilitarian considerations with deontological and ethical rules."

> **"Developing ethically and legally approved organ allocation systems is a must."**

CONCLUSION

Renal transplantation is complex and multifaceted. Improving donor-recipient matching, and reducing the discrepancy between donor organ supply and demand, remains a key challenge for those in the field. With ongoing research and new strategies and approaches, there is hope that this gap can be reduced in the future. ●

Contemporary Acute Kidney Injury Management

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ACUTE kidney injury (AKI) was discussed in a session chaired by Jolanta Malyszko, Medical University of Warsaw, Poland, and Danilo Fliser, Saarland University Medical Centre, Homburg, Germany, at the 60th European Renal Association (ERA) Congress, which took place in Milan, Italy, between 15th–18th June 2023. The moderators started by announcing that ERA has created a new working group on AKI.

ACUTE KIDNEY INJURY PREDICTION THROUGH BIOMARKERS AND CLINICAL MODELS

The first speaker, Greet De Vlieger, Katholieke Universiteit (KU) Leuven, Belgium, explained that AKI is a frequent complication that is often diagnosed late, and is associated with worse outcomes in the short- and long-term; therefore, its prediction is important, even though there is no curative treatment for it.

Subclinical AKI is more difficult to diagnose as there is no gold standard for its diagnosis; however, Kidney Disease Improving Global Outcomes (KDIGO) criteria can be used to diagnose AKI. This is indicated by an increase in serum creatinine or reduction of urinary output. However, the incidence of AKI can vary a lot within a single cohort based on how you apply these criteria.

Different types of biomarkers for AKI prediction include dysfunctional biomarkers, such as serum creatinine, and stress and damage biomarkers, which can be used in the subclinical phase of AKI. Stress biomarkers include tissue inhibitor of metalloproteinases, Dickkopf-3, whereas damage biomarkers that indicate injury to kidney cells include kidney injury molecule-1, IL-18, and neutrophil gelatinase-associated lipocalin.

In a large meta-analysis including over 38,000 patients, the most precise biomarker in predicting AKI was found to be neutrophil gelatinase-associated lipocalin in urine divided by creatinine in urine, whereas for severe AKI the most precise biomarker was tissue inhibitor metalloproteinases-2 x insulin-like growth factor-binding protein 7. A secondary analysis to the SAPHIRE trial showed that combining stress and functional biomarkers gave better accuracy in predicting Stage 2 or 3 AKI within the next 12 hours, and adverse kidney events in 30 days.

De Vlieger also presented the AKI predictor (KU Leuven, Belgium), a machine learning tool developed to predict AKI during the first week of intensive care unit (ICU) stay. This tool demonstrated good accuracy in predicting AKI, which increased as more data were gathered during the patient's stay.

Regarding AKI prediction models, De Vlieger explained that a meta-analysis showed even though 150 prediction models with good accuracy have been used over the years, with a quarter of them externally validated, and 40 of them using machine learning, none of them have actually been implemented in clinical practice. In a study predicting complications after surgery, data collected before and during hospital admission is used to make an estimation before surgery of post-operative complications in addition to a new estimation after surgery.

By using 135 features, this model can quite accurately predict complications after surgery, and it demonstrated a good predictive performance for AKI. Sub-phenotyping of patients in the ICU can be done by using different molecular analysis and biomarkers and machine learning, as well as by combining these two approaches.

In their concluding remarks, De Vlieger emphasised there is still a continuous quest for perfect biomarkers and despite the increased use of machine learning predictions in clinical models, few, if any, are used in clinical practice. De Vlieger predicts that in the future combining biomarkers and clinical models will be the most effective approach and that research will focus on subphenotyping use of machine learning tools and specific biomarkers in AKI phenotypes.

"In the future combining biomarkers and clinical models will be the most effective approach."

ARTIFICIAL INTELLIGENCE GUIDING ACUTE KIDNEY INJURY PATIENT MANAGEMENT

Jay Koyner, University of Chicago, Illinois, USA, discussed artificial intelligence (AI) in medication dosing assistance, clinical decision support, and risk prediction. Koyner emphasised the need for AI in helping improve trends in AKI-associated mortality by citing a recent study that showed a significant but poor decrease in AKI-associated mortality over 11 years in veterans from the USA, emphasising that care of patients with Stage 2 AKI can be improved.

ARTIFICIAL INTELLIGENCE IN CLINICAL DECISION SUPPORT

Koyner went on to present a study that used e-alerts and educational activities to facilitate AKI care across hospitals, which showed improvements in care, even though 30-day mortality and AKI progression remained unchanged. Following implementation of the alert system, the likelihood of AKI recognition and fluid assessment increased, and more medication reviews and urinalyses were performed. In another alert study, no change in the development of AKI was detected but morbidity and mortality were improved in the patient population that was flagged as 'at risk'. In another study, the clinical team was alerted to the presence of AKI, enabling them to enhance care. However, even when orders with one click access to intravenous fluids or diuretics were given, no difference was observed in AKI progression, need of dialysis, death at 14 days, length of stay, or discharge rate. Interestingly, in non-teaching hospitals alerting the staff to the presence of AKI led to more diuretics and fluids being given, demonstrating the need of having AKI-trained staff caring for patients with AKI.

Clinical decision support has been successful in implementing care bundles and has demonstrated decreased mortality in certain studies, not necessarily associated with decreased rate in AKI, but in those specific alerts around nephrotoxin there is a clear decrease in AKI and AKI events.

MACHINE LEARNING

Currently, AKI phenotyping works by defining every type of AKI around changes in creatine whether this is due to a drug, sepsis, or cardiac arrest. Koyner emphasised the need to move away from this, possibly by using machine learning and incorporating all the information found in electronic records. One study used an ICU database to create three separate phenotypes of sepsis-associated AKI, each with different AKI event rates but also event rates regarding other organ system dysfunction. This enabled them to identify those who were most high risk, for example those who had a need for dialysis.

Koyner emphasised that AI tools need external validations and need to demonstrate that they can improve care and outcomes with earlier diagnosis. In their concluding remarks, Koyner explained that combining AI phenotypes and biomarkers has the potential to unlock new pathways to identify and treat AKI and its long-term complications and outcomes.

CLIMATE CHANGE: SUBTROPICAL CAUSES OF ACUTE KIDNEY INJURY IN EUROPE

Vivekanand Jha, The George Institute for Global Health India, New Delhi, India, and Imperial College, London, UK, introduced their talk by emphasising the great increases observed in temperature across Western European countries and the predictions that global temperatures will see new records in the next 5 years. They explained that climate change is going to be the greatest public health challenge of the 21st century, and underlined the high global burden of AKI of 13.3 million cases every year, which is particularly high in tropical developing countries with the majority of global deaths happening in low/middle income countries. Jha explained that AKI in tropical countries is linked to local ecosystem and culture, and that its presentation and outcomes are influenced by health-system level factors, not by individual hospital factors. According to Jha, climate change will have a major impact on AKI incidence; in fact, AKI related to climate change can be called a neglected disease, which needs a higher research focus.

Jha continued by emphasising that "the change that we are seeing is slowly shifting the host, environment, and pathogen equilibrium," explaining that climate change will lead to increased air temperature, change in quality and quantity of drinking water, migration and displacement, air pollution, and pandemics. The increase in urbanisation and the forced and voluntary migration observed both in Europe and the rest of the world will lead to increased frequency and vulnerability to established infectious disease and emergence of new infectious diseases. Jha explained that as a result of climate change and biodiversity loss, a number of infections are likely to increase, many of which have a direct impact on kidney health, such as malaria, dengue, leishmaniases, and severe acute respiratory syndrome.

Europe is increasingly vulnerable to infectious disease breakouts, Jha continued, due to an increasing occupational and residential exposure to vector-borne diseases, lack of natural immunity and vaccine development, and increased local mobility. Lack of flood barriers and ageing water infrastructure increase vulnerability to waterborne diseases, whereas foodborne diseases could develop due to breakdown of cold chain, and suboptimal preparation and processing of food. Change in environmental conditions can lead to changes in vector-host transmission. This, combined with a number of social factors, will lead to many types of kidney disorders for which Europe needs to remain prepared.

Finishing their presentation with a positive tone, Jha explained that there is a lot that can be done if we start now, including vaccine development, systems of monitoring importation risk, and elimination of vector breeding grounds. ●

"The change that we are seeing is slowly shifting the host, environment, and pathogen equilibrium."

Filling the Gap by Targeting the Gut: First Disease-Modifying Treatment Approved for IgA Nephropathy

This symposium took place on 17th June 2023 as part of the 60th European Renal Association (ERA) Congress in Milan, Italy, and virtually

Speakers: Bengt Fellström,[1] Jonathan Barratt[2,3]

1. Uppsala University, Sweden
2. University of Leicester, UK
3. John Walls Renal Unit, Leicester General Hospital, UK

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Keywords: Biomarker, budesonide, chronic kidney disease, corticosteroids, glomerulonephritis, gut–kidney axis, IgA nephropathy (IgAN), kidney failure, Peyer's patch, targeted release.

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Meeting Summary

This symposium took place during the 60th European Renal Association (ERA) Congress, held in Milan, Italy, and virtually. Bengt Fellström, Uppsala University, Sweden, described the relationship between IgA nephropathy (IgAN) and gastrointestinal mucosal reactivity. Fellström then outlined the history of Nefecon (Calliditas Therapeutics, Stockholm, Sweden, and STADA Arzneimittel, Bad Vilbel, Germany), which was developed based on the assumption that the gut plays a major role in the pathophysiology of the disease, and that there was a high unmet need for a well-tolerated and effective therapy. Nefecon was specifically designed to target the origins of IgAN. A Phase IIb clinical trial showed, for the first time, that 9 months of treatment with Nefecon was well-tolerated and effective in patients at risk of disease progression. Jonathan Barratt, University of Leicester, UK, and John Walls Renal Unit, Leicester General Hospital, UK, presented biomarker data supporting the efficacy data in clinical trials, and presented topline data from Part B of the Phase III NefIgArd trial. Specifically, the results demonstrated an average 5.05 mL/min/1.73 m^2 estimated glomerular filtration rate (eGFR) treatment benefit in favour of Nefecon versus placebo over 2 years. This confirmed that the eGFR benefit of 9 months of active treatment with Nefecon was maintained during the observational follow-up. The eGFR benefit with Nefecon versus placebo was consistent regardless of baseline urine protein-creatinine ratio (UPCR). At 2 years, the 30% reduction in UPCR in the Nefecon versus placebo arm was similar to the percentage reduction at the end of the 9-month treatment period, plus 15 months follow-up off treatment. Patients treated with Nefecon experienced decreasing levels of proteinuria while on active treatment and for 3 months afterwards, suggesting a continued biologic effect. Barratt presented UK registry data showing that, despite being treated with the current standard of care for IgAN, three-quarters of adults and half of paediatric patients developed kidney failure or died within 20 years of disease onset. Barratt suggested a paradigm shift in the treatment approach for all patients with IgAN, who have a risk of developing kidney failure in their lifetime.

Nefecon: Rationale, Efficacy, and Safety in the Treatment of Primary IgA Nephropathy

Bengt Fellström

Pathophysiology of IgAN

The pathophysiology of IgAN has been described using the 4-hit hypothesis, where galactose-deficient IgA1 (Gd-IgA1) is formed (hit 1), thereby stimulating the production of anti-Gd-IgA1 autoantibodies (hit 2).[1,2] These combine to form Gd-IgA1 immune complexes (hit 3), which deposit in the mesangial area of the kidney, leading to glomerular injury (hit 4).

Associations of IgA Nephropathy with Gastrointestinal Mucosal Reactivity

Many associations have been demonstrated relating the development of IgAN with gastrointestinal mucosal reactivity, primarily involving B and T cells in the Peyer's patches.[3] Gastrointestinal inflammatory disease (Crohn's disease and ulcerative colitis), characterised by impaired function of the mucosal barrier, is associated with an increased risk of IgAN. For example, patients with coeliac disease have a three-fold increased risk of IgAN.[4] Previous studies have identified key susceptibility genetic loci encoding proteins involved in the immune defence against gastrointestinal mucosal pathogens.[5]

It has also been demonstrated in patients and animal models that there is an abnormal and hyper-reactive immune response to dietary components, including gluten, casein, and soy protein, in the gut mucosa in IgAN.[6-8] It has also been suggested that a defective immune tolerance in patients with IgAN might lead to an abnormal response to microbiota, triggering mucosal-associated lymphoid tissue activation and subclinical intestinal inflammation.[8] The mucosal-associated lymphoid tissue is rich in plasma cells that form antibodies, and it is thought that this is where the Gd-IgA1 molecules are formed.[8]

Nefecon Was Designed to Specifically Target the Origins of IgA Nephropathy

Based upon these findings, and a high unmet need for a well-tolerated and effective treatment, Fellström and colleagues set out to find a compound with a mode of action aimed at specifically targeting mucosal IgA synthesis in the gut. Following release in the ileum, the drug would have a high first-pass metabolism to minimise systemic exposure and side effects.[9]

The active substance budesonide is a highly potent corticosteroid that is absorbed in the ileum and undergoes first-pass metabolism.[10] Budesonide is 90% cleared in first-pass metabolism by the liver, thereby minimising systemic side effects. It acts on the formation of Gd-IgA1 (hit 1) by reducing mucosal B cell activity and reducing the production of aberrant IgA1 compounds (i.e., Gd-IgA1), which ultimately leads to reduced mesangial and glomerular damage.[11] Studies have demonstrated that Nefecon has an acceptable safety profile, with predominantly mild to moderate adverse events (AE) that were reversible upon discontinuation.[9]

Several trials have been conducted using Nefecon, including the Phase IIa pilot study, the NEFIGAN Phase IIb study, and the NEFIGARD Phase IIIa/IIIb trial. A Phase III open-label extension study is ongoing, which will show what effect a second treatment session may have.

The Phase II trial Showed the Safety and Efficacy of Nefecon

The Phase IIa study was an exploratory, open-label, uncontrolled study to evaluate the safety and efficacy of Nefecon.[12] It enrolled 16 patients with IgAN and albuminuria who were on stable renin-angiotensin system (RAS) blockade at three Swedish centres. Patients were treated for 6 months with Nefecon 8 mg/day, and followed up for 3 months. The inclusion criteria were age ≥18 years, biopsy-verified IgAN, proteinuria (urinary albumin >500 mg/24 hours), and serum creatinine <200 µmol/L. The study showed a maximal median reduction in albuminuria of 40% at Month 8, and an improved eGFR, which increased by 8% at Month 6 (p=0.003).

This was followed by NEFIGAN, a randomised, double-blind, placebo-controlled Phase IIb trial examining the efficacy and safety of two doses of Nefecon versus placebo in patients with IgAN at risk of kidney failure. The trial enrolled 150 patients from 62 sites in 10 European countries.[9] The trial design incorporated a 6-month run-in phase, in which RAS blockade was optimised to the maximum allowed or maximum tolerated dose. This was followed by a 9-month treatment phase in which patients were randomised to Nefecon 16 mg/day, Nefecon 8 mg/day, or placebo. The 3-month follow-up phase included a 2-week tapering of the drug to Nefecon 8 mg/day in those randomised to a treatment dose of 16 mg/day, and a 2-week tapering to placebo in the remaining two groups.

Patient demographics and baseline characteristics were well-balanced across the three treatment arms. The trial's primary objective of UPCR reduction at 9 months in all treated patients was met, with a 24.4% reduction in the Nefecon groups versus a 2.7% increase in the placebo group (p=0.007).[9] When the individual doses of Nefecon were examined separately, the reduction in UPCR at 9 months compared with placebo was greater in the group receiving 16 mg/day (-27.3%; p=0.009) compared with those receiving 8 mg/day (-21.5%; p=0.029). The effect of Nefecon was sustained throughout follow up.

The other important finding of the trial was that Nefecon stabilised eGFR during the 9-month course of treatment, while patients treated with placebo experienced a decline in renal function by -9.8%.[9] The study also examined the effects of Nefecon on eGFR according to baseline UPCR (Fellström et al., data on file). Active treatment stabilised eGFR independent of UPCR levels, whereas in the placebo group, higher proteinuria was associated with a stronger decrease in eGFR.

Regarding treatment-emergent AEs, there were no significant changes in body weight, blood pressure, or HbA1c versus placebo, and no serious infections. The most common AEs in the total patient population, including the placebo group, were nasopharyngitis, acne, and swelling of the ankles. A total of 13 serious AEs were reported, of which four were considered to be related to the study drug. Two occurred in the Nefecon 16 mg/day arm; these were deep vein thrombosis and deteriorating renal function. Two occurred in the placebo arm; these were increasing proteinuria and deteriorating renal function. Analysis of glucocorticosteroid AEs showed that the incidence of events was as expected, with an increased level of mild-to-moderate glucocorticosteroid AEs in the Nefecon 16 mg/day group, relative to the other two arms in the study. In summary, the analysis of treatment-emergent AEs and treatment-emergent serious AEs showed no deaths and no serious or fatal infections. There were light-to-moderate glucocorticosteroid-like side effects in a small number of patients. There was no occurrence of *de novo* diabetes nor any increased blood pressure, increase in body weight, osteoporosis, or fractures. The Phase II clinical trial showed, for the first time, that 9 months treatment with Nefecon is well-tolerated and effective in patients with IgAN and at risk of disease progression.

Exploratory Studies Support the Hypothesis that Nefecon Targets the Origins of IgA Nephropathy

Following the NEFIGAN trial, exploratory studies have been performed, showing that 9 months of treatment with Nefecon 16 mg/day resulted in significant changes in several markers of gut-associated lymphoid tissue activity, including mucosal IgA responses to dietary antigens, serum secretory IgA levels, elements of the complement cascade, and chemokines involved in mucosal immune cell trafficking (Wimbury D et al., unpublished data). This was associated with significant reductions in serum levels of Gd-IgA1 and IgA/IgG immune complexes. These results support the hypothesis that Nefecon regulates mucosal immune dysfunction by targeting the gut-associated lymphoid tissue, and exerting a direct disease-modifying effect in IgAN. Further analyses will be performed to better understand the importance of the gut–kidney axis in the development of IgAN.

Considering the 4-hit pathogenesis model of IgAN, the clinical trial results indicate that Nefecon has an effect on hit 1, translating into reduced mesangial and glomerular damage.[1,2] To summarise, there is clinical and experimental evidence of a dysregulated mucosal immune system, particularly within the gut, in IgAN. Genetic aberrations related to human leukocyte antigen, complement, and gastrointestinal inflammatory regulation are enriched in IgAN. The gastrointestinal formation of Gd-IgA1 and subsequent formation of IgG-Gd-IgA1 immune complexes in IgAN was reduced with Nefecon treatment. The NEFIGAN study showed a significant reduction of proteinuria, which translated into stabilisation of eGFR, irrespective of the degree of baseline proteinuria. The early reduction of proteinuria is a useful surrogate endpoint in IgAN, predicting reduced risk of kidney failure, as demonstrated in a meta-analysis.[13] Only mild-to-moderate side effects were observed with Nefecon treatment.

Conclusion

In conclusion, the beneficial results of Nefecon treatment, which targets the mucosal immune system in the distal ileum, support the hypothesis of upstream involvement of gut mucosal immune dysregulation in the development of IgAN. The NEFIGAN trial confirms the validity of treating IgAN by targeting the mucosal immune system in the distal ileum, with a unique formulation depositing a majority of the active drug locally in the gut and minimising systemic corticosteroid exposure.

NefIgArd and Beyond: Treating IgA Nephropathy in 2023

Jonathan Barratt

Exploratory Biomarker Analyses Confirm that Nefecon Targets the Origins of IgA Nephropathy

The Phase IIb NEFIGAN trial was followed by a range of exploratory biomarker analyses to examine the mechanism of action of Nefecon, and to confirm whether it interferes with mucosal immunity (Wimbury D et al., unpublished data). These analyses used serum, plasma, and urine

samples collected at baseline, 9 months, and 12 months during the trial. More than 100 biomarkers were investigated, including chemokines, cytokines (e.g., B cell activating factor/a proliferation-inducing ligand [APRIL]), complement, and urinary markers of tissue remodelling.

Taken together, the biomarker analyses from the NEFIGAN Phase II study showed a disease-modifying effect of Nefecon in IgAN (Wimbury D et al., unpublished data). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways significantly modified by treatment with Nefecon are those related to the intestinal immune network for IgA production. This finding is in line with genome-wide association studies examining risk alleles. A clear pattern emerges of a mode of action that is unique to Nefecon, targeting the mucosal-associated lymphoid tissue within the gut, and mapping to current understanding of the pathogenesis of IgAN. As discussed previously, there were dose-dependent reductions in IgA/IgG immune complexes and Gd-IgA1.[14] These biomarker data support the observed efficacy in clinical trials.

Design of the NefIgArd Phase III Trial

The full results of the Phase III NefIgArd trial were presented for the first time at the 60th ERA Congress, verifying the long-term renal benefit of Nefecon over 2 years.[15] The biomarker analyses performed on the Phase II population are now being repeated in the Phase III population to validate the initial findings.

NefIgArd was a Phase III, multicentre, randomised, double-blind, placebo-controlled two-part trial that tested the efficacy and safety of 9 months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure.[16] NefIgArd enrolled adult patients with IgAN with persistent proteinuria (UPCR: ≥0.8 g/g or proteinuria: ≥1 g/24 hour) despite supportive care optimised to the maximum allowed or maximum tolerated dose for at least 3 months, and an eGFR of ≥35 to ≤90 mL/min per 1.73 m^2. Exclusion criteria included inadequately controlled blood pressure (i.e., systolic blood pressure/diastolic blood pressure: ≥140/90 mmHg), previous kidney transplant, and all secondary forms of IgAN, or any non-IgAN glomerulonephritis.[16]

Part A of the Phase III NefIgArd Trial Confirms the Findings of the Phase IIb NEFIGAN Study

An interim readout (Part A) was performed in November 2020, when the first 199 patients had received treatment for 9 months.[16] This study had a prespecified primary endpoint of 24-hour UPCR, and a key secondary endpoint of eGFR. At 9 months, UPCR was 27% lower in the Nefecon group compared with placebo (p=0.0003). UPCR continued to improve in patients treated with Nefecon; at 12 months there was a 48% reduction in UPCR with Nefecon compared with placebo (p<0.0001). Prespecified analyses demonstrated that in the subgroup of patients with baseline UPCR ≥1.5 g/g, the eGFR benefit was greater in the patients treated with Nefecon compared with the overall population. These results confirmed the findings of the Phase IIb NEFIGAN study, and led to Nefecon being the first drug to be approved by the U.S. Food and Drug Administration (FDA)[17] and the European Medicines Agency (EMA)[18] for the treatment of patients with IgAN at risk of disease progression.

Part B of the Phase III NefIgArd Trial Shows Efficacy and Safety over 2 Years

The full study results (Part B; n=364) were presented at the ERA Congress.[15] The aim was to confirm the long-term renal benefit of the observed reduction in proteinuria. At baseline, the median age was 43 years in the Nefecon group and 42 years in the placebo group, while approximately two-thirds of patients were male (64.3% in the Nefecon group and 67.6% in the placebo group). The median UPCR at baseline was 1.28 g/g in the Nefecon group and 1.25 g/g in the placebo group, and the median UACR was 0.99 g/g in the Nefecon group and 0.98 g/g in the placebo group. The median eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was 56.14 mL/min/1.73 m^2 in the Nefecon group and 55.11 mL/min/1.73 m^2 in the placebo group at baseline. The frequency of systemic corticosteroids of immunosuppressants before randomisation was 8.2% in the Nefecon group and 10.4% in the placebo group. The median time since IgAN diagnosis was 2.4 years in the Nefecon group and 2.6 years in the placebo group.

The primary endpoint was the time-weighted average change in eGFR from baseline over the study period. The results demonstrated a 5.05 mL/min/1.73 m^2 eGFR treatment benefit in favour of Nefecon versus placebo over 2 years (p<0.0001; Figure 1). This confirmed that the eGFR benefit of 9 months of active treatment with Nefecon was maintained during the observational follow-up. The placebo group demonstrated a decline in kidney function, despite being on optimised supportive care. Patients in the placebo group lost 5.85 mL/min/1.73 m^2 of eGFR in 1 year, with a 12 mL/min/1.73 m^2 decrease over 2 years. Treatment with Nefecon halved the degree of kidney function loss over the 2-year period.

The trial also showed that the eGFR benefit with Nefecon versus placebo was consistent regardless of baseline UPCR, meaning that treatment had a protective effect on kidney function in patients with proteinuria above or below 1.5 g/g.

At 2 years, the percentage reduction in UPCR in the Nefecon versus placebo arm was similar to the percentage reduction at the end of the 9-month treatment period (Figure 2). Patients treated with Nefecon experienced decreasing levels of proteinuria while on active treatment and for 3 months afterwards, suggesting a continued biologic effect. From 12–24 months, the level of proteinuria started to increase in those treated with Nefecon, but remained 30–40% lower than at the start of treatment. The open-label extension study will provide further information, when patients are restarted on a new treatment session.

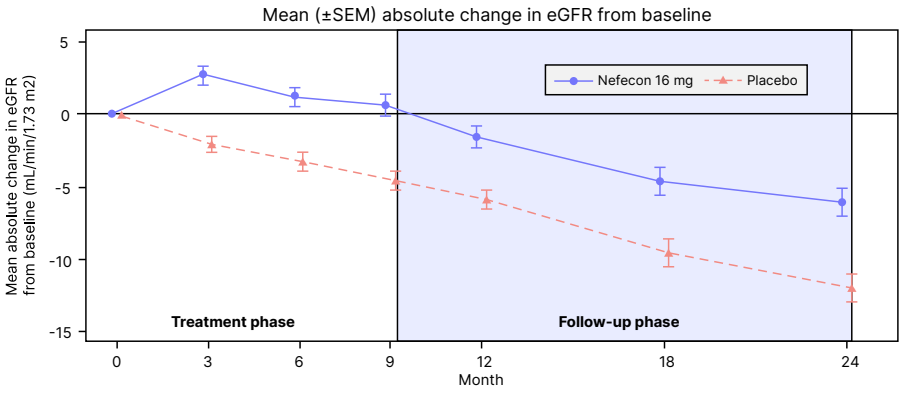
Treatment-emergent AEs were as expected with low systemic exposure of a corticosteroid.[15] Importantly, these events occurred while on active treatment, and were reversible when patients stopped taking the drug. In contrast, the efficacy data showed a continued benefit of treatment for a full 2-year period, including only 9-month exposure to the drug. Biomarker analyses from the NefIgArd Phase III clinical trial are ongoing. The results showed that treatment with Nefecon reduces circulating levels of Gd-IgA1 in patients with IgAN.[19]

Figure 1: Mean (±standard error of the mean) absolute change in estimated glomerular filtration rate from baseline.[15]

Results: efficacy

Primary endpoint: time-weighted average change from baseline in eGFR over the 2-year period

- 5.05 mL/min/1.73 m² eGFR treatment benefit in favour of Nefecon versus placebo over 2 years (p<0.0001)
- eGFR benefit at the end of the 9-month treatment period with Nefecon was maintained during the 15-month observational follow-up



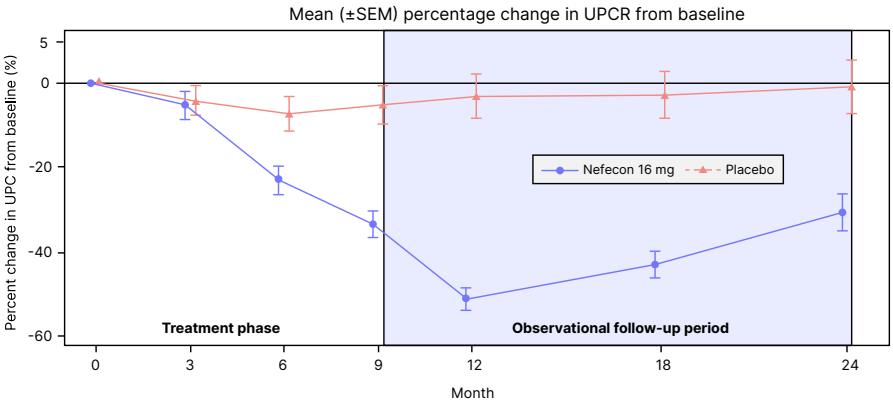
Nefecon 16 mg/day, mL/min/1.73 m²	+0.66	-1.52	-6.11
Placebo, mL/min/1.73 m²	-4.56	-5.85	-12.00
Absolute difference mL/min/1.73 m² (95% CI)	5.21 (3.35–7.58)	4.33 (2.44–6.66)	5.89 (3.35–9.15)

CI: confidence interval; eGFR: estimated glomerular filtration rate; SEM: standard error of the mean.

Figure 2: Mean (±standard error of the mean) percentage change in urine protein-creatinine ratio from baseline.[15]

Results: efficacy

- At 2 years, the percentage reduction in UPCR in the Nefecon versus placebo arm was similar to the end of the 9-month treatment period



Nefecon 16 mg/day, %	-33.6	-51.3	-30.7
Placebo, %	-5.2	-3.2	-1.0
Corresponding percentage reduction, % (95% CI)	30 (20–39)	50 (42–57)	30 (16–41)

CI: confidence interval; SEM: standard error of the mean; UPCR: urine protein-creatinine ratio.

What Do the Results Mean for Clinical Practice Guidelines?

The impact of IgAN can be illustrated using UK registry data in more than 4,000 paediatric and adult patients with IgAN.[20] The data show that, despite being treated with the current standard of care for IgAN, three-quarters of adults and half of paediatric patients develop kidney failure or die within 20 years of disease onset.

In addition, at least 50% of patients diagnosed with IgAN below the age of 50 years are on dialysis before age 60 years. This highlights that while 20 years may seem like a long gap before poor outcomes are experienced, the reality is that kidney failure and death occur while patients are still in their 50s.

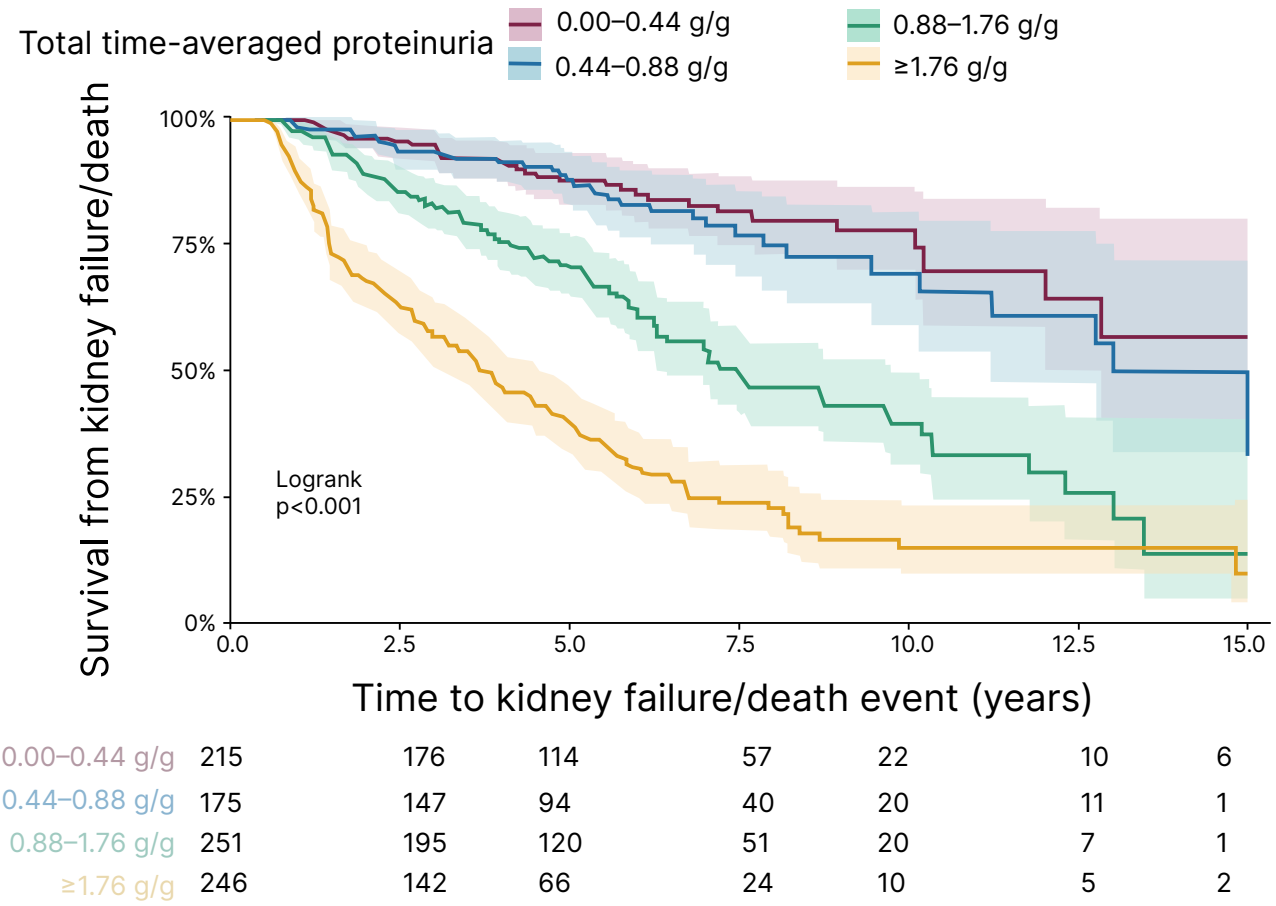
The registry data was also used to model the likelihood of developing kidney failure in a patient's lifetime, dependent on prespecified rates of decline of eGFR. This showed that 100% of patients diagnosed at age 30–<40 years, with an annual eGFR decline of 3–5 mL/min/1.73 m^2, would develop kidney failure in their lifetime. At an annual eGFR decline of 2 mL/min/1.73 m^2, 80% would experience kidney failure. For context, the placebo group in most studies deteriorated at 5–6 mL/min/1.73 m^2 per year. Real-world data showed that at an eGFR decline of 3 mL/min/1.73 m^2, all patients below the age of 50 years developed kidney failure and needed dialysis in their lifetime.

Kaplan–Meier curves of the registry data showed that one in four patients with time-averaged proteinuria 0.5–1.0 g/24 hours developed kidney failure by 10 years (Figure 3). This indicates that it should be reconsidered whether patients achieving <1 g/day are sufficiently treated with supportive care.

Patients with IgA Nephropathy at Risk of Disease Progression Should Be Treated Early and Aggressively

In summary, a diagnosis of IgAN should be viewed in the context of the patient's lifetime, not just the next 5 or 10 years, and treatment should be given to prevent kidney failure in the patient's lifetime. A new mindset is needed of preserving nephrons as soon as diagnosis is made. This suggests that the current treatment paradigm[21] needs to change towards one that is more focused and aggressive. This could include:

Figure 3: Kaplan–Meier survival curve of time to kidney failure/death using total follow-up time-averaged proteinuria.



- A foundation of optimised kidney care with RAS inhibitors for all patients with proteinuric kidney disease. The use of sodium-glucose cotransporter-2 inhibitors, endothelin receptor antagonists, and mineralocorticoid receptor antagonists may also be considered. This treatment will not modify the disease or stop IgA deposition.
- An anti-inflammatory agent, such as a complement inhibitor, for patients with inflammation in the kidney biopsy, as uncontrolled inflammation drives the loss of nephrons.
- All patients will also need a therapy that is directed at B cells and switches off the production of pathogenic IgA. Currently, there are strong data that Nefecon can deliver that goal, as it turns off the production of pathogenic IgA within the mucosal immune system. Repeated treatment with Nefecon to maintain low levels of Gd-IgA1 immune complexes may be required. Studies are ongoing with other potential therapies, including anti-CD38, APRIL, and B cell activating factor/APRIL inhibitors, and results are awaited.

The new paradigm would see all three elements of treatment initiated simultaneously in a multi-targeted approach, based on the current understanding of the pathophysiology of IgAN.

The ultimate aspiration is a precision medicine approach to the treatment of IgAN. Biomarker studies are underway that may help clinicians to direct the right drug to the right patient at the right time in the natural history of the disease.

Question and Answer Session

The symposium concluded with a lively question and answer session. One delegate commented on how Fellström's presentation indicated a 20-year history leading up to the regulatory approval of Nefecon, and congratulated the investigators for successfully completing that marathon. There was an observation from India that perhaps systemic absorption with existing budesonide formulations used to treat inflammatory bowel disease is higher than that presented by Fellström, who had noted that 90% of Nefecon is cleared in first-pass metabolism by the liver, which minimises systemic side effects. Barratt clarified that Nefecon is a very different formulation of budesonide, which currently exists to treat inflammatory bowel disease, and the two cannot be compared due to different pharmacokinetics and absorption.

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Proteinuria as a Surrogate Endpoint for Disease Progression in IgA Nephropathy: Predicting Long-Term Treatment Effects of Sparsentan

These oral poster presentations were given on 16th June 2023 at the 60th European Renal Association (ERA) Congress in Milan, Italy

Speakers:	Alex Mercer,[1] Jonathan Barratt[2,3] 1. JAMCO Pharma Consulting, Stockholm, Sweden 2. Department of Cardiovascular Sciences, University of Leicester, UK 3. Leicester General Hospital, UK

Disclosure:	Mercer has served as a consultant for Travere Therapeutics and Vera Therapeutics. Barratt has served as a medical and/or scientific advisor for Alnylam Pharmaceuticals, Argenx, Astellas Pharma, BioCryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, UCB, Vera Therapeutics, and Visterra; and has received research grants from Argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GlaxoSmithKline (GSK), Novartis, and Travere Therapeutics.
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Keywords:	Disease progression, IgA nephropathy (IgAN), irbesartan, kidney failure, PROTECT study, proteinuria, sparsentan.
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Meeting Summary

IgA nephropathy (IgAN) is a rare, life-limiting disease for which there is significant unmet need. Until recently, drug development for IgAN had been impeded by the requirement for large-scale, long-term clinical trials to measure clinical outcomes. However, the recent establishment of 'reduction in proteinuria' as a surrogate endpoint to predict clinical outcomes in IgAN, as a basis for accelerated drug approval, has transformed the field. At the 60th European Renal Association (ERA) Congress in June 2023, two oral poster presentations focused on the use of early reduction in proteinuria as an endpoint for clinical studies in IgAN. Alex Mercer, Consultant in Clinical Drug Development at JAMCO Pharma Consulting in Stockholm, Sweden, presented data estimating the long-term clinical outcome of reductions in proteinuria (clinically meaningful extensions in time to kidney failure or death), which could help predict the future protective effect of any new intervention on kidney

function. Following this, Jonathan Barratt, Mayer Professor of Renal Medicine at the University of Leicester, and Honorary Consultant Nephrologist at Leicester General Hospital, UK, described findings from the prespecified interim analysis of the Phase III PROTECT study of sparsentan (a novel dual endothelin angiotensin receptor antagonist) in IgAN, which included reduction in proteinuria as a primary endpoint. In patients with IgAN at high risk of disease progression, sparsentan produced a rapid and significant reduction in proteinuria of a level that, according to the study data presented by Mercer, would correspond to a substantially lowered risk of kidney failure or death. Long-term data to confirm this predicted clinical outcome on disease progression are anticipated.

Introduction

IgAN is a progressive, immune complex-mediated glomerulonephritis that is the most common form of primary glomerulonephritis worldwide.[1,2] It is a leading cause of chronic kidney disease and kidney failure.[1,3] The prognosis is poor, with a median length of kidney survival estimated at 11.4 years in the UK National Registry of Rare Kidney Diseases (RaDaR), and almost all patients at risk of progression to kidney failure within their lifetime.[3] Indeed, as most patients with IgAN are diagnosed between 30–40 years of age, the impact of this life-limiting disease is often realised in the mid-adult years.[3-6] Overall, IgAN is a disease with a high level of unmet need.

Focusing on addressing this unmet need, Alex Mercer and Jonathan Barratt presented evidence on the use of proteinuria as a surrogate endpoint for disease progression in IgAN at the ERA Congress, including an interim analysis of the PROTECT study of the dual endothelin angiotensin receptor antagonist, sparsentan, in patients with IgAN.[7,8]

Estimating Delay in Time to Kidney Failure or Death for Treatment Effects on Proteinuria in IgA Nephropathy

Alex Mercer

In their oral presentation,[9] Mercer introduced IgAN as, "a disease in need of new medicines [within] a golden age of drug development." Traditionally, approval of a new drug for chronic kidney disease has required treatment effect to be proven on the composite endpoint of first occurrence of reduction in estimated glomerular filtration rate (eGFR; eGFR: <15 mL/min/1.73 m^2; chronic kidney disease Stage 5), doubling of serum creatinine, and kidney replacement therapy, which has required large-scale, lengthy, randomised controlled trials (RCT). This 'high bar' has proven extremely prohibitive to drug development for rare kidney diseases such as IgAN. However, in a transformative step, meta-regression 'trial level analyses', published in 2016 and 2019, established that an early treatment effect on proteinuria predicts a treatment effect on clinical outcomes in IgAN.[10,11]

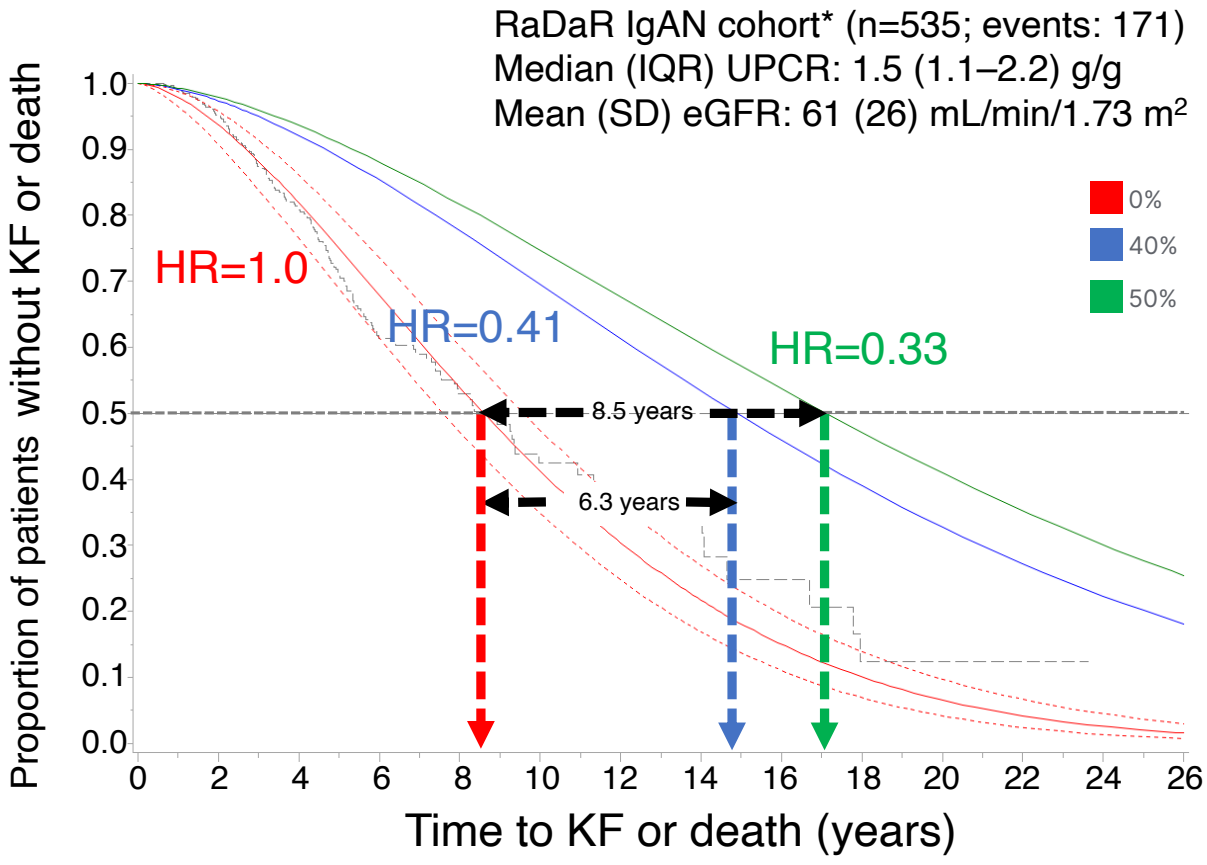
Mercer identified that the acceptance by the USA and European regulatory authorities of 'change in proteinuria over 9 months' as a surrogate endpoint for accelerated/conditional drug approval[10,11] (with full approval reliant on confirmatory clinical data), has enabled studies with smaller sample sizes and an earlier readout. This advance has contributed to the expansion of the IgAN development programme from just one Phase II study in 2013 to 21 studies (Phase II/III) of new medicines in 2023. Indeed, all industry-sponsored Phase III RCTs in IgAN now have a prespecified proteinuria endpoint at approximately 9 months.

Mercer presented findings from a two-step approach that estimated the delay in time to kidney failure or death associated with treatment effects of 40% and 50% reduction in proteinuria at 9 months to allow the estimation of future benefits in ongoing Phase III studies of IgAN.[9] In step one, published findings of a trial-level analysis from 13 RCTs in IgAN (n=1,153)[10] were used to predict the risk (hazard ratio [HR]) that the treatment effect on proteinuria would lead to a doubling of serum creatinine, kidney

failure, or death. In step two, the HRs were used to estimate the delay to kidney failure or death by applying Weibull accelerated failure time modelling to a Phase III representative IgAN population with long follow-up, the UK RaDaR IgAN cohort of adult patients (n=535), of whom 171 had progressed to kidney failure or death. Patients in the cohort were required to have an eGFR ≥30 mL/min/1.73 m^2, and proteinuria equivalent to approximately 1 g/day (urine protein-creatinine ratio [UPCR]: ≥100 mg/mmol).

In step one, 40% and 50% reductions in proteinuria were associated with substantially lowered risks of kidney failure or death, with predicted HRs of 0.41 (95% confidence interval [CI]: 0.26–0.65) and 0.33 (95% CI: 0.16–0.67), respectively. In step two, the predicted HRs for 40% and 50% reductions in proteinuria were applied to the RaDaR IgAN cohort, which had a median UPCR of 1.5 g/g and a mean eGFR of 61 mL/min/1.73 m^2) at baseline, with a median time to kidney failure or death of 8.6 (95% CI: 7.8–9.5) years and a 5-year survival rate of 75%. A 40% reduction in proteinuria (HR: 0.41) prolonged the median time to kidney failure or death to 14.9 (95% CI: 13.6–16.4) years (an increase of 6.3 years) with a 5-year survival rate of 89% (Figure 1). A 50% reduction in proteinuria (HR: 0.33) prolonged the median time to kidney failure or death to 17.1 (95% CI: 15.6–18.8) years (an increase of 8.5 years) with a 5-year survival rate of 91% (Figure 1).

Figure 1: Estimating time to kidney failure or death for predicted hazard ratios associated with treatment effects of 0%, 40%, and 50% reduction in proteinuria.



*Representative Phase III population

eGFR: estimated glomerular filtration rate; HR: hazard ratio; IgAN: IgA nephropathy; IQR: interquartile range; KF: kidney failure; RaDaR: UK National Registry of Rare Kidney Diseases; SD: standard deviation; UPCR: urine protein-creatinine ratio.

Thus, Mercer identified that achieving 40% and 50% reductions in proteinuria at 9 months was predicted to associate with a substantially lowered risk of kidney failure or death, an increased median time to kidney failure or death, and an increased 5-year survival probability.

Mercer concluded that "therapeutic interventions that reduce proteinuria and risk of kidney failure can confer important and clinically meaningful extensions in the time patients are alive and free from kidney failure." Mercer also highlighted that, provided baseline characteristics are comparable, their study findings would allow estimation of future benefit in delay to disease progression for proteinuria results generated in ongoing Phase III RCTs.

Superior Proteinuria Reduction with Sparsentan in IgA Nephropathy: PROTECT Study Interim Analysis

Jonathan Barratt

The PROTECT study of sparsentan in IgAN is one such ongoing, global, Phase III RCT that evaluated early change in proteinuria as a prespecified interim analysis endpoint.[7,8,12] The findings of this interim analysis were presented by Barratt.[13]

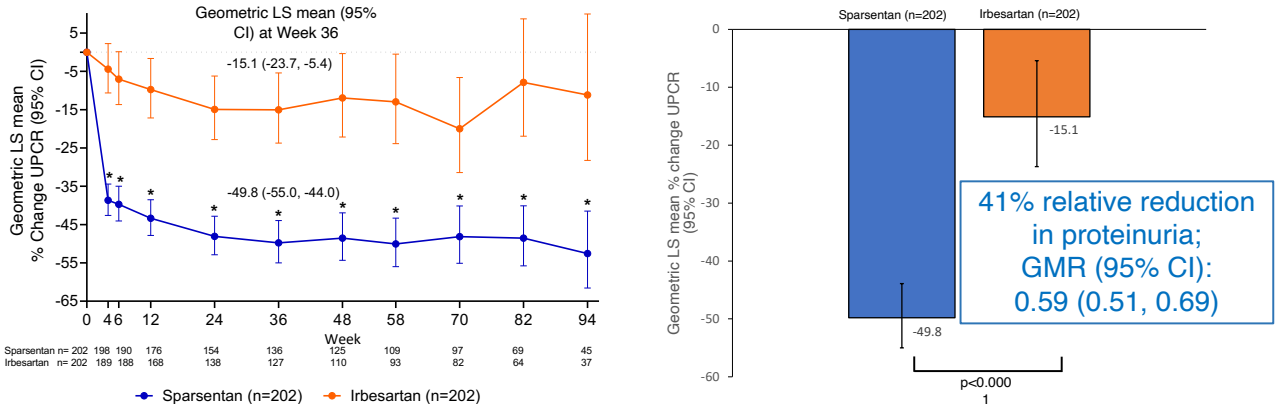
Sparsentan is an oral, non-immunosuppressive, single-molecule dual antagonist that is highly selective for both endothelin (ET-1) and angiotensin II (Ang II) receptors.[14-16] Barratt explained that inflammation and damage of the glomeruli caused by deposition of IgA-immune complexes in the mesangium triggers an increase in production of ET-1 and Ang II.[17-19] Acting via their receptors (ET_A and Ang II receptor Type 1), ET-1 and Ang II work in tandem to amplify this damage, impairing filtration processes and leading to the leakage of blood and protein into the urine.[15,20,21] Increasing proteinuria further amplifies ET-1 and Ang II, exacerbating this cycle of damage, and driving progression towards kidney failure.[15,20-22] Thus, proteinuria has a central role in IgAN disease pathology and, as described above, has been established as a surrogate endpoint for treatment effects on disease progression.[9-11] Sparsentan received accelerated approval from the U.S. Food and Drug Administration (FDA) in February 2023 for the reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression (UPCR: ≥1.5 g/g), with continued approval contingent upon demonstration that sparsentan slows the rate of decline in kidney function (eGFR) in the long term.[16,23]

PROTECT enrolled 404 adult patients with IgAN and persistent proteinuria (≥1 g/day) despite receiving maximised treatment with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, who were at high risk of disease progression.[7,8] Patients were randomised to receive sparsentan 400 mg once daily or current standard-of-care irbesartan 300 mg once daily, for a 2-year (110-week) double-blind treatment period.[7,24] At baseline, patients had a mean age of approximately 46 years, persistent proteinuria (median 1.8 g/day urinary protein excretion; median UPCR: 1.2–1.3 g/g), and existing signs of kidney damage (mean eGFR: 57 mL/min/1.73 m^2), characteristics comparable to those of the UK IgAN RaDaR cohort presented by Mercer et al.[9] As reported by Barratt, a prespecified interim analysis, with primary endpoint of change from baseline to Week 36 in UPCR, was triggered 36 weeks (approximately 9 months) after the 280th patient was randomised. The longer term confirmatory composite secondary endpoint (descriptive only at the interim analysis) was the proportion of patients reaching 40% reduction in eGFR, kidney failure, or all-cause mortality.

Interim analysis showed a marked difference between the treatment groups in proteinuria reduction at Week 36, with sparsentan treatment producing a 41% relative reduction versus irbesartan ($p<0.0001$; Figure 2). According to the findings of Mercer et al.,[9] a 40% reduction in proteinuria would predict a 6.3-year extension in time to kidney/failure death. Moreover, subgroup analysis showed that this treatment effect was irrespective of baseline factors, such as age, sex, eGFR, and level of proteinuria. Examining data available to Week 94, Barratt indicated that the difference in proteinuria reduction appeared as early as Week 4, and was maintained while patients remained on therapy (Figure 2).

This observation was consistent with the time to first complete proteinuria remission (<0.3 g/day), which was also significantly in favour of

Figure 2: Percent change from baseline in urine protein-creatinine ratio (24-hour urine samples) by visit at the prespecified interim analysis of the PROTECT study.



Primary analysis set: 94% of patients treated with sparsentan and 96% of patients treated with irbesartan reached target dose.

*p<0.0001 sparsentan versus irbesartan at each week.

CI: confidence interval; GMR: geometric least squares mean ratio; LS: least squares; UPCR: urine protein-creatinine ratio.

sparsentan over irbesartan (p=0.0002) at the interim analysis, as was the time to first partial proteinuria remission (<1.0 g/day; p<0.0001). Notably, remission events continued to occur throughout the duration of the study, with Barratt highlighting the importance of a benefit that can be accrued throughout the treatment cycle, even when no effect is observed within the early weeks.

Data from the 2-year confirmatory eGFR endpoint analyses and the secondary clinical outcome endpoint of 40% reduction in eGFR, kidney failure, or death, will be available at final analysis once all patients have completed the double-blind period. However, at interim analysis, Barratt reported that 20 patients had reached the composite clinical outcome endpoint, with a numerical difference already apparent between the sparsentan (n=7) and irbesartan (n=13) groups. It was noted that with longer follow-up, this endpoint may deliver valuable information on the link between change in proteinuria and long-term clinical outcomes on disease progression.

In terms of safety (Figure 3), PROTECT raised no concerns at the interim analysis and, overall, there were fewer treatment discontinuations of sparsentan (11%) than irbesartan (19%).

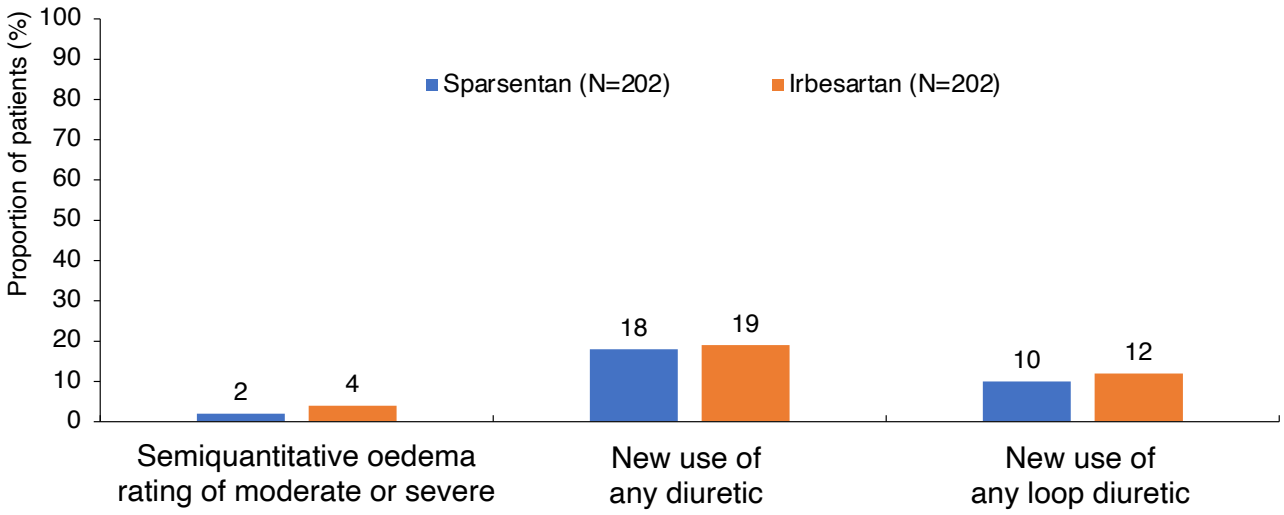
Barratt noted that while there were numerically more episodes of peripheral oedema with sparsentan than with irbesartan, there were no cases of heart failure, oedema-related treatment discontinuations, or fluid retention serious adverse events. Moreover, the treatment groups were comparable in terms of new use of diuretics/loop diuretics.

Hypotension was numerically more frequent with sparsentan than irbesartan, but blood pressure control over the 36 weeks was generally similar in the two groups. The incidence of hyperkalaemia was also comparable between groups, with no hyperkalaemia-related discontinuations. There were few instances of elevated liver enzymes (Figure 3), with all cases being asymptomatic, reversible, and having no concurrent elevation in total bilirubin.

In summary, in a prespecified interim analysis of the PROTECT study, sparsentan produced a significant and clinically meaningful reduction in proteinuria in adults with IgAN and a high risk of progressive kidney disease. The treatment effect was rapid, sustained, and superior to that provided by irbesartan, which is widely regarded as the current standard-of-care therapy. Sparsentan was also well tolerated. With the

Figure 3: Treatment-emergent adverse events with sparsentan and irbesartan at the prespecified interim analysis of the PROTECT study.*

	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAE, n (%)	177 (88)	158 (78)
TEAEs in ≥2% of participants treated with sparsentan, n (%)		
Peripheral oedema (mostly mild, none severe)	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalaemia	27 (13)	21 (10)
Anaemia	10 (5)	5 (2)
Acute kidney injury†	9 (4)	2 (1)
Transaminase elevations >3×ULN	5 (2)	4 (2)



*Median treatment duration: 86.9 weeks.

†Acute kidney injury was typically reported based on changes in serum creatinine between study visits.

TEAE: treatment-emergent adverse event; ULN: upper limit of normal.

PROTECT study ongoing, Barratt said that full 2-year data output on the confirmatory eGFR endpoint is eagerly anticipated later in 2023.

Conclusions

IgAN is a disease with great unmet need for new, effective, and well-tolerated therapies. Proteinuria has been established as a surrogate endpoint for clinical outcomes in IgAN, facilitating clinical study towards accelerated drug approval. Modelling of clinical outcomes based on the IgAN RaDaR cohort have allowed the estimation of future benefits from proteinuria endpoints in Phase III studies in IgAN. In the PROTECT study, sparsentan produced an early, sustained reduction in proteinuria at 9 months that was superior to that of irbesartan, thus predicting a clinically meaningful effect on disease progression that is to be confirmed in long-term analyses.

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Abstract Highlights

The following selected highlights explore several fascinating abstracts that were presented at the 60th European Renal Association (ERA) Congress 2023. Topics covered include vascular access in haemodialysis, renal transplantation, acute kidney injury, IgA nephropathy, and cardiovascular risk in chronic kidney disease.

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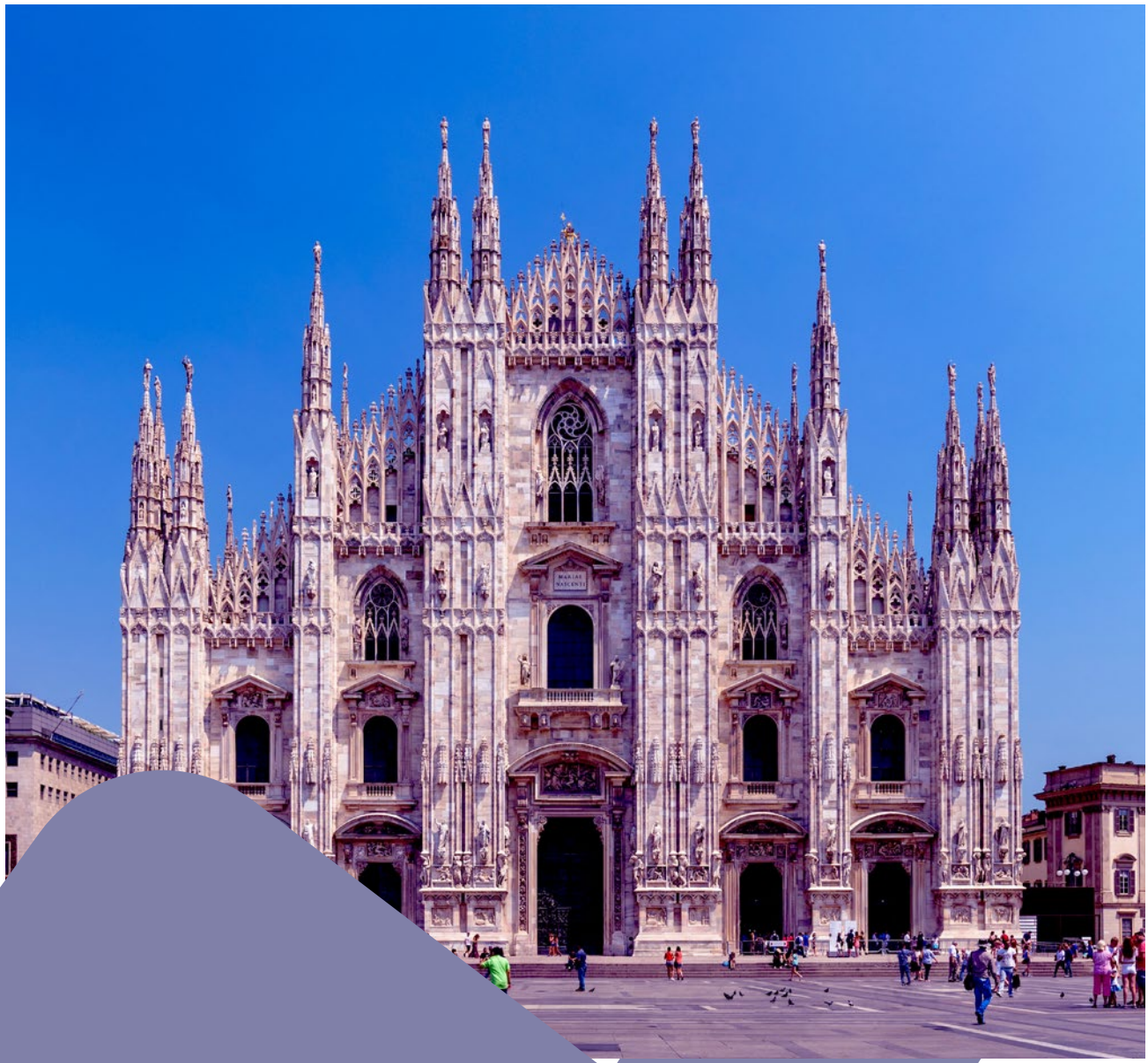


Autosomal Dominant Polycystic Kidney Disease: Identifying Early Disease Progression Risk Factors

RETROSPECTIVE analysis of longitudinal data from patients with autosomal dominant polycystic kidney disease (ADPKD) unveils early-onset hypertension (diagnosis at <18 years of age) as a risk factor for rapidly progressive disease.

The age at which patients with ADPKD reach kidney failure varies, with some patients progressing to renal failure rapidly, whilst others progress slowly. There is an unmet need for early biomarkers that enable clinicians to differentiate between patients who progress rapidly from those who progress slowly. Developing hypertension before 35 years of age was highlighted by the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score as a risk factor for rapid decline in renal function.

In light of this, researchers from multiple centres across the USA and Belgium sought to evaluate data from a subgroup of patients with ADPKD who developed renal failure, defined as chronic kidney disease Stage 5, or the start of renal replacement therapy, before the age of 40 years. The team reviewed data on renal function, comorbidities, and childhood history from 200 patients, and used life table and proportional hazards analysis to evaluate any associations between clinical parameters and time to renal failure.

Median age of ADPKD diagnosis was 22.3 years, and median age for onset of renal failure was 36.2 years. Of the 200 patients, 128 (64%) had a diagnosis of hypertension, and four of these had a diagnosis before the age of 10 years. The researchers found that onset of hypertension before 18 years of age correlated with significantly faster progression to renal failure (univariate hazard ratio: 2.07; 95% confidence interval: 1.32–3.25). The team also noted that median age for first urological event was 27 years, and that 71 patients (35.5%) had a history of urinary tract infections, 67 (33.5%) had haemorrhagic cysts on abdominal imaging, 66 (33.0%) presented with gross haematuria, and 40 (25.0%) presented with renal stones.

The authors concluded that early-onset of hypertension (<18 years of age) was a risk factor for rapid progression to renal failure, and suggested that ambulatory blood pressure monitoring in children with ADPKD may be useful in identifying those at risk of rapid disease progression. ●

"The team reviewed data on renal function, comorbidities, and childhood history from 200 patients."

Predicting Renal Outcomes Through Combined Activity and Chronicity Score

COMBINED assessment of acute inflammatory activity and chronic changes on kidney histology could be used to predict renal outcomes in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis with glomerulonephritis (AAV-GN), according to a study presented at ERA 2023. Previous data has suggested that chronic changes on kidney biopsies could be used to stratify the risk of kidney failure with AAV-GN, and this study aimed to evaluate the impact of inflammatory activity on predictions of renal outcomes.

The retrospective cohort study included 326 patients with AAV and active renal disease who were myeloperoxidase positive, or were serum anti-proteinase 3 anti-neutrophil cytoplasmic antibody-positive and had kidney biopsies available to score. Researchers assessed inflammatory activity through the Activity Index (AI), indicating a ratio between the number of crescents and/or necrosis and the total number of glomeruli, in percent, with the following scores: 0–5=0; 6–10=1; 11–15=2; 16–20=3; 21–25=4; 26–37.5=5; 37.6–50=6; 51–65=7; 66–80=8; 80–90=9; and 90–100=10. The team also evaluated chronicity through the Mayo Clinic Chronicity Score (MCSS), and summed both scores for a combined score. The participants were classified into three classes according to the risk of progression to kidney failure, including low-, intermediate-, or high-risk.

Researchers noted that median estimated glomerular filtration rate correlated with overall risk categories. Those in the high-risk category were more likely to have an estimated glomerular filtration rate <30 mL/min/1.73 m². Those at low risk were more likely to experience renal recovery; however, those at higher risk were more likely to experience kidney failure at 12 months, and to need dialysis. Furthermore, the combined score of AI and MCSS independently predicted risk of kidney failure at 12 months, especially in patients who were classified as high risk, and patients with proteinase 3-anti-neutrophil cytoplasm antibodies.

The team concluded that combined assessment of acute inflammatory activity and chronic changes on kidney histology independently predicted renal outcomes, and that the impact of inflammatory activity is cumulative to chronic changes in patients with AAV-GN. ●

"The participants were classified into three classes according to the risk of progression to kidney failure."

Carotid Plaque Thickness Predicts Cardiovascular Events and Death in Patients with Chronic Kidney Disease

NOVEL research presented at ERA 2023 investigated risk scoring systems in chronic kidney disease (CKD), and how they frequently underestimate elevated cardiovascular (CV) risk. The implementation of the coronary artery calcification score (CACS) has improved the prediction of CV events, and in recent years ultrasound has become an increasingly useful tool allowing for the analysis of carotid arteries to measure maximal carotid plaque thickness (cPTmax). The authors sought to investigate whether cPTmax can be used to predict CV events in patients with CKD for the first time, as well as compare the predictive value of cPTmax and CACS. cPTmax is defined as the radial distance from the media-adventitia interface to the intima-lumen interface towards the centre of the arterial lumen.

> **"The authors sought to investigate whether cPTmax can be used to predict CV events."**

The investigation included 200 patients with Stage 3 CKD. All patients had the thickest part of their carotid artery plaque measured using ultrasound between 2016 and 2017. The authors undertook statistical analysis on the highest cPTmax, giving an intra-observer coefficient of 9%. The patients were then divided into three groups based on their cPTmax score: no plaques; cPTmax 1.0–1.9 mm; and cPTmax >1.9 mm. Additionally, 175 of the patients underwent a non-contrast CT scan of their coronary arteries to calculate their CACS, and were divided into four groups: no calcification; CACS: 1–100; CACS: 101–400; and CACS: >400. The investigators then traced follow-up time, which was defined as the time of first major CV event or death of any cause (MACE).

The results of the investigators' analysis demonstrated an average follow-up time of 5.4 years. CV events were experienced by 20 patients (10%), and 28 patients died (14%). Patients with no plaque at baseline had the lowest risk of MACE, patients with cPTmax 1.0–1.9 mm showed an intermediate risk, and patients with cPTmax >1.9 mm had the highest risk. After adjustment for other factors, such as age, sex, diabetes, smoking, hypertension, and hypercholesterolemia, only patients with cPTmax >1.9 mm demonstrated a significantly increased hazard ratio (of MACE; hazard ratio: 3.2; confidence interval: 1.1-9.3; $p<0.05$). Additionally, the researchers applied C-statistics to assess whether ultrasound or non-contrast CT had a better predictive value for MACE. The analysis found predictive accuracy similar between the two methods (cPTmax [0.21; $p<0.0001$] and CACS [0.21; $p<0.0001$]).

The researchers concluded that the small study indicated that cPTmax and CACS showed equal accuracy and potential for predicting MACE in CKD. However, they highlighted that ultrasound imaging is more convenient, safer, and widely available compared to non-contrast CT. Additional study in larger cohorts is needed to further assess the value of cPTmax in predicting CV risk in CKD.

Is Kidney Replacement Therapy Affected by Arteriovenous Fistula Formation?

TO DATE, several retrospective studies have supported kidney protective effects in arteriovenous fistula (AVF) formation surgery. However, these studies have been limited by biases, including selection bias, and immortal time, in which participants have been unable to experience the study's outcome during a given period of follow-up.

A new study, carried out by the Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, UK, aimed to investigate whether the formation of AVF can delay the start of kidney replacement therapy in patients who have Stage 5 chronic kidney disease. Researchers applied target trial emulation methods, in which the previously mentioned biases are absent.

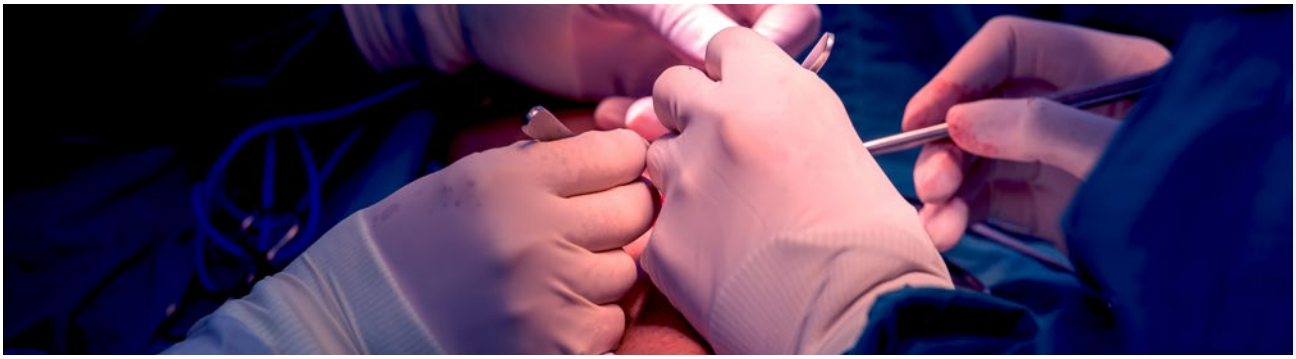
The study included 2,988 adult patients in the Strathclyde Electronic Renal Patient Record database, who attended the 'low clearance' nephrology clinic in the West of Scotland region between 1st January 2010–1st May 2022, and whose estimated glomerular filtration rate (eGFR) was <15 mL/min/1.73m². Patients were excluded if they had prior AVF, or arteriovenous graft formation. The study randomised patients (45% female; mean age: 64) to receive either an AVF immediately, or not to receive one.

Each patient who was given AVF formation was matched to another patient who had not undergone this procedure, but who was still eligible to participate in the study. Patients were matched in age (within a 5-year range), sex, and eGFR (within 0.5 mL/min/1.73m²). Researchers also adjusted for baseline confounders, such as medication use, blood pressure, comorbidities, age, and sex, as well as serum and urine biochemical measurements (eGFR Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI], and for 6 months preceding trial; albumin; C-reactive protein; urine protein to creatinine ratio; haemoglobin; phosphate; ferritin; and adjusted calcium). The study's primary outcome was kidney replacement therapy. Hazard ratios were estimated using estimated restricted mean survival time from Kaplan–Meier curves and Cox regression. A mixed effects model analysed the eGFR slope primary endpoint.

AVF formation was found to be interlinked with a higher risk of kidney replacement therapy (hazard ratio: 1.45; confidence interval: 1.20–1.45; p<0.001), as well as a lower risk of death (hazard ratio: 0.68; p=0.001). The group who received the AVF procedure demonstrated a lower kidney replacement therapy-free survival rate, with an estimated restricted mean survival time of 265 days.

In this study, researchers were unable to identify a kidney protective effect in AVF formation. Their findings prove the usefulness in using target trial emulation to approach research avenues, in which randomised controlled trials are impractical.

"Each patient who was given AVF formation was matched to another patient who had not undergone this procedure."



Shedding Light on The Outcomes and Epidemiology of IgA Nephropathy

FINDINGS from a large retrospective observational study of patients with IgA nephropathy (IgAN) from a UK centre details the disease epidemiology as well as patient outcomes.

The authors reviewed clinical data from 401 patients with biopsy-proven IgAN at their institution between January 2000–December 2019, with the aim of describing the cohort epidemiology, determining the effect of immunosuppression, and assessing patient outcomes, including progression to end-stage kidney disease requiring renal replacement therapy (RRT) and mortality.

Of the 401 patients included, median age was 45 years, 87.5% were White, and 69.6% were male. Median cohort values for creatinine, estimated glomerular filtration rate (eGFR), and urine PCR were 142 µmol/L, 46.7 mL/min/1.73m², and 183 mg/mmol, respectively. Immunosuppression was used in 20.4% of patients in the cohort, and renin-angiotensin system blockade was used in 79.6% of patients. Median follow-up length was 51 months.

Rate of change in eGFR was used to assess chronic kidney disease progression, and all available eGFR measurements were used to generate a linear regression slope. The rate of change in urine PCR was calculated in a similar manner. The median change in urine PCR was -4.46 mg/mmol/year, and the median rate of eGFR decline was -1.31 mL/min/1.73 m²/year. Progression to end-stage kidney disease requiring RRT occurred in 29.7% of patients, and mortality occurred in almost one-fifth of patients (19.7%).

To evaluate the factors associated with mortality, a Cox regression analysis was performed. This identified increasing age, non-White ethnicity, creatinine, urine PCR, hypertension, renin-angiotensin system blockade with angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, diabetes, cardiovascular disease, and biopsy E and T scores as factors associated with mortality. Of note, immunosuppression use was not found to be associated with mortality or need for RRT.

The Cox regression analysis further identified hypertension, creatinine, urine PCR, and use of angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, as factors associated with need for RRT.

> **"Immunosuppression use was not found to be associated with mortality."**

Patients treated with immunosuppression had a higher urine PCR than those treated without immunosuppression, at 301.5 mg/mmol compared with 141 mg/mol ($p<0.001$), and were more likely to have a total MEST score of >2 (42% versus 29.1%; $p=0.041$). Furthermore, patients treated with immunosuppression saw a greater reduction in proteinuria over time compared to those treated without immunosuppression at -16.8 mg/mmol/year and -2.64 mg/mmol/year, respectively. However, no difference was seen in eGFR decline over time between those treated with or without immunosuppression at -1.18 mL/min/1.73 m²/year and -1.32 mL/min/1.73 m²/year ($p=0.703$), respectively.

Overall, the researchers concluded that this large study provides real-world data that will be useful for practicing clinicians, and that whilst immunosuppression was associated with a larger reduction in proteinuria, this did not lead to mitigation of renal function decline.

Which Vascular Access is Best for Older Patients Receiving Haemodialysis?

DETERMINING the best approach for vascular access in patients >75 years of age with end-stage renal disease (ESRD) is challenging. Researchers from the General University Hospital of Alexandroupolis, Athens, Greece, and the Papageorgiou General Hospital of Thessaloniki, Greece, performed a meta-analysis to assess the outcomes following different vascular access procedures in patients ≥75 years with a diagnosis of ESRD.

The authors used MEDLINE and Scopus electronic databases to search for eligible articles published up to October 2021. In total, 12 articles met the inclusion criteria, all of which were retrospective cohort studies. The initial step of the analysis looked at five studies that focused on primary patency rates of autologous versus prosthetic vascular access for haemodialysis. The second step of the analysis reviewed articles that compared primary and secondary patency rates of forearm (distal) versus upper arm (proximal) fistulas.

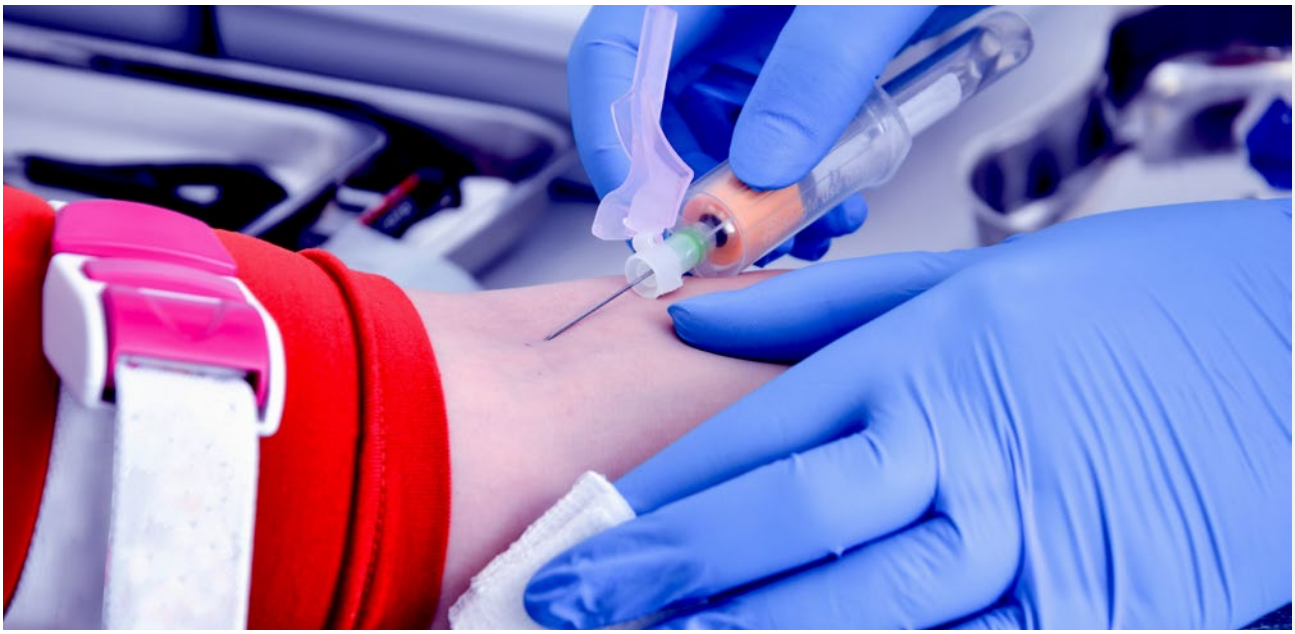
The analysis for the first step showed that 24-month primary failure rate favoured autologous arteriovenous fistula (AVF) access compared with prosthetic vascular access (odds ratio [OR]: 0.56; 95% confidence interval [CI]: 0.38–0.83; p=0.003).

These results signify a patency benefit in use of autologous AVF in patients aged ≥75 years with ESRD.

The analysis for step two revealed that 12-month primary failure rate was in favour of proximal fistulas (OR: 2.1;, 95% CI: 1.53–2.97; p=<0.00001). The secondary patency rate was also superior in proximal autologous fistulas (OR: 1.76; 95% CI: 1.12–2.78; p<0.01), suggesting that proximal AVFs are favourable as the vascular access of choice in patients ≥75 years of age with ESRD.

> **"The secondary patency rate was also superior in proximal autologous fistulas."**

The researchers concluded that whilst there remains no clear answer regarding the best vascular access approach for haemodialysis in older patients, the study analysis highlighted that proximal autologous AVFs have better patency rates compared with distal AVFs, and that creation of autologous vascular access in patients ≥75 years of age should not be excluded. ●



Using Middle Molecule Blood Tests in Incremental Dialysis

A RETROSPECTIVE analysis was conducted to assess the impact of incremental versus conventional haemodialysis initiation. The use of incremental dialysis has shown potential benefits, including improved patient quality of life, reduced treatment burden, and health economic benefits.

The Kidney Disease Outcome Quality Initiative (KDOQI) has recommended the option of incremental dialysis when renal urea clearance (KRU) is ≥2 mL/min, and patients must undertake frequent interdialytic urine collections to monitor residual kidney functions and avoid underdialysis. Due to the inconvenience of this process, some alternative methods of RKF monitoring have been studied, including the assessment of blood levels of middle molecules through β_2 microglobulin (B2M) and β-trace protein.

The study included an analysis of data from 55 patients from a multicentre feasibility randomised controlled trial.

The participants were followed up for up to 12 months, with monthly interdialytic urine collections to assess RKF, as well as monthly B2M and β-trace protein measurements. A middle molecule-based KRU equation and B2M cut-off level was used to predict RKF, and results were compared with the interdialytic reading to assess reliability in identifying patients with the cut-off point of KRU >2mL/min.

Results from the study revealed that the middle molecule-based KRU equation had 62% sensitivity and 84% specificity, and the B2M cut-off level of 0.5 L/day combined predicted KRU >2, with 70% sensitivity and 98% specificity. Overall, this result revealed that 1.8% of patients would have had underdialysis using these methods of monitoring. The researchers concluded that the use of blood B2M level alongside urine volume assessment was a reliable and safe predictor of RKF for incremental dialysis, which would mitigate the need for urine collection. ●

"The study included an analysis of data from 55 patients from a multicentre feasibility randomised controlled trial."

Racial Disparities in Living Kidney Donors

SOME races and ethnicities are disproportionately affected by kidney disease. A new retrospective cohort study, presented at ERA 2023, aimed to determine whether this disparity exists in living kidney donors, by evaluating the association between race/ethnicity and kidney function after donation.

The study included data from the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) on 136,814 living kidney donors undergoing donation between June 1972–September 2022. Researchers used multiple Cox proportional hazard regression analyses to examine time-to-event of >35% rising post-donation serum creatinine from pre-donation serum creatinine. Of the participants, 70% were White, 14% Hispanic, 11% Black, 4% Asian, 0.61% multi-racial, 0.47% American Indian/Alaska Native, and 0.25% Hawaiian/other Pacific Islander. In total, 75% of donors experienced an event during the follow-up time (median 6.27 months), with an incidence rate of 0.09 person-months.

Black patients had a significantly higher risk of increased post-donation serum creatinine >35%, while Hispanic and multi-racial groups had a significantly lower risk (hazard ratio [HR] Black: 1.03; 95% confidence interval [CI]: 1.01–1.06; HR Hispanic: 0.95; 95% CI: 0.93–0.97; HR multi-racial: 0.92; 95% CI: 0.84–0.99). This remained the case after adjusting for gender, USA citizenship, age, pre-donation BMI, education, systolic and diastolic blood pressure, post-donation proteinuria, serum creatinine, history of pre-donation hypertension, and interaction term between race/ethnicity and age. There were no significant differences in risk among other races/ethnicities. The team also noted that age was an effect modifier, leading to attenuated risk for increased serum creatinine >35% in older Asian, Hispanic, and multiracial groups.

"Black patients had a significantly higher risk of increased post-donation serum creatinine >35%."

The team concluded that being Asian was protective, and Black patients were at risk of increased post-donation serum creatinine, compared with White groups. Furthermore, outcomes were not worsened in elderly Asian, Hispanic, and multi-racial living kidney donors compared to younger patients with the same race/ethnicity. ●

Acute Kidney Injury in Hospitalised Patients Remains Unrecognised

UNDIAGNOSED acute kidney injury (AKI), which leads to a higher risk of complications and mortality, is an unrecognised issue in hospitalised patients, according to data presented at ERA 2023. While attempts to point attention to the condition and uniform its diagnosis have been made, recognition of this condition remains a problem.

The study aimed to evaluate the impact of underdiagnosed AKI in hospitalised patients at the IRCSS Policlinico San Martino, Genoa, Italy, between 1st January 2016–31st December 2019. Data including clinical data, length of hospital stay, serum creatinine (sCr), comorbidities, death, and primary diagnoses were analysed. Patients with Stage 4–5 chronic kidney disease were excluded. In the 56,820 remaining patients, the team defined and graded AKI following the Kidney Disease Improving Global Outcomes (KDIGO) criteria, comparing lowest sCr during hospitalisation, representing baseline kidney function, to peak sCr. The cohort was divided into three groups: those with no AKI; those with AKI calculated by sCr changes and formally codified in hospital discharge form (diagnosed AKI); and those with AKI calculated by sCr changes but not codified in hospital discharge form (undiagnosed AKI). Clinical characteristics and outcomes of the three groups were compared.

Data showed an incidence of AKI of 24.5%, with only a small percentage reported in some wards, including 13% in surgical wards, 27% in medical wards, and 19% in intensive care units, compared with 78% in the emergency department. Prevalence of comorbidities, including heart failure, diabetes, and heart failure, as well as sepsis and myocardial ischaemia, was higher in those with AKI (diagnosed and undiagnosed), compared with those without AKI. These patients also had major mortality risk and significantly longer hospitalisation.

> **"These patients also had major mortality risk and significantly longer hospitalisation."**

The team concluded that recognition of AKI in hospitalised patients remains a problem that needs to be faced, as this category of patients is at high risk of complications and mortality. ●

Screening Tool Can Predict Stenotic and Thrombotic Vascular Events

VASCULAR access (VA) risk score could be a useful screening tool to assist decision making, according to research presented at ERA 2023. Alshymaa Eltahan, Salford Renal Department, Northern Care Alliance NHS Foundation Trust, Greater Manchester, UK, and colleagues studied the accuracy of predicting stenotic/thrombotic vascular events with remote monitoring technology that uses VA data routinely collected during haemodialysis treatment. They calculated the access risk score retrospectively in a blinded fashion, using data from all haemodialysis sessions from two satellite units for 12 months.

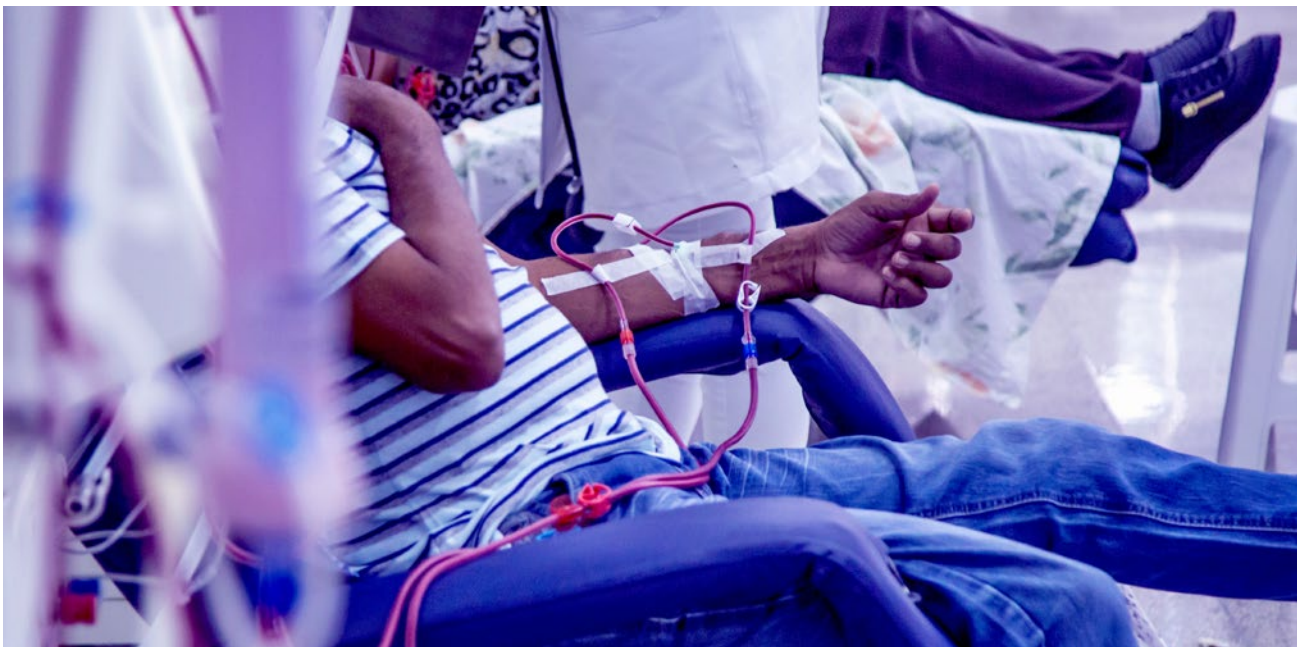
The researchers identified patients with significant VA events, such as thrombosis, and those without an event through electronic records. They calculated the Access Risk Score as an average of the scores from three consecutive treatments, with a high-risk score (HRS) defined as ≥7. Clinically detected malfunctioning fistula information was retrieved from the last clinic letter and multidisciplinary meeting notes before the event. For patients who were event-positive, VA data from the previous 2 months was generated, while data for 5 consecutive months and 1 month follow-up was included for negative patients.

Of the 141 patients with Vasc-Alert (Vasc-Alert LLC, Lafayette, Indiana, USA) data, 60 were dialysed by a tunnelled line. A total of 10 out of 81 patients with arteriovenous fistula or graft had ≥2 HRS 2 months before the vascular event. Of the 46 patients without a vascular event, 15 had ≥2 HRS, while four patients had only the one HRS.

The positive predictive value of HRS ≥2 was 40.0%, while the negative predictive value was 93.9%, with a sensitivity and specificity of 83.3% and 67.4%, respectively. A history of clinically detected malfunctioning fistula and previous access to stenosis was associated with vascular events.

While this research can be a useful tool when screening patients for VA risk stratification, prospective studies are needed to evaluate its usefulness in the VA surveillance pathway. ●

"Prospective studies are needed to evaluate its usefulness in the VA surveillance pathway."



Anaemia of Chronic Kidney Disease: Aligning Patient and Physician Awareness - Interviews with Three Key Opinion Leaders and Patient Advocates

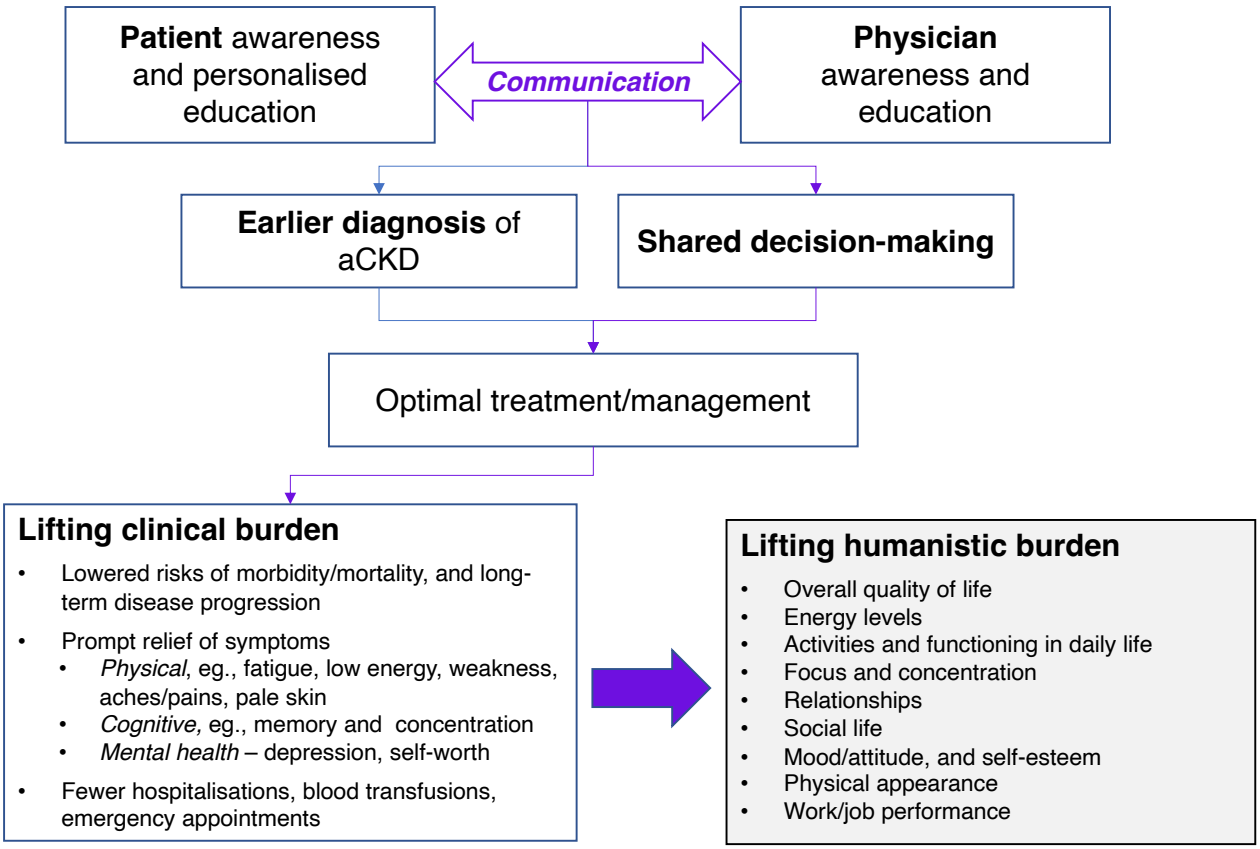
Interviewees:	Christoph Wanner,[1] Daniel Gallego,[2] Jemma Reast[3] 1. University Hospital of Würzburg, Germany 2. European Kidney Patients' Federation (EKPF), Spain 3. London Kidney Network (LKN), UK

Disclosure:	Wanner has received honoraria for participating in steering committees, advisory boards, or lecturing, from Amicus, Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Chiesi, CSL-Vifor, Eli Lilly and Company, FMC, GlaxoSmithKline, Novartis, NovoNordisk, Sangamo, Sanofi, and Takeda. Gallego declares no conflicts of interest. Reast has received speaker fees from GlaxoSmithKline for participation in expert sessions.
Acknowledgements:	Medical writing assistance was provided by Juliet George, Chester, UK.
Disclaimer:	The opinions expressed in this article belong solely to the three named interviewees.
Support:	The publication of this interview feature was supported and reviewed by GSK.
Keywords:	Anaemia of chronic kidney disease (aCKD), disease awareness, education, haemoglobin (Hb), patient empowerment, quality of life (QoL).
Citation:	EMJ Nephrol. 2023; DOI/10.33590/emjnephrol/10305420. https://doi.org/10.33590/emjnephrol/10305420.

Summary

Anaemia is a common and serious complication of chronic kidney disease (CKD) that can greatly impact the daily lives of patients. However, poor awareness around anaemia of CKD (aCKD), from both physicians and patients, may impede its identification and treatment. During interviews conducted by EMJ in April 2023, leading nephrologist Christoph Wanner, University Hospital of Würzburg, Germany, and two patients/patient advocates, Daniel Gallego and Jemma Reast, gave their informed opinions on this topic. From their different viewpoints, they described how greater understanding of symptoms and treatment options could empower patients to make better choices for their own care. At the same time, they considered how greater physician awareness of aCKD, and the human impact beyond haemoglobin levels could influence diagnosis and treatment priorities. Aligning these two perspectives, they also discussed the powerful benefits of improved communication and shared decision-making between patient and physician, and its potential for relieving the burden of aCKD.

Figure 1: Benefits of aligning patient and physician awareness of anaemia of chronic kidney disease.



aCKD: anaemia in chronic kidney disease.

Interviewee Biographies

Christoph Wanner

Professor of Medicine and Chief of the Division of Nephrology and Hypertension, University Hospital of Würzburg, Germany; President of European Renal Association (ERA)

Christoph Wanner's research in the field of chronic kidney disease of diabetic and non-diabetic origin has led to the overseeing of large outcome trials to improve the life of patients with kidney disease and preserve kidney function. Wanner has been Principal Investigator of the 4D study, and steering committee member of the SHARP, EMPA-REG Outcome, EMPA-KIDNEY, and ASCEND trials. Wanner has published more than 900 PubMed-referenced scientific articles. In 2012, they received a doctor honoris causa from the Charles University of Prague, Czechia, and the highest awards from the European Renal Association (ERA) and the German Society of Nephrology.

Daniel Gallego
Patient with CKD, Spain; President of the European Kidney Patients' Federation (EKPF)

Daniel Gallego was diagnosed with CKD in 1993, aged 19 years, following a visit to the emergency department with a suspected sprained ankle. Gallego began haemodialysis in 1995, and received a kidney transplant in 1998, which subsequently failed. They remain on haemodialysis, and have experienced the symptoms of anaemia throughout their life with CKD. Alongside their considerable experience as a patient, Gallego is President of the EKPF, and was formerly President of the Spanish Kidney Patient Federation (Association for the Fight Against Kidney Diseases [ALCER]), working to improve lives and offer hope for people living with CKD.

Jemma Reast
Patient with CKD, UK; advocate for patient-led healthcare, London Kidney Network (LKN), UK

Jemma Reast was diagnosed with CKD aged 2 years, following an acute kidney infection (*E. coli*) in 1997. At age 15 years, Reast's condition went into rapid decline, and they underwent a kidney transplant from their father. Shortly afterwards, they developed haemolytic-uremic syndrome, which caused significant damage and scarring to the donor kidney. Consequently, and with signs of long-term organ rejection, Reast required a second kidney transplant at age 24 years. They remained on peritoneal dialysis for 2 years during the COVID-19 pandemic, during which anaemia was a significant problem, before receiving a transplant from their sister. Reast currently works in healthcare research, and is also an advocate for patient-led healthcare with the London Kidney Network (LKN), UK.

BACKGROUND TO ANAEMIA OF CHRONIC KIDNEY DISEASE

CKD is a complex condition that involves many different body systems and symptoms, alongside the risk of serious complications such as anaemia.[1] Exacerbating the heavy burden of CKD, anaemia can negatively impact morbidity, mortality, and healthcare resources, as well as the daily functioning and emotional health of patients and their families.[2-5] However, differences between patients' and physicians' perceptions around anaemia and its treatment in CKD (aCKD)[6] could affect patient care. To provide insight on this topic, the views of a clinical expert in CKD, Christoph Wanner, and two patients/patient advocates with CKD, Daniel Gallego and Jemma Reast, were sought.

CKD is characterised by a decline in kidney function (measured as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), or by moderately increased or severely increased albuminuria (urinary albumin–creatinine ratio: ≥3 mg/mmol) with well-preserved kidney function.[7] Studies have demonstrated that anaemia of CKD, defined as haemoglobin <13.0/12.0 g/dL for adult males and females who are not pregnant,[8] is associated with an increased risk of CKD progression, major cardiovascular events, and all-cause mortality.[3,5] Wanner explained: "Dysfunction of the heart is the most prominent comorbidity in CKD, and observational studies show that anaemia affects left ventricular function.[9-12] Patients with anaemia of CKD can have a shorter lifespan, due to the considerable comorbidity of cardiovascular disease, and anaemia is a very common complication of CKD." Due to this potentially severe clinical impact, Wanner recommends screening for anaemia from the mild/moderate stages of CKD (Stage 3; eGFR: 30–60 mL/min/1.73 m^2), although they noted it becomes more common as the disease progresses, estimating that 8 out of 10 people who enter dialysis have anaemia.

THE IMPACT OF ANAEMIA FOR PATIENTS WITH CHRONIC KIDNEY DISEASE

Wanner said that tiredness and fatigue, and lack of energy are the two main symptoms reported by patients with aCKD. However, based on their own patient experiences, Gallego and

Reast emphasised that the impact of anaemia goes far beyond a discrete list of symptoms. "Anaemia is so multifaceted, and it can affect not just you but your whole circle," said Reast. "For physical symptoms like extreme tiredness, the impact is not being able to work, or have the energy to do what you want to. I am quite an active person, but when I was at my most anaemic I was struggling with heavy legs and back pains, and couldn't even get up a short flight of stairs. Then there's the cognitive side. People talk about 'brain fog' in CKD, but don't necessarily talk about how it can be connected to, and exacerbated by, anaemia. I would forget words and wouldn't really want to converse, so I just shut myself away. I was lucky that my employer was really understanding, and I was able to get work-related health assessments, but I know a lot of people are not so lucky." Gallego added: "When I was diagnosed, I felt devastated because I didn't want to live with this condition all my life. I felt really, really tired, but didn't know about the importance of haemoglobin or iron. Anaemia is a real disability because you feel powerless, you lack energy and focus, and you are not able to keep up with what you did before, so you feel frustrated and disappointed. Importantly, it also affects physical appearance and self-esteem, which really matter to patients."

Reast was also frank about having struggled with mental health in CKD, describing how fatigue had affected their self-worth: "If you don't feel you can sustain relationships or provide value to other people because you've got no energy, it can be really demoralising because you feel completely worthless. It changes your whole personality." Gallego concurred: "Sometimes the symptoms of anaemia are very similar to those of depression: tiredness, lack of energy, feeling disappointed and frustrated." In a particularly powerful example, Reast described a challenging period pre-transplant when it was not just their own mental health that was affected: "I could barely walk. It was really distressing for me, and also for my boyfriend who was looking after me. He'd previously known me as this really healthy, active person, and due to what he saw me go through, he's had to go to therapy. I think a lot of that was down to me being so severely anaemic."

DIAGNOSIS AND MONITORING OF ANAEMIA

Despite the marked impact of anaemia symptoms on patients' daily lives, the interviewees spoke of how diagnosis and subsequent monitoring of anaemia remains centred on clinical (haemoglobin) testing, highlighting a sharp contrast in patient versus physician perceptions. Wanner observed: "The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for anaemia of CKD were issued over 10 years ago,[8] and over the many years of anaemia treatment [since the arrival of erythropoietin in the 1980s], we have arrived at this broad, easy-going practice in our nephrology clinics, overfamiliarity perhaps, paying less attention, and just measuring haemoglobin because it is easy and cheap. Listening takes time, so there is a tendency not to take account of a patient's signs and symptoms when haemoglobin levels are still within [the accepted] range." Reast's and Gallego's experiences as patients also reflected this situation, with minimal follow-up of their anaemia, aside from blood tests, taken at 3–6 monthly check-ups.

However, all three interviewees felt that change was needed, and that patient-reported signs and symptoms should be considered when assessing anaemia across the course of CKD. "What patients feel should be important, and at the moment doctors have forgotten this," remarked Wanner. Gallego agreed: "There needs to be a focus on the clinical impact of CKD, of course, but once survival is ensured then we need to try to tackle the humanistic burden of this chronic disease. What really matters to the kidney patients is health-related quality of life (QoL), daily life activities, and social and life participation."

This is consistent with the findings of a survey from the International Consortium for Health Outcomes Measurement (ICHOM), in which patients identified fatigue as amongst the most important outcome measures for assessing CKD, alongside survival, daily function/activities, and overall QoL.[13] It was suggested that better awareness amongst physicians of how anaemia presents in patients' daily lives, and the impact this has, could not only improve management, but also help with earlier diagnosis. Wanner explained: "At the moment, nephrologists' time is

greatly focused on addressing the progression of kidney disease because we have fantastic medications, and so anaemia is pushed to the second line. However, if anaemia isn't diagnosed promptly, it can have an impact on the patient's long-term condition. The pathology clearly advances." In short, it is felt that anaemia needs to be a greater priority in the minds of physicians.

PATIENT AWARENESS

In the period around diagnosis, any discussion of anaemia with the patient was said to be largely solution or treatment-based, rather than involving any background or education to help with understanding the condition. In particular, Reast spoke of a disconnect between the symptoms they had experienced, and any knowledge that these were due to anaemia rather than CKD itself: "There was never an obvious link. I was told that my haemoglobin was a bit low, which meant I was anaemic, and I was going to be given treatments to help me have more energy, and it was only brought up when it was a problem. The first time I realised it was related to CKD was when I was waiting for my first transplant and I started receiving [erythropoietin] injections, but it was only a couple of years ago that I really understood that I had anaemia and I also had CKD, and that there was a link between the two. Previously, I had put my anaemia symptoms down to general CKD, and I think many people do that. There's a lot of resignation because CKD is known to be difficult, and the tendency is just to get on with it." Gallego summarised the situation: "You think it's all because of the CKD, and I think we need to change that."

These accounts suggest that patient education around aCKD is currently inadequate. Gallego commented: "Nobody gave me leaflets or information about available resources regarding anaemia, and it is really difficult for CKD patients to find patient-specific materials related to anaemia. Scientific papers and guidelines are too technical and detailed for patient communications." Reast described their knowledge of anaemia as being mostly self-taught, although they acknowledged that receiving all the information at the point of diagnosis would have been overwhelming, and likely too complex to fully comprehend. "I generally learned bits here and there along the way, and through talking to other patients," they said. "Whilst I was on dialysis there was a bit more conversation around anaemia, but I wasn't given anything or referred to any resources on anaemia specifically, so I did my own research because I wanted to know more."

Alarmingly, Reast's initial lack of understanding around anaemia affected their treatment compliance, and led to a crisis point while they were waiting for a transplant: "I didn't do my [erythropoietin] injections the way I should have done. Then, I refused to get the blood transfusions I needed, until it reached the point where they wouldn't let me leave the hospital without giving me multiple units of blood. I was scared. I was on the transplant list and didn't want antibodies to impact my likelihood of being a viable recipient, and that was a barrier in my way of thinking. I was lucky that those blood transfusions didn't cause any antibodies, but I am shocked and sad that I let it go on that long, and also that other people didn't think to intervene sooner or more strongly, or give me more information. Once I understood more, it made my ability to be fully adherent so much easier. I still hated doing the injections, but because I'd seen the benefit, I knew that I had to keep doing them."

Patient Versus Physician Priorities

The gap in patient awareness and education around aCKD may reflect a difference in priorities between patient and physician. Gallego commented: "Clinical impact is really important for the professionals, and I understand why. I think when you report symptoms such as tiredness or lack of energy, the nephrologist does not think about anaemia, but about CKD overall, and the

"Previously, I had put my anaemia symptoms down to general CKD, and I think many people do that. There's a lot of resignation because CKD is known to be difficult, and the tendency is just to get on with it."
- Jemma Reast

reaction is to say that it's just part of the disease." Reast added that physician priorities may also be influenced by the most urgent or controllable needs, especially within a time-constrained consultation: "To an extent, I don't think physician and patient priorities are very different, but it's that there's so much going in CKD. Renal specialists are time-poor, so therefore focus very much on what they can control." Reast continued to explain that patient awareness can also influence physician priorities; for instance, the patient may find it easier to describe or recognise issues such as itching, which may be related to high phosphate levels, or dietary or fluid restrictions, while the signs of anaemia may be harder to identify. Thus, communication and the balance between physician awareness (asking the right questions) and patient awareness (raising the right concerns) are key.

TREATMENT OF ANAEMIA OF CHRONIC KIDNEY DISEASE

The 2012 KDIGO Guidelines for anaemia in patients with CKD recommend iron (oral or intravenous), erythropoietin-stimulating agents, and, in urgent and acute cases, red cell transfusion, as treatment options for aCKD.[8] According to Wanner, most patients with aCKD who require substantial iron treatment will be prescribed an intravenous infusion by their nephrologist. However, they cautioned that while anaemia may be treated well in patients who regularly attend and adhere to hospital outpatient clinics, this applied to only a minority: "Nothing is stated in the general practitioner guidelines about referral of CKD patients due to anaemia. The only recommendation is for kidney function (eGFR falling below 30 mL/min/1.73 m^2), so most patients are not treated."

If treatment is received, then the means of monitoring its effects remain centred on laboratory testing, while measurements of QoL or other patient-reported outcomes are not routinely employed. There was strong consensus that while patient input on QoL would be highly beneficial for optimising treatment, applying standard questionnaires to quantify and track patient outcomes could create challenges. Wanner commented: "We do not listen any more. We do not have patient-reported outcomes. No QoL measurements. You can give patients a form to fill out while they are waiting, which works quite well, but what do you do with this information? There isn't the time. In cardiology, there are heart failure nurses whose main job is to talk to the patients, but we do not have kidney failure nurses in nephrology." In addition, Reast commented: "It's really important that the QoL questionnaire is relevant to the individual, based on their previous/desired level of activity, and I know that some QoL measures are not."

In a complementary approach, all three interviewees suggested that a checklist of simple questions about a patient's life post-diagnosis/treatment, even something as simple as "How are you feeling?" could provide useful, qualitative information about their condition, and guide its management. Reast explained: "Then the connection could be made between what their haemoglobin's doing, how they might be feeling, and what they might be able to achieve. Then it could be a lot better managed. The questions also serve as a reminder that physicians are willing to hear about what an individual is going through and how it affects them, and that there are answers."

Impact of Treatment for Patients

The patient view was clear: optimal treatment of anaemia can be transformative. "If the treatment works well, then in only a few weeks you feel alive again," said Gallego. "You have more energy, and even your physical appearance improves. You feel more confident, with greater self-esteem, and everything improves at the same time: relationships, work, hanging out with friends. Everything comes back into your life and you feel better, happy." Reast was similarly positive about the effects of their anaemia treatment: "Physically and emotionally, I felt so much better, and was able to do much more. Prior to treatment, I couldn't walk for a minute without needing to sit down and afterwards I was able to walk 3 miles slowly, while still on dialysis. My QoL completely changed, as did my energy for things, and that then impacted my view on life. Being able to do a few more of the things

"If the treatment works well, then in only a few weeks you feel alive again." - Daniel Gallego

that I previously had to limit just makes it so much easier to have a positive mental outlook."

Reast also gave an interesting insight on how effective treatment can in itself be a means of patient education: "I struggled with mental health, particularly linked to managing some of the aspects of CKD, so didn't always do the best with compliance [with my erythropoietin injections]. Then, when it was all properly treated, I was quite annoyed at myself, because I felt so much better. Essentially, I had a bit of a wake-up call. Ultimately, I was putting myself in danger, not just in the short-term, but also long-term." Thus, patients could benefit from being better informed about the consequences of non-adherence. Reast also emphasised that a non-judgemental and human-centred approach, looking at underlying needs and wants, would make it easier for patients to "buy into their treatment."

"You have more energy, and even your physical appearance improves. You feel more confident, with greater self-esteem."
- Daniel Gallego

SHARED DECISION-MAKING AND COMMUNICATION

While it is patients who are immersed in the daily burden of anaemia, it is the physician who currently dominates the treatment decision-making process. Patients may often express preferences over side effects or the administration route, but, according to Reast, altering dosing, for example, as a reactive response to such concerns does not constitute true "shared decision-making," as it is not a two-way conversation. Current decision-making practices may also reflect a difference between patient and physician priorities. For example, in a European study of treatment preferences for anaemia of non-dialysis-dependent CKD, patients cited convenience of administration (mode/frequency), and an outcome of increased energy as important treatment attributes for which they would tolerate increased cardiovascular and gastrointestinal risk.[6] In contrast, physicians prioritised clinical efficacy, and while symptom improvement, in particular increased energy, was widely acknowledged as being meaningful for QoL, only a minority recognised mode of administration as being most important to patients.[6]

These differences in viewpoint indicate that empowering patients to contribute to shared decision-making could be influential for the treatment of aCKD. Gallego considered the timescale of this approach: "To empower people you need education, not only information. Knowledge takes time to accumulate, so at [the point of diagnosis] I think it is almost impossible to enable real, shared decision-making, but over the years, with good communication with your nephrologist, you may be able to choose a better approach to improve your anaemia symptoms." Reast described further advantages: "I think there would be a huge benefit of treatment decisions being shared because then you're invested, not just a recipient; you understand the decision, the treatment, and the impact it can have on your life. However, not all specialists welcome patient input, and don't think to bring in the patient as someone who can help control their condition, but I think that's changing." Indeed, Wanner's view is that if a patient appears knowledgeable, then the physician is likely to be more attentive, and offer a more interactive discussion. This is also Reast's experience, as through their own efforts in sourcing information, they have become better informed, and feel that their consultations now involve more shared decision-making: "I feel better able to have these conversations because I've gone out and found out information. I also learned through bitter experience, though obviously I wouldn't want that to be the case for everyone."

Asked for a physician's opinion on whether shared decision-making would be a benefit to aCKD management, Wanner was clear: "Absolutely. Because I have learned that for CKD patients, other forms of intervention and greater care are much more valuable to the patient than 'pill number 11'. Anaemia treatment would fall into the category of 'greater care', because if you talk to the patient about anaemia, many other things come to the fore. I think the communication between professional and patient is most important. Suggesting to the physician that investing in this process will, in the end, create a healthier patient to enter dialysis, and that a healthier patient will survive longer, may

be the psychological approach needed to change practice." Reast reinforced this point, explaining how an open conversation between patient and physician may help to deliver better treatment outcomes by uncovering potential issues and misconceptions. They admitted: "I never found injections easy to do, and I felt angry that there weren't better, more suitable ways of treating anaemia. I think that if [this type of conversation] had been available to me, I would have said: 'My haemoglobin hasn't changed because I have not done my injections; it's not necessarily because the treatment isn't working, it's because I'm struggling.' Taking a couple of minutes to have this sort of conversation would pay off long-term, but I think it can be really difficult because of time pressures."

IMPROVING EDUCATION AND MANAGEMENT AROUND ANAEMIA OF CHRONIC KIDNEY DISEASE

The experiences described here indicate a need for better education around aCKD, directed at both physician and patient. Reast commented: "[Education] definitely has a big impact, because the more aware I am, the more empowered I am to understand and provide benefits for myself and whoever's looking after me, and to work together with my nephrology team. I can knowledgeably look at my haemoglobin level and know how it affects me as an individual. It allows me to look after myself better and reduce my visits to hospital emergency care, to the hospital rapid assessment units, and to my general practitioner for tests."

Improving Physician Education

It was clarified that two main aspects of physician education need to be targeted in aCKD: clinical knowledge of anaemia, and understanding of patient impact and priorities through better communication practices. Concerning this first point, Wanner commented: "We have lost a lot of focus on anaemia in recent years because the erythropoietin-stimulating agent injectables were introduced, and so we knew how to manage patients, and the guidelines were forgotten. It's very difficult to re-educate physicians, but my personal opinion is that if you bring the guidelines to their attention again, a few simple things, cornerstones, the two or three main statements, it may stimulate re-education." Wanner thought that the advent of new oral medications may also bring attention back to the guidelines, and recognition of how anaemia may be better treated. Indeed, the arrival of new data and therapies have prompted an update to the KDIGO Guidelines for anaemia of CKD, last published in 2012, which is currently ongoing.[8,14,15] However, Wanner felt that a bigger stimulation for change could come from the patients: "If they convey the impression that they are not being served well, it would make a greater impact than giving physicians the guidelines to study again," they observed.

As a patient advocate, Gallego gave their view on educating physicians about patient priorities: "We need to educate professionals to tackle the anaemia symptoms in CKD, not only from the clinical perspective, but also around the humanistic burden that really matters to the patients. It is important to let them know that patients are really concerned about anaemia because it is affecting their QoL." Reast added: "The more a physician understands the breadth of impact anaemia can have on someone's life, the more seriously they're going to take it." Gallego commented: "Of course, we need to improve not only the knowledge of the professionals, but also their communication. If you ask the patients more, you will get a lot of feedback in a positive and a negative way. There are three views: one is the professional; the second is that of the patient organisation, patient advocacy; and the third is the patient testimonial, the regular people describing the reality. We joke that professionals give you the news, and patients give you the truth!" Encapsulating the situation, Wanner commented: "We need to encourage more patients to report, and we need to encourage more professionals to ask."

"We need to educate professionals to tackle the anaemia symptoms in CKD, not only from the clinical perspective, but also around the humanistic burden that really matters to the patients." - Daniel Gallego

"We need to encourage more patients to report, and we need to encourage more professionals to ask." - Christoph Wanner

Improving Patient Education

The key needs for patient education are to increase patient knowledge and understanding of the diverse potential symptoms of anaemia and its treatment, and thus empower them towards better communication and shared decision-making. However, the interviewees emphasised that for education to be most effective, it should be personalised. Gallego observed: "If all the information is given at the same time as the diagnosis, it is overwhelming. It takes years to gain knowledge and visit all the resources available, so information should be given repeatedly. Without any doubt, if you know all the possibilities and therapeutic options, you have the tools to choose better for yourself. Every patient is unique, and you need to personalise to every single patient, because what is an advantage for one may be a disadvantage for another." From their physician's view, Wanner said: "We need to educate patients to empower them, but I have so many different patients: those who are quite attentive and ask for their lab results, and others who are not interested. There are also many patients who just look through you, and you see in their eyes that they don't understand. They just need to follow your advice, whereas others would benefit from [more information]."

Wanner also made the important point that it is not always about the education itself, but about engaging patients: "[For example], if patients are given their lab results, they may not immediately understand them, but they come back to you with questions, and then you can engage them. Another [approach] is translating results into something patients can understand, and which is important to them, such as daily functioning." All three experts felt that improved awareness of the effects of anaemia in daily life, including on mental health, was central to improving patient education in aCKD. "A better awareness of all the different symptoms and how they will appear to you, as opposed to a long list of vague symptoms, is so helpful," said Reast. "Having more education and conversations about anaemia is very important, and definitely anchoring it in everyday life. The better the person understands the impact of anaemia on their life if it's left unchecked, the more seriously they're going to advocate for themselves when they see their specialist."

Materials for Patient and Physician Education

For patients, it was emphasised that educational materials should be up-to-date, credible, accessible, and bespoke for patient use, without complicated medical terminology. They should also be delivered through multiple channels (social media, websites, magazines, newspapers, apps, congresses, and meetings) and in a variety of formats (paper-based versus electronic) to create the greatest reach. In general, tools to help people make informed treatment choices were seen as useful, including a means of following and better understanding laboratory results in relation to daily life.

As a patient living with aCKD, Reast described the strengths of visual education with patient testimonies: "Especially when I was really tired, I didn't like reading. Personally, I prefer videos: you get to see the person, you hear their voice, and it's human. You can connect to that, and it has credibility. Hearing someone speak about their experiences, how important it is that anaemia is well managed, and how symptoms appear in everyday life, is so helpful because it just brings it to life." In addition, Gallego and Reast agreed that distinguishing between the symptoms of CKD and the symptoms of anaemia should be a high priority for patient education. "Being able to both actively link anaemia to CKD but also to separate it out is important, so that people don't think all symptoms are due to their CKD," said Reast.

From the physician's perspective, Wanner recommended a "refresher" of key points from the aCKD guidelines, while Gallego suggested a

patient-adapted version of the guidelines could also be useful. In addition, Wanner highlighted a need for tools to aid physician–patient communication during consultations, and also noted: "Patients need to be encouraged to report more about their symptoms, even those they may feel embarrassed about, such as sexual activity, physical appearance, and relationships; whatever they feel is important to them."

In terms of the contribution of patient organisations, Gallego spoke about the role of patient advocacy and the EKPF in delivering support and education: "We aim to help people understand CKD, and to claim equity and access for their treatments and their social rights. We also make sure that professionals and patients are always together at the round table for discussions. But the most important thing we do is to try and give hope. We say to patients that while CKD is tough, you can improve your life, your QoL, and your understanding, and we provide resources to empower them. Our ultimate goal is that they don't need us at all."

CONCLUSIONS: ALIGNING PATIENT AND PHYSICIAN AWARENESS OF ANAEMIA IN CHRONIC KIDNEY DISEASE

The three interviewees provided detailed insights into current awareness of aCKD, and related challenges. It was explained that dissecting out the symptoms of anaemia within CKD, and highlighting their impact on patients' daily lives, is a priority that needs to be better addressed. Although there is some disconnect between physician and patient standpoints, it was felt that both parties require education in order to improve disease management and to address patient QoL. For physicians, this centres on refreshing their knowledge of diagnostic and treatment guidelines, and appreciating the humanistic burden of anaemia beyond clinical (haemoglobin) measures. For patients, education around the recognition and potential relief of anaemia symptoms is key, empowering them to make informed choices and be actively involved in their care. Facilitated by raised awareness and understanding, open communication and shared decision-making between patient and physician could bring substantial benefits to people living with aCKD (Figure 1).

Key takeaways

- Anaemia is a common, serious complication of CKD that raises morbidity and mortality risks, and presents a significant humanistic burden.
- Anaemia affects all aspects of daily living, impacting on physical and mental activities, relationships, and work productivity.
- With prompt recognition and diagnosis, anaemia can be effectively treated, but this requires greater awareness from both physician and patient.
- Physicians need to be better informed about recognising anaemia and realising the significant impact it can have on patients with CKD.
- Patients need more education to identify the symptoms of anaemia, empowering them to raise potential concerns, better understand and adhere to their treatment, and obtain symptom relief and improved QoL.
- More open communication between physician and patient would facilitate shared decision-making, and deliver optimal, personalised care.

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Interviews

Sam Kant, Catherine Quinlan, and Matthew A. Sparks spoke with EMJ, sharing insights into their inspiring careers and research. The experts explored a variety of key topics in the field nephrology, including transplantation, genetic kidney disease, and medical education.

Featuring: Sam Kant, Catherine Quinlan, and Matthew A. Sparks

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Q1 What influenced you to pursue a career in medicine, and then specialise in nephrology?

I always enjoyed science and being part of a bigger community. Medicine combines these two aspects really well. I pursued nephrology because of the most fascinating pathophysiology, which spans so many areas, including acid-base, glomerular disease, dialysis, and transplantation. Above all, it gives us the opportunity to have a long-term association with our patients, from chronic kidney disease to dialysis, and then transplantation. As Atul Gawande aptly put it, medical care has two aspects: incrementalism and heroism. With nephrology, you could be a long-term comrade to patients by providing constant incremental care, but also be there when the heroism of critical care is needed. When I look back in my rear-view mirror, the above decisions were also partly influenced by the fact that I had an early exposure to medicine, having spent a lot of time in the hospital with my father, who had a kidney transplant.

Q2 Your clinical and research interests include renal transplantation, immunosuppression, and opportunistic infections. You co-authored a review in July 2022 on BK virus nephropathy in renal transplant. Could you provide a summary of the findings from this review, and the implications this has for clinical practice?

BK viraemia is a common problem in patients who have received a kidney transplant, mostly as a result of immunosuppression. While there are screening strategies that have been effective in detecting the virus in the post-transplant period, there is a lack of appropriate diagnostic techniques and treatment for the potentially ensuing BK viral nephropathy. The development of BK viral nephropathy has been associated with progressive graft loss. It is encouraging to know that there are clinical trials underway looking at modified T cells and monoclonal antibodies to treat the virus.

Q3 Is there any ongoing or novel research in the field of renal transplant medicine that you are excited about for the future management of patients with kidney transplants?

There is a continued lack of biomarkers to detect early allograft damage and guide immunosuppression. There is a lot of work being done in the space, since this will potentially not only help in enhancing graft longevity and patient survival, but also reduce adverse effects of immunosuppression, including infections, cancers, and metabolic/cardiovascular issues. In addition, there is an increased emphasis on making sure there is equitable access to organs.

Q4 You also co-authored a paper on the principles of immunosuppression in the management of kidney disease. Could you describe the key learning points healthcare professionals working in the field should take away from this article?

Before deciding on immunosuppression for a particular entity of glomerular disease, it is important to not only think about pathogenesis, but also patient profile, such as comorbidities, potential adverse effects, and extent of organ injury. It is also pertinent to think about how we can mitigate these adverse effects, which includes balancing appropriate therapeutic response with risk for toxicity.

"There is continued discovery of new facets with respect to each entity of glomerular disease."

Q5 Another of your clinical interests is glomerular disease, and in 2022, you co-authored an article discussing the advances in the pathogenesis and treatment of immune-mediated kidney diseases. Can you tell us how these advances in pathogenesis have translated clinically, and what this means for patient outcomes?

There is continued discovery of new facets with respect to each entity of glomerular disease. For example, multiple new antigens associated with the development of membranous nephropathy have now been found. The role of complements in anti-neutrophil cytoplasmic antibody-associated vasculitis and IgA nephropathy is being increasingly elucidated. As a result, multiple therapeutics are being based on these targets, which could translate into better outcomes for patients.

Q6 As a transplant nephrologist, can you tell us about some of the biggest challenges faced by both clinicians and patients pre- and post-transplant surgery?

With regards to pre-transplant, for patients on the deceased donor list, the wait time continues to be a big challenge worldwide. With regards to post-transplant, providers need to ensure continued patient education and seamless coordination of care.

Q7 Can you tell us about the evidence surrounding organ donation from deceased patients positive for severe acute respiratory syndrome coronavirus 2, and the current scientific and clinical standpoint on the use of these organs in transplant medicine?

The biggest study so far was done in 2022, looking at COVID-19-positive deceased donors using the Organ Procurement and Transplantation Network (OPTN) database. It showed that transplantation from these deceased donors was not associated with worse graft outcomes or patient survival in the post-transplant period. There is a definite need for long-term follow-up studies, but initial reports do seem encouraging.

Q8 Are you currently working on any projects within either renal transplant research or medical education that you are excited about? Are there any technological advances anticipated in the field of transplant medicine and surgery that you are excited for?

We are currently involved in projects pertaining to biomarkers, the effect of apolipoprotein 1 in kidney transplantation, desensitisation regimes, and BK viraemia/nephropathy. I am looking forward to see how the space of xenotransplantation develops, and endeavours to address inequity and new immunosuppression regimes.

Q9 You are an Organising Committee Member for the National Kidney Foundation (NFK), New York, USA. Can you tell us what your position entails?

As an organising committee member for the scientific meetings, we brainstorm various sessions that would be helpful for healthcare providers in nephrology. For the last 2 years (2022 and 2023), I have been responsible for organising the nephrology board review (US certification) for the NKF Scientific Meetings. In addition, I organise activities focused on trainees, which includes moderating a panel of experts sharing their experience in various fields in nephrology.

"I would encourage trainees of all levels, as well as consultants/attendings, to become a part of the ACP."

Q10 You are Chair of the Early Physicians Council for the American College of Physicians (ACP), which aims to assist younger clinicians with career and personal development. How did you become involved in this, and what are your main responsibilities as Chair?

The ACP plays a very active role in the development of internal medicine/general medicine trainees and supporting attendings/consultants. As a chief resident, trainee engagement and welfare were very important to me, so I became involved with the Chief Residents Association of Baltimore (CRAB), which is facilitated by the ACP Maryland. I now continue to be involved with ACP Maryland as Chair of the Early Career Physicians Council, where I am responsible for organising activities to further the cause of physicians who have finished residency, and have either entered fellowship, or become attendings/consultants. The council forms an important support structure as members transition to the next phase of their careers. To quote the words of Steve Sisson (President-elect of the ACP), we strive to be "of value to the members of ACP".

Q11 You recently presented at the ACP Maryland Williams Conference, on the topic of habits for highly effective students and interns. Can you discuss these habits, and why they are important to clinical practice?

When we transition from medical school to training, there is a perception that medical knowledge is all we need, but this is far from reality. As chief resident, when I looked back at the most successful trainees, they did have some common attributes, which I hoped to distil through this talk. Some of these habits include efficiency, or being adept in using the electronic health record to your advantage, collegial relationships with nurses, being open to opinion, and being wholly present in each clinical encounter.

Q12 In 2020, you received the Maryellen Woodward Governor's Service Award by the Maryland Chapter of the ACP for contributions to the science and patient care. Could you tell us more about this award, and what it meant for you to receive this?

I am just glad to be a part of the ACP and its mission. The leadership continues to be one of the most supportive groups I have come across. I would encourage trainees of all levels, as well as consultants/attendings, to become a part of the ACP. It is a community second to none.

Q13 You recently published an article in the *Washington Post* regarding prevention of kidney disease. Could you please elaborate on this further?

This article was written to raise awareness regarding kidney disease. It outlines risk factors and evidence-based strategies for prevention of chronic kidney disease, and addresses the often debated question of 'how much daily water intake is actually needed'.

Q14 To conclude, what has been your proudest achievement in your career so far?

I am just thankful and consider myself fortunate to have the opportunity to serve patients, and contribute to medical trainees. I do not think any of this would be possible without the excellent mentors that I have had. They surely do help us navigate our career paths, to become better doctors, and better people.

Catherine Quinlan

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Q1 When did you realise that you wanted to pursue a career in paediatric and academic nephrology?

I only ever wanted to be a paediatrician, thanks to *ER*'s Doug Ross, and my first job was on the nephrology service in Temple Street in Dublin, Ireland. In that first week, we started a newborn on dialysis, and it seemed almost magical that a child born with no kidney function could survive to live a normal life, thanks to technology and the work of this incredible team. I knew that this was the career for me.

They were an incredibly inspirational team, and I remember nurses in particular, like Sheila Boyle, who impressed me with their dedication, knowledge, and understanding of patients. Two consultants, Atif Awan and Denis Gill, both had a huge impact, as I saw how much they cared for their tiny patients and how our interventions could completely change their outcomes. I was so inspired by Gill, a Professor of Paediatrics in the Royal College of Surgeons Ireland (RCSI), who had a massive impact on the type of doctor I wanted to be. Gill opened my eyes to how teaching, research, and clinical practice could intersect to create a meaningful and satisfying career. I have been driven to uphold these standards every day of my practice since.

Furthermore, paediatrics is fun! Yes, it is serious, and frequently our patients and families find themselves in circumstances that they could never have imagined, but there are always stickers and bubbles, and a child's attitude that is firmly rooted in the now. Children impacted by kidney disease, and in particular kidney failure, have been dealt a very difficult hand in life. Kidney failure impacts every aspect of their emotional, social, and educational development. Unlike many branches of medicine, in paediatrics it is all personal. We have all been children, we all remember the challenges of childhood and adolescence, and it does not take much imagination or empathy to overlay kidney failure onto our own childhoods, and imagine how challenging it could have been.

I want to do everything in my power to enable children with kidney disease and kidney failure to live their best lives. In my opinion, this starts with making an early and accurate diagnosis so that we can start treatment that delays kidney failure; predicting the future for their families to allow them to dream big dreams that include their child's diagnosis; allowing their parents to make informed reproductive decisions in expanding their family; and, where possible, informing the selection of the best possible kidney donor.

> **"I want to do everything in my power to enable children with kidney disease and kidney failure to live their best lives."**

Q2 Alongside your clinical work, you are the Academic Lead for Graduate Research at the University of Melbourne School of Medicine, Victoria, Australia. What does this role entail?

One of my passions is education and nurturing students through their degrees to become independent researchers. As Academic Lead (Graduate Research) in the Melbourne Medical School, I am working to implement strategies and initiatives that enhance the graduate researcher experience, and improve supervisor capability. These initiatives have included a series of communication workshops and career events, as well as a monthly graduate researcher newsletter focused on promoting opportunities for collaboration and skills development.

Q3 What drove your interest in renal genetics, and how did you come to set up the renal genetics service at The Royal Children's Hospital in Melbourne in 2016?

I am an endlessly curious person, and this drove my interest in renal genetics. More than anything, I want to understand why my patients have kidney disease, and I believe that this understanding leads to better outcomes. At Melbourne Children's there is a lot of support for people with ideas and the ability to follow them through. I was lucky to link up with two fantastic clinical geneticists early on, Sue White and Zornitza Stark, as well as a genetic counsellor, Ella Wilkins, and we opened the doors of our clinical service in 2016 with the support of the Royal Children's Hospital (RCH) Foundation. This service now offers 26 multidisciplinary clinics per year, and provides a new model of care for the diagnosis and management of genetic kidney disease. From the beginning, we have integrated research into our clinical service and have worked closely with Melissa Little at Murdoch Children's Research Institute (MCRI), recruiting patients to kidney organoid modelling projects that have expanded our understanding of the pathogenetic mechanisms of kidney disease.

I am passionate about equity, and my early driver on the research side of the clinic was to generate an evidence base to support an application for federal funding for genetic testing in patients with kidney disease. Within a year, we had the data to support a move into adult services with the support of Melbourne Genomics, and since then we have gone from strength to strength.

Q4 What impact has this service had on patient care since its inception?

Since its inception, our kidney genetics service has reviewed over 500 patients, and we have set a new benchmark for diagnostic yield, while generating the evidence base to support a successful application for federal funding of genetic sequencing for patients with kidney disease in Australia.

Further outputs from the service have included guidelines for the diagnosis and management of patients with kidney disease, the development of visual genomic explainers and decision support tools, the addition of new genes to the PanelApp kidneyome (Australian Genomics, Melbourne, Australia), and the development of a registry of patients with genetic kidney disease.

Q5 You lead the Kidney Flagship at the MCRI. Could you tell us more about the Kidney Flagship, and discuss its aims and goals?

The Kidney Flagship is a multidisciplinary collaboration of clinicians and scientists at Melbourne Children's with a focus on kidneys. The flagship is a comprehensive clinical research pipeline spanning multiple research groups at MCRI, and linking with clinical services at RCH. The flagship built on my ongoing work examining genetic kidney disease from multiple perspectives: clinical outcomes, qualitative assessment, clinical utility, health economics, implementation science, research genomics, pathophysiology, functional genomics, disease modelling, drug screening, and, ultimately, the development of clinical trials.

Our vision is to end kidney failure in childhood, and our mission is to find new ways to prevent kidney failure in childhood while developing better alternatives to dialysis. We are approaching this from five different directions: aiming to empower families to drive research and clinical interventions; to provide an early and accurate diagnosis for children based on research genetics; to develop data-led approaches to manage kidney disease; to discover and repurpose therapies to treat kidney disease; and to develop transplantable stem cell-derived kidneys.

There have been two key papers[1,2] that have been major outputs from the Melbourne Genomics flagship, showing the significant clinical impact of a genetic diagnosis, and which formed a significant portion of Kushani Jayasinghe's PhD under my supervision. The first paper set a new benchmark for diagnostic yield (39%), and the second demonstrated the cost-benefit to the early application of genomic sequencing for children with glomerular disease, demonstrating an incremental cost saving of 3,230 AUD per additional diagnosis when compared to standard of care. These papers formed the evidence summary quoted by the Medical Services Advisory Committee (MSAC) in their recommendation that genomic sequencing for patients with kidney disease should be funded by Medicare in Australia. These papers were also key to the initiation of three new Medicare Benefits Schedule (MBS) item numbers, which fund genomic sequencing for patients suspected to have genetic kidney disease, along with their families and reproductive partners.

I am now fortunate to collaborate with Jayasinghe, as we are working to mainstream genomics in nephrology, and to support all nephrologists in Victoria to request and interpret genetic tests for appropriate patients in general nephrology clinics, another project funded by Melbourne Genomics.

> **"Our mission is to find new ways to prevent kidney failure in childhood while developing better alternatives to dialysis."**

Q6 Your current research focuses on the use of electronic medical record (EMR) data to locate patients at risk of kidney disease. Could you tell us more about this work, and how you foresee this being rolled out across healthcare systems?

I am passionate about achieving an early, accurate diagnosis for children, believing that this leads to the best outcomes. As our hospital moved to an electronic health record (EMR), I realised that there was an enormous amount of healthcare data sitting in the system that could be used to identify children at risk of kidney disease, if we only knew the right question to ask. In collaboration with the Centre for Health Analytics and a brilliant PhD

student, Gráinne Butler, we have utilised data in the EMR to detect a signature for early kidney disease in patients who are undiagnosed and unknown to the nephrology team. This enables us to proactively reach out to patients to offer genomic sequencing.

I believe that data-driven decision-making about healthcare can drive a new era for medical care. The power of data enables us to identify patients before they are symptomatic to proactively intervene early on, so that patients do not have to experience the impact of their disease, and improve outcomes. An example of this in practice at the RCH is the utilisation of EMR data to identify patients with haematuria who have not had follow-up samples or been referred to nephrology. If sustained, haematuria could signify a future risk of adult kidney disease, such as Alport syndrome. Once we have identified these patients, we proactively contact them to arrange a follow-up urine test, offering genomic sequencing to those with sustained haematuria. Through this programme we have identified children with Alport syndrome who were unknown to our nephrology service, or any medical team, enabling us to intervene at an early stage and improve longer-term outcomes for these children.

This programme has the potential to drive a paradigm shift in medicine as we use the power of data to identify patients at risk, rather than waiting for them to develop symptoms. Essentially, we are shifting the focus from treating sick children to working to keep them well, while proactively using the EMR data-lake to identify at-risk patients, rather than waiting for them to be referred to our care.

Q7 You recently co-authored a paper entitled 'Clinical and diagnostic utility of genomic sequencing for children referred to a Kidney Genomics Clinic with microscopic haematuria'. Could you summarise the key findings from this article?

I loved this paper, not least because the lead author, Josiah Shanks, was a medical student when he started the project, and I always enjoy introducing students to the exciting world of research. This was a retrospective review of all patients with microscopic haematuria referred to our Kidney Genomics Clinic from January 2016–December 2021. We demonstrated a substantial diagnostic yield (48%) and clinical utility (60%) of genomic analysis for children with microscopic haematuria.

Q8 What are some of the main challenges in implementing genomic testing into routine nephrology practice?

The challenges differ across the world depending on the availability of genomic sequencing, and the knowledge base of healthcare providers. In Australia, where genomic sequencing is now funded for patients with kidney disease, and where we have been providing nephrology-specific genetic education through the KidGen collaborative for many years, the main challenges remain confidence and finding the time in a busy consultation to appropriately consent, request, and explain genetic testing.

In Victoria, with the support of Melbourne Genomics, we have developed a suite of decision support tools, visual explainers, and an

education programme alongside the development of genomic champions and funded genetic counsellors. At RCH, we are fortunate to have two genetic counsellors, equating to a full-time position, embedded in our nephrology team, providing invaluable support for all the paediatric nephrologists in requesting and interpreting genetic tests on the wards and in the clinic. Recognising the distances that patients can travel in Australia, we have developed our service so that we can provide appointments via telehealth and genomic sequencing on saliva samples that patients collect at home and post to us.

The pace of change in genomics is breathtaking, and I am grateful to work with a flexible team who are endlessly willing to try new approaches to patient care, and research as the knowledge base expands.

Q9 What do you feel are the main gaps within the field of nephrogenetics?

Knowledge, knowledge, knowledge. While the diagnostic yields have increased and there are new therapies available, such as sodium-glucose cotransporter-2 inhibitors and vasopressin 2 receptor antagonists, so many of our patients do not have an identifiable genetic cause, and many do not have an available disease-modifying agent.

I would like to better understand the genetics that underly a predisposition to kidney disease, and the development of data-analytics tools that can be deployed to identify at-risk children before the development of disease. I am excited to think about how the use of data-driven artificial intelligence approaches could make this a reality.

Internationally, the main gap remains equitable access to genomics, including both funded genetic testing and the clinical knowledge required to identify patients who will benefit from a genetic test, provide genetic counselling, and interpret the results. The expansion of genomics education at medical conferences, in undergraduate curricula, and through free online resources, such as GlomCon and NephMadness, will hopefully continue to bridge this gap.

Q10 What direction would you like to see the field of renal genomics take in the future?

I would like to see genomics adopted broadly by nephrologists as another diagnostic tool in our kit, similar to histopathology or ultrasound. Further to this, I would like to see more data-driven approaches to the identification of children at risk of kidney disease, and a shift towards proactive, preventative kidney healthcare in childhood rather than the management of disease.

Q11 To conclude, what has been your proudest achievement in your inspiring career thus far?

I am proud to have developed a kidney genetics service that has provided answers to so many families, and to have developed the evidence base to ensure equitable access to genetic testing for patients with kidney disease across Australia. I am also very proud of my role in developing the Kidney Flagship and in developing data-informed approaches to the early detection of kidney disease.

But if you asked me what makes me happiest at this stage of my career then my answer would be different. Working with children never ceases to be fun and I adore meeting them again as secure, confident adults with the world at their feet. Similarly, I love supporting and nurturing the next generation of researchers, and the achievements of my students bring me the greatest joy. I am fortunate to have been inspired and supported throughout my career by some incredible clinicians, and hope that I will similarly inspire and support the next generation of nephrologists to be the best version of themselves.

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Q1 Could you tell us who or what inspired you to pursue a career in medicine and, more specifically, to become a nephrologist?

Growing up, I did not have much exposure to medicine. There were no physicians, or even anyone in science, in my family, including my extended family. However, I always had a love and fascination with biology. I remember having a two-storey playhouse in the backyard as a child. My sister had the top floor, and I had the bottom. I ended up converting the bottom floor of that playhouse into a laboratory. My parents bought me a microscope that included real glass slides. I loved to look at anything I could find in the backyard under the microscope. I was always exploring new things and was never satisfied with answers. It was fascinating, and I think it is why I pursued a research career, and it is why I love pathology and urine microscopy.

When I was at the University of Arkansas, Fayetteville, USA, I initially focused on a career in music, playing the trumpet. After spending a few years as a music major, I decided to take an immunology course. This was taught by Jeannine Durdik, who is now the Associate Dean in the Fulbright College of Arts and Sciences at the University of Arkansas. I really credit Durdik for inspiring and instilling the confidence in me to pursue a career in science and medicine. I decided to switch my studies to microbiology and immunology, and I joined her research laboratory. I was hooked.

Fast forward to medical school. I was lucky to train at the University of Arkansas for Medical Sciences, where I was exposed to many amazing nephrologists who inspired me to pursue nephrology. Tom Andreoli, Bob Safirstein, Sudhir Shah, Sameh Abul-Ezz, and Michelle Krause each played an important role in my decision to pursue nephrology. I loved everything about it, and the connection to patients in a longitudinal manner. I saw the relationships that nephrologists established with their patients. I also saw a field with many opportunities to innovate. Importantly, I saw the field of nephrology as welcoming and collegial. That was important to me. I have really enjoyed being a nephrologist.

Q2 You have clinical interests in hypertension and cancer-related kidney disease, and in 2021 you co-authored a paper on onco-hypertension as an emerging specialty. Could you summarise the key takeaway messages from this review, and highlight the specific implications for nephrologists?

Onconephrology is an emerging subspecialty of nephrology, and deals with the intersection of nephrology with oncology. I have always had a desire to understand the underpinnings of blood pressure determination and pathogenesis of hypertension. Onco-hypertension was a natural progression in that clinical and research interest. There is an article that examines the emerging field and reviews all of the potential clinical entities one could encounter.[1] It also describes the multitude of anti-cancer agents that can cause or worsen hypertension;[1] however, another article discusses these medications in more detail.[2] Moreover, the article describes how hypertension and anti-hypertensive drugs

have been associated with malignancy. Lastly, the article describes why a multidisciplinary approach to onco-hypertension between oncology, primary care physicians, nephrology, endocrinology, and cardiology is needed.[2]

Q3 You also co-authored a paper on the potential impact of emerging viral infections on hypertension and kidney disease, following the COVID-19 pandemic. How do you think the pandemic impacted kidney healthcare, and what key messages does the paper convey?

So many aspects of nephrology and kidney health were impacted by the COVID-19 pandemic. An article published in 2022 reviews how many viruses contribute to hypertension, cardiovascular disease, and kidney disease.[3] This topic was thrust into the spotlight during the COVID-19 pandemic, and has renewed the interest in research into not only severe acute respiratory syndrome coronavirus 2, but also other viruses, such as HIV, coxsackievirus, cytomegalovirus, hepatitis C, respiratory syncytial virus, Middle East respiratory syndrome coronavirus, and influenza, among others. The key message of the manuscript is that cardiovascular and kidney health can be adversely impacted by a multitude of viruses.[3] It is important that the research community continues to conduct research on this important topic.

Q4 Your academic work has spanned multiple topics within the field of renal medicine. Having published almost 100 academic articles, contributed to several book chapters, and co-authored the book entitled *Nephrology Secrets*, what do you feel are the current gaps in the kidney medicine literature, and what topics within the field warrant greater attention?

This is a tough question because there is so much work that needs to be done. Progress and innovation are always needed. I see a big need for innovation in acute kidney injury, as this remains so common, and is a very challenging clinical entity. We need to invest and deploy upstream screening of kidney disease and applying effective interventions to decrease the kidney failure burden. This is needed. Renin-angiotensin system inhibitors, sodium-glucose co-transporter-2 inhibitors, and aldosterone receptor antagonists have demonstrated efficacy, and now it is time to identify and treat individuals at risk for kidney disease progression aggressively. This will take a very broad and unified effort worldwide.

While glomerular diseases have seen much more attention and focus recently, we still lack targeted therapies in many diseases, such as membranous nephropathy, for example. While biomarker research is exploding in membranous, we are still left with therapies that have not changed much over time. This is true for many glomerular diseases. The burden of hypertension

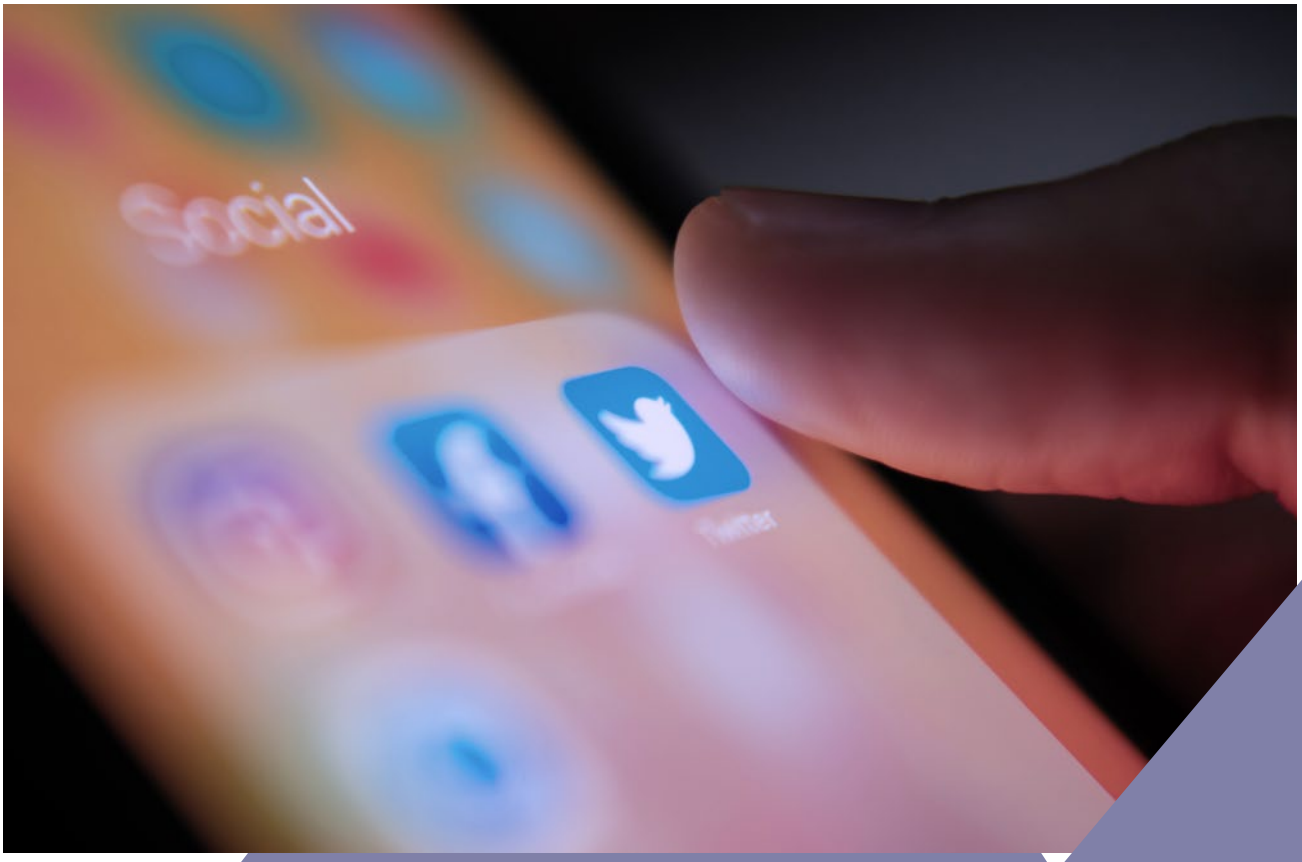
and cardiovascular disease in patients with kidney disease is huge, and continued understanding and effective therapy remains crucial to our patients. It is also important that we continue to advance education in home modalities and, importantly, palliative care in nephrology. These are crucial to patient-centred care. It is apparent that disparities in kidney health is a big problem in nephrology. We need to prioritise research in this area, as the current rates of kidney disease in marginalised groups remains unacceptable.

Lastly, we need to understand how to translate advances in genetics to improvements in therapeutics and clinical outcomes. We are finally in a place where we can test for these diseases, but we are still lacking interventions. This is a necessary and needed next step. It is so exciting to be in nephrology right now. We are making so many important advances. This is just the tip of the iceberg.

Q5 Alongside your clinical work and research, you have a keen interest in medical education. How and why did you become involved in education?

Education is so important. I look at education as my desire to always better myself. Never be satisfied. To this end, I was lucky in that my career intersected nicely with growth of the Internet. I quickly realised that I had a desire to learn, share, and hear from others around the world. I met the late Nate Hellman in 2008 at the very first Origins of Renal Physiology Course at Mount Desert Island in Maine, USA, when we were both fellows. He was the Founder of the Renal Fellow Network, which at the time was one of the few places where you could find free open access medical education (FOAMed). After his untimely passing a few years later, I made it my mission to preserve his legacy and make sure that FOAMed continued and prospered. The rest is history, so they say. I have been

"As social media becomes more and more a part of our daily lives, we need to educate physicians."



fortunate to have a large group of collaborators along the way. There are way too many people to recognise individually. I do want to recognise the impact that Hellman had in the FOAMed movement. We all should be grateful. To this day, nobody has matched the educational output that he achieved. He published a blog post almost every single day in 2009. Incredible.

Q6 On the topic of medical education, you recently co-authored a paper on the engagement of renal fellows in the USA in FOAMed. What were the key findings from this cross-sectional research, and how can these findings be applied on a global scale to improve digital education for healthcare professionals?

An article that was published earlier this year describes the results of a survey administered by the American Society of Nephrology (ASN) to all fellows (adult and paediatric) in the USA in the year 2022.[4] The aim of the survey was to gain a better understanding of how and why fellows are using FOAMed. We were also interested in the barrier and various ways in which it is used to answer clinical questions. We had a survey response rate of about 43%, and found that 74% used FOAMed. Of these FOAMed users, 33% reported that they applied FOAMed knowledge to clinical care. Several barriers to FOAMed use were also identified. Of all of the fellows who answered the survey 27% were unfamiliar with FOAMed, 22% had validity concerns, and 22% lacked a local community of users.[4] I think many of these results can be applied globally but it will be important to survey users from around the world. We intentionally used the ASN Survey and did not distribute via social media, in an attempt to diminish the amount of bias we received from respondents. The entire community has a lot of work to do in this area, but these survey results are a good start.

Q7 Can you tell us more about how social media can be used to enhance clinical education in the field? What avenues of social media do you use in your roles as an educator?

Social media is a means to share and disseminate knowledge. It also allows for a dialogue with others. Importantly, it allows people from all over the world to communicate and share. For me, I enjoy the interactions with others and, importantly, it is a great way to find new information. I also like seeing what is happening in other fields outside of nephrology; this has provided me with many good ideas we can possibility apply to nephrology. Lastly, the use of social media helps one to solidify one's knowledge, as nothing reinforces learning better than sharing knowledge with others and soliciting feedback.

Q8 You are Program Director for the Nephrology Social Media Collective (NSMC) internship, which aims to instil confidence, knowledge, competence, and professionalism in the use of social media, and promote free online medical education. What is the overarching goal of this collective, and how will this be achieved?

The goal of the NSMC internship is to learn by doing. Interns complete four rotations: graphical communication; blogs, tweetorials, and Landmark Nephrology; podcasts; and Nephrology Journal Club on Twitter (San Francisco, California, USA). Our internship allows individuals to learn valuable skills, empowering them to become leaders and effective communicators. We also instil values, so they appropriately use these skills and avoid common pitfalls.

Q9 Do you think there is greater scope for the use of social media in medical education and patient-doctor interactions? Are there any potential pitfalls healthcare professionals should be aware of?

We see patient interactions occurring more and more on social media. This is why it is important to have adequate attention paid to this during medical training. As social media becomes more and more a part of our daily lives, we need to educate physicians about appropriate and inappropriate use of social media. My advice for anyone interested in the professional use of social media is to avoid talking about your patients on social media. I look at anything you do as a risk spectrum, and talking about your patients' medical issues on social media without their consent is very risky, and oftentimes is directly against your employers' policies. All your patient has to do is search your name,

and all of your tweets show up. The patient can easily identify that you are talking about them, even if you remove identifiers. This is especially true if the post occurred just after the clinical encounter. It is also important to remain respectful, and treat everyone as if you are actually meeting them face-to-face. Disagreements happen, but remember to take a step back and learn from everyone. Of course, there are times in which you need to disengage and take a step back. Your social media usage should be a positive aspect of your life and, if it is not, it is okay to stop using it.

Q10 You currently serve as the Program Director for the Nephrology Fellowship Program at Duke University in Durham, North Carolina, USA. Can you tell us how you came to take on this position, and more about what this role entails?

Helping trainees navigate their career path gives me great joy. I also enjoy seeing trainees learn and grow during their journey. In my opinion, there is no better job in the medicine than being a Program Director. I started out as the Associate Program Director a few years after I joined the faculty. My initial role was to administer the core curriculum lecture series and recruit fellows into the programme. Over the next 5 years, I eventually assumed more and more responsibility, and took on the role of Program Director 2 years ago. My job encompasses everything surrounding fellow education, wellbeing, career development, recruitment, and ensuring that our programme meets institutional and national standards. I have a great team, with two Associate Program Directors, Harpreet Singh and Christina Wyatt, and a wonderful Program Co-ordinator. Most importantly, we have amazing fellows. I love my job.

"The burden of hypertension and cardiovascular disease in patients with kidney disease is huge."

Q11 The Duke University Department of Medicine Society for Early Education Scholars (SEEDS) is a newly established programme aimed to assist fellows in planning their careers in clinical education. Were you involved in the establishment of the programme and, as Lead, what are your main responsibilities?

The vision for the SEEDS programme was to invest in clinician educators the same way we invest in physician researchers. Our goal is to equip fellows with the necessary tools to succeed as a clinician educator. The programme spans fellows across the entire Department of Medicine at Duke University, not just nephrology fellows. I co-founded this programme 2 years ago and, as the Lead, my responsivity is to administer the programme. This consists of recruitment, selection, organising lectures, and serving on each of the fellow's longitudinal education projects. The SEEDS programme has been a great addition to our offerings for fellows, and I am excited for the future of SEEDS.

Q12 To conclude, what are your hopes or vision for the future of nephrology patient care and clinician education, and where do you see your educational focus lying in the coming years?

I want to continue working to ensure all fellows have similar opportunities from around the world. It is hard to predict the future, but most of the exciting projects have come from great ideas from trainees that are seized upon. It is important not to be complacent, and talk to and listen to trainees. I do believe that in them holds the next big educational advance, and we do not want to miss it. I am lucky to be a part of this journey.

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The Importance of Medical Nutrition Therapy in Chronic Kidney Disease Management

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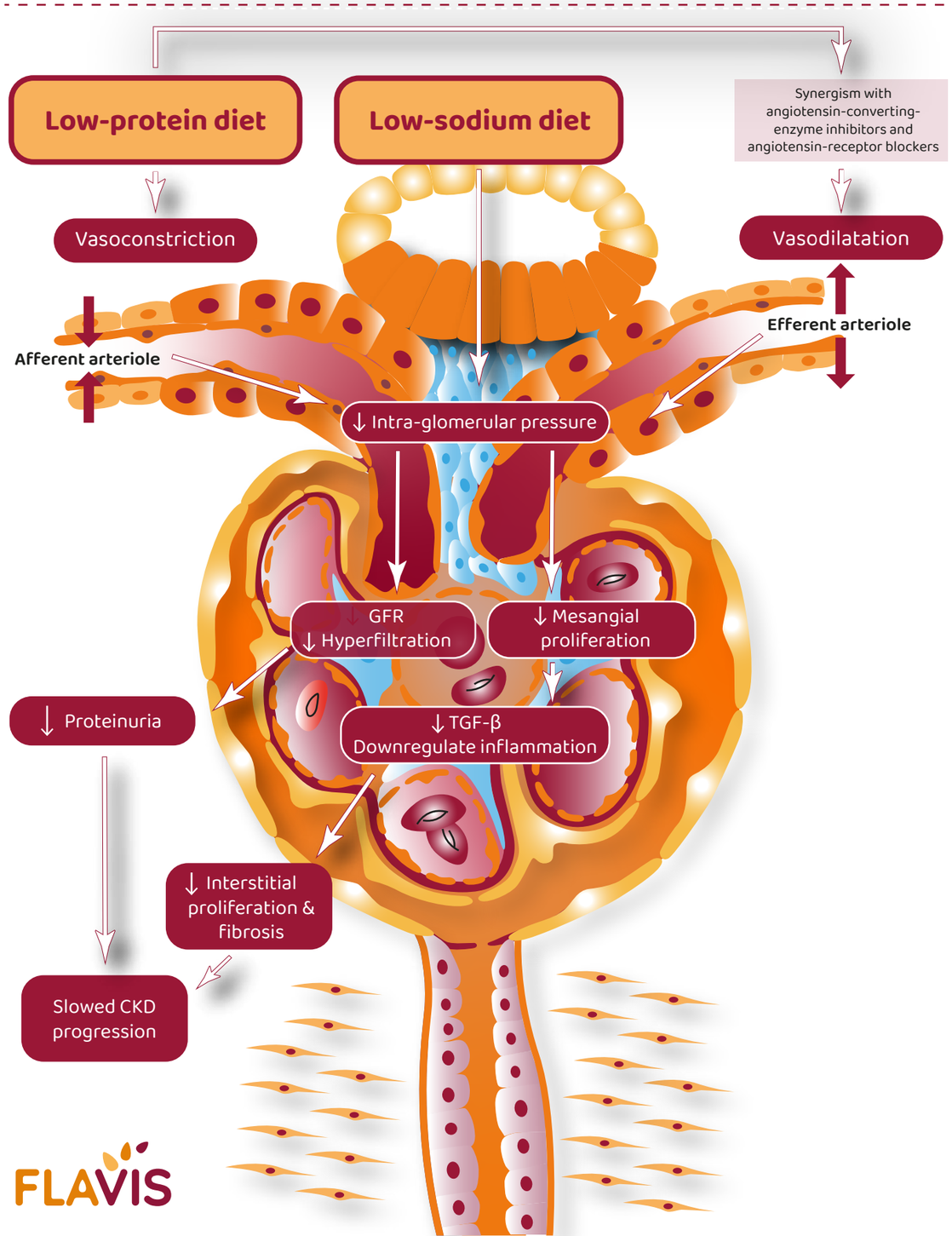
Why should we consider MNT in CKD management?

Current evidence confirms the positive impact of restricted dietary protein on:

- Favourable metabolic surrogates of kidney function, including azotemia, bone and mineral disorder, and acidosis.
- Slowing kidney function loss and the progression of CKD resulted in the delayed commencement of dialysis and prevention of malnutrition.
- Lowering rates of ESRD and death.



Current Nutritional Recommendations in CKD Management

Adults with Stage 3–5 CKD (not on dialysis) who are metabolically stable:

KDOQI 2020 recommends, under close clinical supervision, protein restriction with or without keto acid analogs to reduce risk for ESKD/death (1A) and improve QoL (1C).

A low-protein diet providing **0.55–0.60g** of protein/kg body weight/day

OR

A very low-protein diet providing **0.28–0.43g** dietary protein/kg body weight/day with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60g/kg body weight/day)

Adults with Stage 3–5 CKD (not on dialysis) who have diabetes:

KDOQI 2020 recommends that it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of **0.6-0.8g**/kg body weight/ day to maintain a stable nutritional status and optimise glycaemic control (OPINION).

How can we implement MNT successfully and safely?

Strategies to prevent and treat PEW and increase patient adherence:

- Interdisciplinary and multi-professional approach
- Prescription of a personalised nutritional therapy
- Communication techniques to better support patients involvement
- Use of protein-free medical food to facilitate dietary adherence and prevent PEW

Best Practice in Italy

- Italian nephrologists have a long-standing practice of implementing LPDs in the treatment of patients with CKD.
- The aim is to reduce uraemic symptoms by reducing toxins derived from excess protein intake.
- The Italian experience demonstrates flexibility and innovation in the MNT field, in treating non-dialysis CKD patients, and in using LPDs as a bridge between conservative treatment and the start of chronic dialysis therapy.
- The main goal of this flexible approach is to favour patient compliance, which is a crucial factor in the successful implementation of an LPD programme.

Conclusions

MNT represents a major feature of CKD management, with the goal to delay kidney failure and improve patient QoL.

The 2020 KDOQI recommends protein restriction to patients affected by CKD in Stages 3–5 (not on dialysis) and in CKD 3–5 who have diabetes (not on dialysis).

MNT is not an 'option' in the management of patients with CKD; it is a core element of care similar to drug prescription.

LPDs need to be tailored and patient-centred to ensure adherence, efficiency, and safety.

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Abbreviations:

CKD: Chronic kidney disease; ESKD: end-stage kidney disease; KDOQI: kidney disease outcomes quality initiative; LPD: low-protein diet; MNT: medical nutritional therapy; PEW: protein energy wasting; QoL: quality of life; TGF-β: transforming growth factor beta.

FLAVIS

Hypertension in Patients Receiving Dialysis: A Review of the Current Clinical Approach

Editor's Pick

This review article by Rowan et al. explores the current evidence base regarding the diagnosis and management of hypertension in patients receiving dialysis. Hypertension is a key contributor to morbidity and mortality in this patient population, and its management requires a multifactorial approach. The review covers sodium restriction, dry-weight probing, and different pharmacological therapies for managing hypertension in dialysis, as well as hypertension diagnosis and patient outcomes.

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Abstract

Cardiovascular disease is a leading cause of morbidity and mortality in end-stage renal disease (ESRD). Hypertension plays a major contributory role, resulting in progressive left ventricular hypertrophy, and increasing the risk of sudden cardiac death. The prevalence and pathophysiological mechanisms differ fundamentally from the non-dialysis-dependent population.

Sodium restriction can be as effective as antihypertensive medication in mitigating the haemodynamic effects resulting from impaired sodium handling. Tailoring dialysate sodium may enhance diffusion and facilitate greater sodium elimination where dietary measures alone prove ineffective.

Unlike hypertension in the wider population, volume overload plays a major pathophysiological role in ESRD. Probing dry weight in patients on dialysis who are seemingly euvolaemic enables clinically significant blood pressure (BP) reduction, and translates to improvements in markers of future cardiovascular morbidity and mortality.

Pharmacotherapy remains an important aspect in controlling hypertension in dialysis. Although no large-scale studies have identified the optimal medical therapy, numerous meta-analyses and randomised control trials (RCT) have demonstrated the efficacy of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II

receptor blockers (ARB), calcium channel blockers, β-blockers, and hydralazine/isosorbide dinitrate in the treatment of hypertension in ESRD. Whether the beneficial haemodynamic properties of mineralocorticoid receptor antagonists outweigh the risk of hyperkalaemia is the subject of ongoing RCTs. Numerous meta-analyses have demonstrated that adequate pharmacological control of BP translates to improved cardiovascular morbidity and mortality.

The fluctuation of volume status in the inter/intra-dialytic period complicates the diagnosis of hypertension in ESRD. As with patients not receiving dialysis, 24-hour blood pressure monitoring appears to have the greatest sensitivity in diagnosing hypertension and predicting outcomes from hypertension. Where resources are limited, home BP monitoring appears to have the greatest value.

Key Points

1. Hypertension is a major contributor to morbidity and mortality in end-stage renal disease. The pathophysiological mechanisms driving hypertension are distinct compared to the general population, with fluid overload playing a major role. Other putative mechanisms include vascular stiffness, enhanced sympathetic drive, and aberrant renin-angiotensin-aldosterone system activity.

2. Management is multifactorial, with several strategies unique to dialysis patients. Modulation of dialysate sodium can enhance sodium extraction and improve volume control. Dry weight probing appears to play a leading role in treating hypertension, even in clinically euvolaemic dialysis patients. As with non-dialysis patients, fluid and sodium restriction are essential components in treating hypertension in ESRD.

3. Pharmacotherapy plays a major role in hypertension in advanced kidney disease. Pharmacological management of hypertension is uniquely complex in the dialysis cohort, owing to the greater susceptibility to side effects such as hyperkalaemia, and the influence of medication dialysability. Therefore, management of hypertension in end-stage renal failure must take into account the side effect profile, dialysability, drug efficacy, and intradialytic haemodynamics.

Hypertension is a common complication in advanced chronic kidney disease (CKD), occurring in approximately 80–85% of patients.[1] Blood pressure (BP) control is suboptimal in the majority of these patients. The link between uncontrolled hypertension and mortality among patients with end-stage kidney disease (ESKD) is well documented.[2,3] Much of the research on hypertension has focused on the non-dialysis population, but there are essential differences in the pathogenesis, diagnosis, and management of hypertension in patients receiving dialysis. Unlike the general population, an excess of salt and water play a dominant role in the development of hypertension in the vast majority of patients with ESKD, leading to left ventricular hypertrophy and sudden cardiac death. Numerous randomised control trials (RCT) have shown that salt restriction has a comparable efficacy to the addition of antihypertensive medication in BP control.[4] Consequently, the control of salt and volume overload in these patients is the cornerstone of hypertension management. Renin-angiotensin-aldosterone system (RAAS) activation, sympathetic activation, increased arterial tone, and endothelial dysfunction are also important pathogenic factors for hypertension in patients receiving dialysis. As with patients who are dialysis-independent, antihypertensive pharmacotherapy remains a major strategy in controlling hypertension in ESKD,[5] but differences in the pharmacokinetics and tolerability of certain drugs need to be taken into account. This review aims to highlight the evidence behind the diagnosis and management of hypertension in the dialysis population.

SODIUM RESTRICTION

The morbidity and mortality benefits attributed to dietary sodium restriction have been well

established in cardiovascular disease and CKD.[6] Due to an impaired ability to excrete a sodium load, patients receiving dialysis are considered sodium-sensitive, and yet most patients receiving dialysis consume in excess of the recommended 2 g of sodium per day.[7-8] Increased dietary sodium contributes to hypertension via volume-dependent and independent mechanisms. Raised plasma sodium stimulates movement of water from intra- to extracellular compartments. Hypertonicity also stimulates thirst, again increasing the extracellular fluid compartment and intradialytic weight gain (IDWG). Independent of volume homeostasis, sodium increases medullary vasomotor sympathetic activity due to elevated angiotensin II activity.[9]

Dietary sodium restriction is a particularly important facet of hypertension management in patients with advanced CKD. One RCT reported that sodium restriction was associated with a 7% reduction in systolic BP.[4] The beneficial antihypertensive effects of sodium restriction also translate to patients receiving dialysis.[10] A recent meta-analysis looked at sodium restriction in 71 patients receiving HD, and 20 patients receiving peritoneal dialysis. The mean difference in systolic BP between low and high salt intake groups was -8.4 mmHg and -4.4 mmHg for diastolic BP. Conversely, one of the included RCTs demonstrated that the addition of 3.5 g of salt was sufficient to raise BP by 9/5 mmHg. Restricting dietary salt to <6 g/day can limit inter-dialytic weight gain to 0.8 kg by influencing thirst and extracellular volume.[11] Furthermore, the HEMO study demonstrated that sodium restriction was sufficient to reduce the requirements for ultrafiltration during thrice-weekly dialysis.[12] This highlights the therapeutic role of sodium restriction in managing volume overload, a major contributor to hypertension in ESKD.

DIALYSIS PRESCRIPTION

Research into the augmentation of dialysate sodium to influence inter-dialytic haemodynamics has been a subject of much controversy.[13] Numerous observational studies have linked low dialysate sodium with a reduction in thirst, IDWG, and hypertension, which can improve left ventricular mass index (LVMI), a marker of cardiovascular mortality in patients on dialysis.[14,15] One such observational study including 52 patients receiving dialysis demonstrated that a 3 mmol/L reduction in dialysate sodium was significantly associated with a modest reduction in BP of 5 mmHg, and even 10 mmHg in patients who are hypertensive.[14] This was also associated with a reduction in pre-dialysis serum sodium, but IDWG was unaffected.

Conversely, the DOPPS trial, a large-scale international prospective cohort study which analysed the influence of serum sodium and dialysate sodium on mortality among 11,555 patients receiving dialysis across 12 countries, demonstrated that lower pre-dialysis sodium and lower dialysate sodium (<137 mmol/L) were associated with a higher mortality incidence.[15] A post hoc analysis of the DOPPS trial found that the routine use of sodium profiling (loading of sodium towards the end of dialysis in order to limit intradialytic hypotension) resulted in a 36% increase in all causes of mortality (hazard ratio [HR]: 1.36; 99% confidence interval [CI]), and a 34% increase in cardiovascular death (HR: 1.34; 99% CI).[16] It was postulated that sodium loading resulted in a net sodium gain, culminating in increased thirst, IDWG, and hypertension.

The paucity of RCTs means that the question of dialysate sodium reduction as a means of limiting hypertension in patients receiving dialysis remains unanswered. However, this clinical equipoise is the subject of the ongoing and much anticipated SoLID and RESOLVE trials.[13,17] These multicentred RCTs will seek to provide concrete evidence as to whether the benefits of low dialysate sodium on interdialytic haemodynamics and LVMI outweigh the deleterious effects of an increased propensity towards intradialytic hypotension.

DRY WEIGHT PROBING

Dry weight is defined as the lowest achieved post-dialysis weight without the occurrence of significant signs and symptoms of hypovolaemia or hypervolaemia.[18] A number of studies have shown the importance of achieving dry weight in controlling hypertension in ESKD.[19,20] Extended-duration home haemodialysis (HD) has been shown to achieve satisfactory BP control in the majority of patients without the need for

pharmacotherapy. This is largely due to optimal volume control, although factors such as decreased sympathetic activation may also be at play. These early studies have been validated by the more contemporary DRIP trial.[21] This RCT, involving 150 patients on HD, assessed the influence of dry weight probing versus usual care. One hundred patients were randomised to the ultrafiltration arm achieved a 1 kg reduction in post-dialysis weight at 8 weeks, following a gradual reduction of dry weight. This resulted in a corresponding reduction of ambulatory BP by 6.6/3.3 mmHg compared to the 50 patients randomised to the usual care group.

Therefore, adequate volume control by dry weight probing is one of the pertinent aspects in managing hypertension in ESKD. Agarwal et al. demonstrated that LVMI, a strong prognostic marker for mortality, can be improved with dry weight probing among patients who are on hypertensive dialysis.[22] This study analysed the echocardiographic parameters of the patients included in the DRIP study. LVMI fell by 6.3 g/m^2 over 8 weeks in patients randomised to receive ultrafiltration compared to a 0.3 g/m^2 progression seen in controls. During a post hoc analysis, the HDPAL investigators found that the treatment-mediated decline in LVMI was mitigated when adjusted for systolic blood pressure and inferior vena cava diameter (surrogate markers for volume status).[23] This highlighted that improvements in LVMI were volume-related. An analysis of the DOPPS data suggested that centre-specific practices relating to the management of volume status influence patient outcomes. Centres with a protocol outlining the frequency of dry weight assessment resulted in a reduction in cardiovascular and all causes of mortality (HR: 0.72–0.78; 99% CI: 0.55–0.95 and 0.64–0.94, respectively).[16]

PHARMACOTHERAPY

Hypervolaemia is not the *conditio sine qua non* of hypertension among patients receiving dialysis.[24] One study, involving more than 500 patients receiving dialysis in Europe, demonstrated that 13% of patients were hypertensive but euvolaemic, which emphasises the existence of alternative pathophysiological mechanisms behind hypertension in ESKD. Several meta-analyses have conclusively shown that pharmacotherapy in ESKD improves all causes of mortality.[25,26] However, no specific class of antihypertensive agent has been clearly shown to improve prognosis over another. No study has been powered to observe a difference between classes of antihypertensive agents, nor have there been any head-to-head trials to elucidate the optimal antihypertensive in ESRD.

ACE Inhibitors and Angiotensin Receptor Blockers

Aberrant RAAS activity has been implicated in the propagation of hypertension and cardiovascular morbidity in ESKD.[27] Studies have shown that the RAAS system is twice as active in ESKD compared to healthy controls. Angiotensin II, the major effector molecule of the RAAS system, activates growth factors, elicits myocyte hypertrophy, and fibroblast proliferation (via aldosterone), culminating in left ventricular hypertrophy and fibrosis.[28] Outcome data pertaining to the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in patients on dialysis has yielded mixed results. The FOSIDIAL trial, conducted in patients who are hypertensive and receiving HD, who also have left ventricular hypertrophy, found that fosinopril did not reduce major adverse cardiovascular events or mortality compared with placebo.[29] Similarly, the HDPAL trial showed that lisinopril and atenolol were equivalent in reducing LVMI.[30] However, lisinopril was associated with a greater incidence of MACE, which ultimately resulted in the premature termination of the trial. ARBs may have a more beneficial effect on this population. Losartan, valsartan, and candesartan have all been associated with reduced cardiovascular events and mortality in patients on HD.[31,32] Suzuki et al. reported that ARB therapy was associated with a 49% decrease in MACE and a 36% reduction in all cause-mortality in patients on HD.[32] Shireman et al. suggest that ARBs may be superior to ACE inhibitors, which tend to have a higher dialysability.[33,34] However, a meta-analysis by Tai et al. found that, while ACE-I/ARB therapy reduced LV mass in patients on HD, neither agent significantly improved cardiovascular morbidity or mortality.[35]

During the multicentred STOP ACEi RCT, 62% and 56% of patients in the discontinuation and continuation arms, respectively, progressed to ESRD. The average BP in the discontinuation arm

was higher than the continuation arm. However, the difference was not seen after 15 months of the trial. Notably, the secondary outcomes of cardiovascular events, hospitalisations, and mortality were similar between the two groups.[36]

Despite the cardioprotective effect of ACE inhibitor/ARBs and their apparently favourable impact on LVMI, their use is often limited by their potentiation of hyperkalaemia.[29] However, studies suggest that ACE/ARB therapy may be safe in patients on maintenance dialysis where potassium homeostasis is largely maintained by HD.[37] One RCT analysed the treatment effect of ACE inhibitors, ARBs, and combined RAAS inhibition versus placebo on serum potassium. Of the 62 patients who completed this 3-month trial, none had to discontinue therapy due to hyperkalaemia or another adverse event (Table 1). The serum potassium was equivalent in all

Table 1: A summary of the results of a number of trials looking at the impact of angiotensin-converting enzyme (ACE)/angiotensin II receptor blockers (ARB) therapy in patients on maintenance dialysis.

Trial	HDPAL[30]	Suzuki et al.[32]	Takahashi et al.[31]	FOSIDIAL trial[29]
Agent	Lisinopril versus atenolol	Losartan, candesartan, valsartan versus Control	Candesartan versus control	Fosinopril versus control
Trial Design	Open-label, randomised control	Open label, randomised, prospective	Open label, randomised, prospective	Randomised, double-blind, placebo- controlled
Follow-up (months)	12.0	36.0	19.4±1.2	24.0
(n)	200	366 hypertensive	80 ESRF without CVD	397 LVH±HTN
Statistics	Incidence rate ratio	Cox regression analysis (RR)	Cox proportional hazard (OR)	Cox regression analysis (RR)
1° outcome	Incidence rate ratio Atenolol/lisinopril 1.6 Open label, randomised, prospective hospitalisation (P=0.021) 2.36 CV events (P=0.001) 2.29 All adverse events* (P=0.002)	Relative Risk 0.51 for all CV events (P=0.002) Hazard Ratio 0.64 for all causes of death (P=0.1) ¬®	Odds Ratio 0.29 for MACE (P<0.01)	Relative Risk 0.92 for MACE (P=0.35) ¬®

A number of these trials imply a cardiovascular benefit to ACE/ARB therapy in end-stage renal disease, whereas the HDPAL trial suggests that β-blockade may be more efficacious in reducing cardiovascular morbidity.

*All adverse events: Combined stroke, MI, heart failure, and CV death.

MACE: major adverse cardiovascular events including heart failure, unstable angina, severe arrhythmia, and cardiovascular death.

¬®: No statistical difference

CV: cardiovascular; CVD: cardiovascular disease; ESRD: end-stage renal disease; ESRF: end-stage renal failure; HTN: hypertension; LVH: left ventricular hypertrophy; MACE: major adverse cardiovascular events; MI: myocardial infarction; OR: odds ratio; RR: relative risk.

groups, with no statistical difference between the rates of severe hyperkalaemia.

While these results may seem promising, the highly regulated environment of RCTs makes it difficult to extrapolate the true safety to the wider population.[38] Juurlink et al. observed an increase in hyperkalaemia morbidity and mortality (8.6 and 1.7 per 1000, respectively; P=-<0.001) after the publication of the RALE trial.[38] Furthermore, the HDPAL trial revealed a 3.4-fold increase in hyperkalaemia among the lisinopril arm.[30] More conclusive data encompassing larger, well-powered RCT are required to determine the true treatment effect of ACE/ARB therapy, and whether the benefits outweigh the risks of hyperkalaemia.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers are in widespread use for the management of hypertension in patients on dialysis.[39] One retrospective cohort study involving over 5,500 patients receiving dialysis demonstrated that dihydropyridine versus non-dihydropyridine calcium channel blockers were associated with improved mortality and cardiovascular morbidity outcomes (adjusted HR: 0.77 and 0.86, respectively). The most significant study examining the influence of CCBs in ESRD was concluded in 2008.[40] This RCT, involving 251 patients on hypertensive dialysis, analysed the effects of 10 mg amlodipine on mortality and cardiovascular outcomes in ESRD. Twelve percent of patients assigned to the amlodipine group compared to 17% of the placebo arm over the 19-month follow-up had a primary end point of all causes of mortality; 15% versus 25% achieved a secondary outcome of composite all-cause mortality, cardiovascular event, stroke, or acute limb ischaemia requiring intervention (HR: 0.53; 95% CI: 0.31–0.93; P=0.03). Although all causes of mortality alone were not statistically significant, amlodipine was shown to significantly reduce the composite outcomes of mortality and vascular events.

β-Blockers

In parallel with RAAS inhibitors, β-blockers have also demonstrated cardioprotective properties.[41] The HDPAL trial is the largest head-to-head study between ARB and β-blocker therapy in ESKD.[30] This study concluded that each agent had comparable antihypertensive effects, but thrice-weekly atenolol was associated with lower cardiovascular morbidity and all-cause hospitalisations. This apparent cardiovascular protection may be attributed to improved aortic stiffness, as demonstrated by the secondary analysis of the HDPAL trial.[42]

In addition to antihypertensive properties, β-blockers have a role in the protection against fatal arrhythmia and sudden death.[43] Analysis of the DOPPS study revealed the incidence of sudden death to be as high as 33%, and inclusion of β-blockers were associated with a lower incidence of sudden death (HR: 0.88; 95% CI: 0.78–0.99). Another prospective placebo-controlled trial demonstrated strong evidence for the use of β-blockers in a subpopulation of patients on dialysis with dilated cardiomyopathy.[44] This trial, involving 114 patients, demonstrated a significant mortality benefit following carvedilol therapy with 51% mortality in the treatment arm compared with 73% in the placebo group (HR: 0.51; 95% CI: 0.32–0.82). This was associated with a reduction in maladaptive cardiac remodelling, and improved ejection fraction.

The challenge of studying hypertension in patients on dialysis was demonstrated by the BLOCADE trial.[45] This trial examined the treatment effect of 25 mg BD carvedilol versus placebo. Of 354 eligible patients, 91 consented, and only 49 completed the trial. The major reasons for non-inclusion were clinical instability and current β-blockade. Although large-scale highly powered studies are required to elucidate the most efficacious antihypertensive and cardioprotective agents in ESKD, the experience of the BLOCADE investigators highlights the complexity of establishing such a trial. It may require multicentre international collaboration to answer such questions.

Others (Mineralocorticoid Receptor Antagonists, Hydralazine and Nitrates, and Loop Diuretics)

Numerous studies support the use of mineralocorticoid receptor antagonists in ESRD.[46] The DOHAS trial demonstrated that a low dose spironolactone resulted in a 60% decline in cardiovascular/cerebrovascular events over a

3-year period (HR:0.40; 95% CI: 0.20–0.81). The RALES study demonstrated a low incidence of hyperkalaemia (2%) among study participants.[47] However, subsequent population-based time-series analysis demonstrated a significant increase in hyperkalaemia rates and mortality following this publication.[38] Whether the benefits of mineralocorticoid receptor antagonists outweigh the risks is the subject of the much-anticipated ALCHEMIST trial.[48]

Hydralazine-isosorbide dinitrate (HY-ISD) may also improve cardiovascular outcomes in ESRD.[49,51] The HIDE trial concluded that HY-ISD is safe and tolerable in ESRD.[49] A large retrospective study demonstrated a significant improvement in cardiovascular, as well as all causes of mortality with HY-ISD compared to placebo.[50]

The contribution of extracellular volume overload in the propagation of hypertension in ESRD has been well established.[21] The addition of low-dose diuretics in patients on dialysis with residual renal function can offer additional improvements in natriuresis and volume management.[51] Additionally, they may help maintain urine output in patients on peritoneal and HD, respectively.[51,52] The influence of diuretics on patients receiving hypertensive dialysis requires further studies.

DIAGNOSIS OF HYPERTENSION IN DIALYSIS PATIENTS

Numerous studies have suggested a U-shape associated between pre-dialysis BP and mortality in ESKD.[53] Adequately detecting hypertension is therefore of paramount importance in improving mortality and avoiding harm along the BP spectrum. Recently, however, a lot of focus has shifted towards the setting in which hypertension is diagnosed.[54]

Conventional peri-dialytic BP to diagnose hypertension has several caveats.[55,56] BP variation is common in ESKD, and is closely linked to variations in volume status in the inter- and intradialytic period.[57] Furthermore, one cross sectional study involving 270 patients on dialysis across seven centres demonstrated a significant elevation in pre- and post-dialysis BP (14.3/7 and 13.6/4.4; P=<0.05) when measured via conventional means compared to standard protocol. Secondary analysis of the CLIMB study demonstrated that IDWG was closely associated with BP, further supporting the role of volume in BP variation.[58] Therefore, the use of peri-dialytic BP may not adequately reflect BP in the interdialytic period. Pre- and post-dialysis BP recordings are used as a parameter to reflect cardiovascular stability during dialysis, as opposed to diagnosing and assessing the response of antihypertensive medication.[56] Medications are often held pre-dialysis to prevent intra-dialytic hypotension. The TAKE HOLD trial, which randomised patients on dialysis to take or hold antihypertensive agents with multiple daily dosing, demonstrated a greater propensity for pre-dialysis hypertension in the HOLD arm as part of their secondary outcome analysis; this may suggest a deleterious effect of holding such medications.[59] The strongest evidence against the utility of peri-dialytic BP was provided by a meta-analysis, which looked at 18 studies involving 692 patients on dialysis.[55] This study reported poor concordance between peri-dialytic BP and 44 hour ambulatory blood pressure monitor (ABPM). Numerous studies have also shown poor correlation between BP recorded on dialysis and mortality outcomes.[60]

Relying on peridialytic haemodynamics may also exacerbate hypertension in ESRD. Intradialytic hypotension is a frequent occurrence in this population.[61] A common strategy is to withhold antihypertensives to mitigate the risk of intradialytic hypotension.[62] There is no clear evidence that this strategy accurately mitigates the risk of intradialytic hypotension. Moreover, this may exacerbate interdialytic hypertension and precipitate intradialytic hypertension, which has a strong association with cardiovascular morbidity.[63,64]

As with patients who are not receiving dialysis, ABPM appears to be the most accurate and thus gold standard in diagnosing hypertension in dialysis.[65] The advantages of ABPM include the elimination of white coat hypertension, session-to-session variability in IDWG, and the ability to obtain a high number of readings. Furthermore, ABPM has been shown to predict end-organ damage.[66] One cross-sectional analysis of 140 patients on dialysis demonstrated that ABPM, unlike dialytic BP, closely approximated LVMI, a marker associated with cardiovascular morbidity and mortality. A unique function of ABPM is the

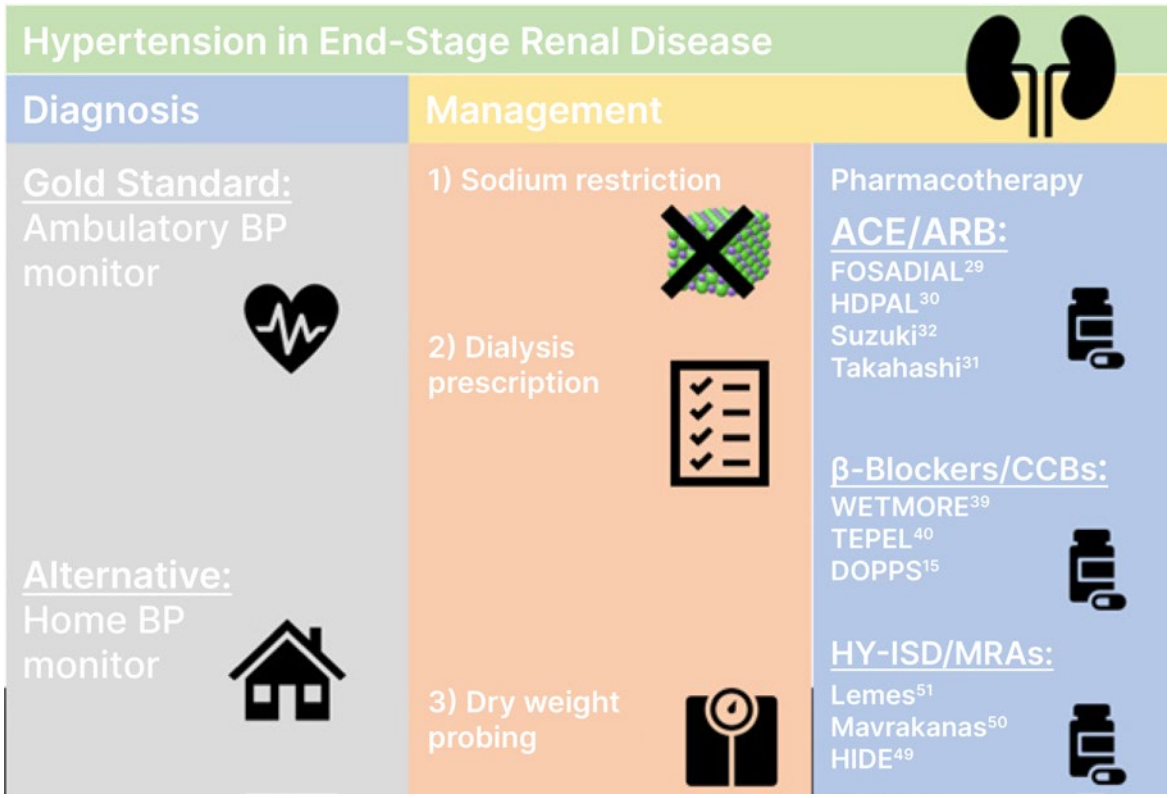
ability to detect nocturnal BP. Dysregulation of the circadian rhythm of BP is increasingly common as renal function declines, and is a function of impaired ultrafiltration or excessive tubular absorption of sodium.[67] There is growing evidence to suggest that 'non-dipping' nocturnal BP is associated with accelerated end-organ damage, the detection of which is greatly enhanced with ABPM.[68]

One of the major disadvantages of ABPM is the lack of availability and timely access to monitoring. With this in mind, one cross-sectional study analysed the utility of home (inter-dialytic) BP monitoring in the diagnosis of hypertension in ESKD.[69] This study demonstrated that home BP measurements were 84.1% sensitive and 80% specific in the diagnosis of hypertension. Moreover, home BP has been shown to be more reproducible than ABPM. Most strikingly, one prospective cohort study involving more than 150 patients on dialysis demonstrated that home BP was accurate in determining risk from cardiovascular death.[3] During this trial, patients were assigned to home BP, ABPM, or standardised and routine dialysis BP monitoring. After the 24-month follow-up period, only the home BP and ABPM groups showed correlation with cardiovascular mortality. Although notably ABPM was of more prognostic value, home BP readings showed that each standard deviation increase in BP corresponded to a 35% increase in cardiovascular mortality (HR: 1.35; 95% CI: 0.99–1.84). This demonstrates the utility of home BP where ABPM is unavailable (Figure 1).

HYPERTENSION AND OUTCOMES IN ESKD

How does adequate diagnosis and management of hypertension translate to cardiovascular outcomes and mortality in ESKD? Early epidemiological studies showed a 'U'-shaped

Figure 1: Summary of diagnosis and management of hypertension in end-stage renal disease.



ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; BP: blood pressure; CCB: calcium channel blocker; HY-ISD: hydralazine-isosorbide dinitrate; MRA: magnetic resonance angiography.

correlation, suggesting that exceeding BP targets may be harmful.[53] Lack of power among RCTs has made it difficult to establish the true effect of hypertension in ESKD.[31,38,44,70] However, recent meta-analyses have shown clear cardiovascular and mortality benefits with antihypertensive therapy.[25,26] The culmination of data from eight and five trials, respectively, have shown that antihypertensive therapy significantly reduces the number of cardiovascular events. Table 2 summarises the findings of these meta-analyses. These meta-analyses have shown that, ultimately, antihypertensive therapy improves cardiovascular mortality and all causes of

Table 2: Treatment effect of antihypertensive therapy on all causes of mortality in end-stage kidney disease is demonstrated in the top half of the table. Treatment effect of antihypertensive therapy on cardiovascular mortality in end-stage kidney disease is demonstrated in the bottom half of the table.

	Study design	Antihypertensive		Hazard Ratio
All-causes mortality				
Cice[44]	RCT	Carvedilol versus placebo	114	0.71 (0.53–0.95)
Cice[71]	RCT	Telmesartan versus placebo	303	0.80 (0.68–0.94)
Zannad[29]	RCT	Fosinopril versus placebo	397	1.09 (0.78–1.52)
Tepel[40]	RCT	Amlodipine versus placebo	251	0.72 (0.39–1.30)
Suzuki[32]	Randomised, open label	ARBs versus conventional therapy	366	0.66 (0.41–1.04)
Li[72]	Randomised, open label	Ramipril versus conventional therapy	60	1.4 (0.3–6.55)
Cardiovascular Mortality				
Cice[44]	RCT	Carvedilol versus placebo	114	0.43 (0.28–0.67)
Cice[71]	RCT	Telmesartan versus placebo	303	0.80 (0.68–0.94)
Zannad[29]	RCT	Fosinopril versus placebo	397	1.05 (0.67–1.68)
Tepel[40]	RCT	Amlodipine versus placebo	251	N/A
Takahashi[31]	Randomised, open label	Candesartan versus conventional therapy	80	N/A
Suzuki[32]	Randomised, open label,	ARBs versus conventional therapy	366	0.60 (0.30–1.19)
Li[72]	Randomised open label	Ramipril versus conventional therapy	60	1.00 (0.15–6.64)

ARB: angiotensin II receptor blocker; N/A: not applicable; RCT: randomised control trial.

mortality (HR: 0.71 (0.50-0.99) and 0.8 (0.66-0.96), respectively).

CONCLUSION

In conclusion, the diagnosis and management of hypertension in ESKD is more complex than for the general population. This is, in part, because of greater variability in BP due to fluxes in volume status and renal sodium handling.[58,67] ABPM appears to confer the best prognostic information, but home BP monitoring can be a useful surrogate where resources are limited.[3] Different pathophysiological determinants dictate hypertension in ESKD, with volume overload playing a major role.[30] Therefore, non-pharmacological interventions such as dietary sodium restriction, extending dialysis time, and altering the dialysis prescription to improve serum sodium diffusion can aid in the management of hypertension.[4,14] Where adequate volume control proves ineffective in managing hypertension, antihypertensive pharmacotherapy is advised.[25,26] Although numerous meta-analyses demonstrate survival benefit with therapy, no trial has demonstrated a clear benefit of one class of antihypertensive over another. Large head-to-head trials will be required to elucidate the optimal medical management of hypertension in ESKD.

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Recent Advances in Targeting Complement in Glomerular Disease

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Abstract

Several diseases are related to complement involvement. In particular, its role is essential for the pathogenesis of several renal disease. On the other hand, the complement role may also be protective, and this possibility should be well known when managing complement inhibitors.

Complement inhibitors are relatively newly discovered therapies that are essential in some diseases, and in others improve the efficacy of the already known therapeutic measures that represent the standard of care.

In the case of glomerular diseases, complement plays a role in almost all diseases. In some diseases, complement abnormalities represent the prevailing factor in the pathogenesis. In such diseases, complement inhibition represents an essential therapy. In other diseases, complement plays an important role, but other factors are involved in the pathogenesis. Clearly, in these diseases, complement inhibition represents a therapy that could be added to the standard of care therapy, according to the physician's judgement. Examples of these diseases are lupus nephritis, thrombotic microangiopathy when associated to some cases of lupus nephritis, and IgA nephropathy. The latter is one of the first primary glomerulonephritides in which a relevant role of complement is documented. These three diseases are the object of this brief review. Particular concern should be given to ongoing clinical trials. Indeed, many of these anti-complement therapies are still in different phases of clinical trials. Finally, particular concern must be ascribed to the problem of associating these emerging therapies to already existing and proven treatments.

Key Points

1. The complement system is involved in several renal diseases. In some disease it is involved deeply, and in such diseases the treatment is principally based on anti-complement drugs. In other glomerular diseases, the complement system is involved marginally.

2. In some renal diseases, principally in autoimmune diseases, the complement system may have a protective role. Indeed, the early complement components have an effect on opsonisation and clearance of immune complexes, apoptotic cells, and cellular debris. Additionally, genetic deficiency of complements 1 and 4 leads to a higher risk of having lupus nephritis. A different protective role exerted by complement is the enhanced immune complexes clearance generated by complement 3b when bound to completment receptor 1 on the erythrocyte surface.

3. Problems in targeting complement in lupus nephritis include which pathway to target, as classical, lectin, and alternative pathways may be involved; which immunosuppressant to use, with a choice between steroids, mycophenolic acid, calcineurin inhibitors, and rituximab; and compatibility of complement therapy with standard of care. Steroids and complement inhibitors are synergistic, while calcineurin inhibitors are synergistic with complement inhibitors. Complement inhibitors may reduce the effect of rituximab.

INTRODUCTION

The complement system has been an appealing drug target for a long time.[1,2] However, early drug development efforts have failed for two reasons: the lack of specificity of the anti-complement drugs, and the insufficient knowledge about the mechanism of action of complement in both health and disease.

COMPLEMENT SYSTEM ABNORMALITIES

Complement system abnormalities may be due to alterations of the different complement proteins, or of the protein system related to complement regulations. Often, these abnormalities are on a genetic basis, and abnormalities frequently involve factor H. They may consist of factor (f) H mutation or presence of anti-fH autoantibodies. Less frequent is a mutation of factor I or of the membrane cofactor protein. Abnormalities of the complement system may concern gain of function of complement (C) 3 or of complement fB. These abnormalities are also on genetic basis.

To date, it is well known that complement is deeply involved in several renal diseases. Such diseases should be divided according to the relevance of complement in their pathogenesis. In several diseases, complement exerts a principal and fundamental role, such as in atypical haemolytic uremic syndrome (aHUS) and in C3 glomerulonephritis. In such diseases, different treatments may be used, ranging from non-specific immunosuppression to newer complement targeting agents. Anyway, such patients should receive anti-proteinuria therapy with angiotensin converting enzyme inhibitors. Non-specific immunosuppression includes steroids, rituximab (RTX), and mycophenolate mofetil (MMF).[3,4] In other diseases, such as systemic lupus erythematosus (SLE); secondary thrombotic microangiopathy (TMA), often associated with lupus nephritis (LN); and several glomerulopathies, such as IgA glomerulonephritis, the role of complement according to new knowledge is particularly relevant, and the anti-complement therapies are more often associated to the standard of care therapies. In this short review, the involvement of complement in diseases such as secondary TMA, SLE, and IgA nephropathy (IgAN) will be treated, looking at the main targeting drugs.

In other renal diseases, complement is similarly involved, even if at a lesser degree, including antineutrophilic cytoplasmic antibody vasculitis, membranous nephropathy, and diabetic nephropathy.[5] First, it should be highlighted that complement activation is not only restricted to the glomeruli within the kidney, but several experimental and clinical data[6-9] have indicated that complement activation may contribute to tubular cell injury. However, it should be observed that some of these studies have been conducted on animals.

An important consideration is that complement has not only a damaging effect, but may also have a protective role against autoimmune diseases. Table 1 documents that the deficiency of some complement proteins leads to disease. In the human, the genetic deficiency of C1 has a 77% risk for SLE, and the genetic deficiency

Table 1: Complement may have a protective role against autoimmune diseases.

Deficient complement component	Human/mouse	Clinical manifestation
C1	Human	LN
C2	Human	Cutaneous lupus
C4	Human	LN
C1q	Mouse	Autoantibodies, proliferative and crescentic GN with C3 glomerular staining
C4	Mouse	Autoantibodies, proliferative GN with C3 and Ig glomerular staining

C: complement; C1q: complement component 1q; GN: glomerulonephritis; LN: lupus nephritis.

of C4 has a 75% risk for SLE.[10] Indeed, the early complement components have an important effect on the opsonisation and clearance of immune complexes, apoptotic cells, and cellular debris, which are all important in the initiation and pathogenesis of LN.

A different protective role exerted by complement is the enhanced immune complexes clearance generated by C3b when bound to complement receptor 1 (CR-1) on the erythrocyte surface. Indeed, immune complexes activate the complement system, and the generated C3b binds to the complexes and to CR-1 present on the surface of erythrocytes. During erythrocyte traffic through sinusoids in liver and spleen, residual phagocytes remove bound immune complexes, leading to their clearance.[11-13]

Several recent studies using transcriptomics techniques to identify complement proteins in kidney biopsies have provided documentation of an increase of messenger RNA of complement proteins in patients with SLE. During inflammation, there is an increase of such proteins, as well as a decrease of messanger RNA of complement regulators such as CR-1.

Through this way, Tempe et al.[14] identified an accelerated intrarenal synthesis of distinct classical and alternative complement pathway components, most associated with impaired renal function. The study documented that glomerular complement synthesis is associated with interferon signalling, while tubulointerstitial complement synthesis is associated with aberrant T cell receptor signalling.

Studies from Parikh et al.[15,16] using transcriptome analysis found that complement molecular profiling of kidney compartments from renal biopsies differentiated responders to treatment and patients affected by lupus flare. These findings may help as a treatment guide and to predict responses better.

Similarly, complement system activation studied by transcriptome analysis allowed identification of complement protein activation in chronic antibody-mediated rejection, and in IgAN recurrence.[17] In summary, all these studies on complement regulation and kidney diseases allow the statement that complement activation in nephrology has a double-edged role.[18]

Standard kidney biopsies may be useful in understanding intrarenal complement activity, but the use of kidney biopsies with complement

staining or transcript analysis adds useful information in understanding the exact role of complement in a particular patient. The use of such techniques may allow moving toward a personalised approach in the management of LN.[19] The study by Gilmore et al.[20] using transcriptome analysis on formalin-fixed paraffin-embedded kidney biopsy tissue revealed which molecular pathways are active in each patient, with LN comporting clinical utility in treatment selection. Similarly, Liu et al.,[21] studying kidneys of patients with LN and New Zealand Black/White mice, found higher expression of C3 and TGF-β1 in the earlier phases of LN. Mejia-Vilet et al.[22] found a significant heterogeneity in immune gene expression in the kidney of patients with LN. This fact might have relevance in treatment decisions. In a similar study, Peterson et al.[23] characterised heterogeneity in the molecular pathogenesis of LN from transcriptional profiles of laser-captured glomeruli.

Finally, Martin et al.[24] found that plasma C4d correlates with C4d deposition in kidneys of patients affected by active LN, and Wang et al.[6] found that membrane attack complex (MAC) deposition in renal tubules is associated with interstitial fibrosis and tubular atrophy.

Tubular complement activation and deposition occurs in proteinuric diseases, and in LN, C5-C9 deposition is associated with tubulointerstitial fibrosis. In addition, there is a subgroup of patients with persistent subclinical inflammation. Such patients have elevated biomarkers (monocyte chemoattractant protein-1) associated with a lower kidney survival.

TARGETING COMPLEMENT IN LUPUS NEPHRITIS

To date, several questions are open in the issue of targeting complement in LN, including which pathway to target; which combination of immunosuppressants to use; when to add anti-complement therapy to standard of care treatment; in which phase of renal disease complement should be targeted; and which new anti-complement compounds to use for LN.

Which Pathway to Target?

Figure 1 shows that all three pathways of complement activation are involved in LN: the classical pathway, the lectin pathway, and the alternative pathway.

A main rule is to avoid the inhibition of the early classical pathway in order to maintain the immune complexes clearance. In the alternative pathway, targets are fB, fD, and properdin. In all pathways, C3 is a possible target. Other targets are the MAC and the anaphylotoxins C3a receptor and C5a receptor.

Which Immunosuppressant?

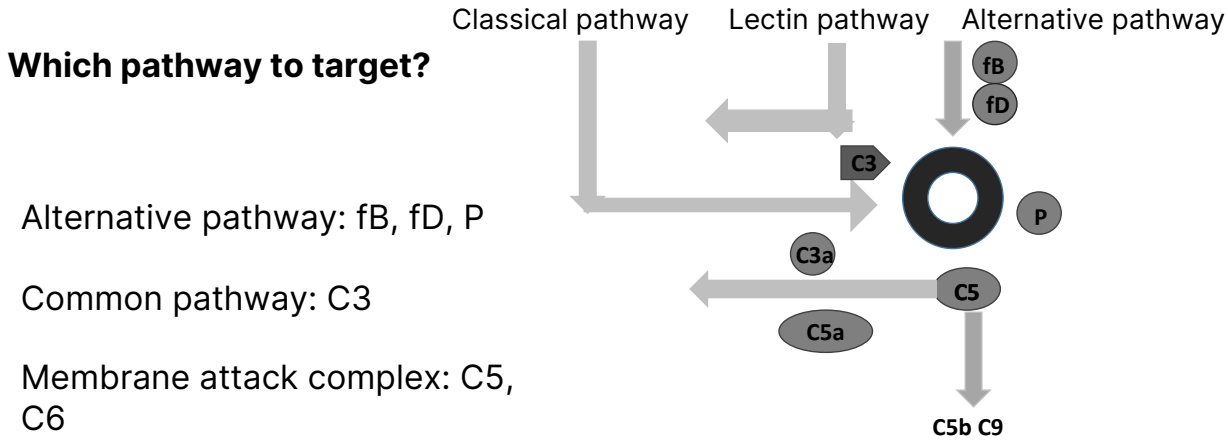
The second question is which is the best immunosuppressant to target complement. A study from Lemercier et al.[25] documented that glucocorticoids modulate the monocyte secretion of C3, fB, and fH, indicating an anti-inflammatory property and a control of complement activation.

A study from Wang et al.,[26] done on animals, documented that a compound of mycophenolic acid, in addition to targeting the proliferation of lympholeukocytes, downregulates complement protein 3 and other pro-inflammatory cytokines, such as TNFα-, IL-6, and TGF-β.

An old study on animals, from Pennington et al.,[27] documented that cyclophosphamide was able to inhibit the synthesis of C2 and C4 in a guinea pig model. A study from Renner et al.,[28] conducted on mice, documented that the treatment of patients with calcineurin inhibitors (CNI) is associated with an increased production of complement-activating endothelial micro particles. The deposition of C3 on the surface of endothelial micro particles was examined by flow cytometry. Complement activation caused by cyclosporine-induced micro particles seems to be due to a decreased binding of factor H.

In a different study,[29] CNI-induced complement activation downregulated the suppressor of cytokine signalling and the complement inhibitors CD46 and CD55. According to these studies, complement activation may contribute to chronic calcineurin inhibitor nephrotoxicity. However, it is only a hypothesis that cyclosporine causes alternative pathway dependent injury in the kidney and vasculature. Moreover, many of these studies were conducted on animals. Additionally,

Figure 1: Complement as a therapeutic target therapy in lupus nephritis.



C: complement; fB: factor B; fD: factor D; P: properdin; R: receptor.

large recent studies have documented the efficacy of CNI in the treatment of LN.[30]

The effect of RTX on LN has been discussed and its efficacy is still controversial.[31] Studies on patients with B cell malignancies treated with RTX[32] did not document RTX efficacy in targeting complement.

Compatibility of Complement Therapy with Lupus Nephritis Standard of Care

According to some studies, several complement proteins are downregulated by corticosteroids,[33] while other studies document an increase of C3 and fB messanger RNA.[25] Overall, the administration of a complement inhibitor to glucocorticoids could synergise with complement inhibition. MMF reduces C3 expression,[26] and the addition of a complement inhibitor could enhance the effect of MMF.

The cited study on cyclophosphamide[27] documents its inhibition on C2 and C4, which has a negative effect on the immune complexes clearance, but the addition of a complement inhibitor acting on a late stage of complement pathway may synergise with the anti-inflammatory effect of cyclophosphamide. CNIs enhance the inflammatory effect of complement in the kidney.

The use of a complement inhibitor could reduce this effect, allowing the use of CNIs in the treatment of LN.

RTX depletes B cells through different mechanisms, among which the complement-dependent cytotoxicity is relevant.[34] The addition of a complement inhibitor to RTX could reduce its effect on B cells through complement-dependent cytotoxicity.

In Which Phase of Renal Disease Should Complement Be Targeted?

Four phases should be distinguished in the development of LN. The first phase is autoimmunity, in which there is loss of self-tolerance; the second phase consists of the asymptomatic immune complexes deposition; the third phase is the inflammatory response that corresponds to clinical LN; and the fourth phase is the repair with development of fibrosis that corresponds to chronic kidney disease. The use of complement inhibitors is more effective when given to patients with active LN with clinical inflammation. The main problem is understanding when this phase occurs. It is best to have biomarkers corresponding to intra-renal complement activation, independent from biomarkers corresponding to systemic complement activation.

Transcriptomic analysis of kidney biopsies documented elevated expression of genes associated with C3 and fD during renal inflammation.[35] Other studies using transcriptomic analysis documented high expression of fB, fH, and properdin in patients with active LN documenting the activation of the alternative pathway.[36] In addition, urine examination may be useful in detecting intrarenal inflammation. Patients with active LN also have urinary C3d[37] and elevated urinary levels of MAC.[38] In conclusion,[5] the renal diseases in which alterations of complement system are present more frequently are aHUS, C3 glomerulonephritis (C3GN), IgAN, and LN.

In aHUS, the most frequent abnormality is the one concerning fH, but less frequently, abnormalities of MCP or fI have been found, and abnormalities of fB or C3 have been encountered with consequent gain of function.

In C3GN, all the described abnormalities can be found, but the more frequent abnormality is the presence of C3 nephritic factor autoantibodies that stabilise C3 convertase.

In IgAN, the abnormal IgA activate the complement system through the alternative or the mannose-binding lectin pathway. In LN, data on humans have documented abnormalities of fB.

Overall, patients who could benefit from anti-complement therapy, looking at the Mayo Clinic Study,[4] are patients with lower serum creatinine at the beginning, less proteinuria at diagnosis, less extensive glomerulosclerosis at renal biopsy, and with a lesser degree of tubular atrophy and interstitial fibrosis.

Complement Targeting Drugs

Dysalarm-322 is a drug still on clinical trial[39] that aims to investigate the role of anti-C1s, anti-high mobility group box 1 protein, and anti-C1q autoantibodies in the pathogenesis of LN. Previous studies[40] have already documented the role of such autoantibodies. Eculizumab, a monoclonal antibody (mAb), principally used for the treatment of aHUS, has also been used for the treatment of LN resistant to other therapies.[41] Ravulizumab, like eculizumab, is a novel humanised mAb that targets C5, and is under investigation for proliferative LN and IgAN.

Narsoplimab is a human mAb acting on the lectin pathway as it binds to the serine protease 2 (MASP-2) that activates the lectin pathway. A Phase II clinical trial is underway to evaluate its efficacy on LN.[42] Iptacopan targets fB and is active on the alternative pathway. To date, a Phase II trial evaluates the efficacy and safety of iptacopan (LNP023) in combination with standard of care for active LN Class III and IV.[43] Pegcetacoplan (APL-2), an inhibitor of C3, is to date being evaluated in several nephropathies, including LN.

Finally, other compounds could have an effect on LN. These compounds are to date the object of clinical trials for other glomerulopathies, but are not yet studied for the treatment of LN.[44]

TARGETING COMPLEMENT IN PATIENTS WITH LUPUS NEPHRITIS AND ASSOCIATED THROMBOTIC MICROANGIOPATHY

Patients with LN and associated TMA should be managed according to the underlying aetiology of TMA, as stated by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2021.[45] Patients with this syndrome should be distinguished according to having low ADAMTS13 levels; normal ADAMTS13 levels and negative antiphospholipid antibodies; or normal ADAMTS13 levels, but positive for antiphospholipid antibodies. The first group of patients should be treated by plasma exchange, glucocorticosteroids, RTX, and caplacizumab (an anti-von Willebrand factor).[46] Patients with normal ADAMTS13 levels should be screened for complement-mediated TMA and treated by eculizumab if positive. Finally, patients positive for antiphospholipid antibodies should be treated like patients with antiphospholipid syndrome nephropathy.

TARGETING COMPLEMENT IN PATIENTS WITH IgA NEPHROPATHY

Among the different glomerulonephritis, pathogenesis of IgAN is deeply involved by complement activation and/or dysfunction.[47]

IgAN is characterised by deposition of immune complexes containing polymeric galactose-

deficient IgA1 in the glomerular mesangium. Polymeric IgA1 and IgA1-containing immune complexes can activate the alternative and lectin pathway, leading to cleavage of intact C3, thereby forming C3a and C3b. C3a is an anaphylotoxin and C3b activates the complement cascade. In addition, fH is a key regulator of the complement system and together with fI, fH cleaves C3b to the inactive form iC3b. In IgAN, fH-related proteins could compete with the regulatory functions of fH, thereby promoting complement activation.

Due to the strong association between glomerular complement activation and IgAN, complement inhibitors are being tested in several clinical trials. Table 2 shows the principal clinical trials to date involved in testing complement inhibitors for the treatment of IgAN.[48-55]

C5a receptor 1 is a complement receptor that regulates the dendritic cells, and is essential to T cell immunity. Ravulizumab, a humanised mAb anti-C5 prevents cleavage of C5 into C5a and C5b. To date, a Phase II study of ravulizumab in proliferative LN or IgAN (SANCTUARY)[48] has the objectives to evaluate the safety and efficacy of ravulizumab administered by intravenous infusion compared to placebo, and demonstrate proof-of-concept of the efficacy of terminal complement inhibition in participants with LN (LN Cohort) or IgAN (IgAN Cohort). Preliminary data have documented its efficacy in reducing proteinuria and improving the estimated glomerular filtration rate (eGFR).

Another oral C5a inhibitor, avacopan (CCX168; NCT02384317),[49] is the object of a pilot study to test its safety, tolerability, and efficacy in reducing proteinuria in patients with IgAN and persistent proteinuria, despite supportive therapy with a maximally tolerated renin-angiotensin-aldosterone system blocker.

Cemdisiran (ALN CC5) is a synthetic, small RNA inhibitor designed to suppress liver production of C5, which may reduce terminal complement pathway activation and subsequent inflammation. A Phase II, double blind controlled study (NCT03841448)[50] aims to evaluate the safety and efficacy of cemdisiran in patients with IgAN.

APL-2 is a peptide inhibitor of C3. A Phase II trial will assess the safety and preliminary efficacy of daily APL-2 subcutaneous infusion administered for 16 weeks with a 6-month safety follow up, in patients with glomerulopathies, including IgAN.[51]

Serum levels of fB are increased in patients with IgAN, correlating with the activation of B cells. Blocking fB has potential pathophysiological importance. IgAN proteinuria reduction after 90 days of treatment with LPN023 (a fB inhibitor) is being tested in a Phase IIa/IIb trial (NCT03373461).[52] IONIS-fB-LRx is an antisense inhibitor of complement fB. It is to date the object of a Phase II study to evaluate the effectiveness and safety in adults with primary IgAN (NCT04014335).[53]

Narsoplimab is a human mAb against MASP-2. MASP-2 is essential for the activation of the lectin pathway that contributes to disease progression of IgAN and is, therefore, a potential drug target. Narsoplimab has been designed to treat diseases mediated by the lectin pathway of complement through inhibition of MASP-2. A first Phase II study was designed to assess the safety and efficacy of narsoplimab (OMS721) in patients with IgAN (NCT03608033).[54] BCX9930 is a fD inhibitor. Its efficacy in C3G, IgAN, and primary membranous nephropathy is evaluated in a long-term study (NCT05162066).[55]

Lafayette et al.[56] published a study evaluating the effects of narsoplimab on patients affected by IgAN. The study concluded that narsoplimab is safe and well tolerated, with a clinical meaningful reduction in proteinuria, and stability in eGFR in high risk patients with advanced IgAN. Similarly, LPN023 is evaluated to control IgAN.[57]

Several of the studies have been the object of pre-emptive publication, including one on ravulizumab,[58] two on iptacopan,[59,60] one on avacopan,[61] and four on narsoplimab.[62-65] In a pilot study by Bruchfeld et al.,[66] the C5a receptor inhibitor avacopan in IgAN documented the improvement of eGFR.

Table 2: Principal studies to test efficacy of complement inhibitors in IgA nephropathy.

Drug	Target	Study description
Ravulizumab	C5 inhibitor	Phase II study of ravulizumab in proliferative LN or IgAN[48]
Avacopan (CCX168)	C5a receptor blocker	Phase II, open-label study to evaluate safety and efficacy of CCX168 in subjects with IgAN[49]
Cemdisiran	Small interfering mRNA inhibitor of synthesis of C5	Phase II study of cemdisiran in adults with IgAN[50]
Pegetacoplan (APL-2)	C3 inhibitor	Phase II study assessing safety and efficacy of APL-2 in glomerulopathies[51]
Iptacopan (LNP023)	Complement fB inhibitor	Phase II study assessing efficacy and safety of LNP023 in patients with primary IgAN (APPLAUSE IgAN [NCT04578834])[52]
IONIS FB-LRx	Complement fB inhibitor	Study assessing efficacy and safety of IONIS-FB-LRx, an antisense inhibitor of complement fB, in adult participants with primary IgAN[53]
Narsoplimab	MASP-2 inhibitor	Study assessing the safety and efficacy of OMS721 in patients with IgAN[54]
LNP023	Factor D inhibitor	Study assessing efficacy and safety of LNP023 in patients with C3 glomerulopathy transplanted and not transplanted (03373461)[55]

fB: factor B; IgAN: IgA nephropathy; LN: lupus nephritis; MASP-2: mannan-binding lectin serine protease 2; mRNA: messenger RNA.

WHICH TREATMENT AFTER KIDNEY TRANSPLANTATION?

It is difficult to give an answer that is valid for any nephropathy. It depends on the type of kidney disease, and the severity of the disease itself.

In the case of LN, the risk of recurrence ranges between 2–30%.[67] In most cases, mild histologic lesions characterise recurrence and only rarely does recurrence lead to graft failure. The post-transplant immunosuppression is probably sufficient to control the disease. Generally, it can be stated that the result of kidney transplantation in LN depends on the clinical conditions at transplantation.

Suarez et al.[68] conducted a study on the recurrence and graft loss of patients affected by C3GN. The lowest incidence of graft loss was in patients treated with eculizumab. Among those who received no treatment because of a stable graft function, the allograft loss was 32% in patients with C3GN, and 53% in patients with dense deposit disease.

No treatment is needed for patients with IgAN, while the problem for patients with aHUS is still not solved, even if many patients try to interrupt the treatment, slowly and with a careful control.

CONCLUSION

In conclusion, the author has several points as final remarks, but several problems still remain to be solved. The current developments show that complement inhibition in renal disease is actively pursued in several clinical studies. The technological advances and clinical experience with eculizumab have led to a new confidence in therapeutic strategies that target the complement system.

The expanding list of trials and the increasing number of complement inhibitors, which are being developed and are tested in preclinical studies, demonstrate that complement inhibition is an option for therapy of glomerular disorders. Given the pathological heterogeneity between, and even within, indications for complement specific therapies, careful patient stratification will be essential to pave the way toward new therapeutic options.

Still unsolved problems are as followed: as aforementioned, for each single renal disease it is possible to target complement in different ways with different drugs and different targets. One problem is deciding which target should be chosen for any disease. A different problem is choosing which inhibitors to choose when having different inhibitors for the same target. Finally, a further problem is to understand how long the anticomplement therapy should be maintained. This point has a particular relevance in consideration of the high cost of such therapies.

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The Effect of Tip Placement on Fibrin Sheath Formation in Poorly Functioning Tunnelled Haemodialysis Lines

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Abstract

Background and Objectives: Fibrin sheath formation is a common cause of haemodialysis (HD) line dysfunction requiring frequent interventional line exchanges. This study assessed HD tip and line placement, line length, and demographics in poorly functioning HD lines due to fibrin sheath formation, to determine if there is a correlation between these factors and repeatedly poor function.

Patients and Methods: Patient medical records were retrospectively reviewed to include those who have had poorly functioning HD lines with fluoroscopic evidence of a fibrin sheath from 2011–2019. Analysis of variance and t-tests were performed to determine the significance of various factors on the time until a line exchange was required.

Results: Patients with an HD tip placed in the inferior vena cava underwent an exchange the soonest (130.23 days), while tips in the superior vena cava went the longest without required intervention (968.80 days; p=0.007). Lines in the left internal jugular vein had the most days without intervention, and lines in the femoral vein had the least (1,132.80 versus 142.50 days, respectively; p=0.007). Furthermore, 19 cm lines went 816.75 days without intervention, and 42 cm lines went 114.73 days without intervention (p=0.049). Intervention-free days decreased if the patient had undergone previous interventions (p<0.001). Patients with diabetes required intervention before those without diabetes (694.09 versus 917.08 days, respectively; p=0.033).

Conclusion: Factors such as HD tip and line placement, line length, previous interventions, and diabetic status demonstrated a correlation with how frequently tunnelled HD lines required intervention due to fibrin sheath formation.

Key Points

1. Identifying the most optimal location for haemodialysis (HD) tip placement could lead to future modifications in HD line insertion techniques and generate a way to reduce the migration of the tip once inserted.

2. Using an individualised approach for each patient on HD based on their comorbidities can be useful in being able to predict when an HD line may fail, and how soon after insertion it may require replacing.

3. Optimising both HD tip and line placement so that they will remain functional for longer before requiring replacement will cut down on overall costs for both patients and hospitals, and improve quality of life for patients.

INTRODUCTION

One of the most common causes of a poorly functioning haemodialysis (HD) line is the formation of a fibrin sheath.[1-3] Tunnelled HD lines contain a Dacron® (Invista, Wichita, Kansas, USA) cuff at the skin entry site, which helps secure the catheter in place due to the fibrosis that occurs in the subdermal tissues.[4-6] This fibrotic process results in the formation of a fibrin sheath, which forms at the cuff and grows centrally towards the tip of the catheter.[7-8] This fibrin sheath can form as early as 24 hours, and begins as platelet aggregation followed by fibroblast conglomeration.[9-11] When the fibrin sheath reaches the tip or inner lumen of the catheter, flow can be impeded. HD dysfunction due to fibrin sheath formation has been reported in 13–57% of patients on HD.[12-14] The fibrin sheath formation additionally acts as a nidus for biofilm formation and infectious complications.[15-17] These sheaths consist of various histological components, such as smooth muscle cells, collagen cells, thrombi, and endothelial cells, which hinders possible treatment and prophylactic options.[18-20] Current prophylactic measures with novel materials and coatings, such as heparin, do not entirely prevent fibrin sheath formation, and treatment options are limited and costly.[15,21,22]

The purpose of this study was to enhance future knowledge on patients on HD, how often their tunnelled HD lines require intervention due to fibrin sheath formation, and if there are any correlations in which patients require more frequent interventions, specifically over-the-wire balloon disruption of the fibrin sheath and line exchange. The variables tested included demographics, other comorbidities, length of HD line used, and HD tip and line placement. The most optimal anatomical location for the HD line tip has been extensively reviewed over the years as proper tip position is essential for efficient HD, with continuing debate on which position has the lowest risk of complications between the right atrium (RA), cavoatrial (CA) junction, and superior vena cava (SVC).[23-25] Current techniques aim for tip insertion in the middle of the RA, but migration after insertion is common.[26-28] The right internal jugular vein (IJV) has been the optimal location for line placement, with femoral and subclavian vein lines used less frequently due to the increased risk of thrombosis and infection.[25,29,30]

The study also aimed to investigate if those who have already had HD line dysfunction due to fibrin sheath formation are more prone to repeat events. There has been evidence that despite intervention by removal of the catheter, remnants of the fibrin sheath can persist in the venous system.[18,31,32] Although noted to be a rare complication, it may be an overlooked complication, as it is often found incidentally on subsequent CT scans and echocardiography.[31,33,34]

Calcified remnants of a fibrin sheath are also often overlooked and misdiagnosed as HD line fractures on imaging.[32,35]

Diabetes has also been associated with HD line dysfunction.[36,37] This has been attributed to the fact that a chronic hyperglycaemic state increases oxidative stress and inflammation, which contributes to a hypercoagulable environment that can cause fibrin sheath formation.[38,39]

METHODS

This retrospective study consisted of 299 consecutive patients from 2011–2019 at a single community hospital who were booked for HD line exchange/fibrin sheath disruption for a poorly functioning HD line, including 162 males and 137 females. Enrolment criteria included males and non-pregnant females over the age of 18 years with clinical evidence of poor HD flows in at least one of the two lumens and fluoroscopic evidence of a fibrin sheath on digital subtraction angiography. Patients with unknown fibrin sheath status were excluded from the study. Meditech (Westwood, Massachusetts, USA) was used to access medical records, including patient demographics and procedure dates. IMPAX (Mortsel, Belgium) was used to access imaging records to confirm HD tip placement. The total number of line exchanges and the time from initial line insertion to when an exchange was required were recorded for each patient. The time intervals between the first three interventions were also recorded for those applicable to investigate if interventions became more frequent after a line exchange occurs.

Fibrin sheath disruption and HD line exchanges were all performed under sterile conditions in the angiography suite by fellowship-trained interventional radiologists. Fibrin sheaths were confirmed by bluntly dissecting the catheter, withdrawing them over a wire, and performing digital subtraction angiography. All HD lines were non-coated HemoStar™ (Bard, New Providence, New Jersey, USA) catheters.

The median age of the study group at the time of their first HD line insertion was 64 years. Other demographic data were also recorded to evaluate if those factors had an impact on line exchanges.

Out of all of the patients, 160 (55%) had diabetes, 17 (6%) were current smokers, 30 (10%) were ex-smokers, 240 (82%) had diagnosed hypertension, 41 (14%) had coronary artery disease, and 87 (30%) had hyperlipidaemia. Of those with diabetes, 140 (88%) also had co-existing hypertension.

HD line characteristics recorded included tip placement, line placement site, and length of line. Intervention fluoroscopy time was also recorded, with a mean time of 1.03 minutes (standard deviation [SD]: 1.71). The possible tip placement positions included the CA junction, RA, SVC, and inferior vena cava (IVC). In total, 56% of the patients had their HD tip placed in the RA, 28% had theirs placed in the SVC, 12% had theirs placed in the CA junction, and 4% had theirs placed in the IVC. The various line placements were the right subclavian vein, right IJV, common femoral vein, and left IJV. The majority of HD lines (85%) were in the right IJV, with 7% placed in the left IJV, 5% placed in the femoral vein, and 2% placed in the right subclavian vein. The majority of HD lines were either 19 cm or 23 cm in length (42% and 50%, respectively), with 4% of lines being between 27–33 cm, and another 4% being >42 centimetres in length.

The variables tested included gender, age at initial insertion, smoking status, intervention fluoroscopy time, and whether the patient had hyperlipidaemia, coronary artery disease, diabetes, or hypertension.

T-tests were used to determine if any of the variables had an impact on either the number of exchanges performed or the length of time until an exchange was required. Analysis of variance (ANOVA) tests were then performed to determine if HD line tip or line placement had an effect. Variables that proved to have a significant impact in the t-test were then grouped separately for further ANOVA tests on tip placement and line placement.

RESULTS

The initial ANOVA test comparing tip placement and length of time between HD line insertion and intervention produced the following results represented by the mean: CA junction: 632.82 days (SD: 747.96); IVC: 130.23 days (SD: 147.89);

RA: 798.51 days (SD: 837.73); and SVC: 968.80 days (SD: 1,006.69); with p=0.007 for this ANOVA.

The initial ANOVA test comparing line placement and length of time between line insertion and intervention yielded the following results represented by the mean: femoral vein: 142.50 days (SD: 133.53); left IJV: 1,132.80 days (SD: 1,380.28); right IJV: 804.42 days (SD: 841.00); and right subclavian vein: 921.86 days (SD: 519.59); with p=0.007 for this ANOVA.

The percentage of HD lines that remained functional at 6 months, 1 year, and 2 year intervals is illustrated in Table 1.

The ANOVA testing the length of the HD line to time until required intervention yielded the following results: 19 cm: 816.75 days (SD: 839.18); 23 cm: 790.71 days (SD: 898.57); 27–33 cm: 458.70 days (SD: 406.20); and >42 cm: 114.73 days (SD: 84.42); with p=0.04 for this study.

The length was then also compared with tip placement by calculating the intervention-free days per cm of line and separating by tip placement. When comparing the two factors using an ANOVA the following results were produced: CA junction: 31.42 days/cm (SD: 36.52); IVC: 4.64 days/cm (SD: 6.78); RA: 35.73 days/cm (41.18); and SVC: 44.31 days/cm (SD: 42.71); with p=0.049.

The ANOVA test comparing the time intervals between the first three interventions produced the following results represented by the mean: line insertion to intervention: 798.45 days (SD: 876.90); first–second intervention: 556.52 days (SD: 584.90); and second–third intervention: 364.96 days (SD: 408.79); with p<0.001.

The ANOVA test comparing tip placement and the mean number of interventions required provided the following results represented by the mean: CA junction: 2.77 days (SD: 2.28); IVC: 2.30 days (SD: 1.44); RA: 2.52 days (SD: 1.91); and SVC: 3.07 days (SD: 2.68); with p=0.15.

The t-tests comparing the length of time between initial line insertion and intervention yielded the following results represented by the means: female gender: 841.64 days (SD: 907.04), and male gender: 762.47 days (SD: 852.14), with p=0.442; age 64 years and below: 886.81 days (SD: 1,434.00), and age 65 and over: 707.08 days (SD: 621.06), with p=0.075; smoking status: non-smoker: 818.63 days (SD: 886.93), and smoker: 691.15 days (SD: 822.24), with p=0.339; blood pressure: no hypertension: 819.45 days (SD: 1,069.19), and hypertension: 791.50 days (SD: 824.86), with p=0.854; diabetic status: no diabetes: 917.08 days (SD: 1,037.64), and diabetes: 694.09 days (SD: 692.81), with p=0.033; no coronary artery disease: 786.58 days (SD: 874.31), and coronary artery disease: 877.03 days (SD: 901.52), with p=0.560; no hyperlipidaemia: 850.02 days (SD: 965.84), and hyperlipidaemia: 673.99 days (SD: 597.91), with p=0.058.

All t-tests testing for any correlation with the number of interventions required produced insignificant values of p>0.05.

After the t-tests, patients were further separated into groups with diabetes and without diabetes, and the ANOVA tests that produced significant results were conducted again.

In patients with diabetes, the ANOVA comparing HD line tip placement and length of time between line insertion and intervention produced the following results represented by the mean: CA junction: 455.24 days (SD: 375.79); RA: 742.52 days (SD: 632.97); SVC: 817.55 days (SD: 632.97); and IVC: 135.70 days (SD: 176.84); with p=0.015.

In patients without diabetes, the ANOVA comparing HD line tip placement and length of time between line insertion and intervention produced the following results represented by the mean: CA junction: 810.41 days (SD: 972.43); RA: 860.18 days (SD: 910.52); SVC: 1,135.18 days (SD: 1,293.57); and IVC: 112.00 days (SD: 63.31); with p=0.264.

In patients with diabetes, the ANOVA comparing HD line location and length of time between line insertion and intervention produced the following results represented by the mean: right subclavian vein: 777.50 days (SD: 526.80); right IJV: 694.05 days (SD: 627.23); femoral vein: 149.92 days (SD: 152.55); and left IJV: 1,257.91 days (SD=1,266.78); with p=0.002.

Table 1: Percentage of haemodialysis lines that remained functional.

	Functional haemodialysis lines		
Tip placement	**6 months**	**1 year**	**2 years**
CA junction	74%	51%	29%
RA	77%	61%	41%
SVC	82%	68%	47%
IVC	23%	8%	0%
Line placement	**6 months**	**1 year**	**2 years**
Right subclavian vein	100%	86%	57%
Right IJV	87%	70%	45%
Femoral vein	25%	6%	0%
Left IJV	90%	65%	50%
Diabetic status	**6 months**	**1 year**	**2 years**
Diabetes	71%	56%	35%
No diabetes	85%	67%	42%

CA: cavoatrial; IJV: internal jugular vein; IVC: inferior vena cava; RA: right atrium; SVC: superior vena cava.

In patients who did not have diabetes, the ANOVA comparing line location and length of time between line insertion and intervention produced the following results represented by the mean: right subclavian vein: 1,114.33 days (SD: 544.41); right IJV: 922.93 days (SD: 1,011.44); femoral vein: 120.25 days (SD: 54.27); and left IJV: 979.89 days (SD: 1,571.96); with p=0.395.

In patients with diabetes, the ANOVA comparing the time between the first three interventions yielded the following results represented by the mean: line insertion to first intervention: 694.09 days (SD: 692.81); first–second intervention: 551.59 days (SD: 617.86); and seocnd–third intervention: 375.09 days (SD: 421.16); with p=0.002.

In patients without diabetes, the ANOVA comparing time between the first three interventions yielded the following results: line insertion to first intervention: 917.08 days (SD: 1,037.63); first–second intervention: 562.73 days (SD: 547.27); and second–third intervention: 350.11 days (SD: 394.16); with p<0.001.

The results of the tests on patients with diabetes versus without diabetes are illustrated in Table 2.

ANALYSIS

There was statistical significance (p<0.05) in the relationships between both HD line tip placement and line placement in regards to the time from HD line insertion until an intervention was required. Patients who had their HD tip placed in the SVC had lines that remained functional the longest, with an average time of 968.80 days until intervention was required, which differs from the current technique that aims for insertion in the RA. The second most optimal location for tip placement was the RA, with an average of 798.51 days until required intervention. Patients with HD line tips that were placed in the CA junction required HD line exchanges at an average of 632.82 days. Patients with their HD tip placed in the IVC required an intervention the soonest, with an average of 130.23 days between line insertion and intervention. The HD lines placed in the left IJV remained functional the longest, with

Table 2: Analysis of variance tests in patients with diabetes versus without diabetes.

Patients with diabetes			Patients without diabetes		
ANOVA	**Mean time until intervention (days)**	**p**	**ANOVA**	**Mean time until intervention (days)**	**p**
Tip placement		0.015	**Tip placement**		0.264
CA junction	455.24 (SD: 375.79)		CA junction	810.41 (SD: 972.43)	
RA	742.52 (SD: 771.14)		RA	860.18 (SD: 910.52)	
SVC	817.55 (SD: 632.97)		SVC	1,135.18 (SD: 1,293.57)	
IVC	135.70 (SD: 176.84)		IVC	112.00 (SD: 63.31)	
Line placement		0.002	**Line placement**		0.395
Right subclavian vein	777.50 (SD: 526.80)		Right subclavian vein	1,114.33 (SD: 544.41)	
Right IJV	694.05 (SD: 627.23)		Right IJV	922.93 (SD: 1,011.44)	
Femoral vein	149.92 (SD: 152.55)		Femoral vein	120.25 (SD: 54.27)	
Left IJV	1,257.91 (SD: 1,266.78)		Left IJV	979.89 (SD: 1,571.96)	
Time between interventions		0.002	**Time between interventions**		<0.001
Line insertion–1st intervention	694.09 (SD: 692.81)		Line insertion–1st intervention	917.08 (SD: 1,037.63)	
1st–2nd intervention	551.59 (SD: 617.86)		1st–2nd intervention	562.73 (SD: 547.27)	
2nd–3rd intervention	375.09 (SD: 421.16)		2nd–3rd intervention	350.11 (SD: 394.16)	

ANOVA: analysis of variance; CA: cavoatrial; IJV: internal jugular vein; IVC: inferior vena cava; RA: right atrium; SD: standard deviation; SVC: superior vena cava.

an average of 1,132.8 days. The 2% of patients with HD lines in the right subclavian vein went an average of 921.86 days before requiring intervention. The majority of patients had their HD lines placed in the right IJV, which had an average time of 804.42 days between insertion and exchange. Those with the line running through the femoral vein required intervention after an average of only 142.5 days.

A correlation was most likely seen between femoral vein lines and IVC tip placement requiring earlier intervention due to the tip of femoral vein lines almost always being placed in the IVC and it being a last-resort option for permanent HD access, suggesting that patients with lines in the femoral vein have all most likely had previous lines elsewhere that failed and have possible damage to those veins.[23,30]

When comparing the length of HD lines and days without intervention, the shorter 19 cm and 23 cm lines went a longer time without required intervention compared with the longer 27 cm and 42 cm lines (p=0.04). This may be heavily affected by the location where these lines are placed. While the 19 cm and 23 cm lines are typically placed in the right IJV, the >42cm lines are placed in the femoral vein, which tends to require intervention sooner.

The ANOVA test comparing the average time between the first three exchanges also proved to be highly significant (<0.001), with the duration of time between exchanges decreasing as the number of exchanges increases. The exact mechanism by which HD dysfunction due to fibrin sheath formation occurs sooner in those who had previous fibrin sheath formation is most likely due to a multitude of factors that can be explored in future studies. It is possible that some of these patients retained remnants of the fibrin sheath after removal of their original HD line that contributed to future HD line dysfunction, although further research would be required to confirm this.[18,31,33]

The total number of exchanges a patient underwent had no significant correlation (p>0.05) with HD tip placement, line placement, health conditions, or demographics. This number is influenced by alternative factors such as patients receiving kidney transplants, death, and the fact that some patients have had an HD line much longer than others.

The only patient factor that had a statistically significant effect on the time until the first intervention was diabetic status (p=0.033), with patients with diabetes requiring an intervention an average of 222.99 days sooner than those without diabetes. This is likely due to the increased inflammation seen in patients with diabetes due to chronic hyperglycaemia.[38]

No significant correlation was found between fibrin sheath formation and smoking status, age at insertion, gender, hyperlipidaemia, hypertension, or coronary artery disease in this study.

When separated, the group with diabetes produced a similar pattern of results as all the initial significant ANOVA tests comparing tip placement, line placement, and time between interventions with significant values (p<0.05). The lines with the HD line tip placed in the SVC remained functional the longest, followed by tip placement in the RA, then the CA junction, and finally the IVC. However, the group without diabetes also yielded similar results, but an insignificant p-value (p=0.264) in the ANOVA comparing tip placement and time until an exchange was required. The results of the initial line placement and time until intervention ANOVA produced different results than the initial test and an insignificant p-value (p=0.395). Regarding the time between interventions, both the group with diabetes and without diabetes produced similar results as the initial ANOVA with highly significant results (p=0.002 and p<0.001, respectively). Both groups demonstrated a decrease in time between interventions for the first three interventions. It is a possibility that the smaller sample size of the group without diabetes may have contributed to insignificant results as the majority (55%) of the group had diabetes.

LIMITATIONS

Possible sources of error in this study include human error in reading the imaging for HD tip placement and errors in information retrieval from patient records. An additional source of possible error is that line exchanges that were performed at other hospitals for these patients could have remained unrecorded in patient files in the Scarborough Health Network (SHN). Patient demographics and health information that were not recorded in patient notes are another possible source. A larger sample size of patients in each variable tested would additionally benefit the validity of this study, as there was an unequal distribution of patients in each test group. Despite a significant p-value, 85% of the patients had their HD lines placed in the right IJV, meaning a larger sample size of patients with alternative line placements would be required to

confidently report findings on the effect of line placement on HD line function.

This sample size was insufficient to compare both combined HD line tip and line placements. The year that each HD line was inserted was also not taken into account in this study, which has had an effect on HD line failure in previous studies.[40] Alternative factors not tested in this study could also have a possible effect on HD dysfunction and fibrin sheath formation, and hence, the results of this study.

CONCLUSION

With millions of people on dialysis worldwide, having the ability to predict the frequency at which tunnelled HD lines will need to be exchanged due to fibrin sheath formation would allow for both physicians and patients to have a better understanding of individualised HD care. In this study, HD line tip placement, line placement, line length, and diabetic status of a patient all had an impact on the dysfunction of HD lines and when an interventional line exchange was required. Tip placement in the IVC, line placement through the femoral vein, and having diabetes were factors that required patients to have more frequent interventions due to poor patency, while patients with tip placement in the SVC and line placement through the left IJV required interventions the least frequently. This challenges the current regimen used of aiming to insert the tip into the RA via the right IJV.

The longer 27 cm and 42 cm lines required an earlier intervention than the 19 cm and 23 cm lines, although the associated line placement could be affecting these results. Tip and line placement proved to be effective predictors, specifically in patients with diabetes. Once a patient had at least one intervention performed, subsequent interventions were required at more frequent intervals for the first three exchanges in this study. None of the variables tested in this study displayed a pattern that could be used to predict the total number of interventions that would be required. Current evidence supports the findings of poorer patency in patients with diabetes and those with HD lines in the femoral vein. Larger studies are required to confirm the findings on how catheter tip placement impacts the frequency of interventions on tunnelled HD lines. Prospective studies conducted in the future could be used to confirm these findings of which tip and line placement have the best outcomes, as well as the impact other patient factors may have on line dysfunction, in order to optimise line insertion techniques. Future studies with a more significant sample size should be used to demonstrate any correlation when comparing both tip and line placement.

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Prevalence of SARS-CoV-2 Cellular and Humoral Immunity Amongst Patients on Dialysis After the First Vaccination Campaign

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Abstract

Background: Immunisation remains critical in prevention of serious COVID-19 infection. This study aimed to characterise the prevalence of humoral and cellular immunity in patients on maintenance dialysis in a nephrology centre 8 months after vaccination onset.

Methods: Real-world single-centre prevalence cross-sectional study enrolling patients on peritoneal and haemodialysis. Humoral response was measured as specific IgG (anti-spike protein receptor-binding domain IgG) and cellular response as T cell reactivity through interferon γ quantification as response to antigen.

Results: Of the 86 patients enrolled, 79.4% and 84.1% showed humoral and cellular immunity, respectively. Anti-spike protein receptor-binding domain IgG correlated with specific T cell reactivity ($\rho=0.58$; $p<0.001$). Vaccinated patients with associated high comorbidity burden and low serum albumin were at risk of absent immunity ($p<0.05$).

Conclusion: The prevalence of humoral and cellular immunity against severe acute respiratory syndrome coronavirus 2 in vaccinated Portuguese patients on maintenance dialysis is high. High comorbidity burden and low serum albumin are risk factors for absent immune response.

Key Points

1. Humoral and cellular quantitative responses to vaccination correlated throughout the study of patients receiving dialysis, suggesting interdependence of the adaptative immune system.

2. High comorbidity burden, quantified through Charlson Comorbidity Index (CCI), correlated with low immunity yield from vaccination in patients receiving dialysis.

3. Adapting isolation and vaccination policies to protect patients receiving dialysis who have high frailty and comorbidities scores is an important factor for a successful vaccination campaign.

INTRODUCTION

Global immunisation against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the standard-of-care in preventing COVID-19 and, in the absence of a specific antiviral therapy, the only effective action against this pandemic. Different vaccines with different action mechanisms have been developed, namely BNT162b2 (Pfizer–BioNTech [New York City, USA, and Mainz, Germany, respectively])[1] and mRNA-1273 (Moderna [Cambridge, Massachusetts]),[2] which are mRNA-based vaccines, as well as ChAdOx1 nCov-19 (AstraZeneca [Cambridge, UK])[3] and Ad26.COV2.S (Janssen Pharmaceuticals [Beerse, Belgium]),[4] which are recombinant adenovirus vectors encoding the SARS-CoV-2 spike glycoprotein.

From the start, the need for mandatory regular contact with health care services, coupled with worse disease severity and increased mortality risk, established patients on maintenance dialysis (MDP) as a high-risk population.[5-7] In this setting, international recommendations, as well as local healthcare authorities, considered immunisation of MDPs a priority, starting the vaccination campaign in February 2021 in Portugal.

As time elapsed, the understanding that the inherent dynamism of a dialysis centre, with a permanent inflow and outflow of chronic patients, has led to a heterogenous dialysis population regarding contact with SARS-CoV-2 and vaccination schemes, or time of inoculation (namely before dialysis initiation, where vaccines unapproved by the Portuguese Dictectorate-General of Health for MDPs were administered). Thus, to rely on a one-time vaccination campaign is insufficient, and follow-up measures for incident patients on dialysis are required.

Aggravating this, end-stage kidney disease (ESKD) associates with immune dysfunction, affecting both the innate and adaptative system.[8,9] Uremic toxins, malnutrition, chronic inflammation, and dialysis technique contribute to this impairment.[10] One of the most important examples is the antigen-presenting dendritic cell, necessary to start antibody production, presenting both a quantitative reduction, while also being dysfunctional in ESKD. It is now proposed as one of the main mechanisms of immunodeficiency in this population.[10-16] Additionally, antigen-specific memory CD4 T cell, responsible for lasting immunity, is also functionally defective and, on a molecular level, dysregulation of toll-like receptors and up-regulation of inflammatory cytokines all contribute to immune system stunning.[17-20] These limitations have raised concerns about the immunogenicity of COVID-19 vaccination in MDPs and on the subsequent preservation of that acquired immunity.

The study aims, primarily, were to quantify the prevalence of humoral and cellular immunity against SARS-CoV-2 in a vaccinated Portuguese MDP cohort, with patients on peritoneal dialysis (PD) and haemodialysis (HD), 8 months after the first vaccination campaign and, secondarily, to compare humoral and cellular responses against clinical and demographic risk factors in the appropriate subgroups.

METHODS

The authors conducted a cross-sectional observational study of all the MDPs in a Portuguese National Health System's medium-sized nephrology department on specific SARS-CoV-2 T reactive cell response and anti-spike

protein receptor-binding domain IgG (IgG S-RBD) titres. This work followed the ethical principles presented in the declaration of Helsinki and informed consent was obtained from every participant in this study. Exclusion criteria were restricted to those who could not provide informed consent.

Blood samples were collected in October 2021 as part of the centre's contingency protocol. Variables, including age, sex, comorbidity burden as measured by Charlson Comorbidity Index (CCI), type of vaccine, dialysis modality, presence of COVID-19 infection in the past, chronic kidney (CKD) staging at vaccination, and analytical results, which included intact parathormone (iPTH), serum albumin (sALB) and C reactive protein (CRP) being used as variables to assess for differences in vaccination response.

Quantification of Humoral Response

Measurement of immunogenicity was performed at the hospital's clinical pathology laboratory. Quantitative determination of SARS-CoV-2 IgG (S-RBD IgG) in the patient's serum was performed by chemiluminescence immunoassay (Maglumi [Snibe, China]), in addition to IgM anti-spike and anti-nucleocapsid for tracking past virus contact. Results were measured as AU/mL. Response was considered significant for values over 1 AU/mL, in accordance with manufacturer specifications.

Quantification of Cellular Response

For determination of the activity of SARS-CoV-2-reactive T cells, the EUROIMMUN (Lübeck, Germany) Quan-T-Cell ELISA was used, an interferon (IFN) γ released assay (IGRA) based test. Heparinised whole blood was incubated into three stimulation tubes: BLANK, no T cell stimulation, for determination of the individual IFN-γ background; TUBE, specific T cell stimulation using antigens based on the SARS-CoV-2 spike protein; and STIM, unspecific T cell stimulation by means of a mitogen, for control of the stimulation ability. The obtained plasma was analysed by ELISA and the SARS-CoV-2 specific IFN-γ-release assay was quantified automatically, in mIU/mL. The IFN-γ concentration of the TUBE after BLANK subtraction was evaluated in order to obtain information on a past pathogen contact with SARS-CoV-2, or an immune reaction following vaccination. In accordance with the manufacturer's recommendations, concentrations between 100–200 mIU/mL were considered borderline, with under 100 mIU/mL being negative and over 200 mIU/mL positive.

Statistical Analysis

Statistical analysis was carried out using Microsoft (Redmond, Washington, USA) Excel 2016 and IBM (Armonk, New York, USA) SPSS Statistics 25 software.

Descriptive analysis was performed using means with standard deviation for continuous variables (median with interquartile range [IQR] for skewed distribution), and categorical variables using absolute and relative frequencies. For comparative analysis, specific statistical tests were performed based upon the nature of the variables: continuous/continuous–correlation with Spearman for skewed and Pearson for parametric variables; binomial/continuous–differences in median with Mann–Whitney U for skewed distribution and means with Student's t-test, if parametric; and binomial/binomial–Fisher's exact test and Phi coefficient, if significant.

Variables that were significantly different between immune and non-immune subgroups, cellular or humoral, were pooled together and binary regression analysis was performed to assess their contribution to the likelihood of absent immunity.

RESULTS

A total of 88 patients were enrolled, with 86 getting screened for immune response, 65 (75.6 %) patients from HD and 21 (24.4 %) from PD. Patients who refused vaccination (2) were excluded after initial recruitment. Descriptive analysis, including results from demographic, clinical, and immunity related variables, is summarised in Table 1.

The group's mean age was 69.6 years (standard deviation [SD]: 12.8), with 30 female patients (34.9%). CCI mean was 6.7 (SD: 2.5), and 39 (45.3%) had diabetes. Regarding manufacturer, 78 (90.7%) patients received the BNT162b2 (Pfizer–BioNTech) vaccine, 6 (7.0%) the ChAdOx1 nCov-19 (AstraZeneca), and 2 (2.3%)

Table 1: Descriptive group and subgroup analysis.

	Complete sample (n=88)	Subgroup B (n=68)
Age (years), mean (SD)	69.9 (12.7)	70.2 (13.2)
Sex (female/male), n (%)	30 (34.1); 58 (65.9)	23 (33.8); 45 (66.2)
Modality		
HD, n (%)	67 (76.1)	49 (72.1)
PD, n (%)	21 (23.9)	19 (27.9)
Dialysis vintage at vaccination (months), mean (SD)	N/A*	29.7 (26.7)
Diabetes, n (%)	38 (43.2)	31 (45.6)
CCI, mean (SD)	6.8 (2.5)	6.8 (2.5)
Nephrosclerosis, n (%)	24 (27.3)	18 (26.5)
Immune disorders, n (%)	7 (8.0)	2 (2.9)
CKD stage at vaccination		
Maintenance dialysis, n (%)	79 (89.8)	68 (100.0)
Stage 5 CKD, n (%)	9 (10.2)	0 (0.0)
Time from vaccination to immune status evaluation	N/A	8 months
Vaccine		
BNT162b2 (Pfizer–BioNTech [New York City, USA, and Mainz, Germany, respectively]), n (%)	78	68†
ChAdOx1 nCov-19 (AstraZeneca [Cambridge, UK]), n (%)	6	0
Ad26.COV2.S (Janssen Pharmaceuticals [Beerse, Belgium]), n (%)	2	0
None, n (%)	2	0
Contact with SARS-CoV-2		
COVID-19 infection, n (%)	3	0
Asymptomatic, n (%)	4	0
Humoral response		
S-RBD IgG (AU/mL), median (IQR)	4.6 (14.0)	4.6 (11.4)
NR, n (%)	19.0 (21.6)	14.0 (20.6)

Table 1 continued.

	Complete sample (n=88)	Subgroup B (n=68)
Cellular response		
GRA (mUI/mL), median (IQR)	574.8 (1,376.9)	530.0 (914.9)
NR, n (%)	14.0 (15.9)	10.0 (14.6)
Laboratory variable		
sALB, mean (SD)	3.5 (0.5)	3.6 (0.4)
iPTH, mean (SD)	301.1 (317.7)	328.6 (331.5)
CRP, mean (SD)	1.1 (1.5)	1.0 (1.6)

*Both groups included patients who were not on dialysis.

†Administered at the same time.

CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; CRP: C-reactive protein; HD: haemodialysis; IGRA: interferon γ release assay; S-RBD IgG: anti-spike protein receptor-binding domain IgG; IQR: interquartile range; iPTH: intact parathormone; N/A: not applicable; NR: non-responsive; PD: peritoneal dialysis; sALB: serum albumin; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation.

the Ad26.COV2.S (Janssen Pharmaceuticals). Time and CKD stage at vaccination differed, with 68 patients receiving vaccination in February, integrated in initial MDP vaccination protocols, while the remaining 18 received it later, with nine still on Stage 5 CKD before dialysis initiation (10.5%) and the remaining nine after dialysis start. Mean time to immune evaluation in these 18 patients was 4.4 months (SD: 1.9). A total of seven patients (8%) had a history of COVID-19 infection confirmed via PCR of a nasopharyngeal swab.

Regarding immune response, humoral response, through IgG S-RBD quantification, showed a median of 5.6 AU/mL (IQR: 14.4 AU/mL), with 19 patients (22.1%) not achieving humoral response cut-off; and cellular immunity, as quantified through T cell reactivity, revealed a median of 598.7 mUI/mL (IQR: 1,440.4 mUI/mL), with 14 patients (16.3%) showing no reactivity (<100 mUI/mL) and 9 (10.5 %) resulting in inconclusive with intermediate results (100–200 mUI/mL). IgG S-RBD levels correlated positively with IFN-γ-release assay results (ρ=0.56; p<0.001). A total of 12 patients (14.0%) were concomitantly negative for humoral and cellular immunity.

Patients with an history of contact with SARS-CoV-2 showed the highest values of specific IgG (median: 476.7 AU/mL versus 4.0 AU/mL), as well as T cell reactivity (median: 2,440.6 mUI/mL versus 695.4 mUI/mL), though none of these differences were statistically different (p=0.07 and p=0.33, respectively). Receiving the vaccine before dialysis start (in non-dialysis ESKD [N=9]) was associated with no cellular response when compared with vaccination in patients who were already on dialysis (Phi=0.44; p=0.006), which was not verified for humoral response (p=0.4).

Subgroup Analysis

A total of 68 patients (77.3% of the original sample) satisfied the selection criteria, having received 2 doses of BNT162b2 at vaccination campaign onset (February 2021), while already being on dialysis and with no clinical or laboratory findings compatible with virus contact. Mean age was 70.2 (SD: 13.2), 33.8%

female, and 72.1% were on HD versus 27.9% on PD. In these patients, immunogenicity analysis, dating approximately 34 weeks from vaccination, revealed a serologic median of 4.6 AU/mL (IQR: 11.4 AU/mL) and cellular response median of 530 mIU/mL (IQR: 914.9 AU/mL). Quantitative humoral and cellular response correlated positively (p=0.5; p<0.001). Humoral and cellular responses were negative in 20.6% and 14.7%, respectively. Compared with humoral responders, non-responders presented higher CCI (8.6 versus 6.4; p=0.005), lower sALB (3.4 versus 3.7; p=0.03), and lower iPTH (95.4 versus 241.9; p=0.03), while CRP and age alone were not significantly different. On the cellular dimension, non-responders showed higher CCI (9.4 versus 6.2; p<0.001) and lower sALB values (3.2 versus 3.7, p<0.001).

When comparing complete absence of immune response in these patients (humoral and cellular concomitantly; verified in nine patients) with the remaining subgroup, even those who just achieved response in one type of the adaptative immunity, complete non-responders had higher CCI (9.4 versus 6.3; p=0.001) and lower albumin (3.2 versus 3.7; p=0.003). A binary logistic regression was performed to ascertain the effects of CCI and sALB on the likelihood that patients had no humoral and cellular response concomitantly. The model was statistically significant ($\square^2$[2]=24.1; p<0.001) and explained 62.0% (Nagelkerke R^2) of the variance in non-responding while also correctly classifying 91.2% of cases. Higher levels of CCI (odds ratio: 1.9; 95% confidence interval: 1.1–3.4; p=0.03) increased the likelihood of complete absence of immune response whereas higher sALB decreased it (odds ratio: 0.02; 95% confidence interval: 0.02–0.20; p=0.01).

Further exploratory analysis was performed using the subgroup B, but specifically for differences in dialysis modalities. Patients on PD were significantly younger (61.1 versus 73.8 years; p<0.001), with lower CCI (5.4 versus 7.4; p=0.005) and higher iPTH levels (550.8 versus 242.4; p<0.001). CRP (0.7 versus 1.1; p=0.4) and sALB (3.5 versus 3.6; p=0.3) levels and were not significantly different. Regarding immune response, specific IgG titres were higher in the PD subgroup (median: 6.3 versus 3.0 AU/mL; p=0.36) and a lower rate of IgG under 1 AU/mL (10.5% versus 26.1%; p=0.1), although neither were statistically significant. T cell reactivity quantification values were statistically higher among patients on HD (median: 297.1 mUI/mL versus 695.4 mUI/mL; p=0.03), but there was no difference in the rate of cellular response under the 100 mUI/mL cut-off (20.0% versus 17.9%; p=1).

DISCUSSION

This study showed a high prevalence of humoral (78.9%) and cellular (83.7%) immunity 8 months after vaccination campaign onset in Portuguese MDPs, regardless of the time of vaccination, manufacturer, or previous contact with the virus. Humoral and cellular quantitative responses correlated throughout the study, suggesting interdependence of the adaptative immune system instead of two separate dimensions. The prevalence of patients with known contact with SARS-CoV-2 was low (8%) and does not translate the true incidence during this 8-month period, given the high mortality of COVID-19 in patients on dialysis.[5-7] Similarly, interpretation of the results must consider that patients without response to vaccination were at risk of death by COVID-19 since vaccination campaign onset, which was not quantified in this cross-sectional study. Previous COVID-19 infection elicited the highest values of humoral and cellular response, though was not significantly different from non-infected, supporting the main limitation throughout all comparative analysis in this study: small sample size.

Vaccination in patients with ESKD who were pre-dialysis was associated with absence of cellular response (p=0.006), even though the time from vaccination to the immune status evaluation was shorter when compared with MDPs vaccinated in February. It is relevant to note that these patients were not exclusively vaccinated with BNT162b2 but also with ChAdOx1 nCov-19 and Ad26.CoV2.S, whereas those already on MDP were all given the BNT162b2, which was the only vaccine approved for patients on dialysis in Portugal.

Higher and untreated levels of uraemia, persistent volume overload with resulting gastrointestinal endotoxemia, decreased clearance of proinflammatory cytokines, and oxidative stress can set up the substrate for increasing circulating inflammatory cytokines

and the resulting T cell dysfunction.[21-23] However, even after dialysis is initiated, the presence of a vascular/peritoneal access or contact with extracorporeal components still contributes to chronic inflammation.

Moreover, studies regarding hepatitis B vaccination have suggested a decrease in immune response proportional to the degree of kidney failure, with patients on dialysis yielding the worst immunogenicity,[24,25] establishing that even small levels of residual kidney function ameliorate inflammatory status in MDP.[22,26] Therefore, the association between pre-dialysis ESKD, and absence of cellular immunogenicity verified in this study, could result from other factors beyond those related to CKD. Despite the limitations already mentioned, this finding of an improved response in patients on dialysis when compared with imminent pre-dialysis ESKD has not yet been reported, and may support a heavy contribution of uraemia and an exacerbated inflammatory state in immune system dysfunction.

Concerning vaccination response and immunogenicity, multiple studies have looked at early humoral response in MDP. One of the largest by Stumpf et al.,[27] with a cohort of 1,256 patients on dialysis, described a rate of seroconversion of over 95% and cellular response of 78% after 8 weeks of first vaccination, establishing its efficacy in this population. A more recent study by Sibbel et al.[28] provided real-world evidence of its effectiveness in lowering death and hospitalisation among MDPs. However, early follow-up of elicited immunogenicity quickly showed a steeper decline compared to healthy controls, leading to the conclusion of a shorter longevity of immune protection in MDP.[29-34]

In this cohort, subgroup analysis focused on this dimension, given the obvious confounding factors of utilising the complete sample (different times of vaccination, different manufacturers, and patients, with elicited immune response by direct contact with the virus). From this perspective, comparative analysis was performed only after grouping patients to attain a homogeneous group, improving the ability to address factors differentiating immune status and, so, the authors aimed to evaluate specific response to BNT162b2 and factors relating to the waning of its immunogenicity in MDPs after 8 months, since it constituted the sole stimulus (two separate doses in February 2021) for immunogenicity in this subgroup.

The results point to absent immunity of one in five patients for humoral and one in seven for cellular response. Again, these results are prevalence based and do not consider vaccinated patients who died during this period. Hence, the true value of immunity waning is probably higher. The relevance of the subgroup analysis, however, is not only to establish the prevalence of immunity but to assess for risk factors, an important and interesting addition in this part of the study. Here, and against several previous reported studies, age alone did not contribute to the lack of immunity. Instead, high CCI, comprising not only age but several disorders, including cardiovascular and connective tissue diseases, was systematically associated with overall lower immune assessed response. In a similar fashion, low sALB was also associated with this outcome, and both risk factors contributed independently to the likelihood of absence of both humoral and cellular elicited immunity.

The present study can be a step forward in the understanding and management of this and the subsequent pandemics, proposing the use of CCI and sALB as surrogate markers and valuable tools to predict lower response to vaccination and faster waning of immunity. Again, new studies with larger sample size or meta-analysis are required to establish this relation.

Dialysis modality also contributes to immune impairment differently. PD specific factors include intra-abdominal catheter; high glucose/glucose degradation products or endotoxins on dialysate; constitutive complement activation; and repetitive peritonitis and exit-site infection.[21,22,35] For the population on HD, the factors include central venous catheter as vascular access; the use of conventional HD over haemodiafiltration; the use of bioincompatible dialysis membranes; and complement activation during session secondary to loss of inhibitory molecules.[36-38] Regardless of this knowledge, there is still no evidence on which modality associates with the lowest immune dysfunction.

In subgroup analysis C, comparison between vaccinated patients on PD and HD in February was remarkable for lower levels. A lower rate of humoral immunity was seen in the HD subgroup, with one in four not achieving 1 AU/mL compared with one in 10 in the PD subgroup, even though the difference was not significant.

As previously discussed, comorbidity burden and sALB correlated with immune response. The first was significantly lower in PD, which can be responsible for this immunity difference. On the cellular side, however, the difference abates in rate of reaching cellular responsiveness threshold, and is even quantitively lower in the PD subgroup, this time significantly. Advances in immunology understanding have differentiated subtypes of T cells into central memory, mainly localised to the lymph nodes and those that lack immediate effector function, and effector memory T cells (TEM), peripherally localised and responsible, after stimulation, for immediate production of IFN-γ, which enhances antigen-specific adaptive immune response and is the response quantified with IGRA. Roberts et al.[39] have studied the peritoneal effluent and established not only the existence of highly specialised resident TEM population in the peritoneal cavity of patients on PD (a first line of defence against pathogens), but also the selective recruitment of TEM cells from peripheral blood, including those produced through vaccination, to the peritoneal cavity. Consequently, the fact that IGRA was measured in peripheral blood samples may lead to falsely reduced values, a direct result of the constant recruitment of TEM cells to the peritoneum. Other studies, not restricted to TEM and immediate IFN- γ, but focusing on thymic epithelial cells are important to further understand long-standing cellular immunity in patients on PD.

Despite the limitations of the authors' study, mainly related to sample size, there are many important and interesting new findings such as dialysis centres maintain high rates of immunity after 8 months of vaccination; humoral and cellular quantification correlate positively; vaccination in immediate pre-dialysis ESKD is suggested as yielding worst immunogenicity compared with MDP; high comorbidity burden and low sALB are independent risk factors for low acquired immunity in MDPs and can be used as predicting markers of patients that will show deficient immunogenicity yield; and patients on PD show a relative reduction in cellular response when using IGRA as a quantifying method, which favours the specific TEM abnormalities verified in this specific modality.

CONCLUSION

This study supports a high prevalence of both humoral and cellular immunity against SARS-CoV-2 among real-world vaccinated Portuguese dialysis centres, even 8 months after vaccination campaign onset. Moreover, the intertwining of both adaptative immunity dimensions, humoral and cellular, is highlighted through multiple correlations.

High comorbidity burden, and specifically CCI as a quantifying tool, is suggested as a surrogate marker to predict lower response or faster waning immunity after vaccination. In a holistic approach, other markers of frailty like low serum albumin may also play a role in the creation of a risk stratification panel to identify possible non-responders and those at risk of faster immunity waning, particularly when direct immune response assays are unavailable.

Taken together, these results suggest the need to adapt protocols based not only on vaccination status, but also on patients' individual risk of no-response and of faster waning immunity. Vaccination remains the single most important measure in COVID-19 prevention, requiring that new incident patients on dialysis be procured and vaccinated to maintain high immunity rates across institutions.

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Steroid-Dependent Nephrotic Syndrome in a Child After an Allogeneic Bone Marrow Transplant: A Case Report

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Abstract

Nephrotic syndrome is a frequently encountered disease in children. It is mostly responsive to high-dose steroids, with some requiring steroid-sparing immunosuppressive regimens, or further, a renal biopsy if resistant to steroid therapy. However, nephrotic syndrome in children post-allogeneic bone marrow transplant is rarely encountered. The authors report here a child who developed nephrotic syndrome post-allogeneic bone marrow transplant for β-thalassaemia major, with the suspicion of graft-versus-host disease that was difficult-to-treat, who had frequent relapses with multiple hospital admissions, and prolonged treatment course. For the last 5 years, the disease has been in remission, on a low dose of prednisolone and mycophenolate mofetil-based maintenance immunosuppressive treatment.

Key Points

1. Patients who have had a bone marrow transplant can present with nephrotic syndrome, which can be a presentation of graft-versus-host disease.

2. After a bone marrow transplant, patients who present with nephrotic syndrome have been managed by nephrologists using conventional therapies such as prednisolone and calcineurin inhibitors.

3. This case report presents the successful management of a child post-bone marrow transplant, who presented with difficult-to-manage nephrotic syndrome while on conventional therapies. The patient was successfully manged using mycophenolate mofetil and very low dose prednisolone, and has been in remission for the last 5 years.

CASE REPORT

The authors present a case report of a child presenting with difficult-to-manage, steroid-sensitive, frequently relapsing nephrotic syndrome in the setting of a prior bone marrow transplant for β-thalassaemia major. Informed consent was duly obtained from the parents in advance of writing this case report.

A 6-year-old female presented with generalised body swelling. They were diagnosed with steroid-sensitive, frequently relapsing/steroid-dependent nephrotic syndrome in the past, and had been managed at different health facilities with repeated courses of high-dose prednisolone. Multiple immunosuppressive drugs were used in addition to prednisolone therapy, including cyclosporine, tacrolimus, and levamisole as steroid-sparing agents. The lowest dose of prednisolone required to maintain remission was 20 mg/day, along with steroid-sparing agents. On examination, the patient had bilateral gross pedal and peri-orbital oedema, with cushingoid features. The rest of their systemic examination and vital signs were normal.

Previously, the patient had been diagnosed with β-thalassaemia major, at the age of 3. In 2013, they underwent a successful allogeneic bone marrow transplant using the conditioning protocol of matched related donor bone marrow stem cell transplant, consisting of rabbit anti-thymocyte globulin-fresenius, busulfan, methotrexate, and cyclophosphamide therapy. Graft-versus-host disease (GvHD) prophylaxis was given with cyclosporine, methotrexate, and methylprednisolone. Granulocyte colony stimulating factor was administered post-transplant, with desirable blood count results.

Post-bone marrow transplant, the course was complicated by mucositis, diarrhoea, weight loss, haematuria, mood disturbance, cerebellar signs, and one instance of infection-related fever, which was treated by a course of antibiotics (ceftriaxone, amikacin, and meropenem). The patient also received two packs of red cell concentrate and nine packs of platelets during during their stay in hospital. They were discharged on ciclosporin and methylprednisolone, in tapering dose, as well as an antiviral, antifungal, *pneumocystis jirovecii* pneumonia prophylaxis (co-trimoxazole), and other supportive therapy.

The patient's course remained stable for 8 months after the bone marrow transplant, after which they developed steroid-dependent, frequently relapsing nephrotic syndrome. They were managed at different centres, multiple times with prednisolone monotherapy, with subsequent additions of levamisole, and later with calcineurin inhibitors (ciclosporin and tacrolimus) and prednisolone continuously for almost 3 years.

The patient's laboratory work-up showed a urine dipstick of 3+ proteins, with the 24-hour urinary protein test in the nephrotic range, hypoalbuminemia, and deranged lipid profile with normal renal function. They were on cyclosporine 4 mg/kg/day, with unsuccessful tapering-down of prednisolone due to relapse of nephrotic syndrome every time the steroid dose was reduced to below 20 mg/day. The patient was diagnosed with steroid-dependent, frequently relapsing nephrotic syndrome, with the possibility of GvHD as the underlying cause of the nephrotic syndrome.

Renal biopsy was not performed in this case, as the patient was diagnosed with steroid-sensitive nephrotic syndrome with steroid-dependent, frequently relapsing course. They had definite remissions on high doses of ciclosporin and prednisolone, but would relapse on dose tapering. Such patients are considered to have minimal change disease (MCD), where conventional light microscopy and immunofluorescence microscopy are normal, even if a kidney biopsy is undertaken. According to standard practice, a kidney biopsy is only performed in patients with steroid-resistant nephrotic syndrome to find underlying causes other than MCD, such as focal and segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, etc. The temporal association of steroid-sensitive nephrotic syndrome after bone marrow transplant in this patient raised the possibility of GvHD affecting the kidney and manifesting as nephrotic syndrome. However, the occurrence of steroid-sensitive nephrotic syndrome as an independent entity could not be ruled out.

Calcineurin inhibitors were stopped, considering the already protracted use without sufficient efficacy. Further options included cyclophosphamide; however, this was avoided in this case due to potential adverse consequences for the bone marrow transplant, infections, fertility, and risk of future malignancies. Instead,

mycophenolate mofetil 600 mg/m^2/day (weight: 25 kg; height: 4 ft; body surface area by the Du Bios method: 0.9 m^2; mycophenolate mofetil 500 mg/day) was initiated. The patient was restarted on high dose prednisolone 2 mg/kg/day with gradual tapering, along with mycophenolate mofetil, with regular follow-up and frequent urine dipstick checks. Prophylactic influenza and pneumococcal vaccinations were also given, along with calcium supplements.

This patient has remained in complete remission, with no relapses since. Their prednisolone has been reduced to 5 mg on alternate days successfully. Their renal function tests, serum albumin level, and blood counts are normal, and symptoms of generalised body oedema and cushingoid features have completely disappeared. The patient has been on mycophenolate mofetil maintenance (500 mg/daily) with 5 mg prednisolone on alternate days for the last 5 years, is in complete remission, and has had no relapses.

DISCUSSION

Nephrotic syndrome, with an incidence of 1.15–16.90/100,000 children, is the most common glomerulopathy in children.[1] Approximately 70–90% of children with this condition are less than 10 years of age.[2] Among adults, 10–15% of patients with nephrotic syndrome have MCD as an underlying aetiology.[3] In adults with MCD, 25% are found to experience a frequently relapsing course, whereas 30% develop steroid dependency.[4] Clinically, nephrotic syndrome presents as massive proteinuria and hypoalbuminemia, along with oedema and hyperlipidaemia.

Food, allergen inhalation, insect bites, and vaccinations have been reported as possible aetiology.[5] Recent advances in treatment regimens, especially since the 1970s, have improved overall survival and reduced mortality previously caused by complications, such as infections, thromboembolisms, and renal failure.[1] Nephrotic syndrome is labelled as an idiopathic condition when there is no known underlying aetiology. In the majority of paediatric patients, idiopathic nephrotic syndrome is an MCD, which is treated with steroids.

Renal biopsy is only done when idiopathic nephrotic syndrome is resistant to treatment, which in most cases turns out to be focal segmental glomerulosclerosis,[6] while few can be IgA nephropathy, complement 3 glomerulopathy, or membranous nephropathy.

Kidney Disease Improving Global Outcomes (KDIGO) recommends high dose prednisolone as a first-line therapy for MCD.[4] The majority of patients attain full and sustained remission,[1] while some can have a chronic and relapsing course.[3] For those with infrequent relapses, a short repeat course of full dose corticosteroids is recommended. However, for individuals with frequent relapses, who are steroid-dependent, or in whom steroids are contraindicated or not recommended, the addition of immunosuppressive therapy (levamisole, calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide, or rituximab) as steroid-sparing therapy is recommended, in order to minimise steroid doses.[7,8]

GvHD is a life-threatening complication in patients after a bone marrow transplant due to immune dysregulation.[9] It can be acute GvHD less than 100 days post-transplant, or chronic GvHD more than 100 days post-transplant.[8] GvHD involves reconstruction failure of the central immune system in the recipient, causing the donor immune system to react against the recipient organs. There can be a loss of peripheral tolerance due to the reduction of regulatory immune cells (T, B, or natural killer cells).[10] Organs such as the skin, eyes, liver, haematological system, genital and gastrointestinal tract, and rarely kidneys can be affected.[9] So far, only around 50 cases of nephrotic syndrome secondary to chronic GVHD have been reported.[9]

Only topical treatment is sufficient in case of mild chronic GvHD. On the other hand, if chronic GvHD has multi-organ involvement, immunosuppressive treatment is a must. This includes a corticosteroid (prednisone 1 mg/kg/day) as the first-line agent, with or without a calcineurin inhibitor, allowing dose reduction of corticosteroids to avoid long-term complications of steroid use. However, 50–70% of patients develop a steroid-refractory or steroid-dependent disease. There are numerous drug options that may be considered in this group of patients.

These include high-dose steroids, mycophenolate mofetil, rituximab, methotrexate, cyclophosphamide, mammalian target of rapamycin inhibitor, and pentostatin. The latest emerging

therapies include: belumosudil, a selective rho-associated protein kinase inhibitor; bortezomib, a reversible proteasome inhibitor with B cells and plasma cells inhibition property; pomalidomide, an inhibitor of T cell activation; abatacept, an inhibitor of T cell activation; tocilizumab, a humanised IgG1 IL-6 receptor antibody; ruxolitinib, an oral selective JAK1/2 inhibitor; and ibrutinib, a Bruton's tyrosine kinase inhibitor.[11,12]

Literature shows how nephrologists have been using different regimens of immunosuppressant drugs to treat GvHD-causing nephrotic syndrome. In 2017, Zhang et al.[13] reported a case of an adult patient who was treated for secondary steroid-resistant membranous nephropathy post-haematopoietic stem-cell transplantation (HSCT; identical sibling) for monoblastic leukaemia. Rituximab was added to cyclosporine and prednisolone. Although the proteinuria stabilised, nephrotic syndrome persisted despite albumin infusions. Mesenchymal stem cells were administered from a third-party donor (dose: 1×106 cells/kg/infusion; a total of 6 doses at weekly intervals). The patient achieved remission, with no relapses. Cyclosporine and prednisolone were tapered down and stopped. It was speculated that mesenchymal stem cells could modulate nephrotic syndrome after allogeneic-haematopoietic stem-cell transplantation by suppressing B cell proliferation (both regulatory B cells and regulatory T cells) and inhibiting inflammatory cytokine production by monocytes and natural killer cells.[13]

In March 2020, a survey was conducted regarding prophylaxis and treatment of acute GvHD in the paediatric population, where data was taken from European Society for Blood and Marrow Transplant (EBMT) centres in 26 countries. In paediatric patients with acute GvHD, prednisolone remained the first-line agent, at a dose of 1–2 mg/kg/day (Grade 1 or 2 involvement of the skin only). For more severe acute GvHD, intravenous methylprednisolone, at the dose of 2 mg/kg/day in two doses, was preferred. The survey showed variability in second-line treatment of acute GvHD in children, except for mycophenolate mofetil and extracorporeal photopheresis.[14]

In September 2020, the first case of MCD in an adult after HSCT, associated with post-transplant lymphoproliferative disorder, was reported. This patient was managed with rituximab (3 weekly doses of 375 mg/m^2). The patient was continued on cyclosporine and budesonide for skin and gastrointestinal GvHD once remission was achieved with rituximab. The authors reported that membranous nephropathy caused nephrotic syndrome following HSCT in two-thirds of cases, while MCD complicated 0.4% of Hodgkin lymphoma cases.[15] In 2021, another adult case was reported.[10] The patient underwent syngeneic HSCT for T-lymphoblastic lymphoma and developed nephrotic syndrome 24 months later, which turned out to be atypical membranous nephropathy. This patient gained complete remission after treatment with glucocorticoids combined with cyclophosphamide and cyclosporine.[10]

In March 2022, a report was published regarding the management of two adult patients who developed MCD secondary to chronic GvHD after allogeneic-HSCT for myelodysplastic syndrome. The onset of nephrotic syndrome coincided with the tapering of calcineurin inhibitors in both patients. One patient had had chronic GvHD of the lungs previously. One patient was treated with corticosteroids alone, while tacrolimus was added to corticosteroids for the second patient. Complete remission was achieved in both cases with no relapse.[16]

The authors of this article reported a rare case of a child who developed frequently relapsing/steroid dependent, steroid-sensitive nephrotic syndrome, post-allogeneic bone marrow transplant for β-thalassaemia major, managed successfully with prolonged immunosuppressive therapy with mycophenolate mofetil and low dose prednisolone, and is still on maintenance immunosuppressive therapy for the last 5 years without any relapses.

In conclusion, steroids remain the first-line of management in both acute and chronic GvHD causing nephrotic syndrome post-bone marrow transplantation, while mycophenolate mofetil can be used as an add-on steroid-sparing agent in patients who do not respond to conventional steroid-sparing agents such as levamisole and calcineurin inhibitors. Further clinical research is recommended regarding different treatment options for MCD caused by GvHD in children, with better responses, and aiming for a shorter duration of therapy and minimal relapses. This will help achieve early remission and limit the possibility of drug-related side effects.

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