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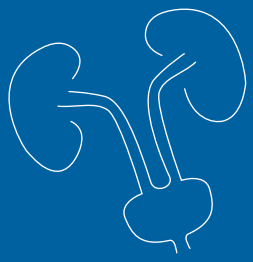

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1. Roxadustat shows increases in Hb regardless of prior roxadustat use in CKD

Roxadustat treatment increased haemoglobin (Hb) levels in individuals with chronic kidney disease (CKD) who previously had roxadustat treatment or were naïve. Anaemic conditions were improved for patients regardless of dialysis status.

Anaemia is a prevalent condition for individuals with CKD, and is associated with poor quality of life and faster progression to end-stage kidney disease. Roxadustat is known to increase red blood cell production and affects iron metabolism. A phase 3 clinical trial showed that roxadustat increased Hb levels in individuals with CKD [1].

The current phase 4 trial was a multicentre, open-label, prospective study conducted at 61 institutions across China [2]. The primary endpoint was a safety analysis. Secondary endpoints included measures of Hb and quality of life (not presented in this session). The safety analysis was conducted on 2,021 patients; 193 had previously been treated with roxadustat, 1,804 were naïve. All participants received at least 1 additional dose of roxadustat. The study included a 70–120 mg oral dose of roxadustat 3 times a week for 52 weeks. In the roxadustat-naïve population, the mean ± SE Hb level at baseline was 96.94 ± 0.33 g/L.

In total, 10.8% of patients experienced drug-related treatment-emergent adverse events (TEAEs). The most common drug-related TEAEs were nausea (1.3%), hypertension (1.0%), and insomnia (0.9%). Roxadustat treatment led to increased Hb levels, with a peak at week 12. The difference from baseline over weeks 24–36 was 14.20 ± 0.38 g/L. The estimated percentage of patients with Hb ≥100 g/L was 83.3% between weeks 24–36. Increases in Hb were sustained regardless of dialysis status. In the group previously treated with roxadustat, moderate increases in Hb (around 10 g/L) were also observed and sustained.

1. Chen N, et al. N Engl J Med 2019; Sept 12. DOI: 10.1056/NEJMoa1813599.
2. Du X, et al. A National, Multi-Center, Prospective Study Evaluating the Long-Term Safety and Effectiveness of Roxadustat for Anemia Treatment in Patients with CKD (ROXSTAR Registry). TH-PO980, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

2. Aldosterone synthase inhibition reduces albuminuria in CKD

An aldosterone synthase inhibitor, provisionally named BI 690517, reduced urine albumin to creatinine ratio (UACR) on its own and together with empagliflozin in chronic kidney disease (CKD).

Despite treatment with available therapies such as sodium-glucose cotransporter 2 (SGLT2) inhibitors like empagliflozin, people with CKD are at high risk for progression. Overproduction of aldosterone is known to accelerate CKD progression.

"This phase 2 clinical trial (NCT05182840) assessed the safety and efficacy of an aldosterone inhibitor, BI 690517, with or without empagliflozin in participants with CKD," Prof. Katherine Tuttle (University of Washington, WA, USA) explained [1]. The trial included 714 patients with CKD; approximately 70% had type 2 diabetes. They were first randomised to 10 mg empagliflozin (n=356) or placebo (n=358). After 8 weeks, each group was subdivided into 3 groups receiving BI 690517 (3 mg, 10 mg, or 20 mg), or a placebo. The second leg lasted 14 weeks. The primary endpoint was a change in UACR in the last 14 weeks. Secondary endpoints included the proportion of patients with ≥30% or ≥15% change in UACR and changes in estimated glomerular flow rate (eGFR). Baseline characteristics were similar across all groups.

Participants with and without empagliflozin had a decrease in UACR with BI 690517, with the 10 mg and 20 mg BI 690517 dosages resulting in similar effects. The highest percentage of patients with UACR reduced ≥30% was in the 10 mg BI 690517 plus empagliflozin group, where 70% of the patients met that endpoint. There were no unexpected adverse events. BI 690517 will be further tested in the EASi-KIDNEY phase 3 clinical trial that will begin recruiting in 2024.

1. Tuttle KR, et al. Aldosterone Synthase Inhibition with or Without Background Sodium Glucose Cotransporter 2 Inhibition in CKD: A Phase II Clinical Trial. FR-OR111, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

3. Low doses of zibotentan with dapagliflozin improve albuminuria in patients with CKD

Dapagliflozin administration with zibotentan decreased urine albumin to creatinine ratio (UACR) in patients with chronic kidney disease (CKD). A low dose of zibotentan did not lead to increased fluid retention.

Prof. Hiddo Heerspink (UMC Groningen, the Netherlands) presented the results of the phase 2 ZENITH-CKD trial (NCT04724837)

[1,2]. Previous studies found that the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduced the risk of a composite kidney endpoint [3]. Another trial with the endothelin receptor antagonist atrasentan showed a reduced risk of a composite kidney outcome and reduced albuminuria. However, endothelin receptor antagonists can cause fluid retention, which may lead to heart failure. "In the SONAR trial with atrasentan, there was indeed a tendency towards an increased risk of heart failure," Prof. Heerspink explained [4]. The researchers hypothesised that using dapagliflozin may ameliorate the fluid retention caused by endothelin receptor antagonist like zibotentan.

The ZENITH-CKD trial included part A (5 mg of zibotentan or placebo, plus 10 mg dapagliflozin) and part B (0.25 mg or 1.5 mg zibotentan or placebo, plus 10 mg dapagliflozin). Part A was discontinued at an interim analysis point due to safety concerns and updated clinical guidelines, making part B the main study. The study enrolled 447 participants from 18 countries and over 160 sites. The primary outcome was UACR change.

Dapagliflozin alone reduced UACR by 28.3%. Zibotentan (0.25 mg) decreased UACR by an additional 27.0% (90% CI -38.4 to -13.6; P=0.002), and 1.5 mg zibotentan decreased the UACR by an additional 33.7% (90% CI -42.5 to -23.4; P<0.001). Fluid retention was similar in the 0.25 mg zibotentan group and the dapagliflozin alone group. Lower doses of zibotentan with dapagliflozin may thus be a viable treatment regimen for CKD; a new, phase 3 clinical trial called 'ZENITH High Proteinuria' is now recruiting.

1. Heerspink HJ, et al. ZENITH-CKD: A Phase 2B Study of Zibotentan in Combination with Dapagliflozin and Dapagliflozin Alone in Patients with CKD. FR-OR112, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Heerspink HJ, et al. Lancet. 2023;Nov 3. DOI:10.1016/S0140-6736(23)02230-4.
3. Heerspink HJ, et al. N Engl J Med 2020;383:1436–1446.
4. Heerspink HJ, et al. Lancet. 2019;May 11;393(10184):1937–1947.

4. Spironolactone failed to reduce major adverse cardiac effects in patients with CKD on haemodialysis

Spironolactone did not reduce the rate of major adverse cardiac events (MACE) for patients with chronic kidney disease (CKD) undergoing haemodialysis. An analysis of the individual components of the primary endpoint did show a significant reduction in the incidence of hospitalisation for heart failure.

Overactivation of the mineralocorticoid system plays a role in the pathology of cardiac disease and subsequent epidemiology of cardiac death in patients with CKD. "We, therefore, investigated the effects of the steroidal mineralocorticoid receptor antagonist spironolactone on cardiovascular outcomes in a high-risk haemodialysis population," Prof. Patrick Rossignol (University Hospital of Nancy, France) described the overarching goals of the double-blind, randomised, placebo-controlled, phase 3 ALCHEMIST trial (NCT01848639) [1].

ALCHEMIST assessed the efficacy of spironolactone on MACE (defined as non-fatal myocardial infarction and acute coronary syndrome, hospitalisation for heart failure, non-fatal stroke, or cardiovascular-induced death) in haemodialysis patients with pre-existing cardiovascular risk. The primary endpoint was time to first event. The 644 participants recruited from 64 sites in 3 countries were randomised 1:1 to spironolactone or placebo for 4 weeks and had a follow-up period of 2–4 years. Doses were titrated up to 25 mg per day.

The primary endpoint was not met: spironolactone did not reduce the time to first cardiac event (HR 0.996; 95% CI 0.729–1.362; P=0.982). An additional analysis showed that time to hospitalisation for heart failure was the only cardiac outcome that significantly favoured the spironolactone group compared with placebo (HR 0.412; 95% CI 0.171–0.995; P=0.049). A subgroup analysis of the primary outcome revealed a significant age effect, with individuals >75 years showing an increased likelihood of MACE compared with those ≤75 years (HR 1.50; 95% CI 0.93–2.41). Hyperkalaemia was slightly more prevalent in the spironolactone group compared with the placebo group (12.0% vs 9.8%).

1. Rossignol P, et al. ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST): Primary Results. FR-OR113, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

5. Efficacy of bardoxolone methyl for DKD, without increased cardiac risk

Bardoxolone methyl slowed the decline of the estimated glomerular flow rate (eGFR) in patients with diabetic kidney disease (DKD). It did not increase the risk of severe cardiac events, which had been observed in previous trials.

"Bardoxolone methyl is an activator of NRF2 [nuclear factor erythroid-2-related factor 2] and has been shown to continuously increase eGFR calculated by serum creatinine in previous trials, in patients with DKD," said Dr Tadao Akizawa (Showa University School of Medicine, Japan) [1]. While the phase 2 TSUBAKI trial (NCT02316821) indeed showed increased eGFR, the phase 3 BEACON trial (NCT01351675) was terminated early because of severe cardiac events [2,3].

The current AYAME study was a phase 3, double-blind, placebo-controlled trial that again assessed bardoxolone methyl for DKD. Participants were randomised 1:1 to

bardoxolone methyl (n=507) or placebo (n=506). The primary endpoint was time to onset of a ≥30% decline in eGFR from baseline or progression to end-stage kidney disease (ESKD). The key secondary endpoint was time to onset of a ≥40% decline in eGFR or progression to ESKD.

The primary endpoint was met; fewer participants receiving bardoxolone methyl reached a 30% decrease in EGFR or ESKD compared with placebo, and this was statistically significant (30.2% vs 45.3%; HR 0.56; 95% CI 0.45–0.69; P<0.0001). The secondary endpoint was also met: compared with 34.0% of the placebo arm, only 24.1% of bardoxolone methyl-treated participants had either >40% decrease in eGFR or ESKD (HR 0.69; 95% CI 0.55–0.87; P=0.0018).

Severe adverse effects were similar between the bardoxolone methyl and placebo-treated groups. Importantly, no increase was observed in the incidence of cardiac events in the bardoxolone methyl treatment group.

1. Akizawa T, et al. AYAME Study: Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Bardoxolone Methyl in Diabetic Kidney Disease (DKD) Patients. FR-OR110, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Nangaku M, et al. Kidney Int Rep. 2020;5(6):879-890.
3. de Zeeuw D, et al. N Engl J Med 2013;369(26):2492-503.

6. New approaches to successful vascular access

Patient education, timely referrals, knowing all options for vascular access, and training frontline staff are important approaches to successful vascular access in dialysis patients.

In a session on finding success in vascular access in dialysis patients, Dr Vandana Niyyar (Emory University, GA, USA) asked: "What do we mean when we say we want success? For me, that means providing the right access to the right patient, at the right time, for the right reasons. And then, once we define it, how can we achieve it and maintain it in the long term?" [1].

Dialysis has worse survival outcomes than invasive cancers, and there is often a discrepancy between what's most important to the patient and to the clinician. Vascular access needs to be individualised to the patient, and patients need to be active decision-makers in their care. Patient education is associated with a 2-fold increase in the patient choosing arteriovenous fistula or arteriovenous graft.

Dr Niyyar reviewed strategies to optimise functional access as a nephrologist. She highlighted vessel preservation and timely referrals. At the nephrology level, doctors must appropriately refer patients to surgery. At Emory, her team was able to institute an automatic notification system for a nephrology consult for anyone scheduled to receive a peripherally inserted central catheter (PICC) line. Understanding all line options for specific vascular access is necessary, and institutional guidelines for treatment and follow-up are recommended.

Dr Niyyar's team trained front-line haemodialysis staff to assess fistulas for maturity and use ultrasound to guide cannulation at Emory dialysis. This included 4 outpatient units and 150 patients. Diameter measurements were at 2 cm, 4 cm, and 6 cm from the anastomosis. At 4–6 weeks, maturity was examined, and if mature, scheduled for cannulation. Overall, 40 patients were cannulated, and there was only 1 case of infiltration. Ultrasound was useful for assessing maturity and doing the procedure, but Dr Niyyar stressed this is an adjunct — not a replacement — for physical examination.

1. Niyyar VD. Keys to Success in Managing Vascular Access in Dialysis Patients. ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

7. Patient care technicians improve haemodialysis patient outcomes

Having fewer patient care technicians (PCTs) for every haemodialysis patient is associated with increased mortality and hospitalisation, and decreased incidence of kidney transplantation.

PCTs are pivotal in dialysis care. They operate haemodialysis machines with prescribed treatment parameters, manage cannulation, and monitor vitals. Turnover and variation in the number of PCTs on site can compromise consistent, high-quality care.

Dr Laura Plantinga (Emory University, GA, USA) presented the results of a retrospective cohort study that assessed the association of patient:PCT ratios with health outcomes within 1 year of starting in-centre haemodialysis [1]. The data was accessed from the United States Renal Data System (USRDS), and it included 200,863 patients who started in-centre haemodialysis from 2016–2019 and received haemodialysis for a minimum of 90 days. The mean age was 63 years. Patient:PCT ratio was calculated by dividing the total number of patients receiving in-centre haemodialysis by the number of full-time equivalent PCTs reported on the last day of the year prior. Outcomes included mortality, first transplantation, first all-cause hospitalisation, and first hospitalisation caused by sepsis, fluid overload, or vascular access.

The quartile of patients with the highest patient:PCT ratio had an increased incidence of mortality (IRR 1.07; 95% CI 1.02–1.12; P<0.001), all-cause hospitalisation (IRR 1.05; 95% CI 1.02–1.08; P<0.001), fluid overload hospitalisation (IRR 1.05; 95% CI 1.02–1.08; P<0.001), sepsis hospitalisation (IRR 1.08; 95% CI 1.03–1.14; P<0.001), and vascular access hospitalisation (IRR 1.15; 95% CI 1.03–1.28; P<0.001). Overall, this quartile had a decreased incidence of transplantation (IRR 0.80; 95% CI 0.71–0.91; P<0.001).

Dr Plantinga concluded that "dialysis PCTs may play an important – and often overlooked – role in the quality of care delivered to US patients receiving in-centre haemodialysis. Increased PCT patient loads may result in worse patient outcomes."

1. Plantinga L, et al. Higher Patient-to-Patient Care Technician Ratios Associated with Worse Outcomes Among US In-Center Hemodialysis Patients. TH-OR45, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

8. Haemodiafiltration increases longevity compared with haemodialysis, but does it improve patient satisfaction?

Due to the many variables that may impact health-related quality of life in both haemodiafiltration and haemodialysis, investigators of the CONVINCE trial were also interested in measuring patient-reported outcomes (PROs). Overall, patients described a significant deterioration of health. Differences in PROs between haemodiafiltration and haemodialysis have not yet been reported.

The CONVINCE trial (NTR7138) was a multinational, open-label, randomised-controlled clinical trial that assessed the survival of patients with kidney failure at 30 months following high-dose haemodiafiltration compared with high-flux haemodialysis. Inclusion criteria for CONVINCE included renal replacement therapy (RRT) for more than 2.5 years. The study consisted of 677 patients receiving haemodialysis and 683 patients receiving haemodiafiltration. In the trial, haemodiafiltration showed a reduced risk of death compared with haemodialysis (HR 0.77; 95% CI 0.65–0.93) [1].

A further important consideration when comparing treatments is patients' feelings of well-being, both physically and emotionally. The presented study aimed to assess PROs in the CONVINCE cohort, using the Patient-Reported Outcome Measurement Information System (PROMIS) [2]. PROMIS examines 8 domains: social participation, depression, anxiety, cognitive function, physical function, pain interference, sleep disturbance, and fatigue. PRO assessments were collected for 84% of the participants. Assessments were taken before randomisation, and then every 3 months for 3 years. This amounted to 10,681 total analysable questionnaires. The omnibus test was used to determine significance.

Overall, all domains of PROMIS revealed a significant deterioration of health throughout the study. The domains with the lowest scores were physical function with a mean T-score ± SD of 44.0 ± 9.9, sleep (49.0 ± 9.3), and anxiety (49.4 ± 9.3). Differences between the haemodiafiltration and haemodialysis groups will be reported in an upcoming paper.

1. Blankestijn PJ, et al. N Engl J Med 2023; Aug 24. DOI: 10.1056/nejmoa2304820
2. Rose M, et al. Patient-Reported Health Status of Adults with Kidney Failure Receiving Hemodiafiltration vs. Hemodialysis: Results from the CONVINCE Randomized Controlled Clinical Trial. TH-PO1134, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

9. Donor stem cells may reduce lifelong immunosuppressant use following transplant surgery

In an update on the phase 3 MDR-101-MLK trial, more than 48% of recipients with MDR-101 infusion were off of immunosuppressants for 2 years.

"Patients who undergo kidney transplantations currently require lifelong immunosuppressant therapies," stated Prof. Daniel Brennan (Johns Hopkins Medicine, MD, USA). "MDR-101 is intended to induce mixed chimerism and immune tolerance, to allow for elimination of all immunosuppressants while preserving transplant function and averting transplant rejection," he explained [1].

The open-label, international, multicentre, phase 3 MDR-101-MLK trial (NCT03363945) randomised participants 2:1 to the investigational arm (n=20) and control arm (n=10). The control arm received institutional standard of care, including immunosuppressants. For the investigational arm, donors were HLA-matched, ABO-identical, and living-related. Recipients had no prior transplantation, no other underlying kidney disease, nor prior immunosuppressant treatment. The MDR-101 product criteria were ≥4 x 10^6 CD34-positive stem cells/kg and 1 x 10^6 CD3-positive T cells/kg. Participants received total lymphoid irradiation of 10 x 120 cGγ and 5 doses of rabbit anti-thymocyte globulin at 1.5 mg/kg. Mixed chimerism of ≥5% of donor white blood cell count in the whole blood was required. Following transplant surgery, a single infusion of MDR-101 was given at day 11. If mixed chimerism was reached and there was no rejection at 6 months, immunosuppressants could be tapered over 6 months. Participants were followed for an additional 2 years.

Mixed chimerism was achieved in 19 (95.0%) participants at 6 months and 17 (85.0%) at 1 year. Of the 19 participants taken off immunosuppressants, 100% underwent complete withdrawal, and 17 patients remained off immunosuppressants for a full year after withdrawal. Following withdrawal, 12 patients stayed off immunosuppressants for 2 years. Transplants were well tolerated by patients' immune systems.

1. Kaufman D, et al. MDR-101-MLK Update: Operational Immune Tolerance Achieved in Living Related HLA-Matched Kidney Transplant Recipients. FR-OR115, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

10. A systems approach to kidney transplantation disappoints

The use of a province-wide, multisystem approach did not increase steps toward kidney transplantation. The COVID-19 pandemic may have disrupted implementation.

Advanced chronic kidney disease (CKD) is treated most effectively with kidney transplantation, which ultimately saves the healthcare system money from dialysis costs. Yet, due to access barriers, many kidney transplant-eligible patients will never receive a kidney transplant.

Dr Amit Garg (McMaster University, Canada) and colleagues designed a multicomponent intervention to address barriers that prevent kidney transplantation [1,2]. The components included administrative support, educational resources for healthcare professionals, patients, and donors, a patient support group called the 'Transplant Ambassador Program,' and reports on each patient's progress. This was a "pragmatic, cluster-randomised trial to determine if renal programme-wide use of this multicomponent intervention was superior to usual care in helping eligible patients complete up to 4 key steps towards receiving a kidney transplant," Dr Garg explained. The 4 steps were referral to a transplant centre, having a contact for living donor evaluation, addition to the donor waitlist, and receiving a transplant. All 26 CKD renal programmes in Ontario were randomly assigned to multicomponent intervention or usual care groups. Participants were 18 to 75 years old, had no recorded contraindication to transplantation, had an estimated glomerular flow rate <15 mL/min/1.73 m^2, and had a >25% 2-year chance of receiving renal replacement therapy.

Approximately 10,000 participants were included in each group, and they were followed for a median of 2.1 years. The number of steps completed did not differ between the multicomponent intervention or usual care groups (HR 1.00; 95% CI 0.87–1.15). Dr Garg reflected that, even though the intervention did increase access to transplantation or living donation, the COVID-19 pandemic played a significant role in patients' access, and he "believes that several aspects of our systems approach remain sensible."

1. Garg AX, et al. Effect of a Multi-Component Intervention to Improve Patient Access to Kidney Transplantation and Living Kidney Donation. FR-OR114, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Garg AX, et al. JAMA. 2023;Nov 3. DOI:10.1001/jamainternmed.2023.5802.

11. RMC-035 reduces long-term adverse kidney events following cardiac surgery

RMC-035 treatment did not reduce acute kidney injury (AKI) 72 hours post-cardiac surgery. It did reduce major adverse kidney events (MAKE) and rescued the estimated glomerular flow rate (eGFR) over 90 days.

AKI and subsequent kidney failure are major adverse events that can happen following cardiac surgery. RMC-035 is a biologic that imitates alpha-1-microglobulin activity.

AKITA (NCT05126303) was a multicentre, randomised, placebo-controlled phase 2 study [1]. Its primary endpoint was reduced AKI development with RMC-035 within 72 hours following coronary bypass surgery and/or valve surgery, and/or aortic repair. Secondary endpoints included change in eGFR based on serum creatinine and MAKE. MAKE was defined as death, dialysis post-surgery, or ≥25% eGFR from baseline on days 30 or 90. Participants were treated with 5 intravenous treatments of RMC-035 (n=89) or placebo (n=89). Patients with a starting eGFR >60 mL/min/1.73 m^2 were started at a dose of 1.3 mg/kg. Patients with eGFR between 30–60 mL/min/1.73 m^2 were started at 0.65 mg/kg.

Similar percentages of patients developed AKI within 72 hours of surgery in the RMC-035-treated and the placebo arm, so the primary endpoint was not met (50.6% vs 39.8%; RR 1.30; 90% CI 0.99–1.71; P=0.12). Secondary endpoints were met 90 days following the intervention. The mixed model for repeated measures (MMRM) eGFR was 4.3 mL/min greater in the RMC-035 group compared with placebo (P=0.063). The percentage of MAKE was reduced in the RMC-035 group at 6.7%, compared with 15.9% of the participants experiencing severe events in the placebo arm (RR 0.41; 90% CI 0.19–0.88; P=0.047). Treatment-emergent adverse events (TEAEs) occurred at comparable rates in RMC-035 and placebo groups (85.4% vs 75.0%). More infusion-related reactions (IRR) occurred in the group receiving the drug.

Thus, in a small trial, RMC-035 demonstrated to be a well-tolerated drug for reducing MAKE following cardiac surgery. It was not effective for preventing AKIs immediately following surgery.

1. Zarbock A, et al. Results of a Randomized Placebo-Controlled Double-Blind Adaptive Phase 2 Study (AKITA) Evaluating RMC-035 for the Prevention of AKI in Patients Undergoing Cardiac Surgery. TH-PO1160, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

12. Obinutuzumab attenuates kidney decline in lupus nephritis

Obinutuzumab was shown to reduce the decline in estimated glomerular flow rate (eGFR) in patients with lupus nephritis. It also decreased the incidence of unfavourable kidney outcomes.

Obinutuzumab is a type 2, optimised, anti-CD20 monoclonal antibody that kills B cells effectively. The recently published, double-blind, phase 2 NOBILITY study (NCT02550652) randomised patients with lupus nephritis 1:1 to either 100 mg of obinutuzumab (n=63) or placebo (n=62) [1,2]. Doses were administered at weeks 0 and 2, followed by doses at weeks 24 and 26. Both groups continued with the standard of care, which included a mycophenolate-based lupus regimen. Complete renal response (CRR) was significantly improved in the obinutuzumab group up to 2 years later [1].

Dr Brad Rovin (Ohio State University, OH, USA) and colleagues presented a post hoc analysis of NOBILITY, investigating other kidney outcomes [2]. This included the time to first unfavourable kidney outcome and eGFR slope between week 12 and week 104.

Unfavourable kidney outcomes were reduced in the obinutuzumab group (HR 0.40; 95% CI 0.20–0.80). The adjusted mean difference in eGFR at 2 years was 9.7 mL/min/1.73 m^2 (95% CI 1.7–18; P=0.017), favouring the obinutuzumab group. Obinutuzumab annual slope difference of eGFR was -0.43 (95% CI -3.16 to 2.31); this was -4.52 (95% CI -7.41 to -1.66) for placebo.

While Dr Rovin noted that these data should be viewed cautiously since they are post hoc and that the work needs to be tested prospectively, he concluded that "these data suggest better long-term preservation of kidney function with obinutuzumab." The phase 3 REGENCY trial (NCT04221477) will prospectively evaluate obinutuzumab for lupus nephritis, and it has finished recruiting.

1. Furie RA, et al. Ann Rheum Dis. 2022 Jan;81(1):100-107.
2. Rovin B, et al. Kidney-Related Outcomes in Patients with Active Lupus Nephritis Treated with Obinutuzumab: A Post Hoc Analysis of the Phase 2 NOBILITY Trial. TH-OR30, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.

13. Clinical benefits of sparsentan for patients with FSGS

In the largest study of focal segmental glomerulosclerosis (FSGS) ever conducted, sparsentan significantly reduced proteinuria compared with the active control irbesartan. The estimated glomerular flow rate (eGFR) was not changed.

Despite currently available treatments, patients with FSGS are likely to progress to kidney failure. "Patients with FSGS who have nephrotic-range proteinuria have an over 50% risk of reaching end-stage kidney disease within 5 to 10 years of their diagnosis," Prof. Michelle Rheault (University of Minnesota, MN, USA) explained [1,2]. Sparsentan, a dual endothelin and angiotensin receptor antagonist, has previously been shown to reduce proteinuria in patients with FSGS in a phase 2 trial.

Prof. Rheault presented the results of the current phase 3, double-blind, active-controlled, global DUPLEX study (NCT03493685), which evaluated sparsentan compared with the angiotensin receptor blocker irbesartan. Inclusion criteria were a primary FSGS confirmed by biopsy or genetic testing, urinary protein creatine ratio (UPCR) ≥1.5 g/g, and eGFR ≥30 mL/min/1.73 m^2. The participants were randomised 1:1 to sparsentan (n=184) or irbesartan (n=187) for 108 weeks. Sparsentan and irbesartan were started at 400 mg/day and 150 mg/day and were titrated to 800 mg/day and 300 mg/day, respectively. The primary endpoints were the slope of eGFR, depicting changes over the trial period, and the proportion of patients achieving UPCR ≤1.5 g/g, with a ≥40% reduction. The population was young, with a mean age for each group around 42 years.

The eGFR chronic slope from week 6 to week 108 was 0.9 (95% CI -1.27 to 3.04). No eGFR-related endpoints were statistically significant. At 108 weeks, 37.5% of the participants receiving sparsentan had achieved partial remission, compared with 22.6% of those taking irbesartan (RR 1.60; 95% CI 1.13–2.25). "Proteinuria decreased rapidly in both groups, with larger reductions seen in patients treated with sparsentan," Prof. Rheault said. The sparsentan group was more likely to go into complete remission of proteinuria at any point during the trial (RR 2.47; 95% CI 1.37–4.45). Adverse events were comparable in both groups.

1. Rheault MN, et al. Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Focal Segmental Glomerulosclerosis (FSGS): Results from the Phase 3 DUPLEX Trial. FR-OR108, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Rheault MN, et al. N Engl J Med 2023;Nov 3. DOI:10.1056/NEJMoa2308550.

14. Sparsentan outperforms irbesartan for treatment of IgAN

Sparsentan met all primary and secondary endpoints for the treatment of patients with immunoglobulin A nephropathy (IgAN). Sparsentan reduced proteinuria and slowed the rate of estimated glomerular flow rate (eGFR) decline.

Patients with IgAN have an activated endothelin and renin-angiotensin-aldosterone system, involved in kidney fibrosis and inflammation. "We postulated that treatment with sparsentan, a dual endothelin and angiotensin receptor antagonist, would be more effective in reducing proteinuria and preserving kidney function in patients with IgAN than treatment with an angiotensin receptor blocker alone," said Prof. Brad Rovin (Ohio State University, OH, USA) [1,2].

The PROTECT trial (NCT03762850) was a phase 3, double-blind trial that randomised participants 1:1 to sparsentan (n=202) or irbesartan (n=202) for 110 weeks. The primary endpoint was a change in urine protein creatinine ratio (UPCR) at week 36. The secondary endpoint was a change in eGFR measured by chronic and total eGFR slope.

At week 36, participants receiving sparsentan had a 41% relative reduction in proteinuria compared with those receiving irbesartan (least squares mean ratio 0.59; 95% CI 0.51–0.69; P<0.0001), and that difference was maintained throughout the 110 weeks. More patients receiving sparsentan achieved complete proteinuria remission (i.e. <0.3 g/day) than those receiving irbesartan (31% vs 11%). eGFR slope declined less in the sparsentan group (-2.7 mL/min/1.73 m^2/year; 95% CI -3.4 to -2.1) than in the irbesartan group (-3.8 mL/min/1.73 m^2/year; 95% CI -4.6 to -3.1), and this difference was statistically significant (P=0.037).

Using a composite kidney failure endpoint of a 40% reduction of eGFR, end-stage kidney disease, or death, sparsentan outperformed irbesartan (RR 0.68; 95% CI 0.4–1.2). Irbesartan-treated participants were also more likely to start immunosuppressive therapy during the trial (OR 2.87; 95% CI 1.09–7.57). Adverse events were similar between the 2 groups.

Overall, the PROTECT trial met its primary endpoints and showed favourable outcomes for sparsentan compared with irbesartan in all its endpoints.

1. Rovin BH, et al. Pivotal Results of the Phase 3 PROTECT Trial of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Immunoglobulin A Nephropathy (IgAN). FR-OR109, ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Rovin BH, et al. Lancet. 2023;Nov 3. DOI:1016/S0140-6736(23)02302-4.

15. Small molecule PGE1 shows promise for nephronophthisis treatment *in vitro* and *in vivo*

Prostaglandin E1 (PGE1) treatment in nephronophthisis (NPH) patient urine-derived epithelial cell lines (URECs) rescued ciliary deficits. In a knockout mouse model of NPH, treatment improved renal tubular dilatations.

NPH is an autosomal recessive ciliopathy that causes up to 15% of paediatric cases of end-stage kidney disease. Pathologically, it is characterised by severe renal fibrosis cortical cysts. There are over 25 genes involved in NPH, making early diagnosis and treatment challenging in the clinic. Prof. Sophie Saunier (Inserm, France) researches the genetic and molecular basis of NPH [1].

In a genetic analysis of 834 patients with NPH, the most frequently mutated gene was *NPHP1* (52.8%). To understand cellular and molecular changes with *NPHP1* mutations, URECs from NPH patients with *NPHP1* mutations were created. Compared with URECs from control patients, there were significantly fewer ciliated cells in the *NPHP1* URECs.

Prof. Saunier's group also investigates small molecules for potential NPH therapies. They screened 1,120 compounds from the Prestwick Chemical Library on *Nphp1* knockdown cell lines. Of 51 compounds that rescued ciliogenesis and migration phenotypes, they evaluated 11 of their hits in the *NPHP1*-mutated patient URECs and validated 1 compelling compound: PGE1/alprostadil. PGE1 is an analogue of prostaglandin E2. Treating *NPHP1*-mutated patient URECs with PGE1 led to significant increases in the percentage of ciliated cells. PGE1 also increased actin cytoskeletal remodelling [2].

In addition to the *in vitro* exploration of PGE1 treatment on NPH phenotype, Prof. Saunier wanted to assess the drug's efficacy *in vivo*. Using a CRISPR/Cas9 homozygous deletion of the *NPHP1* start codon, the researchers generated *Nphp1* knockout mice. The knockout mice presented with significant renal tubular dilatations at 2 months and 5 months. The animals were treated with 80 µg/kg of PGE1 or saline intraperitoneally daily between months 1 and 5, and found that PGE1 treatment decreased the number of severe tubular dilatations. PGE1 may thus be an interesting candidate for clinical trials of NPH.

1. Saunier S. Ciliary Disease and Potential Therapeutic Mechanisms. ASN Kidney Week 2023, 2–5 November, Philadelphia, PA, USA.
2. Garcia H, et al. Proc Natl Acad Sci USA. 2022;119(18):e2115960119.