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HIGHLIGHTS CONFERENCE REPORT

This Highlights report includes:

- FLOW-trial: Semaglutide improves kidney and cardiovascular outcomes in type 2 diabetes and CKD
- Preview of the new KDIGO Guidelines for ADPKD, available later in 2024
- TATH trial: Twice-weekly haemodialysis can be an alternative to thrice-weekly regimen
- The majority of real-world patients with CKD are not eligible for SGLT2 inhibitor trials
- Atrasentan shows positive interim results in IgA nephropathy: ALIGN phase 3 trial

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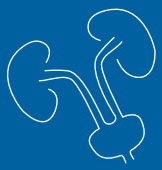

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Chronic kidney disease

FLOW-trial: Semaglutide improves kidney and cardiovascular outcomes in type 2 diabetes and CKD

The phase 3 FLOW trial confirms: glucagon-like peptide 1 receptor agonist semaglutide has shown significant improvement in kidney and cardiovascular outcomes in participants with type 2 diabetes and chronic kidney disease (CKD).

The phase 3, global, randomised, controlled FLOW trial (NCT03819153) randomised 3533 participants 1:1 to semaglutide 1mg weekly or placebo, with all participants receiving background standard-of-care therapy. The trial design, primary, cardiovascular, and safety outcomes were presented by multiple speakers at the ERA 2024 [1–4].

The FLOW trial included adults with type 2 diabetes (HbA1c ≤10%), who had additional CKD (eGFR of 50–75 mL/min/1.73 m², urinary albumin-to-creatinine ratio between >300 and <5,000 mg/g, or eGFR of 25 to <50 mL/min/1.73 m², urinary albumin-to-creatinine ratio between >100 and <5,000 mg/g). The primary endpoint was the time-to-first occurrence of persistent ≥50% eGFR reduction from baseline, kidney failure (persistent eGFR <15 mL/min/1.73 m², dialysis or kidney transplant), kidney-related mortality or cardiovascular death.

The trial was stopped early as it reached the prespecified boundaries of superiority of the new treatment: After a median of 3.4 years, 18.7% of participants receiving semaglutide reached the primary endpoint compared with 23.2% of participants receiving placebo (HR 0.76; 95% CI 0.66–0.88; P=0.0003). 12.3% of participants with semaglutide versus 14.7% of control participants achieved the composite outcome excluding cardiovascular death (HR 0.79; 95% CI 0.66–0.94), while the mean loss of kidney function rate was -2.19 mL/min/1.73 m²/year compared with -3.36 mL/min/1.73 m²/year (1.16 mL/min/1.73 m²/year difference; P<0.001) [1].

Semaglutide also showed significantly lower rates of major adverse cardiac events (12.0% vs 14.4%; HR 0.82; 95% CI 0.68–0.98; P=0.029) compared to placebo [3]. Overall, serious adverse events were more common in the placebo group (53.8% vs 59.6%), with infections, infestations, and cardiac adverse events as the most common adverse events in both groups [4].

"The FLOW trial demonstrated a 24% lower risk of the primary outcome with the consistency of the kidney components of the primary outcome", concluded Prof. Vlado Perkovic (University of New South Wales, Australia), the lead investigator of the trial [2]. These results are particularly promising in combination with the similar safety outcomes in the two groups.

1. Pratley R, et al. FLOW trial design and baseline characteristics. Plenary Session, ERA 2024, 23–26 May, Stockholm, Sweden.
2. Perkovic V, et al. FLOW primary efficacy results. Plenary Session, ERA 2024, 23–26 May, Stockholm, Sweden.
3. Mahaffey KW, et al. FLOW CV outcomes. Plenary Session, ERA 2024, 23–26 May, Stockholm, Sweden.
4. Mann JFE, et al. FLOW safety outcomes. Plenary Session, ERA 2024, 23–26 May, Stockholm, Sweden.

Early phase data show albuminuria improvement with avenciguat

The soluble guanylyl cyclase activator avenciguat improved albuminuria and slightly increased hypotension in participants with chronic kidney disease (CKD) according to early phase pooled data from a phase 1b and phase 2 trial.

Data were pooled from a phase 1b trial with participants with diabetic CKD (NCT03165227) [1] and a phase 2 trial with non-diabetic CKD (NCT04736628). Inclusion criteria were an eGFR between ≥20 and <90 mL/min/1.73 m², a urine albumin-creatinine ratio between ≥200 and <3,500 mg/g and receiving a maximally tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. 500 participants were randomised (1:3) to avenciguat (1, 2, or 3 mg 3 times daily) or a corresponding placebo. The primary endpoint of the pooled analysis was the 10-hour urine albumin-creatinine ratio at week 20 [2].

Avenciguat reduced the 10-hour urine albumin-creatinine ratio at week 20 irrespective of the regimen dose. Corrected by placebo values, avenciguat reduced the 10-hour urine albumin-creatinine ratio by a geometric mean of -15.5% (95% CI -26.4 to -3.0; P=0.02), -13.2% (95% CI -24.6 to -0.1; P=0.0479) and -21.5% (95% CI -31.7 to -9.8; P<0.001) for the 1, 2, and 3 mg dose regimens, respectively, with no difference between participants with or without diabetes. Furthermore, 39.7%, 37.7% and 48.3% of participants receiving avenciguat 1, 2, and 3 mg achieved ≥20% reduction from baseline in urine albumin-creatinine ratio at week 20, compared with 22.9% with placebo. Hypotension was reported more commonly with avenciguat (5.6%–9.5%) versus placebo (2.5%) and discontinuations due to adverse events were more common in the avenciguat arm (4.0%–8.7% vs 3.3%). However, serious adverse events and adverse events of special interest tended to be similar between the avenciguat and placebo groups.

"Avenciguat was effective in reducing albuminuria in participants with diabetic and non-diabetic CKD with the highest effect seen with the 3 mg dose regimen", concluded Prof. Hiddo J.L. Heerspink (University Medical Center, the Netherlands). These results support avenciguat dose selection in future trials.

1. Cherney DZI, et al. Diabetes Obes Metab. 2023;25(8):2218–2226.
2. Heerspink HJL, et al. Efficacy and safety of avenciguat in diabetic and non-diabetic kidney disease: Pooled analysis from two Phase II randomised controlled clinical trials. Abstract #79, ERA 2024, 23–26 May, Stockholm, Sweden.

Rilparencel leads to kidney function stabilisation in CKD and type 2 diabetes

Rilparencel, a cell-based therapy using *ex vivo* cultured expansion of autologous cells from percutaneous kidney biopsies, showed a slowing of eGFR decline in participants with stage 3–4 chronic

kidney disease (CKD) and comorbid diabetes in the phase 2 REACT trial.

The current multicentre, open-label, phase 2 REACT trial (NCT02836574) included participants aged 30–80 years, with type 2 diabetes and stage 3–4 CKD (eGFR between ≥20 and <50 mL/min/1.73 m²), and without renal dialysis. Following baseline biopsy, participants were randomised to an active cohort (receiving 2 rilparencel doses immediately, n=39) or to a deferred group (receiving 2 rilparencel injections 12 months after baseline, n=34). The time between rilparencel doses was 3–6 months. All participants received background standard-of-care therapy. The primary efficacy endpoint was a change in kidney function determined by serial eGFR measurements [1].

The deferred cohort served as the control group for the active cohort for the initial 12 months of the trial. At 12 months after baseline and before the deferred start of rilparencel, the mean eGFR reduction was -3.7 mL/min/1.73 m² in the active group compared with -4.3 mL/min/1.73 m² in the deferred group (P<0.05). Upon the start of rilparencel, the deferred group's eGFR stabilised, with a mean decline of -1.1 mL/min/1.73 m². The significant differences were maintained in a post-hoc analysis in participants with eGFR < 30 ml/min/1.73 m². In total, 3 serious adverse events (AEs) related to the biopsy and 10 AEs related to study injections were observed and none of them were linked to rilparencel. Non-serious AEs, potentially linked to rilparencel, included kidney fibrosis and indeterminate renal vessel occlusion/vasospasm.

"Our data suggest that rilparencel may preserve kidney function in patients with type 2 diabetes and moderate-to-severe chronic kidney disease", said Dr Joseph Stavas (ProKidney LLC, NC, USA). "Rilparencel is under further investigation in an ongoing global phase 3 study program."

1. Gerber D, et al. Rilparencel renal autologous cell therapy for patients with Stage 3-4 CKD and type 2 diabetes: Results from a phase 2 clinical trial. Abstract #8, ERA 2024, 23–26 May, Stockholm, Sweden.

The majority of real-world patients with CKD are not eligible for SGLT2 inhibitor trials

Kidney outcome trials of sodium-glucose transport protein 2 (SGLT2) inhibitors in participants with chronic kidney disease (CKD) might not be representative of real-world populations due to including patients at higher risk for kidney adverse outcomes. According to a real-world analysis, less than 10% of English primary care patients would have been eligible for inclusion in phase 3 SGLT2 inhibitor trials.

The recently published cross-sectional analysis from the Oxford-RCGP RSC network included adults with chronic kidney disease who were treated in primary care in England [1]. Using this database, Dr Anna Forbes (University of Oxford, United Kingdom) and her colleagues explored SGLT2 inhibitor trial eligibility criteria as well as clinical characteristics. In total, 516,491 adults with CKD were identified in the database, 32.8% of whom (n=169,443) had comorbid type 2 diabetes [2]. Of the total CKD cohort, 2.23% of patients would have been eligible for the Dapa-CKD trial (NCT03036150), 7.98% for the EMPA-KIDNEY trial (NCT03594110) and 0.92% for the CREDENCE trial (NCT02065791). In the analysed comorbid type 2 diabetes sub-cohort, 4.74%, 13.05% and 2.80% would have been eligible for Dapa-CKD, EMPA-KIDNEY, and CREDENCE respectively, while 1%, 5.50% and 0% of the sub-cohort with CKD and no type 2 diabetes would have been eligible for the Dapa-CKD, EMPA-KIDNEY, and CREDENCE trials, respectively. The major reasons for trial ineligibility included not receiving a renin-angiotensin system (RAS) inhibitor, and not meeting the albuminuria criteria for inclusion (insufficiently high albuminuria or lack of assessment). Compared with the EMPA-KIDNEY trial, real-world patients with CKD tended to be older, with a higher mean eGFR value, lower urine albumin-creatinine ratio and less likely treated with a RAS inhibitor (45.1% vs almost all in EMPA-KIDNEY).

"SGLT2 inhibitor outcome trials represent only a subgroup of people with chronic kidney disease at high risk for adverse kidney events, alleviating the interpretability of the results", concluded Dr Forbes.

1. Forbes A, et al. Nephrol Dial Transplant 2024; Mar 22. DOI: 10.1093/ndt/gfae071.
2. Forbes A, et al. SGLT2 inhibitor kidney outcome trials: Under-representation of the majority of people with chronic kidney disease in real-world clinical practice. Abstract #58, ERA 2024, 23–26 May, Stockholm, Sweden.

Kidney Transplantation and Dialysis

CD38 inhibition by felzartamab promising for resolution of antibody-mediated rejection following kidney allografts

The novel anti-CD38 antibody felzartamab has an acceptable safety profile and partially resolves antibody-mediated rejection activity following kidney allografts in a phase 2 trial.

Antibody-mediated rejection is a leading cause of allograft rejection and is associated with poor long-term outcomes in patients receiving kidney transplantation [1]. The current double-blind, parallel-group, pilot trial (NCT05021484) randomised participants following kidney allografts 1:1 to 24 weeks of felzartamab or placebo. All participants underwent a biopsy at the end of treatment (24 weeks) and another at 52 weeks. Inclusion criteria were donor-specific positive active or chronic active antibody-mediated rejection, eGFR >20 mL/min/1.73 m², and timing of the transplantation at least 6 months before study inclusion. The primary outcome was safety and tolerability, and the secondary outcomes covered the evolution of antibody-mediated rejection. Dr Katharina A. Mayer

(Medical University of Vienna, Austria) presented the results [2].

With 11 participants included per treatment group, 1 placebo participant developed graft loss at week 14 due to antibody-mediated rejection. Treatment-emergent adverse events were more common with felzartamab (90.9% vs 63.6%), which could be traced back to infusion-related reactions (72.7% vs 0%). "However, the infusion-related reactions were mild-to-moderate in severity, were limited to the first dose of felzartamab and were generally easy to treat. We did not have any treatment-related discontinuations due to infusion-related reactions or any other adverse event", highlighted Dr Mayer. The week 24 biopsy showed resolution of antibody-mediated rejection in 81.8% of participants with felzartamab versus 20.0% of participants with placebo (61.8% difference; 95% CI 18.6–100; RR 0.23; 95% CI 0.06–0.83). Of the 9 felzartamab participants showing a resolution, 33% had a recurrence of antibody-mediated rejection at the week 52 biopsy.

"We demonstrate that felzartamab had an overall acceptable safety profile when given on top of baseline immunosuppression to kidney transplant recipients", summarised Dr Mayer. "Our preliminary efficacy data was promising and will be followed up in future trials."

1. Irish W, et al. Transplantation. 2021;105(3):648–659.
2. Mayer KA. Randomized Phase 2 trial of felzartamab in humoral transplant rejection. Abstract #80, ERA 2024, 23–26 May, Stockholm, Sweden.

Clazakizumab improves albumin and inflammation in participants undergoing haemodialysis

Clazakizumab, a monoclonal antibody targeting IL-6, reduced inflammatory marker levels and increased serum albumin with manageable safety in participants with atherosclerotic cardiovascular disease receiving haemodialysis, according to phase 2b data.

The POSIBIL$_6$ESKD trial (NCT05485961) is a phase 2b/3 trial enrolling participants with a history of atherosclerotic cardiovascular disease, with/without diabetes and a hs-CRP >2 mg/L who are receiving maintenance dialysis. In the presented phase 2b dose-ranging trial part, participants were randomised 1:1:1:1 to 2.5, 5, or 10 mg IV clazakizumab every 4 weeks, or placebo. The primary endpoint was the change from baseline at week 12 in hs-CRP. In total, 127 participants were included [1].

All 3 clazakizumab doses decreased mean hs-CRP levels which was sustained over time. After 12 weeks, the geometric mean change in hs-CRP was -86%, -90% and -92% with clazakinumab 2.5, 5, and 10 mg, respectively, while the placebo group led to a 19% increase in hs-CRP. Twelve weeks of clazakizumab increased serum albumin by 0.28, 0.25, and 0.21 g/dL (2.5, 5, and 10 mg, respectively), compared with a 0.04 g/dL increase with placebo. "In clinical practice, I very rarely see an increase of serum albumin much greater than 0.2 or 0.3 g/dL, especially considering the time course of 6 months, let alone 3 months", highlighted Prof. Glenn Chertow (Stanford University School of Medicine, CA, USA), placing the findings into context. In terms of safety, clazakinumab led to 2 episodes of grade 3 neutropenia and 2 episodes of thrombocytopenia which were managed by withholding the investigational treatment. Furthermore, serious infections were observed in all clazakizumab groups and incidences increased with increasing doses.

"Low-dose clazakizumab reduced inflammatory markers associated with cardiovascular disease and increased serum albumin in a small cohort of participants receiving haemodialysis with background inflammation", summarised Prof. Chertow. "A phase 3 trial using 5 mg clazakizumab is underway."

1. Chertow G, et al. A Phase 2b/3 trial assessing IL-6 inhibition with clazakizumab in patients with cardiovascular disease or diabetes on dialysis: Results from Phase 2b. Abstract #7, ERA 2024, 23–26 May, Stockholm, Sweden.

TATH trial: Twice-weekly haemodialysis can be an alternative to thrice-weekly regimen

The TATH trial revealed, that a reduction to a twice-weekly haemodialysis schedule did not increase mortality or hospitalisation rates compared with 3 times weekly dialysis, suggesting twice-weekly intervention as a potentially simpler regimen.

A twice-weekly haemodialysis schedule may be a preferred option for patients, considering e.g., cost, travel time, or preference. The prospective, multicentre, non-randomised TATH trial (NCT03415776) compared twice-weekly versus 3 times weekly dialysis, with cross-over permitted to limit attrition for participants who had started haemodialysis between January 2018 and August 2021. Participants who were terminally ill were excluded. The primary endpoint was all-cause mortality at 2 years. Due to the COVID-19 pandemic, recruitment rates were low, and the trial was terminated early: Of the total 806 planned participants, 132 were included in the 3 times weekly and 71 in the twice-weekly group [1].

Baseline characteristics were balanced between groups, but more patients in the twice-weekly group (41%) versus the thrice-weekly group (25%) had employment and worked at the time of dialysis. "Survival rates did not differ between twice-weekly and thrice-weekly dialysis groups after 2 years follow-up (HR 0.84; 95% CI 0.37–1.90)", said Dr Mabel Aoun (Saint Joseph University of Beirut, Lebanon), who presented the results.

The number of deaths numerically decreased from 31 deaths with the 3 times weekly regimen and 15 deaths with the twice-weekly regimen. However, sudden cardiac deaths were more common in the twice-weekly (53.3%) compared with the thrice-weekly regimen (12.7%). With the trial taking place during the COVID-19 pandemic, the rate of infection-related deaths was high (26.7% vs 38.7% in the twice- vs thrice-weekly groups). The groups did not differ regarding rates of uncontrolled hypertension, cumulative erythropoietin dose or cumulative number of hospital admissions at the 2-year cut-off point.

"Participants receiving twice-weekly haemodialysis had similar survival and hospitalisation rates at 2 years compared with participants on a thrice-weekly schedule", summarised Dr Aoun.

1. Aoun M, et al. Twice Against Thrice-weekly Hemodialysis: the TATH trial. Abstract #1809, ERA 2024, 23–26 May, Stockholm, Sweden.

KIR-HLA class I mismatch could be involved in antibody-mediated rejection of transplanted kidneys

Recent cohort data shows that microvascular inflammation is more commonly present in kidney transplant recipients with inhibitory KIR-HLA class I mismatch and that these participants have shortened graft survival.

The genetic mismatch between natural killer cell immunoglobulin-like receptors (KIRs) and HLA class I molecules has been proposed to be involved in antibody-mediated graft rejection in kidney transplantation. The current study investigated KIR-HLA class I mismatch in a cohort of kidney transplant recipients who did not receive thyroglobulin or rituximab. All recipients underwent KIR genotyping, and all recipients and donors HLA class I genotyping. Per protocol, all graft recipients underwent biopsies at 12- and 36-months following transplant. Microvascular inflammation, composed of glomerulitis and peritubular capillaritis scores was determined for all biopsies. Of all kidney transplant recipients, 23 participants presented with a microvascular inflammation score ≥2 and 57 control participants with a score ≤1 in any biopsy.

Individual mismatch inhibitory KIR-HLA class I interactions did not seem to affect microvascular inflammation scores. However, the proportion of participants with ≥1 inhibitory KIR-HLA class I mismatch was higher in the group with microvascular inflammation scores of ≥2 (73.9%) versus microvascular inflammation scores of ≤1 (50.9%). The participants presenting with microvascular inflammation scores of ≥2 and inhibitory KIR-HLA class I mismatch also showed significantly lower graft survival compared with participants with lower/absent mismatch (P=0.0488). This phenomenon was not observed in participants with activating KIR-HLA class I mismatch. However, overall, more participants with microvascular inflammation scores ≥2 showed total (inhibitory and/or activating) KIR-HLA class I mismatch than participants with low inflammation scores (87% vs 59.7%; P=0.0183). Finally, graft survival was also lower in participants with microvascular inflammation scores of ≥2 and any KIR-HLA class I mismatch (P=0.0278).

"The presence of genetic inhibitory KIR-HLA class I mismatch is more frequent in kidney recipients with microvascular inflammation. Our results support that KIR-HLA class I mismatch favours the development of microvascular inflammation", concluded Ms Judith Federico-Vega (Hospital del Mar Research Institute, Spain).

1. Federico-Vega J, et al. KIR-HLA-I genetic mismatch and the development of antibody-mediated rejection and microvascular inflammation after renal transplantation. Abstract #2461, ERA 2024, 23–26 May, Stockholm, Sweden.

IgA Nephropathy

Atrasentan shows positive interim results in IgA nephropathy: ALIGN phase 3 trial

The endothelin A receptor antagonist atrasentan improves 24-hour proteinuria with favourable safety in IgA nephropathy, according to the ALIGN phase 3 trial.

The ongoing, randomised, double-blind, controlled ALIGN trial (NCT04573478) randomised adult participants with IgA nephropathy 1:1 to 132 weeks of atrasentan versus placebo. Participants had a biopsy-proven IgA nephropathy, received renin-angiotensin system inhibitors, and showed a total urine protein ≥1 g/day and an eGFR ≥30 mL/min/1.73 m². The primary endpoint was 24-hour urine protein-creatinine ratio at week 36. The current interim analysis was presented by Prof. Hiddo J.L. Heerspink (University Medical Center Groningen, the Netherlands) and included 135 participants receiving atrasentan and 135 participants with placebo [1].

Following 36 weeks of treatment, atrasentan significantly reduced proteinuria characterised by 24-hour urine protein-creatinine ratio (mean change -38.1% vs -3.1%; -36.1% difference; 95% CI -44.6 to -26.7; P<0.0001) compared to placebo. Differences in proteinuria were seen from week 6 onwards and were maintained through week 36. No change in proteinuria was observed in the placebo group. A sensitivity analysis taking into account prohibited medication use (immunosuppressants or sodium-glucose transport protein 2 inhibitors), chronic dialysis, or kidney transplant showed results consistent with the primary analysis. Adverse events more commonly reported with atrasentan were nasopharyngitis, peripheral oedema, fluid retention, vasodilation/hypotension, anaemia, and pyrexia. Overall, 5.9% of participants with atrasentan and 6.5% of participants with placebo had serious adverse events. 3.5% of participants in each group discontinued treatment due to adverse events.

"Atrasentan was well-tolerated, has a favourable safety profile, and was superior to placebo in reducing proteinuria at week 36, the primary pre-specified endpoint of the phase 3 global ALIGN trial", concluded Prof. Heerspink. The ALIGN trial is ongoing and the final results of the primary analysis of eGFR are awaited.

1. Hiddo JL Heerspink, et al. ALIGN Phase 3 primary endpoint analysis: atrasentan shows significant reduction in proteinuria in patients with IgA nephropathy. Abstract #109, ERA 2024, 23–26 May, Stockholm, Sweden.

Zigakibart slows down eGFR decline in IgA nephropathy

Zigakibart is a monoclonal antibody targeting the A-PRoliferation-Inducing Ligand (APRIL), which is involved in the pathogenesis of IgA nephropathy. Phase 1/2 data from the ADU-CL-19 trial showed that zigakibart preserves kidney function in participants with IgA nephropathy.

The ADU-CL-19 trial (NCT03945318) is an ongoing, phase 1/2 trial investigating zigakibart in participants with IgA nephropathy, a total protein excretion of ≥0.5 g/24h or 24-hour urine protein-creatinine ratio ≥0.5 g/g, and an eGFR ≥30 mL/min/1.73 m². The trial enrolled two cohorts: Cohort 1 received intravenous zigakibart 450 mg every 2 weeks. After the new formulation became available (after 24 weeks, participants of this group switched to 600 mg zigakibart subcutaneously administered every 2 weeks. Cohort 2 received subcutaneously administered 600 mg zigakibart every 2 weeks. The primary endpoint was safety and tolerability, and 40 participants were included in the trial [1].

The 24-hour urine protein-creatinine ratio declined over the initial 52 weeks of therapy in both cohorts, reaching a mean -53.4% reduction. "For the treatment of IgA nephropathy, we aspire to maintain kidney function", explained Prof. Jonathan Barrat (University of Leicester, United Kingdom). Indeed, zigakibart maintained eGFR levels over the first year of treatment in both the overall population of the trial and the individual cohorts. Zigakibart was overall well-tolerated. While adverse events (AEs) were observed, none led to treatment discontinuation or deaths. Most AEs were infectious events (as expected, as the trial was run during the COVID-19 pandemic). However, 7 participants also developed injection site reactions which were considered treatment-related. Only one serious AE was reported (amnesia) which was not considered to be treatment-related and did not lead to study drug discontinuation.

"In this trial, zigakibart reduced proteinuria, preserved kidney function in terms of a stable eGFR over the 52-week study period, and presented with an acceptable safety profile", said Prof. Barrat. "We are currently evaluating zigakibart in the BEYOND phase 3 study (NCT05852938) which is open and recruiting".

1. Barrat J, et al. One year of zigakibart treatment shows clinically meaningful proteinuria reductioon and good tolerability in a Phase 1/2 study of IgA nephropathy. Abstract #55, ERA 2024, 23–26 May, Stockholm, Sweden.

Long-term atacicept shows continued benefit in IgA nephropathy

Atacicept continued to show improvement in urine protein-creatinine ratio and eGFR stabilisation in participants with IgA nephropathy in the open-label extension of the recently published phase 2b ORIGIN trial.

Atacicept is a dual inhibitor of B-cell Activating Factor (BAFF) and A PRoliferation-Inducing Ligand (APRIL) investigated in the phase 2b ORIGIN trial (NCT04716231). This multinational, randomised dose-range study randomised participants 1:1:1:1 to 36 weeks of atacicept 25 mg, 75 mg, or 150 mg every week or placebo. Inclusion criteria were the presence of IgA nephropathy confirmed by kidney biopsy, a high risk of disease progression, eGFR ≥30 mL/min/1.73 m², 24-hour urine protein-creatinine ratio of >75 mg/g or 24-hour total urine protein >75 g, and a stable treatment with renin-angiotensin-aldosterone system inhibitors. As recently published, atacicept met its primary endpoint of 24-hour urine protein-creatinine ratio reduction at week 24 in the 116 randomised and treated participants [1]. Prof. Richard Lafayette (Stanford University, CA, USA) presented the 72-week interim results of the open-label extension of the trial [2].

At 72 weeks, 106 participants had completed the open-label extension. Participants who had switched to atacicept by that time had a mean -59% change from baseline in galactose-deficient IgA1 compared to -62% for participants with continuous atacicept. Furthermore, haematuria decreased in 59% of participants switching to atacicept compared with 81% of participants receiving continuous atacicept treatment. The mean urine protein-creatine ratio decreased by 47% from baseline in participants who switched to atacicept and by 45% in patients receiving continuous atacicept by week 72, and eGFR values stabilised in all participants. Atacicept was well-tolerated during the open-label extension, with only 1 participant discontinuing treatment due to adverse events. There were no signals of increased infections.

"Participants treated with atacicept had consistent and sustained reductions in their galactose-deficient IgA1, haematuria and urine protein-creatine ratio, and they have consistent and stable eGFR", summarised Prof. Lafayette, adding that participants who switched to atacicept demonstrated similar results. "These data provide strong confidence in the ongoing phase 3 trial."

1. Lafayette R, et al. Kidney Int. 2024;105(6):1306–1315.
2. Lafayette R, et al. Phase 2b ORIGIN study open label extension with atacicept in patients with IgA nephropathy and persistent proteinuria: Week 72 interim analysis. Abstract #812, ERA 2024, 23–26 May, Stockholm, Sweden.

APPLAUSE-IgAN: Iptacopan improves proteinuria in IgA nephropathy

Interim results from the ongoing phase 3 APPLAUSE-IgAN trial showed that iptacopan significantly improved proteinuria with acceptable safety in participants with IgA nephropathy versus placebo.

Iptacopan is a complement factor B inhibitor which showed significant improvement in haemoglobin levels without transfusion in 2 recent phase 3 trials in participants with paroxysmal nocturnal haemoglobinuria [1]. The current APPLAUSE-IgAN (NCT04578834) investigates a 24-month treatment with iptacopan compared with placebo in a phase 3, multicentre, randomised, double-blind phase 3 setting in participants with primary IgA nephropathy. Eligibility criteria were biopsy-confirmed IgA nephropathy and a 24-hour urine protein-creatinine ratio ≥1 g/g despite maximally tolerated renin-angiotensin system inhibitors with/without sodium-glucose transport protein 2 (SGLT2) inhibition. The interim analysis's primary endpoint was a reduction in urine protein-creatinine ratio

from baseline at month 9. The analysis included 250 participants for efficacy and 443 participants for safety (based on the study population at data cut-off) and Prof. Vlado Perkovic (University of New South Wales, Australia) presented the results [2].

Iptacopan met the primary endpoint of the interim analysis at 9 months: 24h urine protein-creatinine ratio was reduced by 43.8% with iptacopan versus 9.0% with placebo, corresponding to a 38.3% difference between groups (95% CI 26.0–48.6; P<0.0001). These reductions in proteinuria were consistent among subgroups characterised by sex, geographic region (Asia vs non-Asia), various baseline urine protein-creatinine ratio categories, eGFR categories (30 to <45 vs <30 mL/min/1.73 m²), and participants with/without baseline use of SGLT2 inhibitors. In total, 8.1% of participants reported serious adverse events with iptacopan compared with 5.0% with placebo. Upper respiratory tract infections were more common with iptacopan (9.0% vs 7.2%), while adverse events such as nasopharyngitis (5.0% vs 7.2%), headache (4.1% vs 5.4%) and hypertension (1.8% vs 5.9%) were more common in the placebo arm. There were no deaths reported for either treatment regimen [2].

To conclude the interim analysis of APPLAUSE-IgAN showed the superiority of iptacopan over placebo in reducing proteinuria after 9 months of treatment in participants with IgA nephropathy. Overall, iptacopan was well-tolerated. The study is currently ongoing with a total treatment duration of up to 2 years [2].

1. de Latour RP, et al. N Engl J Med. 2024;390(11):994–1008.
2. Perkovic V, et al. Efficacy and safety of iptacopan in patients with primary IgA nephropathy: Interim analysis results of the Phase 3 APPLAUSE-IgAN study. Abstract #456, ERA 2024, 23–26 May, Stockholm, Sweden.

Cardio-Renal Interplay

Semaglutide improves renal outcomes in overweight/obese participants with cardiovascular disease and no diabetes

Semaglutide compared with placebo showed significant renal improvement on top of the recently established cardiovascular improvements in participants with overweight/obesity and cardiovascular disease enrolled in the SELECT trial.

The SELECT trial (NCT03574597) is a randomised, double-blind, multicentre, phase 3 trial of semaglutide versus placebo which enrolled participants with BMI ≥27 kg/m² and established cardiovascular disease but no diabetes to assess cardiovascular outcomes [1]. The current renal prespecified analysis, presented by Prof. Helen M. Colhoun (The University of Edinburgh, United Kingdom), used a 5-point composite endpoint defined as death due to kidney causes, initiation of chronic kidney replacement therapy (dialysis or transplant), onset of persistent eGFR <15 mL/min/1.73 m², persistent eGFR reduction from baseline of ≥50%, or onset of persistent microalbuminuria. These analyses were performed on the entire cohort of SELECT (n=17,604) [2].

The time-to-occurrence of the 5-component kidney endpoint was significantly longer with semaglutide compared with placebo. After a median follow-up of 182 weeks, 1.8% of participants receiving semaglutide and 2.2% receiving placebo achieved the composite endpoint (HR 0.78; 95% CI 0.63–0.96; P=0.02). When analysing the individual components of the composite endpoint, the efficacy results were mainly driven by improvement in time-to-onset of eGFR reduction from baseline of ≥50% (HR 0.57; 95% CI 0.27–1.14; P=0.11) and time-to-onset of microalbuminuria (HR 0.80; 95% CI 0.64–1.00; P=0.05). No kidney-related deaths were observed for either group. Semaglutide further led to a treatment benefit of 0.75 mL/min/1.73 m² (95% CI 0.43–0.96; P<0.001) in eGFR and -10.7% (95%CI -13.2 to -8.2; P<0.001) in urinary albumin-creatinine ratio at week 104, compared with placebo.

"In the absence of diabetes, 2.4 mg of semaglutide weekly reduced the composite kidney endpoint by 22% and had beneficial effects on eGFR and urine albumin-creatinine ratio", summarised Prof. Colhoun. "These data add to the growing body of evidence on the potential kidney benefit of semaglutide".

1. Lincoff AM, et al. N Engl J Med. 2023;389(24):2221–2232.
2. Colhoun HM, et al. Effect of semaglutide on kidney outcomes in people with overweight or obesity and established cardiovascular disease in the SELECT trial. Abstract #2496, ERA 2024, 23–26 May, Stockholm, Sweden.

Discrepancy between cardiovascular RCT participants and real-life CKD patients could limit generalisability of RCT results

Participants with chronic kidney disease (CKD) from a real-life population cohort were mostly ineligible for randomised controlled cardiovascular trials (RCTs) that drive contemporary clinical guidelines. The studied real-life population with CKD presented with better cardiovascular risk factor control than participants included in the RCTs.

RCTs often use stringent inclusion criteria, which could limit the applicability of results for routine clinical practice. Julia M.T. Colombijn (University Medical Centre Utrecht, the Netherlands) presented the results of a pilot study which estimated the eligibility of participants with CKD from a real-life population cohort for major routine cardiovascular outcome clinical trials [1].

The eligibility criteria were extracted from 46 trials, selected from KDIGO and ESC clinical guidelines, covering a total of 321,674 participants with interventions like renin-angiotensin-aldosterone system inhibitors, beta-blockers, aldosterone receptor antagonists, diuretics, antiplatelets, anticoagulants and sodium-glucose cotransporter-2 inhibitors. The extracted eligibility criteria were modelled on participants from the real-life population cohort, meaning all participants from the Utrecht Patient Oriented Database between 2012 and 2019. From this real-life population, n=9,005 participants with CKD were included (eGFR <60 mL/min/1.73 m^2 or urine albumin-creatinine ratio ≥3 mg/mol) and rates and reasons for ineligibility were determined.

The median rate of ineligibility for clinical trials was 99%. Reasons for ineligibility included demographic characteristics, presence of comorbidities, co-medication use, kidney-related and laboratory or physical examination reasons. Compared with participants in the selected RCTs, participants in the overall Utrecht cohort tended to have fewer comorbidities such as diabetes (27% vs 53%), previous myocardial infarction (3% vs 9%), or heart failure (17% vs 28%). However, Utrecht cohort participants who were eligible for clinical trials had higher rates of common comorbidities such as hypertension, previous myocardial infarction, stroke or heart failure compared to those in the trial populations. Furthermore, participants from the real-life Utrecht population tended to have lower blood pressure, Hb1Ac values, urine albumin-creatinine ratios, and body mass index.

"In Utrecht, we have over 95% ineligibility rates for patients from routine clinical practice for the RCTs on which the KDIGO and ESC guidelines are based. For these trials, the kidney-related criteria were the reasons for ineligibility in about 60%", concluded Ms Colombijn. "Real-life patients appeared healthier with better cardiovascular risk factor control than the participants included in RCTs."

1. Colombijn JMT, et al. Generalisability of cardiovascular RCTs to patients with chronic kidney disease in clinical practice: a comparison between RCTs and real-world data. Abstract #615, ERA 2024, 23–26 May, Stockholm, Sweden.

MERCURI-1: Perioperative empagliflozin shows renal protection following cardiac surgery

Perioperative use of the sodium-glucose transport protein 2 (SGLT2) inhibitor empagliflozin led to lower rates of acute kidney injury with improved glycaemic control in participants undergoing elective cardiac surgery, according to the MERCURI-1 trial.

The MERCURI-1 trial (EudraCT 2021-003172-13), a single-centre, open-label, randomised, parallel-group, phase 4 pilot study, investigated the potential protective effect of perioperative empagliflozin on renal injury in participants undergoing elective cardiopulmonary bypass-assisted cardiac surgery. Participants with diabetes, a body-mass index <25 kg/m^2 eGFR <30 mL/min/1.73 m^2, and/or ongoing SGLT2 inhibition were excluded from the trial. Participants were randomised to empagliflozin 10 mg daily (starting 3 days before surgery and ending 2 days after surgery, n=25) or a standard-of-care control (n=30). The primary endpoint was the difference between the renal injury biomarker neutrophil gelatinase-associated lipocalin (NGAL) at post-operative day 2. Dr Lars Snel (Amsterdam University Medical Centre, the Netherlands) presented the results [1].

On post-operative days 1 and 2, NGAL concentrations did not differ between groups. Following surgery, the rates of acute kidney injury were significantly lower with empagliflozin (20%) versus control (66.7%), corresponding to a 47% reduction in kidney injury (95% CI 24–70%; P=0.001). Post-operative glycaemic control was significantly improved with empagliflozin compared with control, with lower peak glucose levels (P=0.007), and fewer participants presenting with hyperglycaemia (P=0.029) and receiving insulin (P=0.023). None of the participants developed hypoglycaemia in either treatment group. As participants fasted before surgery, the administration of an SGLT2 inhibitor could promote the development of ketone bodies. However, ketoacidosis rates did not differ between treatment groups.

"This is the first clinical trial of perioperative SGLT2 inhibitor use as opposed to pre-operative SGLT2 inhibition. Our data suggest that acute SGLT2 inhibition protects from renal injury in participants undergoing cardiac surgery", highlighted Dr Snel. The results are currently further tested in the larger, double-blind, phase 4 MERCURI-2 trial (NCT05590143) with results expected in 2025.

1. Snel L, et al. Empagliflozin limits AKI incidence and severity following cardiac surgery: an open-label phase IV randomized pilot study. Abstract #976, ERA 2024, 23–26 May, Stockholm, Sweden.

Simulated head-to-head comparison of SGLT-2 inhibitors and GLP-1R agonists in type 2 diabetes

Head-to-head clinical trials comparing sodium-glucose transport protein 2 (SGLT-2) inhibitors to glucagon-like peptide-1 receptor (GLP-1R) agonists for kidney protection in patients with type 2 diabetes are not available. An observational study showed a slight improvement in acute kidney injury but also slightly increased mortality rates following SGLT-2 inhibitor treatment compared with GLP-1R agonists.

Adverse kidney outcomes are frequent complications in diabetes mellitus type 2 and are currently treated with SGLT-2 inhibitors or GLP-1R agonists. So far, clinical trials comparing the kidney protective effects of these two agents are however lacking. Dr Uffe Heide-Jørgensen (Aarhus University, Denmark) and team emulated a clinical trial from nationwide Danish population-based registries registry data. Trial participants included were adults with type 2 diabetes, an eGFR ≥30 mL/min/1.73 m^2 and a urine albumin-creatinine ratio <300 mg/g. Treatment consisted of SGLT2 inhibitors or GLP-1R agonists starting in January 2014 to November 2020. Participants with chronic kidney dialysis, kidney failure or transplant were excluded from the analysis. To address potential confounders arising from the lack of randomisation, the stabilised inverse probability of the treatment weighting method was used. The primary outcome was acute kidney injury estimated from

laboratory measurements. A total of 36,331 participants receiving SGLT2 inhibitors and 18,822 participants receiving GLP-1R agonists were included.

Using an intention-to-treat analysis, there was an approximately 20% lower ratio of acute kidney injury events with SGLT2 inhibitors compared with GLP-1R agonists after 1 year of treatment (95% CI 0.74–0.90), This trend continued at 3 years and 5 years of treatment.

The results were consistent favouring SGLT2 inhibitors in subgroups characterised by sex, age (<65 vs ≥65 years), albumin-creatinine ratio, and presence of cardiovascular disease. As an exception, no differences between treatment regimens were observed in the subgroup of participants with an eGFR < 60 mL/min/1.73 m^2. Numerically, the mortality rate was higher in participants receiving SGLT2 inhibitors compared with GLP-1R agonists (ratio 1.05; 95% CI 0.99–1.09).

"SGLT2 inhibitors are associated with a slightly higher mortality compared with GLP-1R agonists, but with somewhat lower rates of acute kidney injury", said Dr Heide-Jørgensen. "The lower incidence of acute kidney injury was largely consistent across subgroups."

1. Jensen SK, et al. Initiation of SGLT2i vs GLP1-RA and incidence of AKI in persons with type 2 diabetes mellitus. Abstract #462, ERA 2024, 23–26 May, Stockholm, Sweden.

Other Nephrology

Preview of the new KDIGO Guidelines for ADPKD, available later in 2024

The first-ever upcoming KDIGO guidelines for adult and children autosomal-dominant polycystic kidney disease (ADPKD) were introduced at the conference and extracts are presented here.

The current guidelines for clinical practice of ADPKD are based on consensus statements released in 2015 [1]. So far, KDIGO guidelines have not been established on this subject. ADPKD Guideline co-chair Dr Vicente Torres (Mayo Clinic, Rochester, MN, USA) and Dr Djalila Mekahli (KU Leuven, Belgium) presented the upcoming recommendations for ADPKD diagnosis and management. Some aspects are covered in this report.

Nomenclature: For adults, following a diagnosis of ADPKD and genetic testing, KDIGO recommends a nomenclature which contains the pathogenic gene name (*PKD1*, *PKD2*, or confirmed minor gene): "ADPKD/gene". If no genetic testing is performed or no gene is identified, the nomenclature should follow the same style [2].

Diagnosis: The initial diagnosis of ADKPD will be based on 3 diagnostic pillars as per the new KDIGO guidelines, similar to the earlier consensus statement [2]:

- ADKPD phenotype (bilateral kidney cysts, usually with kidney enlargement, often with liver cysts and other extrarenal manifestations)
- Absence of other kidney cystic disease
- With/without family history

Regarding the identification of rapidly progressing ADPKD, upcoming KDIGO guidelines recommend the Mayo Imaging Classification [3] for the prediction of decline in kidney function and evolution to kidney failure. Other markers which can be added are total kidney volume, genetic testing, ProPKD score, family history (age at kidney failure), eGFR decline, chemical biomarkers and other imaging biomarkers.

Diagnosis of paediatric ADPKD is faced with particular challenges as predictive factors for eGFR decline in children are not well established because the decline tends to be slower. The diagnostic routine is recommended similarly to adult conditions. However, kidney ultrasound is also recommended for parents in case of multiple cysts if no known family history exists. Furthermore, as hypertension is a common occurrence in paediatric ADPKD, blood pressure measurements should be carried out starting at 5 years of age. Additionally, Dr Mekahli presented a new ultrasound model called the Leuven Imaging Classification which can be used to complement the Mayo Imaging Classification but will require further validation in larger cohorts [4].

Management: The upcoming KDIGO guidelines contain general updates regarding management. Hypertension, often associated with ADPKD, and the use of lipid-lowering agents such as statins should be managed similarly to recommendations for chronic kidney disease [5]. For rapidly progressing ADPKD, tolvaptan is recommended in adults with an eGFR ≥ 25 mL/min/1.73 m² and risk of rapid progression (based on Mayo class or eGFR decline ≥ 3 mL/min/1.73 m²/year). MTOR inhibitors, metformin, statins, sodium-glucose transport protein 2 inhibitors, somatostatin analogues and ketogenic interventions are not recommended for slowing eGFR decline [2]. At the current stage, there is insufficient clinical trial data with tolvaptan in children, so this agent is not recommended [2].

The fully updated ADPKD guidelines will be published later in 2024.

1. Chapman AB, Kidney Int. 2015;88(1):17–27.
2. KDIGO update - PKD guidelines 2024. Session S0.6, ERA 2024, 23–26 May, Stockholm, Sweden.
3. Bais T, et al. Clin J Am Soc Nephrol. 2024;19(5):59 –601.
4. Breysem L, et al. Clin J Am Soc Nephrol. 2023;18(5): 581–591.
5. KDIGO Working Group. Kidney Int. 2024;105(4S): S117–S314.

APPEAR-C3G: Iptacopan shows promise for complement 3 glomerulopathy

The APPEAR-C3G showed that the complement inhibitor iptacopan can improve proteinuria and delay the decline in eGFR in participants with complement 3 glomerulopathy.

Complement 3 glomerulopathy (C3G) is a rare renal disease characterised by the accumulation of C3 fragments in glomeruli, which in time can lead to end-stage kidney disease [1]. APPEAR-C3G (NCT04817618) trial is a randomised, double-blind, parallel-group, multicentre phase 3 trial of iptacopan versus placebo on top of supportive. Adults with biopsy-confirmed C3G and a urine protein-creatinine ratio ≥1.0 g/g and eGFR ≥30 mL/min/1.73 m² were included. The initial treatment period consisted of 6 months of randomised iptacopan (38 participants) versus placebo (36 participants), after which all participants received 6 months of iptacopan. The primary endpoint was 24-hour urine protein-creatinine ratio reduction after 6 months of therapy [2].

"The trial met its primary endpoint with a statistically significant and clinically meaningful reduction in proteinuria at 6 months", said Prof. David Kavanagh (Newcastle University, United Kingdom), who presented the results. Overall, iptacopan led to a 30.2% reduction in 24-hour urine protein-creatinine ratio compared with a 7.6% increase with placebo after 6 months (mean 35.1% difference; P=0.0014). Iptacopan led to higher proportions of participants achieving both ≤15% degradation in eGFR and ≥50% reduction in urine protein-creatinine ratio (29.7% vs 5.6%; OR 7.145; 95% CI 1.429–35.723; P=0.0166). Furthermore, 6-month treatment with iptacopan reduced nephrotic-range proteinuria (31.6% vs 41.7%, iptacopan vs placebo) and led to a numerical improvement in eGFR scores. In total, 15.8% and 13.9% of participants had adverse events suspected to be related to iptacopan and placebo, respectively, while serious adverse events were reported in 5.3% and 2.8%, respectively. However, there were no treatment discontinuations due to adverse events or deaths during the study.

"The study demonstrated a clinically significant and meaningful reduction on top of the standard-of-care with eGFR improvement", finalised Prof. Kavanagh. "The safety profile was favourable in participants with C3G".

1. Schena FP, et al. Int J Mol Sci. 2020;21(2):525.
2. Kavanagh D, et al. Efficacy and safety of iptacopan in patients with C3 glomerulopathy: results from the phase 3 APPEAR-C3G trial. Abstract #98, ERA 2024, 23–26 May, Stockholm, Sweden.

Anti-nephrin autoantibody positivity describes a unique subclass of podocytopathies

Autoantibodies targeting nephrin could be detected in approximately 70% of adults with untreated minimal change disease and 90% of children with idiopathic nephrotic syndrome. Anti-nephrin autoantibody presence correlated with disease activity and its presence may suggest a new subclass of podocytopathies.

Podocytopathies are a group of glomerular diseases in which podocyte damage leads to proteinuria. These are rare diseases with causes which are not currently fully understood [1]. The current multicentre cohort aimed to detect anti-nephrin antibodies and included 357 adults (with diseases such as minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, IgA nephropathy, ANCA-associated glomerulonephritis and lupus nephritis), 182 children (all with idiopathic nephrotic syndrome), and 67 adults and 50 children as controls. Prof. Tobias B. Huber (University Medical Center Hamburg-Eppendorf, Germany) presented the results [2].

Anti-nephrin autoantibodies were detected in 44% of adult cases of minimal change disease, and in 9% of primary focal segmental glomerulosclerosis, but were rare in non-primary focal segmental glomerulosclerosis and membranous nephropathy, with no detections in other studied conditions or control participants. Among participants with minimal change disease, 69% of participants who were not nephrotic and did not receive immunosuppressants showed anti-nephrin autoantibody positivity. Moving to children, anti-nephrin autoantibodies were detected in 52% of cases with idiopathic nephrotic syndrome, with an increase in proportion in children who were not nephrotic and did not receive immunosuppressant therapy (90%). "Furthermore, there was a strong correlation between the detection of anti-nephrin antibodies and proteinuria, and thus disease activity", elaborated Prof. Huber. The presenter also described several patient cases where anti-nephrin antibody detection was employed to switch immunosuppressive treatment to agents such as cyclosporin or rituximab and where this switch induced long-term remission [2].

"These results suggest a novel disease entity of anti-nephrin podocytopathy appearing in 70% of untreated minimal change disease cases and 90% of idiopathic nephrotic syndrome", concluded Prof. Huber.

1. Kopp JB, et al. Nat Rev Dis Primers. 2020;6(1):68.
2. Huber TB, et al. Autoantibodies targeting nephrin in podocytopathies. Late Breaking Clinical Trials I, ERA 2024, 23–26 May, Stockholm, Sweden.

Active vitamin D plus low-dose prednisolone is an alternative to high-dose prednisolone in minimal change disease

Low-dose prednisolone plus alfacalcidol is non-inferior in inducing remission but presents with fewer adverse events compared with the guideline-recommended high-dose 1 mg/kg/day prednisolone, according to results from the ADAPTinMCN trial.

ADAPTinMCN (NCT03210688) is an ongoing investigator-initiated, Danish, multicentre, prospective, open-label, randomised, controlled trial including adult participants with biopsy-proven minimal change disease and nephrotic syndrome. Participants were randomised 1:1 to prednisolone 1 mg/kg/day or prednisolone 0.5 mg/kg/day plus 0.5 µg alfacalcidol. The primary endpoints were the rate of and time to remission, defined as urine albumin-creatinine ratio <300 mg/g and/or <400 mg/g present at 2 consecutive tests. A total of 35 participants were included per treatment group and Dr Tilde Kristensen (Regional Hospital Viborg, Denmark) presented the results [1].

Remission was achieved in 89% of participants with high-dose prednisolone and 83%

receiving low-dose prednisolone plus alfacalcidol. The median time-to-remission was 23 days (interquartile range [IQR] 12–43) in the high-dose prednisolone group and 25 days (IQR 15–35 days) in the low-dose prednisolone plus alfacalcidol group. However, as expected, the median cumulative prednisolone doses were significantly lower in the low-dose prednisolone plus alfacalcidol group (1,413 mg [IQR 834–2,061] vs 2,240 mg [IQR 1,380–4,310]; P=0.002). Nine treatment-related adverse events (AEs) were reported in the high-dose group compared with only one in the low-dose prednisolone plus alfacalcidol group. Also, other, milder, treatment-related AEs were more common in the high-dose prednisolone group. Finally, serum Ca^{2+} and vitamin D levels did not differ between treatment groups at baseline or remission.

"In participants with minimal change disease, treatment with low-dose prednisolone in combination with alfacalcidol is non-inferior to prednisolone 1 mg/kg/day", concluded Dr Kristensen. "The 2 treatment strategies are equally efficient regarding the rate-of-remission and time-to-remission, but severe AEs were more common in the high-dose group". These results raise the question of whether guidelines for the treatment of minimal change disease in adults should be changed to low-dose prednisolone alternatives.

1. Kristensen T, et al. Lower dose prednisolone and alfacalcidol is noninferior to high dose prednisolone in minimal change disease – a randomized controlled trial. Abstract #3, ERA 2024, 23–26 May, Stockholm, Sweden.

Claudin-1 is a potential antibody target for crescent glomerulonephritis

Claudin-1, the target of lixudebart, showed mechanistic involvement in decreasing kidney function and preclinical data support claudin 1 as a therapeutic target in crescent glomerulonephritis.

Claudin-1 is a transmembrane protein involved in fibrotic pathways and extracellular matrix remodelling in immune-mediated kidney disease. It is targeted by lixudebart, a drug currently assessed for its potential in anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA-associated vasculitis) in the phase 2 RENAL-F02 (NCT06047171) trial.

Dr Jean-Daniel Delbet (Paris Centre de Recherche Cardiovasculaire, France) and his team investigated the mechanistic role of claudin 1 in crescentic glomerulonephritis, which is characterised by extensive glomerular parietal epithelial cell proliferation forming a crescent, which evolves into fibrotic lesions. Using the OPAL multiplex technique, the researchers determined claudin 1 expression in parietal epithelial cells in two cohorts (33 participants with ANCA-associated vasculitis and 29 with IgA nephropathy). Separately, an anti-claudin 1 antibody was tested in a nephrotoxic nephritis mouse model of crescentic glomerulonephritis (knockout mice expressing human claudin 1, n=20 each receiving control and the antibody) [1].

"We found that the proportion of claudin 1-positive cells increases with the development of histological extra-capillary glomerular lesions and we identified a subpopulation of activated parietal epithelial cells that express both claudin 1 and CD44", explained Dr Delbet. This subpopulation of claudin 1 and CD44 double-positive cells was associated with lowered eGFR (<30 mL/min) at diagnosis for both participants with IgA nephropathy (P<0.01) and ANCA-associated vasculitis (P=0.02). Transcriptome analysis of the activated parietal epithelial cells compared to normal kidney samples (junctional claudin 1 in Bowman's capsule) and participants with ANCA-associated vasculitis (exposed claudin 1 from cellular crescents) revealed that the activated parietal epithelial cells overexpressed genes related to the extracellular matrix and fibrosis. In the mouse model of crescentic glomerulonephritis, the anti-claudin 1 antibody led to a significantly decreased urine albumin-creatinine ratio and significantly blunted glomerular scarring by decreasing collagen IV deposition.

"We showed that parietal epithelial cells retain claudin 1 expression when forming extra-capillary glomerular crescents and that the subpopulation of double-positive (claudin 1 and CD44) cells may be associated with poor renal outcomes in human glomerulonephritis," concluded Dr Delbet.

1. Delbet JD, et al. Novel therapeutic for crescentic glomerulonephritis through targeting CLDN1 in parietal epithelial cells. Abstract #2837 ERA 2024, 23–26 May, Stockholm, Sweden.

Rituximab protocol based on PLA2R1 epitope spreading outperforms the standard GEMRITUX protocol in membranous nephropathy

A personalised treatment regimen based on PLA2R1 epitope spreading analysis can offer improved remission rates in participants with membranous nephropathy, according to a recent phase 2 trial.

The discovery of the M-type phospholipase A2 receptor (PLA2R) as the primary target in membranous nephropathy greatly advanced basic and clinical research [1]. The current multicentre, randomised, clinical trial (NCT03804359) analysed the clinical remission effect of a personalised treatment scheme based on the presence or absence of baseline PLA2R1 epitope spreading in participants with membranous nephropathy compared to the standard GEMRITUX protocol. Prof. Barbara Seitz-Polski (Université Côte d'Azur, France) presented the results [2].

The personalised treatment regimens (n=33) under investigation were: participants without PLA2R1 epitope spreading at baseline received the GEMRITUX protocol and participants with epitope spreading at baseline or who had persistent nephrotic syndrome at month 6 were treated immediately with 2 high-dose rituximab infusions. The control GEMRITUX protocol (n=31) entailed symptomatic treatment for 6 months, with 2 additional rituximab infusions after 6 months if persistent nephrotic syndrome was present. Outcome measures were clinical remission, defined as a urine protein-creatinine ratio <0.3 g/g, with a normal serum albumin and eGFR >60 mL/min/1.73 m², or partial clinical remission (urine protein-creatinine ratio <3.5 g/g with ≥50% improvement from baseline, improvement or normalisation of serum albumin and stable serum creatinine).

A significantly higher proportion of participants receiving the personalised regimen achieved partial clinical remission (69% vs 34%; P=0.0105) at month 12 compared with the GEMRITUX regimen. "It is important to note that we have the same level of spontaneous remission for participants who were never treated in the personalised arm compared to the GEMRITUX arm, showing that we did not overtreat participants", added Prof. Seitz-Polski. The personalised versus GEMRITUX regimen led to significantly improved kidney function assessed by variation between baseline and month 12 in creatinaemia (P=0.0323) and eGFR (P=0.0303). The adverse event rates between both study groups did not differ (P=0.6071).

"Personalised rituximab treatment based on PLA2R1 epitope spreading recognition was superior to the standard protocol in achieving remission and gain in eGFR at 12 months. Participants with multiple domain recognition should be treated immediately with high doses of rituximab to increase their chances of remission", concluded Prof. Seitz-Polski.

1. Beck Jr LH, et al. N Engl J Med. 2009;361(1):11–21.
2. Seitz-Polski B, et al. Protocol based on PLA2R1 epitope recognition is superior to standard protocol in achieving remission in PLA2R1-associated membranous nephropathy. Abstract #992, ERA 2024, 23–26 May, Stockholm, Sweden.

The REACT score predicts relapse in ANCA-associated vasculitis

A new risk score called REACT can predict relapses following cyclophosphamide in participants with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, data from a multinational retrospective cohort study suggests.

"Cyclophosphamide use is associated with sustained remission induction in ANCA-associated vasculitis. Several clinical factors, however, likely co-affect this risk for relapse", started Dr Gianmarco Lugli (Meyer Children's Hospital IRCCS, Italy) and introduced the reasoning for performing a retrospective study, using 3 national cohorts from Italy, Ireland, and Spain, to establish a relapse risk score for ANCA-associated vasculitis patients.

The retrospective study included 593 participants (261 with microscopic polyangiitis, 259 with granulomatosis with polyangiitis and 73 with eosinophilic granulomatosis with polyangiitis), of whom 552/593 (93%) had remission, and 271/552 (49%) developed relapse. Cohort participants were eligible for inclusion if they were adults with a diagnosis of granulomatosis with polyangiitis, microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis (with a Five-Factor Score >0), received induction with cyclophosphamide (both oral and intravenous were eligible) and had a follow-up of at least 12 months. Relapse was defined as at least 1 new vasculitis event after remission of ≥3 months [1].

Although organ involvement varied among participants with different ANCA-associated vasculitis, kidney involvement was present in 80% of the cohort. The median cohort relapse-free survival time was over 24 months; however, participants with eosinophilic granulomatosis with polyangiitis had longer relapse-free survival than those with microscopic polyangiitis and granulomatosis with polyangiitis (P<0.0001). Multivariate analyses showed that IgG class ANCA directed to proteinase 3 (PR3) levels, intravenous cyclophosphamide, cardiovascular involvement, arthralgias/arthritis and the absence of rapidly progressive glomerulonephritis were all independent predictors of relapse. Based on these data, a "Relapse Evaluation And Cyclophosphamide Treatment (REACT) score" (range 0–7) was created, whereby all independent predictors were weighted with 1 point, except intravenous cyclophosphamide and cardiovascular involvement, which received 2 points. REACT scores identified 138 (27%) of participants as low-risk (scores 0–1), 252 (59%) as moderate-risk (scores 2–3), and 115 (22%) as high-risk (scores ≥4) categories which could significantly predict relapse-free survival on Kaplan-Meier analysis.

"The REACT score could be employed at diagnosis to predict the risk of relapse, but the score will require future external validation," concluded Dr Lugli.

1. Lugli G, et al. Development of a relapse risk score in patients with ANCA-associated vasculitis treated with cyclophosphamide induction. Abstract #1484, ERA 2024, 23–26 May, Stockholm, Sweden.