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Trends in General Medicine

Update in Nephrology

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ABSTRACT

Background: *This timely update in nephrology is based on the proceedings of The American Society of Nephrology (ASN) Kidney Week that was held in San Diego, California between October 23, and October 27, 2024. The meeting had 4 sessions dedicated to high-impact clinical trials and late-breaking science.*

Methods: *This update will present 12 studies including 10 clinical trials. Each trial was published in a major peer-reviewed journal on the day of the presentation. This will provide the reader with the opportunity to refer to the published study in its entirety. IgA nephropathy (IgAN) management was a major theme in the meeting, and 5 clinical Trials on that topic are included. Other topics included in this review cover kidney transplantation, sodium-glucose cotransporter 2 (SGLT2) inhibitors in chronic kidney disease (CKD), acute kidney injury (AKI), the role of APOL-1 risk variants, semaglutide in non-diabetic CKD patients, potassium binders in hemodialysis patients, and blood pressure management strategies in non-cardiac surgery patients.*

Results: *For each study a brief background will be provided, followed by the results of each individual study, then a conclusion and a statement about the study limitations.*

Conclusions: *This update is a window into recent progress in renal medicine. Advances in basic science are propelling novel medications in the field of nephrology with the potential of impacting direct patient care. The excitement in the renal community is palpable.*

Keywords

Chronic Kidney Disease, CKD-MBD (Mineral and Bone Disorders), Acute Kidney Injury, Glomerulonephritis, Hypertension.

Introduction

Kidney Week is a premier annual nephrology meeting organized by the American Society of Nephrology (ASN). The meeting is attended by a large number of renal physicians and scientists. This is a timely update on recent clinical and basic science advances in nephrology. Prior Kidney Week meetings dedicated one session to late-breaking clinical trials. The 2024 Kidney Week had 4 such sessions. Two high-impact clinical trials, and two late-breaking science oral sessions. In the 4 sessions, 30 oral abstracts were presented, each followed by a discussion of the respective study. These studies reflect the most recent advances in the diagnosis and treatment of kidney disease. This update will present 12 studies in including 10 clinical trials. These studies were chosen because their importance warranted their simultaneous publication on the day of presentation in a major peer-reviewed medical journal. This assures that the trial data are complete and that the trial manuscript was subjected to a rigorous peer-review process. Each study review will include a quick background, followed by a study summary, a conclusion, and finally a statement regarding the study limitations.

Microvascular Inflammation of Kidney Allografts and Clinical Outcomes

Background: Microvascular inflammation is the characteristic histologic lesion of antibody-mediated kidney allograft rejection, a major cause of kidney allograft failure [1].

The Banff Classification of Allograft Pathology classifies biopsies from solid organ transplants. The new update included two new

diagnostic entities: microvascular inflammation (MVI) without evidence of an antibody-mediated response (donor-specific antibody [DSA] negative, and complement component C4d [C4d] negative), and probable antibody-mediated rejection (probable AMR, DSA positive and C4d negative) [2].

Study summary: The authors classified approximately 16,000 kidney biopsies from more than 30 kidney transplantation centers in North America and Europe using the 2022 Banff classification [3]. The above-mentioned two novel phenotypes were diagnosed in about 5% of the biopsies. Of note, most of those cases were considered non-rejection prior to the new classification. In patients with MVI without evidence of an antibody-mediated response the hazard ratio for allograft loss compared to non-rejection cases was 2.1 (95% confidence interval [CI], 1.5 to 3.1). In patients with probable AMR the hazard ratio for allograft loss was 1.7 (95% CI, 0.8 to 3.5) which is similar to non-rejection cases. The median follow-up post allograft biopsy was 5.0 years.

Study conclusion: This large study confirms the importance of identifying patients with MVI (DSA negative, C4d negative) due to increased risk of graft loss.

Limitations: Immunosuppressive medications varied among centers and were not systematically recorded in the database at each participating location. The study, therefore, cannot assess the relation between clinical outcome and specific treatment.

Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease

Background: Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. The EMPA-KIDNEY trial was published in 2023 [4]. It showed that in patients with chronic kidney disease (CKD) at risk for disease progression, empagliflozin treatment lowered the risk of cardiovascular death and kidney disease progression over a median follow-up of 2.0 years. Current study was done to determine the effects of empagliflozin after drug discontinuation.

Study summary: Patients from the original trial were followed for an additional two years. Open-label prescribing of an SGLT2 inhibitor including empagliflozin was permitted [5]. About three-quarters (4891 patients) of the original study subjects were enrolled. The use of open-label SGLT2 inhibitors in this post-trial interval was not different (about 40%) between the original two groups (empagliflozin and placebo). The primary outcome of the study was cardiovascular death or kidney disease progression from the beginning of the active trial interval to the end of the post-trial interval (median of 4 years). During the combined trial periods, the risk of the composite of death or end-stage kidney disease (ESKD) was 16.9% in the empagliflozin group and 19.6% in the placebo group (hazard ratio, 0.81; 95% CI, 0.72 to 0.90). The risk of cardiovascular death was 3.8% in the empagliflozin group and 4.9% in the placebo group (hazard ratio, 0.75; 95% CI, 0.59 to 0.95). There was no difference between the two groups regarding non-cardiovascular death. During the post-trial period, hazard ratio for the same composite was 0.82 (95% CI, 0.70 to 0.96).

Study conclusion: In patients with CKD at risk for disease progression, empagliflozin treatment continues to show renal and cardiac benefits for up to one-year post empagliflozin discontinuation. The mechanism of this lasting effect is unclear.

Limitations: Patients from Japan were not included. Creatinine measurement was done locally and not centrally. Data regarding hospitalization were not collected.

IgA Nephropathy Trials Background

Up to 20-40% of patients with immunoglobulin A (IgA) nephropathy (IgAN) progress to ESKD within 20 years from disease onset [6]. The "4-hit" hypothesis was proposed to elucidate the pathophysiology of IgAN [7]. First, galactose deficient IgA1 (gd-IgA1) is produced by B cells (B lymphocytes) in the Peyer's patches in the distal ileum and in the mesenteric lymph nodes. Second, anti-gd-IgA1 IgG or IgA1 autoantibodies are produced. Third, circulating immune complexes are formed in the plasma. Fourth, these immune complexes are not cleared efficiently from the plasma, and they deposit in the glomerular mesangium with subsequent complement activation leading to inflammation, interstitial fibrosis, and renal injury. Additionally, two factors are essential in maintaining B cell pool, B-cell-activating factor (BAFF), and A proliferation-inducing ligand (APRIL). Both are produced by the intestinal epithelial cells and dendritic cells. BAFF and APRIL levels in the serum are increased in IgAN. Higher BAFF levels are associated with the severity of histological injury [8,9]. Each FDA (US Food and Drug Administration)-approved or investigational agent for IgAN targets one of the above processes or factors. Currently there are three FDA approved agents for IgAN. All reduce proteinuria in IgAN. Sparsentan is an endothelin and angiotensin II receptor antagonist. Targeting these two receptors is renoprotective. Budesonide delayed release capsules (nefecon) target the production site of gd-IgA1 in the distal ileum. In addition to reduction in proteinuria, nefecon prevents eGFR decline [10]. Iptacopan inhibits the effects of the alternative complement pathway by binding complement Factor B.

As of October 2024 there are 32 clinical trials listed at ClincialTrials.gov investigating treatments for IgAN [11]. Investigational agents for IgAN in phase 3 clinical trials include: ravulizumab (C5 inhibitor), atrasentan (endothelin receptor antagonist), zigakibart (anti-APRIL monoclonal antibody), and atacicept (Anti-B-lymphocyte stimulator [BLys] and APRIL inhibitor) [12]. Felzartamab is an investigational monoclonal antibody targeting CD38 on plasma cells. It reduced proteinuria in IgAN in a phase 2 trial (IGNAZ study, ASN, Kidney Week, 2024, Abstract: SA-0R101). In January 2024, a phase 2 trial of sibeprenlimab, a humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL, showed significant reduction in proteinuria in patients with IgAN [13].

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

Study summary: The trial included 222 patients with biopsy-proven IgAN. All patients were optimized on supportive treatment (angiotensin converting enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARBs]) and continued to have a 24-hour urine protein-to-creatinine ratio (UPCR) ≥1 g/g [14]. Patients were randomized to receive 200 mg of Iptacopan or placebo twice daily for 2 years. A planned interim analysis was done at 9 month. It showed that the mean 24-hour UPCR was 38.3% (95% CI, 26.0 to 48.6) lower with iptacopan compared with placebo. Iptacopan was well tolerated with no difference in adverse events or safety issues in the two groups. The study is still ongoing to determine the effect of Iptacopan on renal function after 2 years of therapy.

Study conclusion: Iptacopan inhibits the alternative complement pathway by binding to Factor B resulting in significant reduction in proteinuria in patients with IgAN on optimized medical therapy.

Limitations: Proteinuria is a surrogate end point, the effect on hard end points such as prevention of eGFR decline will be available in the future. The data are forthcoming.

Efficacy and Safety of Ravulizumab in IgA Nephropathy: A Phase 2 Randomized Double-Blind Placebo-Controlled Trial

Study summary: This is a phase 2 trial investigating the role of ravulizumab, a second-generation complement C5 inhibitor humanized monoclonal antibody in the management of IgAN. This is an analysis from the Study of Ravulizumab in Proliferative Lupus Nephritis or IgA Nephropathy. In this trial, 43 patients were randomized to ravulizumab intravenously every 8 weeks, and 23 patients to placebo for a total of 26 weeks [15]. All patients had biopsy proven IgAN, eGFR ≥30 ml/min per 1.73 m^2, proteinuria ≥1 g/d, and were on supportive treatment with ACE inhibitors or ARBs. All subjects received open-label ravulizumab from week 26-50. At 26 weeks the ravulizumab group had a greater reduction in proteinuria (-41.9%, 95% CI, -50% to -32%) versus placebo (-16.8%, 95% CI, -31.8% to 1.6%). At 50 weeks, proteinuria reduction was sustained in patients who were initially on ravulizumab and was achieved in patients who were on placebo and the switched to ravulizumab. Adverse events were similar in both groups. A phase 3 trial is currently enrolling patients.

Study conclusion: Ravulizumab, a C5 inhibitor, leads to significant reduction in proteinuria in patients with IgAN.

Limitations: this a phase 2 trial with a small number of subjects (N=43), most patients were white (70%), follow up duration was short, and information on eGFR trajectory is not available.

The Selective Endothelin Receptor Antagonist SC0062 in IgA Nephropathy: A Randomized Double-Blind Placebo-Controlled Clinical Trial

Study summary: This is a phase 2 trial investigating the role of SC0062 a selective endothelin receptor type A antagonist in the management of IgAN. This was a dose finding trial in patients with biopsy-proven IgAN with UPCR ≥ 0.75 g/g or proteinuria ≥1 g/24 hour [16]. Patients were on supportive treatment with ACE inhibitors or ARBs. The study enrolled 131 patients, 34 patients randomized to placebo, and 97 to SC0062, 33 patients to 5 mg, 32 patients to 10 mg, and 32 patients to 20 mg. At 24 weeks, placebo-corrected proteinuria changes with 5 mg, 10 mg, and 20 mg SC0062 were −22.4% (95% CI, −42.2 to 4.3), −30.9% (95% CI, −48.6 to −7.0), and −51.6% (95% CI, −64.2 to −34.6), respectively. There was no difference in adverse events among treatment groups including peripheral edema.

Study conclusion: In this phase 2 trial, SC0062, a novel selective endothelin receptor type A antagonist reduced proteinuria in patients with IgAN without increasing the risk of peripheral edema.

Limitations: this a phase 2 trial with a relatively small number of subjects (N=131), follow up duration was short, and information on eGFR decline is not available.

Atrasentan in Patients with IgA Nephropathy

Study summary: This phase 3 study reported on 270 patients with biopsy-proven IgA nephropathy, proteinuria ≥1 g/24 h, and eGFR ≥30 ml/min/1.73 m^2 [17]. Subjects were randomized to 0.75 mg of atrasentan a selective oral endothelin receptor antagonist type A or placebo for 132 weeks. A prespecified interim analysis was done at week 36 showed a greater decline in proteinuria (UPCR) in the atrasentan arm (−38.1%) compared with placebo (−3.1%), (95% CI, -44.6 to -26.4). There were more cases of fluid retention in the atrasentan arm (19) compared to placebo (8), but no cases of heart failure or severe edema.

Study conclusion: Atrasentan, a selective oral endothelin receptor antagonist type A, significantly reduced proteinuria in patients with IgAN compared to placebo.

Limitations: The study duration was only 36 weeks. The majority of patients (>90%) were Asian or White. The results cannot be generalized to other ethnic groups or to patients with proteinuria <1 g/24 h.

Long-Term Results from an Open-Label Extension Study of Atacicept for the Treatment of IgA Nephropathy

Study summary: Atacicept is a fully humanized fusion protein inhibiting BAFF and APRIL. After completion of 36-week double-blind trial, subjects were enrolled in this 60-week open-label extension trial [18]. The duration of the study was 96 weeks, and it enrolled 113 patients. In the extension trial subjects self-injected 150 mg of atacicept subcutaneously once a week. Atacicept results in UPCR reduction (−52%±5%). Additionally, it reduced gd-IgA1 serum levels and hematuria. eGFR slope remained stable.

Study conclusion: Use of Atacicept, a BAFF and APRIL inhibitors, resulted in proteinuria, IgA1 serum level, and hematuria reduction; and eGFR stabilization in patients with IgAN.

Limitations: This is a phase 2 trials with a relatively small number

of patients (N=113). It was open-label with no placebo arm, and only 13% of patients were on an SGLT2 inhibitor at baseline.

Early, Individualized Recommendations for Hospitalized Patients with Acute Kidney Injury

Background: In hospital-acute kidney injury (AKI) is associated with significant morbidity and mortality. Diagnostic and therapeutic recommendations sent via electronic health record (EHR) could impact clinical outcomes.

Study summary: A kidney action team sent alert recommendations via EHR covering several entities (testing, medications, volume status, potassium, and acid-base) [19]. The recommendations were sent within one hour of AKI detection. About 4000 patients in 7 hospitals were randomized to the intervention versus usual care. There was no difference between the 2 groups regarding the need for dialysis or mortality over the following 14 days.

Study conclusion: Alert recommendations by a kidney action team in hospitalized patients with AKI do not reduce the need for dialysis or mortality.

Limitations: It is not clear whether the recommendations given were implemented or whether they were implemented in a timely manner. Subjects were not enrolled at all hours or on weekends.

APOL1 Bi- and Monoallelic Variants and Chronic Kidney Disease in West Africans

Background: Apolipoprotein L1 gene (*APOL1*) risk variants are found in Africans and individuals of African ancestry such as Black Americans. The two risk variants are G1, and G2. Persons with G1/G1 alleles, G2/G2 alleles, or G1/G2 alleles are at increased risk of CKD due to HIV nephropathy, focal segmental glomerulosclerosis (FSGS), and hypertension [20]. In the US, the prevalence of two APOL1 risk alleles in African Americans is approximately 13% [21].

Study summary: The goal of this case-control study was to determine the association of APOL1 variants with CKD in West Africans [22]. The study enrolled 8355 subjects with stages 2 through 5 CKD, biopsy-proven glomerular disease, or no kidney disease. Subjects were from Ghana and Nigeria. The prevalence of one APOL1 risk allele (G0/G1, or G0/G2) was 43%, and of two risk alleles 30%. Subjects with two APOL1 risk alleles had a higher odds of CKD (OR 1.25, 95% CI, 1.11 to1.40), and of FSGS (OR 1.84, 95% CI, 1.30-2.61) compared to subjects with one or no risk alleles. Subjects with one risk allele had a higher odds of CKD (OR 1.18, 95% CI, 1.04-1.33) and FSGS (OR 1.61, 95% CI, 1.04 to 2.48) compared to subject with no risk alleles.

Study conclusion: In this West African population, the presence of one or two APOL1 risk alleles is associated with higher odds of CKD and FSGS.

Limitations: patients were recruited from Ghana and Nigeria; therefore, the results may not be generalizable to other West African countries. Further studies are needed to determine the effect of APOL1 risk variants on progression of CKD.

Semaglutide in Patients with Overweight or Obesity and Chronic Kidney Disease Without Diabetes: A Randomized Double-Blind Placebo-Controlled Clinical Trial

Background: In patients with type 2 diabetes and CKD, semaglutide reduces the risk of major renal events (dialysis, transplantation, an eGFR of <15 ml/min/1.73 m^2, ≥ 50% reduction in eGFR from baseline, or kidney-related death), and death from cardiovascular causes [23]. The effect of semaglutide in patients with CKD without diabetes is unknown.

Study summary: 101 subjects were enrolled [24]. Body mass index was ≥27 kg/m^2, all patients had CKD (eGFR ≥25 ml/min per 1.73 m^2), and urine albumin-to-creatinine ratio (UACR) ≥30 and <3,500 mg/g. Subjects were randomized to weekly 2.4 mg subcutaneous semaglutide injection or placebo for 24 weeks. Reduction of UACR in the semaglutide group compared to placebo was -52% (95% CI, -65% to -33%). Semaglutide resulted in more gastrointestinal adverse events.

Study conclusion: Semaglutide reduced albuminuria in overweight or obese patients with CKD without diabetes.

Limitations: patients with eGFR <25 ml/min/1.73 m^2 were excluded, follow up duration was for 24 weeks only, the number of participants was rather small (n=101).

A Sub-Study of the POISE-3 Randomized Trial Examined Effects of a Perioperative Hypotension-Avoidance Strategy Versus a Hypertension-Avoidance Strategy on the Risk of Acute Kidney Injury

Background: AKI is common post-operative complication. It is unknown whether a peri-operative hypotension-avoidance strategy versus a peri-operative hypertension-avoidance strategy reduces the incidence of postoperative AKI.

Study summary: A pre-specified substudy of the POISE-3 trial was done [25]. Over 7000 patients from 22 countries were enrolled if they were ≥ 45 years old on at least one antihypertensive medication. All patients underwent non-cardiac surgeries. Target intra-operative mean arterial pressure (MAP) was ≥80 mmHg in the hypotension-avoidance strategy, and ≥60 mmHg in the hypertension-avoidance strategy. Inhibitors of the renin-angiotensin-aldosterone system were held in the hypotension-avoidance strategy. Antihypertensive medications were continued in the hypertension-avoidance group. There was no difference in the risk of AKI in the two groups.

Study conclusion: In non-cardiac surgery patients there was no difference in post-operative AKI (about 15% in both groups) with hypotension-avoidance or hypertension-avoidance strategies. Holding inhibitors of the renin-angiotensin-aldosterone system pre-operatively conferred no benefit.

Limitations: The study had a very limited participants with stage 4-5 CKD (eGFR<30 ml/min/1.73 m^2). AKI was defined based on serum creatinine; no biomarkers of renal tubular damage were checked.

Effects of dialysate potassium concentration of 3.0mEq/l with sodium zirconium cyclosilicate on dialysis-free days versus dialysate potassium concentration of 2.0mEq/l alone on rates of cardiac arrhythmias in hemodialysis patients with hyperkalemia

Background: The optimal management of serum potassium and dialysate potassium in hemodialysis patient is unclear. Hypokalemia is a risk factor for atrial fibrillation (AF) and cardiac arrhythmias [26,27].

Study summary: The study enrolled 88 patients on thrice weekly hemodialysis and hyperkalemia on two pre-dialysis measurements [28]. All patients had an implantable cardiac loop recorder placed. The intervention was sodium zirconium cyslosilicate (SZC) 5-15 g on non-dialysis days to maintain a predialysis serum K 4.0-5.5 mEq/L. Patients were randomized to group A: 2.0K/2.5Ca mEq/L dialysate without SZC for 8 weeks, followed by 3.0K/2.5Ca mEq/L dialysate with SZC for an additional 8 weeks, or group B (the reverse order of group A). AF was lower with 3.0 K/SZC versus 2.0K/no SZC (rate ratio 0.52, 95% CI, 0.41 to 0.65), the same was true for clinically significant cardiac arrhythmias (rate ratio 0.47, CI 0.38 to 0.58). Hypokalemia was less frequent with 3.0 K/SZC (33 patients) versus 2.0 K/no SZC (58 patients).

Study conclusion: In hyperkalemic hemodialysis patients combining SZC on non-dialysis days with potassium 3.0 mEq/L bath reduces clinically significant cardiac arrhythmias and AF, compared to potassium 2.0 mEq/L bath and no SZC.

Limitations: The number of participants is small, the follow up duration is short, and the treatment group assignment was not blinded.

Conclusion

The advances in the field of nephrology are accelerating. The mechanisms of various glomerular and genetic renal diseases are being elucidated. These advances in basic science are propelling novel medications with the potential of impacting patient care. The excitement in the renal community is palpable. The road ahead is still full of challenges including the prohibitively high prices of newer medications which is a formidable obstacle in countries with limited resources; the need to extend the trials to prove a positive effect on hard endpoints such as eGFR slope, the need for kidney replacement therapy, hospitalizations, and cardiovascular death; designing comparative head-to-head or drug combination clinical trials; and examining the role of new therapies in combination with new standard of care medications such as SGLT-2 inhibitors, and non-steroidal mineralocorticoid receptor antagonists that were not available or commonplace at the time of study enrollment.

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