American Society of Nephrology Kidney Week 2019

Key outcomes and highlights

High Impact Clinical Trials

Pooled Efficacy and CV Safety Results of Roxadustat in the treatment of Anemia in CKD patients on and not on dialysis (Provenzano et al.)

- Roxadustat is an oral hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that stimulates erythropoiesis and regulates iron metabolism by mimicking the body's natural response to low oxygen
- **Study populations:**
  - Non-dialysis dependent (NDD) CKD pool: placebo comparator
  - Dialysis dependent (DD) CKD pool: epoetin alfa comparator
    - Incident dialysis (ID) pool: clinically important subgroup of DD pool
- Pooled analysis of global phase 3 trials on Roxadustat: number of patients 4277 in NDD pool and 3880 patients in the DD pool.
- NDD group: Primary efficacy endpoint (change in Hb from baseline to Hb averaged over weeks 28-52) was met in individual studies and pooled analyses, showing roxadustat to be superior to placebo, regardless of iron repletion. Mean change in Hb 1.85 (Roxadustat) vs. 0.13 (placebo); $p < 0.001$.
- DD group: Roxadustat achieved larger Hb increase over epoetin alfa in individual studies and in pooled analyses (mean change in Hb 1.22 vs. 0.99, $p < 0.001$)
- Roxadustat achieved higher Hb increase in patients with inflammation (CRP >ULN) and in patients without inflammation (CRP ≤ ULN), compared to epoetin alfa. Less IV iron was required in roxadustat patients than in patients on epoetin alfa
- Cardiovascular safety endpoints: Risk of MACE (Major Adverse Cardiovascular Events) and all-cause mortality in roxadustat patients were not increased when measured against comparators in both dialysis and non-dialysis patients.
- In the incident dialysis group, there was 30% lower risk of MACE in Roxadustat group compared with EPO group

Angiotensin-Neprilysin Inhibition in Heart failure with preserved ejection fraction (Solomon 2019)

- 4800 patients followed for 36 months
- Comparator: valsartan vs. valsartan / sacubitril (entresto)
- Primary outcome: No difference in heart failure admissions or CV death
- Renal outcomes: Entresto group showed an attenuation in decline in renal function; reduced composite renal outcome 1.4 vs 2.7%, HR 0.5, p=0.002
- Benefits of cardiovascular outcomes were more pronounced in those patients with lower baseline eGFRs (note: patients with eGFR <30 were excluded)

Dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF)

(McMurray 2019)

- Phase 3 placebo controlled trail, 4774 patients
- Comparator: Dapagliflozin (DAPA) 10mg daily vs. placebo
- 45% of patients had T2DM
- Reduced primary endpoint (composite of worsening heart failure or CV death) in DAPA group (6.3% vs. 21.2% HR 0.74, p<0.001)
- Lower renal composite outcome but not statistically significant (1.2% vs. 1.6%, HR 0.71, p=ns)

Difelikefalin in Haemodialysis patients for pruritis - KALM-1 Phase 3 study (Fishbane 2019)

- Difelikefalin is a peripherally restricted and selective agonist at the kappa opioid receptor.
- It does not bind to the mu receptor and therefore does not have the euphoric effects of usual opioid agonists, furthermore it doesn't cross the blood brain barrier.
- Double blinded-placebo controlled randomised trial of 378 Haemodialysis patients with moderate or severe pruritis randomised to Difelikefalin 0.5mg/kg IV after dialysis vs. placebo
- Results: The imputed percentage of patients with ≥ 3 points decrease in the Worst itching Intensity numerical Rating Scale (WI-NRS) was 49.1% in the difelikefalin group compared with 27.9% in placebo group (p<0.001)

NOBILITY trial for obinutuzumab vs standard of care in Lupus nephritis – Phase 2 Trial (Schindler 2016)

- Obinutuzumab is an anti-CD20 type II monoclonal
- 104 week trial, obinutuzumab 1000mg vs. standard MMF + steroids
- Lupus proliferative GN patients, RPGN or chronic damage excluded based on biopsy
- Overall response 51% vs. 29% at 76 weeks favouring obinutuzumab group
- Complete renal response 40% vs 18% at 74 weeks favouring obinutuzumab group
- 104 week data will be available soon

Athena trial

- Mycophenolate vs. Azathioprine in low dose cyclosporine (CsA) and steroid free renal transplant patients with low immune risk
- Chronic allograft nephropathy at 3 years and incidence of biopsy proven rejection did not differ between the two groups
- However, it was a small powered study with high overall rates of chronic allograft nephropathy and 30% rates of rejection in both arms

References

Solomon, S., McMurray, J., Anand, I., Ge, J., Lam, C., Maggioni, A., … Lefkowitz, M. (2019). Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. The New England Journal of Medicine, 381(17), 1609–1620. https://doi.org/10.1056/NEJMoa1908655

McMurray, J., Solomon, S., Inzucchi, S., Køber, L., Kosiborod, M., Martinez, F., Langkilde, A. et al. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine, 381(21), 1995–2008. https://doi.org/10.1056/NEJMoa1911303

Fishbane, S., Jamal, A., Munera, C., Wen, W., & Menzaghi, F. (2019). A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. The New England Journal of Medicine. https://doi.org/10.1056/NEJMoa1912770

Schindler, T., Rovin, B., Furie, R., Leandro, M., Clark, M., Brunetta, P., & Garg, J. (2016). AB0423 Nobility, A Phase 2 Trial To Assess The Safety and Efficacy of Obinutuzumab, A Novel Type 2 Anti-CD20 Monoclonal Antibody (MAB), in Patients (PTS) with ISN/RPS Class III or IV Lupus Nephritis (LN). Annals of the Rheumatic Diseases, 75(s2), 1051–1051. https://doi.org/10.1136/annrheumdis-2016-eular.2397