Tyrosine kinase inhibition shows promise in diabetic nephropathy

JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial


Diabetic nephropathy is the most common cause of chronic kidney disease worldwide and a dominant cause of end-stage renal disease (ESRD). In addition to angiotensin system inhibitors (ACE and ARB), sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are also now known reduce albuminuria and improve renal outcomes. However, additional therapies are still needed. Diabetic nephropathy is characterised by inflammation, partly mediated by the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway. Baricitinib is an oral, small-molecule inhibitor of JAK1 and JAK2. This randomized, placebo-controlled, double-blind, dose-ranging Phase 2 trial was conducted to test the efficacy of baricitinib in participants at high risk for progression of diabetic nephropathy. One hundred and twenty-nine participants with an eGFR of 25–70 ml/min/1.73m² and macroalbuminuria were randomized in equal numbers to placebo or one of four different doses of baricitinib (0.75mg daily, 0.75mg twice daily, 1.5mg daily and 4mg daily). The 4mg baricitinib arm experienced a 41% (95%CI 7, 62; P=0.022) decrease in urine albumin–creatinine ratio at 24 weeks (UACR) compared with placebo. Significant decreases in UACR were also observed with the 1.5mg daily dose. In addition, there was dose-dependent decrease in inflammatory biomarkers (urinary CXCL10, urinary CCL2, plasma sTNFR1 and sTNFR2, SAA, ICAM1 and VCAM1). Anemia was more common in the 4mg dose group than placebo (8/25 participants vs. 1/27). Although this targeted approach has yielded promising results in this small early phase study, it remains to be seen if baricitinib will eventually find a place among the small number of agents with proven ability to modify the course of diabetic nephropathy.

Despite lowering HbA1c, linagliptin provides no benefit in patients with T2DM and CKD

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial


Given the high risk of cardiovascular events in patients with type 2 diabetes (T2DM) it is essential that the cardiovascular risks and benefits of novel hypoglycemic agents are well understood. Previous studies have suggested that the dipeptidyl peptidase-4 (DPP-4) inhibitor, linagliptin, might result in a lower incidence of adverse cardiovascular and renal outcomes. To test this hypothesis the CARMELINA study investigators randomized 6979 participants with a history of vascular disease and renal disease (either eGFR 45-75 ml/min/1.73m² with albuminuria >200mg/mmol or ≤ 45 ml/min/1.73m² with at least microalbuminuria) to 5mg linagliptin or placebo. Over a median of 2.2 years of follow up, HbA1c was lower by 0.36% (95%CI 0.29, 0.42) in the linagliptin group. However, there was no difference in time to the primary outcome of cardiovascular death, myocardial infarction or stroke (absolute incidence rate difference 0.13 per 100 patient-years [95%CI -0.63, 0.90]), nor were there differences in the incidence of adverse renal events (ESRD, renal death or ≥ 40% decline in eGFR) (absolute incidence rate difference 0.22 per 100 patient-years [95%CI -0.52, 0.97]). There was a significant reduction in the incidence of albuminuria progression (-3.18 per 100 patient-years [95%CI -5.59, -0.97]). No differences in adverse events or overall mortality were
observed. These results are consistent with the results of previous large studies finding no clear cardiovascular benefits with DPP-4 inhibitors. Some, but not all, DPP-4 inhibitors have been shown to reduce albuminuria, however no impact on hard renal endpoints has yet been reported.

**Intensive immunosuppression improves short-term remission rates in lupus nephritis**

*Combined immunosuppressive treatment (CIST) in lupus nephritis: a multicenter, randomized controlled study*


Many patients with lupus nephritis (LN) still fail to achieve remission with standard treatment of glucocorticoids and either mycophenolate or cyclophosphamide. Novel biological agents hold promise but are expensive. An, et al. sought to determine if a more intensive immunosuppressive regimen with lower cost existing agents could improve outcomes. They enrolled 191 participants with a clinical diagnosis of systemic lupus erythematosus and at least 1.5g/day proteinuria (with or without hematuria or biopsy proven LN). Nineteen-five were randomized to cyclophosphamide, hydroxychloroquine and an additional agent (mycophenolate [n=30], azathioprine [n=9] or leflunomide [n=57]), and 96 to cyclophosphamide alone. Both groups received glucocorticoids. At 24 weeks, complete remission (proteinuria < 150mg/day and normal renal function and urine sediment) was more frequent in the combination immunosuppression arm vs. cyclophosphamide alone (39.5% vs. 20.8%; P<0.05). Similarly, treatment failure (i.e. lack of at least partial remission) was less frequent (12.8% vs. 31.2%; P<0.001). No difference in severe adverse events was reported. This trial is limited by the lack of biopsy confirmed diagnosis and the loss of 28 participants (15%) to follow up. Its relatively small size and short duration of follow up also mean that the long-term effects from combined immunosuppression cannot be assessed. While the results suggest that remission may be achieved earlier with more intensive immunosuppression, it is not clear if long-term achievement and maintenance of remission would be improved with this approach.

**New calcimimetic on the block demonstrates efficacy**

*Head-to-head comparison of the new calcimimetic agent evocalcet with cinacalcet in Japanese hemodialysis patients with secondary hyperparathyroidism*


Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease. First line therapy of phosphate binders and vitamin D receptor activators may be insufficient to prevent progression of SHPT or may result in side effects. Cinacalcet – a calcimimetic agent – results in higher achievement of target serum PTH, calcium, and phosphorus levels and reduces the need for parathyroidectomy. This double-blind study randomized 639 hemodialysis patients with PTH > 240 pg/ml (>25 pmol/l) (after at least 2 weeks cinacalcet wash-out) to evocalcet, a new oral calcimimetic agent, or cinacalcet. Both agents were titrated to effect according to study protocol. The evocalcet group was similar to the cinacalcet group with 72.7% and 76.7% of participants achieving the primary endpoint of a mean intact parathyroid hormone level of 60-240 pg/ml [6-25pmol/l]. The between group difference of -4.0% (95%CI -11.4%, 3.5%; P=0.002) was within the prespecified non-inferiority margin. Evocalcet was superior when it came to gastrointestinal-related adverse events with a between-group difference of -14.2% (95%CI -20.9%, -7.5%; P<0.001). The study was limited by loss to follow up of 18% of the cohort, although multiple imputation of missing data did not change the outcome. This study suggests that evocalcet is as effective as cinacalcet in achieving target PTH, although long-term data and, ultimately, evidence of improvements in hard clinical endpoints is still lacking.
Topiroxostat may reduce albuminuria in chronic kidney disease
Renoprotective effects of topiroxostat for Hyperuricaemic patients with overt diabetic nephropathy study (ETUDE study): A prospective, randomized, multicentre clinical trial
Previous studies have suggested that lowering of uric acid may slow progression of chronic kidney disease (CKD), although the results of ongoing trials are required to clarify this issue further. Topiroxostat, a selective xanthine oxidase inhibitor, has been shown not only to lower uric acid levels, but also to decrease the urinary albumin-creatinine ratio (UACR). The ETUDE study compared the effects of high or low-dose topiroxostat when added to standard therapy in hyperuricemic patients with diabetic nephropathy at high risk of progression. Eighty participants with an eGFR ≥ 20 ml/min/1.73m² and macroalbuminuria were randomized to high dose topiroxostat (160 mg daily) or low dose (40mg daily). Compared to baseline, those in the high dose arm had a significant reduction in UACR after 24 weeks (-13.8 mg/mmol [95%CI -27.1, -0.6; P=0.041]), with a non-significant decrease in UACR with the low dose (40mg) arm (-22.8 mg/mmol [95%CI -47.2, 1.6; P=0.067]). This small study is limited by the lack of a placebo arm or blinding. Moreover, the reductions in UACR were small and the long-term safety and efficacy remains unclear.