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Introduction: Suboptimal glycemic control is often associated with albuminuria and decline in estimated GFR (eGFR) in patients with diabetic kidney disease (DKD). Sodium-glucose linked transporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors have individually been shown to exert benefit on glycemic control and/or albuminuria in patients with DKD. We assessed the effects of the SGLT2 inhibitor dapagliflozin (dapa) alone and in combination with the DPP4 inhibitor saxagliptin (saxa) on albuminuria and HbA1c in patients with Type 2 diabetes and DKD.

Methods: The trial enrolled patients from nine countries (Australia, Canada, Japan, Republic of Korea, Mexico, South Africa, Spain, Taiwan, and the United States of America). Inclusion criteria comprised urinary albumin-to-creatinine ratio (UACR) 30–3500 mg/g, eGFR 25–75 mL/min/1.73 m2, HbA1c 7–11%, and stable doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and glucose lowering treatment for ≥12 weeks. After a 4-week single blind placebo run-in period, 448 eligible patients were randomized (1:1:1) to dapa 10 mg, dapa 10 mg/saxa 2.5 mg combination or placebo once daily for 24 weeks. Type 1 error control allowed for separate comparisons between dapa and placebo separate hierarchical test procedures were used for inference. The primary endpoint for dapa was percent change in UACR from baseline to Week 24; co-primary endpoints for dapa/saxa were percent change in UACR from baseline and change from baseline in HbA1c. Primary comparisons with placebo corresponded to Week 24 differences in least square mean estimates obtained from mixed models for repeated measures. Safety was assessed throughout (adverse events [AEs] and laboratory data).

Results: Both dapa alone and dapa/saxa significantly reduced UACR compared to placebo. This effect was sustained over the study period; at Week 24, change in UACR versus placebo was −21.0 (−34.1–−5.3; p = 0.011) and −38.0% (−48.2–−25.8; p < 0.001) for the two arms, respectively. Dapa/saxa also significantly reduced HbA1c compared to placebo: at Week 24, change in HbA1c was −0.58% (−0.80–−0.37); p < 0.001. Dapa and dapa/saxa were well-tolerated and no new drug-related safety signals were observed. AEs occurred in 79 (54.5%), 104 (68.4%) and 81 (54.7%) patients in the dapa, dapa/saxa and placebo arms, respectively, and serious AEs in 12 (8.3%), 13 (7.9%) and 16 (10.8%) patients; 4 (2.8%), 7 (4.6%) and 8 (5.4%) patients discontinued due to AEs. Two deaths occurred, one in each treatment group.

Conclusions: Both dapa and dapa/saxa conferred significant improvements in albuminuria, with dapa/saxa additionally conferring a clinically significant reduction in HbA1c at Week 24 in patients with DKD.

The DELIGHT study (clinicaltrials.gov NCT02547935) was sponsored by AstraZeneca.

SAT-302 INHIBITION OF COMPLEMENT CSA/C5A RECEPTOR 1 DECREASES RENAL INJURY IN DIABETIC KIDNEY DISEASE VIA METABOLIC REPROGRAMMING

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Introduction: The complement system plays a central role in the activation of innate immunity, inflammation and tissue remodelling. The complement fragment CSA/C5a receptor CSAr1 is a key inflammatory and tissue remodelling. We have shown complement activation in patients with diabetes including renal deposition of the canonical CSA receptor CSAr1 and CSA/C5r1 activation in experimental diabetes. This study aimed to determine whether genetic deletion or pharmacological inhibition of CSAr1 could confer renoprotection in diabetes.

Methods: Streptozotocin (STZ)-induced diabetic C57BL/6 mice were treated with the highly selective CSAr1 antagonist, PMX53 (2mg/kg/day) in drinking water for 24 weeks (n=10). CSAr1 deficient mice (C5ar1−/−) and their wild type littermates were rendered diabetic with STZ and followed for 24 weeks (n=10). Kidney injury was assessed by urinary albumin excretion and glomerulosclerosis (GSI). Immunohistochemistry for Collagen IV, FoxP3+ regulatory T cells and F4/80+ macrophages was performed. Transcriptomics of renal cortex was performed by RNA-sequencing using the Illumina platform and pathway analyses using Gene Set Enrichment Analysis. Lipidomics of renal cortex was performed using liquid chromatography electrospray ionization tandem mass spectrometry.

Results: Diabetic C5ar1−/− mice showed protection against renal injury with decreased albumin excretion. Treatment of diabetic mice with PMX53 led to a reduction in albuminuria, inhibition of glomerular injury and resolution of inflammation via a decrease in F4/80+ macrophages and activation of FoxP3+ regulatory T cells. Transcriptomic analyses showed that the diabetes gene signature was reversed by PMX53. Pathways that were reduced by PMX53 in diabetic mice were related to mitochondrial function and lipid metabolism. The top gene downregulated in the diabetic kidney was acyl-CoA dehydrogenase 10 (Acad10), which participates in fatty acid β-oxidation in mitochondria. Blockade of C5ar1 signalling in diabetic mice restored Acad10 expression. Lipidomics analyses revealed a dysregulation of acylcarnitine profile in the diabetic kidney, as well as pathological

160°C for 1 hour), with or without 25% resistant starch (RS) for 10 weeks. All diets were isocaloric. 24-hour urine was collected for the assessment of albuminuria. At 16 weeks of age, intestinal permeability was assessed in vivo by the clearance of FITC-labelled dextran (500mg/kg body weight). Cecal contents were collected and the V3-V4 region of the bacterial 16S rRNA gene were sequenced.

Results: The high AGE diet exacerbated albuminuria in diabetic mice (874±115 vs 536±196μg/24h, P < 0.05, db/db H vs db/db L), and this was attenuated by RS (874±115 vs 515±72μg/24h, P < 0.05, db/db H vs db/db H+RS). Db/db mice had increased gut permeability compared to db/m mice (3.28±0.32 vs 1.05±0.11μg/ml, P < 0.01, db L vs db/m). Furthermore, the high AGE diet increased gut permeability of db/db mice (3.43±0.43 vs 2.38±0.32μg/ml, P < 0.05, db/db H vs db/db L), an effect not observed in high AGE and RS-fed db/db mice (2.38±0.32 vs 2.77±0.30μg/ml, P > 0.05, db L vs db/db H+RS). In db/db mice, a high AGE diet was associated with an increase in the Firmicutes/Bacteroidetes (F/B) ratio (0.82±0.2 vs 0.33±0.1, P < 0.05, db/db H vs db/db L), which was ameliorated by supplementation with RS (0.82±0.2 vs 0.21±0.1, P < 0.01, db/db H vs db/db H+RS).

Conclusions: A high AGE diet led to increased intestinal permeability, an increase in F/B ratio, and worsening albuminuria in db/db mice. Resistant starch was protective against high AGE induced albuminuria in db/db mice. These preliminary studies support the notion that dietary AGES contribute to renal disease via alterations in gut homeostasis and suggest a potential role for resistant starch as a renoprotective agent.