Prophylactic and therapeutic tenapanor are vascular protective in a rat model of chronic kidney disease

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Overview and conclusions

- Tenapanor is a minimally systemic, small-molecule inhibitor of the sodium/hydrogen exchanger NHE3. Tenapanor is in development for renal and constipation-related indications.
- We evaluated the cardiovascular protective effects of prophylactic (Px) and therapeutic (Tx) tenapanor in a rat model of renal-insufficiency-induced, salt-sensitive arterial hypertension and chronic kidney disease (CKD).
- Compared with healthy controls (HCs), disease controls (DCs) had abnormal levels of urinary biomarkers and increased blood pressure, as well as impaired arterial vasorelaxation and vasoconstrictor function, and endothelial dysfunction at week 2 and week 6.
- Px tenapanor prevented and Tx tenapanor reversed existing renal-insufficiency-associated, disease-control-induced proteinuria and albuminuria, as well as reducing urinary sodium and phosphate excretion.
- At week 6, Px and Tx tenapanor treatment normalized or reduced arterial hypertension, vascular stiffness, vasoconstrictor function, and endothelium dependent and independent vasorelaxation.
- The benefit of Tx treatment was similar to that elicited by Px use, suggesting potential for reversal of existing disease.

Background

- Tenapanor (AZD1722, RDX7951) is an inhibitor of NHE3 (also known as SLC9A3).
  - NHE3 plays an important role in intestinal sodium/hydrogen homeostasis.
  - Preclinical and volunteer studies have shown that tenapanor treatment reduces absorption of dietary sodium and phosphate. (See Fillis et al. for oral presentation and other papers at this meeting.)
- By reducing absorption of sodium and phosphate, it may be hypothesized that treatment with tenapanor has the potential to influence a number of pathways involved in increasing cardiovascular risk in patients with CKD (Figure 1).
- The aim of this study was to investigate the cardiovascular protective effects of Px and Tx tenapanor in a rat model of renal-insufficiency-induced, salt-sensitive arterial hypertension and CKD.

Methods

- 5/6 nephrectomized Sprague-Dawley rats were fed 4% NaCl chow to induce salt-sensitive hypertension.
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- The aim of this study was to investigate the cardiovascular protective effects of Px and Tx tenapanor in a rat model of renal-insufficiency-induced, salt-sensitive arterial hypertension and CKD.

Results

- Tenapanor is a minimally systemic, small-molecule inhibitor of the sodium/hydrogen exchanger NHE3. Tenapanor is in development for renal and constipation-related indications.
- We evaluated the cardiovascular protective effects of prophylactic (Px) and therapeutic (Tx) tenapanor in a rat model of renal-insufficiency-induced, salt-sensitive arterial hypertension and chronic kidney disease (CKD).
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References


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Disclosures