Reaching a XENITH in cardiorenal protection

Zibotentan, a developmental endothelin A receptor antagonist, in combination with dapagliflozin in SGLT2 inhibitor-naïve patients, was effective in reducing albuminuria in people with chronic kidney disease (CKD) already on optimised RAAS blockade in the XENITH-CKD trial published in the *Lancet*. In this randomised, active-controlled, phase 2b clinical trial, adults with CKD, an eGFR of ≥20 mL/min/1.73 m² and a uACR of 150–5000 mg/g (approximately 17–565 mg/mmol) were randomised to 12 weeks of treatment with zibotentan 1.5 mg daily (high dose; *N*=179), zibotentan 0.25 mg (low dose; *N*=91) or placebo (*N*=177), all in combination with dapagliflozin 10 mg daily, and in addition to full doses of an ACE inhibitor or ARB if tolerated. At 12 weeks, compared with placebo, there was a significant 33.7% reduction in uACR in the high-dose zibotentan group and a 27% reduction in the low-dose group. Fluid retention had been identified in previous studies of endothelin A antagonists; therefore, weight and B-type natriuretic peptide were monitored during the study and demonstrated fluid retention event rates of 18% with high-dose zibotentan and dapagliflozin, 9% with low-dose zibotentan and dapagliflozin, and 8% with dapagliflozin alone.

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Chronic kidney disease (CKD) is defined as an eGFR <60 mL/min/1.73 m² or a urinary ACR >3 mg/mmol persisting for at least 90 days. If albuminuria is present, current management includes blood pressure control, RAAS blockade with an ACE inhibitor or ARB, and an SGLT2 inhibitor to slow CKD progression and help reduce the high cardiovascular risk (NICE, 2021; NICE, 2022). However, in clinical studies, people with CKD managed with optimal RAAS blockade and an SGLT2 inhibitor continue to have high residual risk of renal progression and cardiovascular death; therefore, additional treatments are needed. Finerenone should also be considered to reduce CKD progression and cardiovascular risk for those with type 2 diabetes and albuminuria (NICE, 2023).

Endothelin 1 is a potent vasoconstrictor discovered more than 30 years ago and involved in the development and progression of CKD and its associated cardiovascular complications. In the SONAR study, atrasentan, an endothelin A receptor antagonist, reduced renal events in people with type 2 diabetes (Heerspink et al, 2019). However, studies of endothelin A or mixed endothelin A/B receptor antagonists have failed to show benefits for cardiovascular disease, so these agents are currently only licensed for pulmonary arterial hypertension and scleroderma digital ulceration.

The phase 2b clinical trial reviewed here, ZENITH-CKD, compared treatment for 12 weeks with two different doses of zibotentan, an endothelin A receptor antagonist currently in development, in 477 people with CKD. Participants were required to have an eGFR ≥20 mL/min/1.73 m² and significant albuminuria, with a uACR of 150–5000 mg/g (approximately 17–565 mg/mmol). All were being treated with optimal doses of an ACE inhibitor or ARB at study initiation.

Zibotentan 1.5 mg or 0.25 mg once daily, both combined with dapagliflozin 10 mg once daily, was compared with dapagliflozin 10 mg daily plus placebo. The primary outcome was change in uACR, as a measure of CKD progression.

Results

At the end of the 12 weeks of treatment, compared to participants treated with dapagliflozin 10 mg alone (*N*=177), uACR

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was 34% lower in the group treated with zibotentan 1.5 mg and dapagliflozin (*N*=179), and 27% lower in those treated with zibotentan 0.25 mg and dapagliflozin (*N*=91). These benefits occurred in people with and without type 2 diabetes and in those with an eGFR above or below 45 mL/min/1.73 m^2. However, the trial was short and had a surrogate endpoint, so long-term benefits on renal outcomes are unknown.

Fluid retention is recognised as a treatment-limiting side effect of endothelin receptor antagonists, and in this study there was no difference between the group receiving low-dose zibotentan/dapagliflozin or dapagliflozin/placebo, with rates of 9% and 8%, respectively. However, increased rates of fluid retention (18%) and a small number of heart failure events were seen in those receiving zibotentan 1.5 mg and dapagliflozin. In the discussion, the authors felt that careful dose-ranging studies would be needed to optimise benefit while minimising fluid retention, and that this class of drug may need to be co-prescribed with a diuretic in some cases, as well as with an SGLT2 inhibitor to minimise fluid retention and heart failure.

Compared with dapagliflozin alone, both doses of zibotentan appeared to reduce systolic blood pressure (by 3.6 and 7.6 mmHg with the low and high doses), diastolic blood pressure (3.0 and 5.4 mmHg, respectively) and LDL-cholesterol. However, it was felt that the reduction in albuminuria was due to endothelin inhibition rather than to any blood pressure-lowering effect. Endothelin A receptor antagonism has previously been demonstrated to reduce LDL-cholesterol by reducing PCSK9 concentrations (Farrah et al, 2019).

Commentary

Writing in an accompanying comment, Dhaun and Chapman (2023) identified that there were more people with known heart failure in the dapagliflozin/placebo group than in the other two groups. Additionally, in view of previous concerns regarding fluid retention triggering heart failure in those treated with endothelin receptor antagonists, those with increased B-type natriuretic peptide (BNP) levels were excluded from the study, whereas BNP would not routinely be measured in people with CKD. They also cautioned that to fully interpret the blood pressure and lipid-lowering data, it would be important to know about new treatment initiations during the 12 weeks of the study. They also raised the question of whether sequential initiation of RAAS, SGLT2 and endothelin inhibition may be as effective as and more economical than initiating the SGLT2 and endothelin inhibition at the same time, as was done in this study; however, this would require head-to-head trials to determine. In the meantime, zibotentan will progress to phase 3 studies alongside use of RAAS and SGLT2 inhibitors.

We already have work to do to make certain that we diagnose CKD promptly, code accurately, ensure blood pressure targets are met, titrate RAAS blockade up to optimal doses and ensure that SGLT2 inhibitors are prescribed irrespective of their need for glucose lowering, as well as identifying those with type 2 diabetes and albuminuria who would additionally benefit from finerenone. It is likely that an audit would reveal that we all have people who would benefit from timely reviews and optimisation of lifestyle and current medications. Let's ensure we tackle this while awaiting further evidence on this new use for endothelin receptor antagonists. ■

Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD)

Click here to access the study in full

Dhaun N, Chapman GB (2023) Endothelin antagonism: Stepping into the spotlight. *Lancet* 2 Nov [Epub ahead of print]. https://doi.org/10.1016/S0140-6736(23)02419-4

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