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RESEARCH LETTER

Effects of atrasentan on markers of liver function in patients with type 2 diabetes and chronic kidney disease

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1 | BACKGROUND

Some endothelin receptor antagonists (ERAs), whether targeting only the endothelin A receptor or both endothelin A and B receptors, are associated with elevated markers of liver injury.[1] The hepatotoxicity has generally been modest; however, one ERA, sitaxsentan, caused serious drug-induced liver injury (DILI), resulting in fatalities.[2] The mechanism of ERA hepatotoxicity is not fully understood but probably relates, at least partly, to effects on hepatobiliary transporters and metabolism.[3] In addition, ERA chemical structure may be a factor. Bosentan, a sulphonamide-based ERA, is associated with an increased incidence of elevated liver transaminases (> 3 x the upper limit of normal [ULN]).[1] By contrast, macitentan, a sulphatide-based ERA, is not associated with elevated markers of liver injury.[1] Further, ambrisentan, a carboxylic acid-based ERA, is associated with reduced episodes of elevated liver transaminases.[1] Studies using cultured human hepatocytes have corroborated these clinical observations, finding that bosentan > macitentan > ambrisentan reduced hepatobiliary transporter activity (and presumably promoted intracellular bile salt accumulation).[3] Atrasentan is a selective endothelin receptor A antagonist that reduces the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease (CKD)[4]; however, no studies have reported the hepatotoxic effects of atrasentan, a carboxylic acid. Consequently, the current study assessed the effects of atrasentan on markers of liver function and liver-related adverse events.

2 | METHODS

This study constitutes a prespecified analysis of the SONAR trial; the primary results, study design and patient characteristics have been described.[4] The trial was conducted at 689 clinical practice sites in 41 countries; the ethics committees from each participating centre approved the study protocol before any study-specific procedures commenced. Inclusion criteria included age 18-85 years, presence of type 2 diabetes, an estimated glomerular filtration rate (eGFR) of 25-75 mL/min per 1.73m^2, a urine albumin-to-creatinine ratio (UACR) of 300-5000 mg/g and brain natriuretic peptide (BNP) of less than 200 pg/mL. All patients were on stable doses of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks prior to enrolment. Exclusion criteria included alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevated to at least three times ULN, or advanced liver disease with a life expectancy of less than 1 year. All patients initially received 0.75 mg/day atrasentan during a 6-week enrichment period. Patients with 30% or higher (responders, N = 2648) and less than 30% (non-responders, N = 1020) UACR reduction from baseline with no signs of fluid retention (defined as an increase in body weight ≥ 3 kg or increase in BNP ≥ 300 pg/mL) were randomly assigned to 0.75 mg/day atrasentan or placebo. The median total follow-up period was 2.2 years.

The effects of atrasentan compared with placebo on the mean change from baseline in ALT, AST, alkaline phosphatase (ALP) and bilirubin were assessed using an ANCOVA model adjusted for the respective baseline values. Data for responders and non-responders were combined. We summarized investigator-reported liver-related treatment-emergent adverse events (TEAEs) by treatment group and searched for potential cases of Hy's law (AST or ALT > 3 x ULN and total bilirubin > 2 x ULN, absence of evidence of cholestasis, and no other explanation for liver injury). The liver-related TEAEs were self-defined by healthcare providers.

TABLE 1 Baseline characteristics of study participants

	Atrasentan, n = 1834	Placebo, n = 1834
Age, y	64.6 (8.8)	64.4 (8.8)
Female sex, n (%)	458 (25.0)	488 (26.6)
Systolic blood pressure, mmHg	133.3 (15)	133.3 (15)
Diastolic blood pressure, mmHg	71.7 (10)	71.4 (10)
HbA1c, %	7.6 (1.4)	7.6 (1.5)
eGFR, ml/min/1.73m^2	42.3 (14)	42.4 (14)
UACR, mg/g (median)	838	826
Liver disease, n (%)	103 (5.6)	101 (5.5)
Hepatitis, n (%)	45 (2.5)	31 (1.7)

Note: Values in parentheses are standard deviation unless stated otherwise.
Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; UACR, urine albumin-to-creatinine ratio.

3 | RESULTS

A total of 3668 subjects were randomized to atrasentan (N = 1834) or placebo (N = 1834). At baseline, the mean (SD) age was 64.5 (9) years, eGFR was 42.3 (14) mL/min/1.73m^2 and median UACR was 829 (25th to 75th percentile 457-1556) mg/g. At baseline, 204 (5.6%) and 76 (2.1%) participants reported liver disease (excluding hepatitis) and hepatitis, respectively (the specific aetiologies of liver disease or hepatitis were not reported). There were no differences between atrasentan and placebo groups at baseline in any of the above variables (Table 1). Atrasentan compared with placebo statistically significantly reduced ALT, AST and ALP (Table 2). The numbers of participants with a liver-related TEAE in the atrasentan and placebo groups were not significantly different: 57 (3.1%) and 52 (2.8%), respectively, resulting in an exposure-adjusted incidence rate of 1.6 and 1.4 per 100 person-year follow-up, respectively. No cases meeting Hy's Law or with rare, severe, DILI were observed with atrasentan treatment in SONAR.

4 | DISCUSSION

In this post hoc analysis of the SONAR trial, patients with type 2 diabetes and CKD, who are at high risk of liver disease, had no evidence

TABLE 2 Effect of atrasentan on markers of liver function

	Atrasentan, n = 1834	Placebo, n = 1834	*P*
Alanine transaminase (U/L)			
Baseline, mean (SD)	21.8 (14)	21.1 (13)	
End of treatment, mean (SD)	19.5 (12)	20.5 (16)	
Change from baseline, mean (95% CI)	−2.2 (−2.7, −1.6)	−0.7 (−1.3, −0.1)	
Difference, mean (95% CI)	−1.5 (−2.3, −0.7)		< .001
Aspartate transferase (U/L)			
Baseline, mean (SD)	20.9 (10)	20.3 (9)	
End of treatment, mean (SD)	19.9 (11)	20.4 (10)	
Change from baseline, mean (95% CI)	−0.9 (−1.3, −0.5)	0.0 (−0.4, 0.4)	
Difference, mean (95% CI)	−0.9 (−1.5, −0.3)		< .003
Alkaline phosphatase (U/L)			
Baseline, mean (SD)	76.9 (32)	77.3 (28)	
End of treatment, mean (SD)	84.1 (41)	89.3 (38)	
Change from baseline, mean (95% CI)	7.1 (5.8, 8.5)	12.0 (10.6, 13.4)	
Difference, mean (95% CI)	−4.9 (−6.8, −2.9)		< .001
Bilirubin (μmol/L)			
Baseline, mean (SD)	2.1 (0.8)	2.1 (0.8)	
End of treatment, mean (SD)	2.1 (0.8)	2.2 (1.9)	
Change from baseline, mean (95% CI)	0.0 (−0.1, 0.0)	0.0 (0.0, 0.1)	
Difference, mean (95% CI)	−0.1 (−0.2, 0.0)		< .240

Abbreviations: CI, confidence interval; SD, standard deviation, U, units.

of liver function abnormalities or liver-related adverse effects during treatment with the endothelin A receptor antagonist atrasentan.

Atrasentan treatment was associated with a modest reduction in ALT, AST and ALP levels compared with placebo. Whether this effect is biologically significant is unknown; however, given that activation of liver endothelin A receptors can elicit pleiotropic effects on hepatic vascular smooth muscle and stellate cells, including vasoconstriction, proliferation, inflammation and fibrosis,[5] it is possible that atrasentan confers at least a small degree of liver protection in patients with type 2 diabetes and CKD.

The current findings raise the possibility that atrasentan treatment will manifest similar liver safety in other forms of CKD. In this regard, ongoing clinical trials are evaluating the effects of atrasentan on kidney outcomes specifically in patients with IgA nephropathy (ALIGN, NCT04573478), and in a basket trial involving patients with IgA nephropathy, focal segmental glomerulosclerosis, Alport syndrome and patients with type 2 diabetes with CKD who are treated with sodium-glucose cotransporter inhibitors (AFFINITY, NCT04573920). Of note, sparsentan, a combined endothelin A and angiotensin AT1 receptor antagonist, was recently given accelerated approval by the US Food and Drug Administration (FDA) for the treatment of IgA nephropathy.[6,7] Importantly, the FDA mandated a Risk Evaluation and Mitigation Strategy for potential hepatotoxicity based on concerns over a class effect of ERAs on liver function, although sparsentan treatment did not alter markers of hepatotoxicity.[7] Given that the renoprotective effects of other ERAs are being tested in CKD (e.g. zibotentan in diabetic CKD [ZENITH, NCT04724837]), this issue of ERA-induced hepatoxicity is assuming increasing clinical importance, particularly in the treatment of patients with CKD. The current data from a large international randomized controlled clinical trial provide reassuring evidence that atrasentan does not cause liver injury.

AUTHOR CONTRIBUTIONS

Drs. Kohan and Heerspink made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. Drs. Liew, Tang and Barratt made substantial contributions to analysis and interpretation of data. All authors were involved in drafting or revising the manuscript for important intellectual content.

CONFLICT OF INTEREST

DEK has served as a consultant and member of advisory boards for AstraZeneca, Chinook Therapeutics, Idorsia, Janssen, and Travere Therapeutics. AL has served as a consultant and member of advisory boards for Alnylam Pharmaceuticals, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer-Ingelheim, Chinook Therapeutics, Dimerix Limited, Eledon Pharmaceuticals, George Clinical, GlaxoSmithKline, Kira Pharmaceuticals, Prokidney, Otsuka Pharmaceuticals and Visterra Inc, Zai Lab Co. Ltd; has received Speaker's honorarium from AstraZeneca, Baxter Healthcare, Boehringer-Ingelheim, Chinook Therapeutics and Otsuka Pharmaceuticals; and has served as a member of Data Safety and Monitoring Committee for Dimerix Limited and Zai Lab Co. Ltd. SCWT has served as a consultant and advisory board member for Eledon Pharmaceuticals and Travere Therapeutics, and received Speaker's honorarium from AstraZeneca, Baxter Healthcare, Boehringer-Ingelheim, GSK and Novartis. JB has received consultancy fees and grant funding from Travere Therapeutics and Chinook Therapeutics. HJLH has consulting relationships with AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli-Lilly Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundi Pharma, Novo Nordisk, Novartis and Travere Therapeutics. He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk (all payments to his institution).

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15103.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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