

Introduction

The selective endothelin receptor A antagonist (ERA) atrasentan reduced the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease (CKD).

Rare, but serious drug induced liver injury (DILI) has been previously reported with some ERAs, possibly due to chemical structure and modulation of hepatobiliary transporters, hepatic metabolism and/or hepatic clearance pathways.

Suspicion of DILI is based on the presence of hepatocellular injury with jaundice (Hy's Law) without an identifiable underlying cause of liver injury.

We assessed the effects of atrasentan on markers of liver function and liver-related adverse events, including DILI.

Material and methods

We performed a pre-specified analysis of the SONAR trial where patients with:

- eGFR 25-75 ml/min/1.73 m² and
- urinary albumin-to-creatinine ratio (UACR) 300-5000 mg/g

were randomized (1:1) to:

- atrasentan 0.75 mg or
- placebo

The effect of atrasentan compared to placebo on the mean change from baseline was assessed using an ANCOVA model adjusted for the respective baseline value in:

- Alanine Aminotransferase (ALT)
- Aspartate Aminotransferase (AST)
- Alkaline Phosphatase (ALP)
- Bilirubin

We summarized investigator reported treatment emergent liver-related adverse events (TEAE) by treatment group and searched for potential cases of Hy's law.

Baseline Characteristics

We randomized 3668 participants to atrasentan (N=1834) or placebo (N=1834).

Baseline Characteristics	
Mean (SD) age	64.5 (9) years
eGFR	43.3 (14) mL/min/1.73 m ²
Median UACR	829 mg/g (25th to 75th percentile 457-1556 mg/g)

Results

- At baseline, 204 (5.6%) and 76 (2.1%) participants reported liver disease (excluding hepatitis) and hepatitis respectively.
- Median follow-up was 2.2 years.

Atrasentan compared to placebo statistically significantly reduced ALT, AST and ALP (Table 1).



The number of participants with a liver-related TEAE in the atrasentan and placebo group were not significantly different.

Rare, severe, DILI was not observed with atrasentan treatment in SONAR.

	atrasentan	placebo
Liver-related TEAE	57 (3.1%)	52 (2.8%)
Exposure adjusted incidence rate per 100 person-year follow-up	1.6	1.4

Conclusion

In patients with type 2 diabetes and CKD, who are at high risk of liver disease, there was no evidence of liver function abnormalities or liver related adverse effects with atrasentan treatment.

H.J.L. Heerspink PhD¹
A. Liew MD PhD²
S.C.W. Tang MD PhD³
J. Barratt MD PhD⁴
D. Kohan MD PhD⁵

¹Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, The Netherlands

²Mount Elizabeth Novena Hospital, Singapore

³Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

⁴Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

⁵Division of Nephrology, University of Utah Health, Salt Lake City, Utah, USA

Correspondence:

¹ h.j.lambers.heerspink@umcg.nl