JOURNAL OF HEPATOLOGY

Seladelpar in patients with primary biliary cholangitis: Need for a closer look!

To the Editor:

We read with great interest the study by Bowlus *et al.*, wherein the authors reported on the anticholestatic properties and safety profile of seladelpar at increasing doses (from 2 to 10 mg) in patients who are ursodeoxycholic acid (UDCA) intolerant or incomplete responders.[1] However, the following points warrant a closer look.

Firstly, the mean BMI of the cohort was 27.4, which is independently associated with steatosis, bile duct damage and advanced fibrosis. A previous study showed that 52% of patients with primary biliary cholangitis (PBC) and a BMI >25 had advanced fibrosis.[2] Seladelpar is a PPAR delta agonist which has been shown to improve non-alcoholic steatohepatitis in an animal model[3]; PPAR delta agonists have also been reported to have antifibrotic properties.[4] Monitoring liver stiffness and controlled-attenuation parameter values may have shown that seladelpar has a dual role in overweight patients with PBC.

Secondly, patients in the 5 mg cohort appeared to have more advanced disease: mean alkaline phosphatase levels were higher, mean platelet counts were lower, and a higher percentage of patients in this cohort had cirrhosis. This may have confounded the efficacy of seladelpar in this cohort.

Thirdly, mean pruritis visual analogue scale score was 26 in all cohorts. Why anti-pruritic medications were not given in such patients needs to be mentioned. Also, pruritis as an adverse event was reported in around 24% patients; differences in the distribution and duration of seladelpar- *vs.* PBC-related pruritis should be characterised and defined.

Lastly, PPAR delta is expressed not only on hepatocytes but also on Kupffer cells and cholangiocytes, and seladelpar is proposed to have a disease-modifying effect in PBC.[5] Whether seladelpar should be used in the first-line or as an add-on to UDCA for patients with PBC should be assessed.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed equally.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.04.039.

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Keywords: Seladelpar; PPAR delta; PBC; UDCA; Fibrosis.
Received 27 April 2022; accepted 30 April 2022; available online 17 May 2022
https://doi.org/10.1016/j.jhep.2022.04.039