Avacopan-induced liver injury: an uncommon but emerging concern?

Sirs,

It has been three years since the FDA approval of avacopan as an add-on therapy for severe ANCA-associated vasculitis (AAV), followed promptly by the European Medical Agencies (EMA) (1). Avacopan represents a milestone in the treatment of AAV as it is the first drug specifically developed for vasculitis, offering a glucocorticoid-sparing option (2-4) that mitigates the significant risk of steroid-related toxicities.

Avacopan's use relies solely on one Phase 3 randomised control trial (RCT; ADVOCATE), limited to a 1-year treatment period (2). While demonstrating efficacy and safety in remission induction and maintenance of AAV, absence of additional parallel trial and long-term data raises concerns about the robustness of its safety profile. Safety liver signals were observed in nine avacopan patients (5.4%), leading to discontinuation in five cases (resolved post-withdrawal). In contrast, six prednisone patients had no discontinuations. This prompted FDA and other agencies to issue warnings regarding liver function abnormalities.

Multiple reports have since detailed avacopan-associated drug-induced liver injury (AA-DILI), including some severe cases (5-11). Several Japanese cases reported vanishing bile duct syndrome (VBDS), a rare, often fatal condition leading to liver failure (LF) and death (9-11). Mori and colleagues found 9 out of 22 patients (40.9%) developed DILI, mainly those on cyclophosphamide, with one VBDS case resulting in death (9). Two additional VBDS cases have been reported and all three cases found portal inflammation with focal necrosis on biopsy (9-11).

It is noteworthy that Yamaguchi *et al*. described an elderly Japanese woman with persistent liver injury likely attributable to avacopan. Despite discontinuing avacopan for two months and resolving jaundice, her liver function did not entirely normalise, prompting a liver biopsy that revealed portal inflammation with focal necrosis. Similar to the VBDS cases, the authors felt that the histology findings were consistent with acute hepatitis-like DILI; although, these features may also be seen in autoimmune hepatitis (12-13).

Real-world evidence from the US and Europe shows 3.2 and 6.5% of avacopan patients developed transaminitis or liver injury, leading to discontinuation, aligning with the ADVOCATE trial (14-17). Notwithstanding, a Spanish study of 29 patients on avacopan found no evidence of liver injury, highlighting outcome variability across populations (18).

To mitigate risk, the FDA recommends liver function tests before commencing avacopan and 4-weekly monitoring, especially during the first six months, avoiding use in patients with pre-existing liver disease. Additionally, careful consideration of drug interactions, particularly with CYP3A4 modulators, is advised (19). Kataoka *et al*. proposed a novel approach using gradual dose escalation with ursodeoxycholic acid to reduce AA-DILI risk (20).

Animal and *in vitro* studies have not clarified the mechanism of AA-DILI, leaving its pathophysiology uncertain (21). Concomitant potentially hepatotoxic therapies like cyclophosphamide and statins further complicate causality assessments. While avacopan shows plausible liver injury signals, Hy's law composite for predicting acute LF progression by DILI were not confidently met in many studies (21). Moreover, Uchida *et al*. observed a range of causality scores (3–8 points) using the Roussel Uclaf Causality Assessment Method, indicating at least possible causality but subject to significant variability and subjectivity (8, 22-23).

Avacostar- a post-authorisation real-world study is currently enrolling patients (Germany and the UK) to assess avacopan's long-term safety and efficacy (24). This will provide invaluable insights into identifying liver toxicity and potential risks beyond 1-year treatment, fulfilling the EMA requirements. A similar study, particularly among Japanese patients is warranted given the apparent increased susceptibility to severe DILI in this population.

While avacopan advances AAV treatment, concerns of AA-DILI persist. Future research should focus on identifying risk factors, clarify mechanisms, and assess long-term safety in diverse populations. RCTs and broader real-world studies are essential to characterise avacopan's hepatotoxic potential and develop risk-minimisation strategies.

J. Sern[1,2], *MBBCh*
K. Ravintharan[1,2], *MBBCh*
F. Adeeb[1,3], *MBBCh, CSCST, FRCPI, PhD*

[1]Department of Medicine, Royal College of Surgeons in Ireland and University College Dublin, Ireland;
[2]Department of Medicine, Malaysia Campus (RUMC), Penang, Malaysia;
[3]Rheumatology, Department of Medicine, Pantai Hospital Penang, Malaysia.

Please address correspondence to:
Fahd Adeeb
Department of Medicine,
Rcsi & Ucd Malaysia Campus (RUMC),
Georgetown, Penang,
Malaysia.
E-mail: m.fahd@rumc.edu.my
ORCID iD: 0000-0002-9444-0810

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