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PEER-REVIEW REPORT

Name of journal: *World Journal of Experimental Medicine*

Manuscript NO: 101771

Title: Bile acid therapy for primary biliary cholangitis: Pathogenetic validation

Provenance and peer review: Unsolicited article; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08148815
Position: Peer Reviewer
Academic degree: N/A
Professional title: N/A
Reviewer's Country/Territory: United States
Author's Country/Territory: Russia

Manuscript submission date: 2024-09-25

Reviewer chosen by: Yu Bai

Reviewer accepted review: 2024-10-11 03:13

Reviewer performed review: 2024-10-21 23:00

Review time: 10 Days and 19 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Understanding the causes and mechanisms of diseases is essential for effective treatment. In the case of PBC, a chronic liver disease with no known cause, treatment has been largely symptomatic. However, significant progress has been made in the development of bile acid-based therapies that can slow the disease's progression. Research into the properties of bile acids and how liver and bile duct cells (hepatocytes and cholangiocytes) respond to them has played a crucial role in advancing treatment options. For the past 35 years, UDCA, a hydrophilic bile acid, has been the primary drug used to treat PBC. In recent years, however, the range of bile acid-based treatments has expanded to include other hydrophilic bile acids, such as OCA, TUDCA, and norUDCA. These therapies address the underlying mechanisms of cholangiocyte damage, which are central to the early stages of PBC. Each of these bile acids offers unique therapeutic benefits, with their effectiveness rooted in an improved understanding of PBC's pathogenesis. This review, authored by Vasily Ivanovich Reshetnyak and Igor Veniaminovich Maev, highlights the pathogenetic rationale for using hydrophilic bile acids and their derivatives in treating PBC. It emphasizes the mechanisms that explain the therapeutic potential of each bile

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acid, offering valuable insights into their specific roles in PBC management. In the Conclusion part, the authors proposed some concepts based on the current literature, the discovery of impaired mechanisms of bicarbonate formation by cholangiocytes in PBC, through decreased activity of inositol-1,4,5-trisphosphate receptor isoform 3 and chlorine/bicarbonate anion exchanger 2, caused by increased miR-506 activity. This discovery could provide a rationale for the future development of new drugs aimed at locally reducing miR-506 activity or activating the AE2 anion exchanger in cholangiocytes. It is likely to become one of the new therapeutic approaches in treating PBC or complement existing methods that use hydrophilic bile acids. In sum, the authors provide a comprehensive overview of how bile acid therapy, particularly with UDCA and its derivatives, is validated by current understanding of PBC's pathogenesis. While some minor revisions may be required, for instance, "which is connected with her metabolism" in page 9, the review successfully captures the progress in bile acid-based treatment for PBC.