A change of paradigm in PBC: Pursuing normal alkaline phosphatase

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Commentary

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterised by a chronic and destructive lymphocytic cholangitis of the small bile duct, with variable risk of progression.[1] Ursodeoxycholic acid (UDCA) is the first-line licensed disease-modifying treatment. Add-on therapy with obeticholic acid (OCA) is recommended for patients who do not respond to UDCA. Moreover, off-label therapy with the pan-PPAR agonist bezafibrate is recognised as an alternative and triple combination therapy -including UDCA, OCA, and fibrates- can normalise biochemical liver tests in difficult-to-treat PBC.[2] Lack of response to treatment identifies patients at higher risk of poor liver related outcomes and is currently depended on Alkaline Phosphatase (ALP) levels after 1 year of treatment. ALP is indeed a well recognize surrogate marker of response and outcome.[3] Eight binary criteria have been developed to evaluate biochemical response to UDCA and therefore to predict liver transplant-free survival of PBC patients. Of note, definition of incomplete response differs among different criteria, with Paris-2 including the lowest ALP threshold (below 1.5 times the upper limit of normal) to define response to UDCA.[4] While this might have large implications in the number of patients eligible for second and third-line therapies, clinical guidelines generically recommend the use of binary criteria but lack to refer to a specific one.[5]

In a recent issue of eBioMedicine, Jones and colleagues use the serum proteome of patients on stable therapeutic dose of UDCA for at least 1 year to explore the biological impact of the main UDCA response criteria.[6] They identify a group of seven immune markers that remained significantly elevated in responders to UDCA, regardless of the used response criteria, while patients with normal ALP had lower levels. These results are in line with epidemiological data from a large patient cohort from the Global PBC Study Group demonstrating that normal ALP are associated with the lowest risk for liver related outcomes in patients with PBC.[7] Moreover, the biological basis and molecular mechanisms underlying UDCA response have remained poorly investigated. The strong correlation between serum chemokine components and levels of ALP supports a direct link between the cholestatic injury and the immune processes. It is well accepted that the pathogenesis of PBC is the result of the interaction of immune and biliary pathways, leading to an interdependent and chronic cycle of cholestasis and liver fibrosis.[8] The signature identified by the Jones and colleagues include chemokines (CXCL11, 9 and 10), cytokine modulators (IL-4RA, IL-18-R1), the High Affinity Scavenger Receptor CD163, and Angiotensin Converting Enzyme 2 (ACE2). All markers that have been involved in the pathogenesis of PBC in independent studies. This study strongly suggests a relationship between the existing biochemical response criteria and disease activity.

The treatment scenario in PBC is rapidly changing with three lines of therapy available and a significant number of clinical trials currently ongoing. The authors herein challenge the current use of ALP for PBC risk assessment leading to a paradigm shift in PBC that might have real-life implications in the number of patients starting second- of third-line therapies. As the authors point out, these results are in line with the response criteria for remission in autoimmune hepatitis. Indeed, the definition of remission have been modified over the years and now includes normal transaminases[9] because abnormal these liver enzymes are associated with poor clinical outcomes.

In conclusion, the results of the present study, despite the limitations, confirm that treatment goals in PBC should aim at full disease control and that normalisation of ALP should be the treatment target.

Contributors

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Declaration of interests

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