JHEP|Reports

Challenges in the diagnosis and management of AIH-PBC syndrome

To the Editor:

We have read with great interest the article by Stoelinga *et al.*[1] on the diagnostic criteria and long-term outcomes in autoimmune hepatitis-primary biliary cholangitis (AIH-PBC) variant syndrome under combination therapy, published in *JHEP Reports*. We are grateful to the authors for this novel piece of evidence on a quite enigmatic condition. We would like to offer some comments to highlight the challenges in studying such a difficult clinical phenotype.

One of the most debated aspects of AIH-PBC management is whether Paris criteria should be used in clinical practice.[2] Although the Paris criteria are highly specific, they may exclude patients with milder presentations. In other words, the relatively high cut-offs for AST, ALT, and IgG in these criteria tend to identify patients with severe PBC and AIH, potentially overlooking those with mild overlap manifestations, *e.g.* AIH with mild biliary damage or PBC with mild hepatitis, who would actually benefit from an effective combined treatment.[3]

In their work, Stoelinga *et al.* report that 55 out of 83 patients (76%) did not meet the Paris criteria; yet, clinicians still prescribed ursodeoxycholic acid along with immunosuppression to all these patients outside Paris criteria. Paris-positive and Paris-negative individuals were different on baseline histology, since the former had more liver inflammation and fibrosis. However, when evaluating treatment response at 12 months (*i.e.* complete biochemical response for the AIH component, Paris-II criteria for the PBC component), the rates were similar regardless of the Paris criteria status. This finding prompted the authors to conclude that, regardless of disease onset, biochemical response might not be affected by the Paris status. To us, these data seem to suggest that Paris criteria capture a more inflamed group of cases within a spectrum of disease, but without a significant consequence on treatment response. Notably, the authors recognize that the retrospective nature of the study only allows for inference of an association, since they could not exclude that differences in the treatment regimens were present.

To further explore the phenotypic landscape of this syndrome, the authors presented a comparison between the previously mentioned 83 patients with AIH-PBC and 74 with a diagnosis of PBC associated with elevated ALT and/or IgG levels who were not considered as having AIH-PBC overlap by clinicians, and therefore not treated with a combination regimen. Unfortunately, no histological data were available on the latter cohort. We might speculate that the 74 patients with PBC and elevated IgG/ALT, who were not classified as having AIH-PBC overlap by clinicians, have *de facto* Paris criteria-negative AIH-PBC.

Furthermore, the same cohort of "non-overlap" PBC showed higher mortality rates than that of AIH-PBC, and the authors suggest that this may be due to the absence of immunosuppressive therapy. From our perspective, it is crucial to ascertain whether these patients got access to and received second-line PBC therapies (*e.g.*, obeticholic acid or fibrates).[4,5] Secondly, the analysis lacked appropriate adjustment for cirrhosis, which was more frequent in the 'pure' PBC cohort, and potentially confounds the real differences between the two groups. Notably, when authors corrected for age, the mortality difference disappeared, which suggests the need for further analyses.

In conclusion, we thank Stoelinga *et al.* for their novel and valuable insights into AIH-PBC variant syndrome. The inherent complexity of studying this group of patients, with its difficult-to-categorize characteristics, underscores the great effort required. We would also like to draw attention to the ongoing international Delphi process, promoted by a consortium of experts from the ERN-RARE LIVER network, the IAIHG, and the Global PBC Study group. This initiative has the ambitious aim of standardizing the definition, diagnosis, and treatment of this syndrome, with the ultimate goal of improving the long-term outcomes for patients with this complex overlap condition.

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Received 17 September 2024; Accepted 18 September 2024; Available online 23 September 2024
https://doi.org/10.1016/j.jhepr.2024.101224

Financial support

The authors thank AMAF Monza ONLUS, AIRCSS and IPSEN for the unrestricted research grants. This research was partially supported by the grants: Italian MUR Dipartimenti di Eccellenza 2023–2027 (l. 232/2016, art. 1, commi 314–337), Italian MUR PNRR PE06 "HEAL ITALIA – Health Extended ALliance for Innovative Therapies, Advanced Lab-research and Integrated Approaches of Precision Medicine" - Spoke 4 - Precision Diagnostics, Italian MUR PRIN 2022 PNRR P2022H7JYZ "Non-invasive biological and molecular characterization of autoimmune liver diseases and variant syndromes''.

Conflict of interest

AG has received grant/research support from Ipsen and consulted for Ipsen, CAMP4 Therapeutics and Signanthealth; MC has received grant/research support from Genetic Spa and Intercept and served on an advisory board and/or been a consultant (paid or unpaid) for Advanz, Albireo, AMAF, Calliditas, CymaBay, Echosens, EpaC, Falk, Genetic Spa, GSK, Ipsen, Kowa, Mayoly, Mirum, Perspectum, PSC Pediatric Foundation, and Zydus. PI has received grant/research support from Bruschettini and Intercept and served on an advisory board and/or been a consultant (paid or unpaid) for Advanz, AMAF, Calliditas, Cymabay, EpaC, Falk, Gilead, GSK, Ipsen, Mirum, Zydus.

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

Authors' contributions

Drafting of the manuscript: AG, MC, Critical revision of the manuscript for important intellectual content: all authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101224.

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