EDITORIAL

Immunoglobulin A antibodies: prognostic tools with unknown mechanism in primary sclerosing cholangitis

Maria Papp[1,2], David Tornai[1,2]

1 Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
2 European Reference Network on Hepatological Diseases, ERN RARE-LIVER, Debrecen, Hungary

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by Wunsch et al

We read with great interest the study by Wunsch et al[1] published in this issue of *Polish Archives of Internal Medicine*, which validated the prognostic ability of 2 previously identified serological markers, immunoglobulin (Ig) A type anti-gliadin (AGA) and anti-actin antibodies (AAA) in primary sclerosing cholangitis (PSC). While the validation of prior findings from Tornai et al[2] in a large cohort (n = 624) is an important step forward in the prognostication of PSC, the study falls short of exploiting the full potential of this large patient population and does not provide novel insights into the clinical and mechanistic implications of these antibodies.

The clinical characteristics of patients in the study of Wunsch et al[1] is comparable to that of Tornai et al[2] with similar rates of cirrhosis (22.1% vs 20.3%) and slightly lower prevalence of concurrent inflammatory bowel disease (IBD) (66.5% vs 75.4%). However, notable differences were detected in antibody positivity rates between the 2 cohorts (AAA, 12% vs 28.4%; AGA, 14.6% vs 9%), which may reflect geographic differences but also could be due to the small number of patients (n = 67) in the Hungarian cohort resulting in less representative antibody frequencies. The follow-up periods also differed significantly, with the study by Wunsch et al[1] having a much shorter follow-up duration (median [interquartile range], 18.5 [8–33] vs 99 [14–106] months).

A significant limitation of the Polish study[1] is a missed opportunity for comprehensive subgroup analyses, which could have provided valuable mechanistic insights. The substantial cohort size would have permitted robust investigation of antibody associations with the presence and severity of cirrhosis, decompensation rates or fibrosis status, and cirrhosis development in noncirrhotic patients. Similarly, associations of antibody frequencies and levels with IBD phenotype and disease activity could have provided supportive evidence for the gut failure hypothesis. These aspects are of special interest, since the gut-liver axis is thought to be a driver of PSC pathogenesis,[3] yet the relationship between IBD and PSC outcomes is complex and may vary based on the type of IBD.[4] The results of the study by Wunsch et al[1] could have possibly provided clues for the existing controversies. Moreover, since cirrhosis also contributes to further intestinal injury, it remains uncertain whether the observed associations are attributable to the factors intrinsic to the primary disease (PSC) or to the consequences of cirrhosis progression. Notably, both antibodies are more prevalent in cirrhosis[5] and AGA IgA is associated with portal hypertension,[6] while AAA IgA correlates with liver-oriented scores and decompensated clinical stage of cirrhosis.[5] Given that cytoskeletal F-actin is released into the extracellular space from damaged cells, the formation mechanism of AAA IgA is easily understood in enteropathies. However, in conditions such as PSC and cirrhosis, where multiple organs are affected, these mechanisms warrant further investigation. Nonetheless, extracellular F-actin acts as a damage-associated molecular pattern molecule, initiating antigen cross-presentation to CD8+ T cells. In mice, gut-activated CD8+ T cells can migrate to the liver and trigger immune-mediated cholangitis, potentially representing a pathogenic mechanism in PSC.[7]

The statistical approach also raises methodological concerns. While the multivariate Cox regression incorporated the model of end-stage liver disease score, the exclusion of the MAYO score, or other validated PSC specific prognostic tools,[7] limits comprehensiveness of the risk assessment. Furthermore, while the methodology section mentions the inclusion of laboratory

Correspondence to:
Maria Papp, MD, PhD, DSc, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, 98 Nagyerdei krt., Debrecen H-4032, Hungary, phone: +3652258598, email: papp.maria@med.unideb.hu
Received: January 15, 2025.
Accepted: January 16, 2025.
Published online: January 30, 2025.
Pol Arch Intern Med. 2025; 135 (1): 16938
doi:10.20452/pamw.16938

parameters in the Cox regression, no such parameter was indicated in Table 3 in the original article. It is not clear whether the table is supposed to show only (almost) significant predictors, but if so, the authors probably did not perform logarithmic transformation on continuous variables, as it is not mentioned in the methods. Such a procedure is usually necessary for biological variables that often follow log-normal distribution.

Finally, the authors made a factually inaccurate statement regarding secretory IgA findings. While they stated that Tornai et al[2] demonstrated a predominance of the secretory type among AGA IgA in PSC, this observation was actually made for antiglycoprotein 2 (GP2) IgA antibodies in a different study by the same group.[8]

Nevertheless, the confirmation of the prognostic ability of these antibodies in a large, independent cohort represents a significant advancement, since management of PSC urgently needs diagnostic and prognostic markers. Three IgA antibodies, including anti-GP2, have been already identified by Tornai et al[2] (AAA, AGA, and anti-GP2)[2,8-11] and validated by Wunsch et al.[1,12] While these studies established their individual prognostic utility, a model that integrates these markers could enhance risk stratification and clinical decision-making in PSC. Therefore, combined prognostic ability of these IgA antibodies would be a valuable focus for future research.

In summary, the study is in line with efforts for continued investigation of serological markers in PSC. While it is successful in its primary aim, it also represents a partially missed opportunity to advance our understanding of the mechanistic role of these antibodies in PSC pathogenesis and to provide clues for their link with clinical outcomes. Future studies should address these knowledge gaps through comprehensive subgroup analyses. Evaluation of combined marker panels could ultimately facilitate improved patient stratification and personalized therapeutic strategies in PSC management.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

HOW TO CITE Papp M, Tornai D. Immunoglobulin A antibodies: prognostic tools with unknown mechanism in primary sclerosing cholangitis. Pol Arch Intern Med. 2025; 135: 16938. doi:10.20452/pamw.16938

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