Project X: Variant syndromes of primary biliary cholangitis and autoimmune hepatitis – interface activity determines long-term outcome

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Background and preliminary data:
Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are autoimmune liver diseases. In PBC, the small intrahepatic bile ducts are damaged, leading to chronic cholestasis and eventually liver cirrhosis. Ursodeoxycholic acid (UDCA) is the first-line treatment for PBC, preventing liver damage through its choleretic effect and by modulating bile acid composition. Immunosuppressive treatment is not recommended for PBC. In AIH, immune cell infiltrates in the liver exhibit the characteristic histological pattern of interface hepatitis. This is characterized by lymphocyte and plasma cell infiltrates exceeding the portal tract into the liver lobule with a finger-formed pattern. Patients with autoimmune hepatitis (AIH) usually require lifelong immunosuppressive therapy to halt the autoimmune reaction and prevent liver damage. First-line treatment consists of steroids to induce remission and azathioprine to maintain remission.
PBC and AIH can share serological and histological characteristics. In the past, the term and concept of an “overlap” were used to describe cases in which a patient simultaneously meets the diagnostic criteria for two distinct diseases, while maintaining separate disease boundaries. In contrast, the term and concept of a “variant” has been introduced more recently to define a disease subtype in which one condition predominates while the classical disease exhibits atypical features. The most relevant consequence of diagnosing a variant syndrome is a change of treatment, which adds UDCA treatment to an AIH patient and immunosuppressive treatment to a PBC patient. Patients with a PBC-AIH variant have a worse prognosis than classical PBC patients.
Due to diagnostic uncertainties and heterogenous opinions on terminology and pathomechanistic concepts, PBC-AIH variant syndrome represent one of the most controversial entities in hepatology. Recently, an international, multi-society consensus approach on the definition, diagnosis and treatment of a PBC-AIH variant syndrome has been finalized and was co-coordinated by the project leader. The main results of this consensus process are displayed in Figure 1 and the manuscript is currently under re-submission. One of the most relevant recommendations defines the presence of severe interface hepatitis (≥3/4 according to the Ishak modified Histologic Activity Index) as an indication to start immunosuppression in a patient with PBC. This recommendation is still based on expert opinion from hepatologists and liver pathologists and requires validation through clinical studies. In addition, further experimental data are needed to characterize the immune cell composition of the interface area, which could enable more targeted treatments for patients.

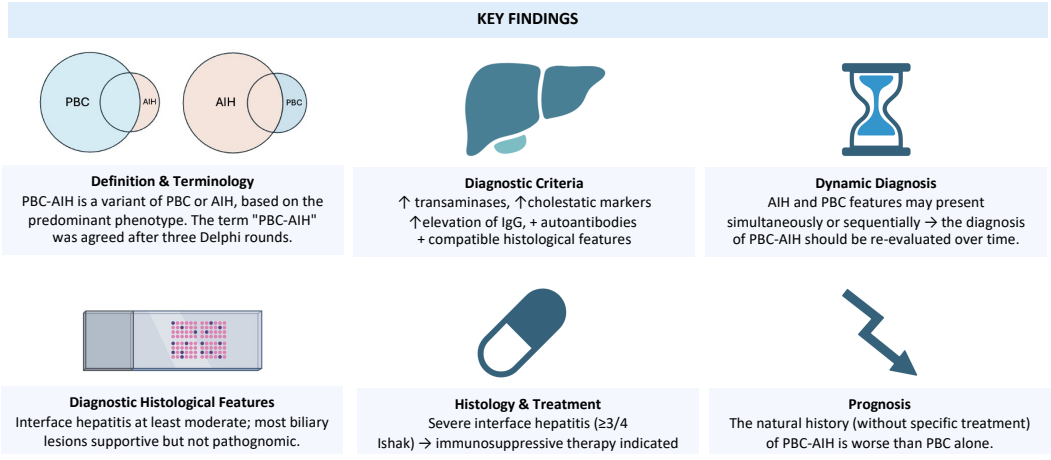

Figure 1: Preliminary results of the Delphi Consensus on PBC-AIH, Alessio Gerussi A*, Sebode M*, et al., re-submitted (*shared first authorship)

Hypothesis: The long-term outcome of a PBC-AIH variant syndrome is determined by severe interface hepatitis

Aims and Work Programme:

1. to define the indication for immunosuppressive treatment in patients with PBC-AIH variant syndrome by a comparative cohort analysis
2. to identify specific pathophysiological mechanisms and prognostic markers for PBC-AIH variants by spatial analysis of histological immune-cell composition of the interface area

In Aim #1, the clinical part of the project, a cohort of patients with PBC-AIH variant syndrome treated with immunosuppression will be analyzed and compared to a cohort of PBC-AIH variant not receiving immunosuppressive treatment. Primary and secondary outcomes are defined as transplant-free survival and progression of liver fibrosis assessed by transient elastography. The YAEL outpatient clinic of the I. Department of Medicine of the UKE is one of the largest outpatient clinics worldwide for patients with autoimmune liver diseases. PBC and AIH patients from the UKE have been enrolled into large-scale international retrospective and prospective registry studies. This ensures that a sufficient number of patients will be identified. Traditionally, at the UKE, PBC patients with interface hepatitis are treated with immunosuppression at a low threshold, whereas international collaborating centers apply a higher threshold of inflammatory activity before initiating immunosuppressive therapy. These two different cohorts of PBC-AIH variants will be characterized by parameters such as histological severity of interface activity, laboratory markers of inflammation and cholestasis and histological and non-invasive grading of liver fibrosis. The outcome of these cohorts will be analyzed under the impact of different treatment regimens in order to provide risk stratification. Thereby, we intend to define the subgroup of PBC-AIH variant patients that benefit from immunosuppressive treatment and to support the respective recommendations provided by the recent consensus process.

In Aim #2, the experimental part of the project, we intend to map the interface area on a subcellular proteogenomic level in order to characterize the immune cell composition that specifically defines patients with PBC-AIH variant syndrome. On H&E fixed histological slides of liver biopsies from patients with variant syndromes, an antibody-based profiling (targeted proteome and phospho-proteome) with subcellular resolution following the principles of iterative indirect immunofluorescence imaging will be performed (so-called PathoPlex, pathology-oriented multiplexing). This aim will be achieved in collaboration with Victor Puelles, III. Department of Medicine, UKE, and Marina Zimmermann, Institute of Medical Systems Bioinformatics, Centre for Molecular Neurobiology, and implemented in Project A08 of the current CRC1700 (with Puelles, Zimmermann and Sebode being PIs of Project A08). The main objective of Project A08 is to dissect the disease-specific and prognostic spatial data of classical AIH and thereby will provide relevant control groups for analyses of PBC-AIH variants. We intend to identify pathophysiological pathways and prognostic markers that will serve for a more specific treatment of patients with PBC-AIH variants.

Project-related publications: (max. 5)

1) Gerussi A*, Sebode M*, et al. Definition, Diagnosis, and Treatment of Primary Biliary Cholangitis - Autoimmune Hepatitis: An International Multisociety Delphi Consensus. *Re-submitted.*
2) Kuehl M, … Sebode M, ..., Puelles V. Pathology-oriented multiplexing enables integrative disease mapping. Nature. 2025;644:516-526.
3) Sebode et al. S3-Leitlinie „Seltene Lebererkrankungen (LeiSe LebEr) – Autoimmune Lebererkrankungen von der Pädiatrie bis zum Erwachsenenalter“ der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) [S3 guideline "Rare liver diseases (LeiSe LebEr) - Autoimmune liver diseases from paediatrics to adulthood" of

the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS)]. Z Gastroenterol. 2025;63:604-688.
4) Schregel I, …, Sebode M, …, Schramm C. Unmet needs in autoimmune hepatitis: Results of the prospective multicentre European Reference Network Registry (R-LIVER). Liver Int. 2024;44:2687-2699.
5) Lohse AW, Sebode M, et al. Consensus recommendations for histological criteria of autoimmune hepatitis from the International AIH Pathology Group: Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology: Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology. Liver Int. 2022;42:1058-1069.