Review

JOURNAL OF HEPATOLOGY

Unmet clinical need in autoimmune liver diseases

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Summary

Despite recent advances in understanding and treatment, there remain significant areas of unmet clinical need in each of the autoimmune liver diseases (AILDs). The evolving research landscape and emerging large patient cohorts are creating unique opportunities to translate science into new therapies and care pathways, with the potential to significantly improve the lives of AILD patients. However, the areas of unmet need represent real challenges, which need to be addressed, if this vision is to be realised. This review describes the areas of unmet need in AILD in adults relating to diagnostic and prognostic assessment, primary therapy, symptom management, trial design and delivery, and structured care delivery, with the aim of focusing future research prioritisation.

Introduction

Autoimmune liver diseases (AILDs) are all rare diseases (defined as having a prevalence <50 per 100,000 population) but result in significant morbidity and mortality. Across primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and IgG4-related diseases (IgG4-RD) there are significant areas of unmet need. Some are shared, others are disease specific (Fig. 1 and Table 1). As the research landscape in AILD evolves in parallel with high throughput genomic, proteomic, metagenomic and metabonomic platforms, the evolution of large national and international patient cohorts is being accompanied by opportunities to translate science into new therapies and care pathways. Alongside this upswing in activity, there is an opportunity to focus thoughts on the unmet needs of patients, from the initial point of accurate and timely diagnosis, to the management of end-stage liver disease and co-existent symptoms. In this review we attempt to define and delineate the areas of unmet need in AILD, which relate principally to an improvement in primary therapy, symptom management, trial design and delivery, and structured care delivery.

Key Points

- In PBC, biomarkers for high risk disease, predictive markers of UDCA non-response and secondary therapies for non-responders and/or alternative first-line therapies for patients at high risk of non-response, are needed
- A better understanding of the place of steroid therapy in overlap syndromes and for the particular role of budesonide is required
- In PSC, recognised primary therapy still does not exist and biomarkers for early stage disease, high risk patients, and enhanced cancer risks are needed
- In AIH, stratification criteria are required to enable identification of high risk patients
- In IgG4 disease, accurate diagnostic markers and evidence-based maintenance regimens are lacking
- In all AILDs, therapies are needed for the often life-changing systemic symptoms, such as pruritus and fatigue

Keywords: Unmet clinical need; Autoimmune liver diseases; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune hepatitis; IgG4 disease; Stratified care delivery.
Received 19 June 2014; received in revised form 4 September 2014; accepted 5 September 2014

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Abbreviations: AILD, autoimmune liver disease; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; HCV, hepatitis C virus; ALP, alkaline phosphatase; APRI, aspartate transaminase to platelet ratio; DMARDs, disease modifying anti-rheumatic drugs; DILI, drug-induced liver injury; AMA, anti-mitochondrial antibody; LPA, lysophosphatidic acid; ASBTi, apical sodium-dependent bile acid transporter inhibitor; MARS, molecular adsorbent recirculating system; HCC, hepatocellular carcinoma.

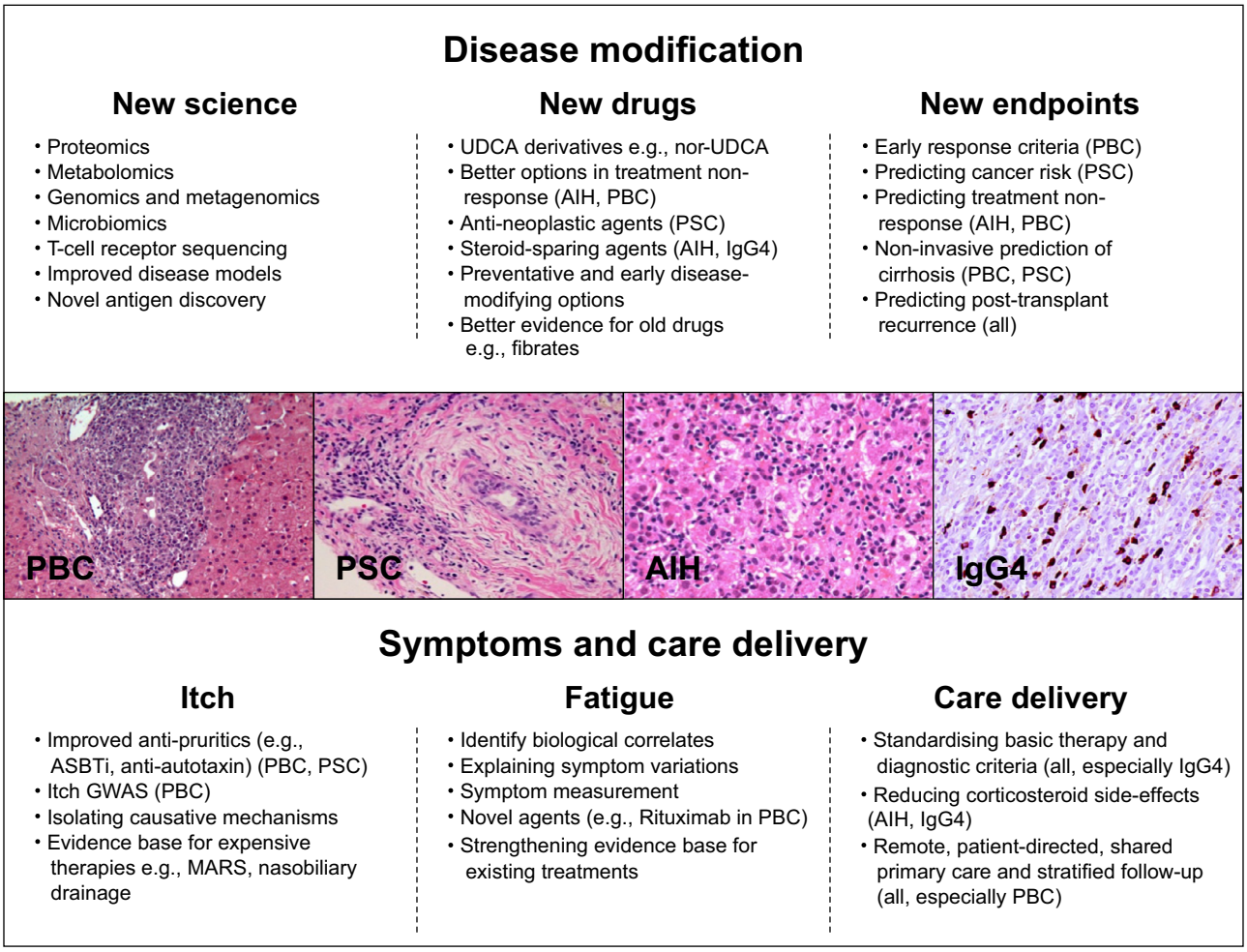

Fig. 1. Summary of unmet needs in autoimmune liver disease. Conditions in brackets following bullet points denote areas of particular need (PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; IgG4, immunoglobulin G subclass 4 associated disease). Central panels show typical histological findings on haematoxylin and eosin stained liver sections (PBC, PSC, and AIH) or haematoxylin with anti-IgG4 secondary staining (IgG4). UDCA, ursodeoxycholic acid; ASBTi, apical sodium-dependent bile transport inhibitors.

Challenges in diagnosis and prognosis

In PBC, a key challenge in the area of diagnosis is the significance of anti-mitochondrial antibodies (AMA, or anti-M2 detected by ELISA) detected in the absence of liver biochemical abnormality. Early studies, performed on a cohort of 29 patients who underwent liver biopsy assessment, suggested that the majority of such AMA-positive patients with normal liver function tests (LFTs) had histological features of mild PBC (83%), and the majority went on to develop characteristic biochemical abnormalities (83%) or symptoms of PBC (76%) over a prolonged follow-up. None, however, became cirrhotic or died of the complications of PBC [1]. More recent population-based studies have suggested a prevalence for AMA in the normal population of 0.1–1% [2–4] with up to half of the AMA-positive subjects in the larger cohorts having biochemical abnormality. Long-term natural history studies are required, with baseline evaluation of the population, to identify processes and markers, associated with the subsequent development of clinically significant PBC. This will enable identification of the subgroup with enhanced risk of disease development and potential preventative approaches able to change the natural history.

In both PBC and PSC, specific questions arise with regard to the issue of so-called "overlap syndromes" with AIH and their diagnosis; a key question if specific therapy is to be considered [5–7]. Each disease naturally encompasses a heterogeneous group of patients with variations in the classical clinical, biochemical, serological, and histological findings, which can lead to difficulties in diagnosis. The classical features of AIH are elevated aminotransferases, raised IgG, positive auto-antibodies [8], and interface hepatitis with portal plasma cell infiltrate on biopsy [9]. The histology findings, however, are not specific for the diagnosis of AIH and the International Autoimmune Hepatitis Group (IAIHG) states that a diagnosis of AIH should not be made when definite bile duct pathology or granulomas are present [10]. Czaja *et al.* found that 24% of patients with "classical AIH" had biliary changes on biopsy, including destructive cholangitis, ductopenia, and non-destructive cholangitis [11] but concluded on further investigation that these patients lacked the features of PBC [12]. Conversely, the "florid duct lesion", classically found in PBC, is not always present and granulomatous cholangitis was seen in only 32% of PBC patients in one study [13]. In PSC, the classical histology findings are portal tract inflammation with lymphocytic infiltration in the bile ducts and ductular