Preface
The Evolving Landscape of Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by the destruction of intrahepatic bile ductules, resulting in chronic cholestasis, that can progress to advanced fibrosis, cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC), and if untreated, requires liver transplantation. Ursodeoxycholic acid (UDCA) has been an effective first-line agent for this condition for approximately three decades; however, approximately one-third of patients are not complete responders to UDCA. The second-line treatment agent obeticholic acid is associated with significant side effects, including worsening pruritus and hyperlipidemia, and is contraindicated in patients with portal hypertension and/or hepatic decompensation. Over the past 5 years, there has been a rapid evolution in our understanding of the epidemiology, genetics, and pathophysiology, and an increase in the number of potential agents and therapeutic targets for PBC. This issue of Clinics in Liver Disease addresses the evolving landscape of PBC.

One of the most interesting aspects of PBC is the sex predisposition among women. Although contemporary epidemiologic studies indicate that PBC is more common among men than previously thought, we now have a better understanding of the progression of PBC among men. Recent studies have shown that men are more likely to present at a more advanced stage of disease, but even among patients presenting with compensated cirrhosis, male sex is associated with higher overall and liver-related death, compared with women.

Genome-wide association studies (GWAS) have identified a number of HLA and non-HLA loci showing strong association with PBC. Approximately 20 novel risk loci have been identified in a recent international meta-analysis, pointing to a total of 22 genes. Although due to its female preponderance, genetic loci located on the X chromosome may be an obvious target in genetic studies, X chromosome is often less studied in many existing GWAS analyses. Recent studies have linked loci located on
the X chromosome to PBC, and it is hoped, these data will improve our understanding of the female predisposition to this disease. Genetic studies have suggested that IL-12 and IFN-γ are two key drivers of immune-mediated cholangitis, as observed in both human and animal models of PBC.

Another area of development in PBC has been in risk-stratification scores. While many of the commonly used scores in the past, including the Toronto and Paris classifications, dichotomized patients with PBC into UDCA responders and non-responders, there has been an evolution in our understanding that even patients who do not normalize their alkaline phosphatase derive some benefit with treatment and are now referred to as partial responders. Instead of dichotomous variables, we now also have continuous scores, including the GLOBE score and UK-PBC scores, which help to calculate the 5- and 10-year survival in patients with PBC. Because many of the traditional prognostic scores describing UDCA response were calculated at 12 and 24 months after initiation of UDCA therapy, there is now a move to define response to therapy sooner, as early as 3 or 6 months after treatment. This has the benefit of moving to a second-line agent sooner, without allowing patients to progress for months, on an ineffective treatment.

An important complication of PBC is HCC, which has an incidence of as high as 13 per 1000 person-years in patients with PBC cirrhosis, and 2.7 per 1000 person-years among patients with PBC without cirrhosis. HCC in PBC is more common among men, as well as among those with cirrhosis, with some studies suggesting that treatment with UDCA and UDCA response may reduce risk. While some guidelines recommend HCC surveillance in men with PBC in the absence of cirrhosis, there are limited data currently to support this recommendation.

While UDCA remains the first-line agent for PBC, obeticholic acid and bezafibrate are both evolving as alternative second-line agents. Bezafibrate may have an additional benefit of reducing pruritus, and studies combining bezafibrate and obeticholic acid are currently ongoing. As pruritus is now being recognized as an important and disabling symptom in PBC, efforts are underway to develop newer agents to treat this debilitating symptom. In addition to bezafibrate, alternative treatments for pruritus include anion exchangers, rifampin, selective-serotonin receptor uptake inhibitors, and opioid receptor antagonists. Newer agents, such as the apical sodium-dependent bile acid transporter inhibitors, that act by decreasing bile acid accumulation and thereby reducing bile toxicity are now being investigated.

Clinical trials in the field of PBC treatment have expanded greatly, with a number of agents, chiefly PPAR agonists and NOX 1/4 inhibitors, holding the most promise to prevent disease progression and in the improvement of symptoms.

There are a number of PPAR agonists with varying activity against the different isoforms. While fenofibrate predominantly binds to PPAR-alpha, bezafibrate binds to the alpha, gamma, and delta isoforms, seladelpar binds only to the delta isoform. Elafibranor is a dual PPAR-alpha and -gamma agonist, and saroglitazar binds primarily to alpha and gamma isoforms. Several of these agents, having shown promising results in phase II studies, are currently in phase III studies. There is much to look forward to in patients with PBC, as our understanding of genetics, pathophysiology, and immunology improves, and a large number of potential treatments are being investigated in clinical trials.

I would like to thank the authors, who are leading experts in the field of PBC, assembled from 10 institutions in six different countries in the United States and Europe. It is
my hope that readers will find this issue comprehensive, state-of-the-art, clinically relevant, and useful, to better manage their patients with PBC.

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