Updates on primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a rare disease, which currently bears one of the biggest needs in hepatology. Neither the cause nor the pathogenesis of the disease are known. The diagnosis is essentially based on magnetic resonance cholangiopancreatography showing bile duct strictures, with the exception of small-duct PSC. The disease is twice as prevalent in men than in women, and the median age at diagnosis is approximately 40 years. The expression and evolution of the disease are notoriously variable and difficult to predict. The only treatment that seems to improve liver tests is ursodeoxycholic acid (UDCA), but despite 2 decades of clinical research, there is still no evidence from randomized trials that UDCA is truly beneficial in improving transplant-free survival in PSC patients. Surrogate endpoints for clinical trials are still poorly validated. Considerable efforts have been provided in recent years to promote significant progress in the understanding and in the treatment of PSC. Several phases II and III clinical trials aimed at evaluating new drugs are ongoing. The prognostic values of histologic and imaging scoring systems are also being progressively established.

In this issue of *Current Opinion in Gastroenterology*, Bowlus (pp. 71–77) provides an update on the epidemiology and natural history of PSC. The incidence rate of the disease seems to increase. Nonetheless, the last prevalence of PSC found in North American and European large population-based studies is lower than previous estimates from specialized centers, approximating 4–6 per 100 000 subjects. Overall, prognosis is also better than previously thought. Most notably, it is highly variable, largely depending on age, race, inflammatory bowel disease (IBD) association, stricture location and degree, autoimmune hepatitis overlap and IgG4 level status. The relations of PSC with IBDs and the risk of colorectal cancer are now better characterized. With the development of liver transplantation, the frequency of death due to liver failure has decreased among PSC patients, liver transplant-free survival ranging between 15 and 20 years, whereas cholangiocarcinoma, most often of hilar location, remains a leading cause of death, with a cumulative risk around 15%.

Ehlken *et al.* (pp. 78–84) have reviewed current advances with respect to cholangiocarcinoma diagnosis and they discuss a rational approach on how to perform surveillance of cholangiocarcinoma in PSC patients. The incidence of cholangiocarcinoma does not correlate with the duration of disease, and approximately one-third of cholangiocarcinomas are detected within the first year after the diagnosis of PSC. Thereafter, yearly incidence of cholangiocarcinoma is approximately 0.5%. Therefore, no evidence-based recommendation has been provided for cholangiocarcinoma surveillance, contrasting with clear guideline recommendations for the surveillance of gallbladder carcinoma. Risk factors for cholangiocarcinoma in PSC are increasingly identified, some of which suggest an implication of the gut–liver axis. Novel approaches include serum biomarkers, urine and bile proteomics, brush cytology combined with in-situ hybridization and the detection of genetic aberrations, cholangioscopy and probe-based confocal laser endomicroscopy. The authors describe the surveillance strategy they propose in their center for cholangiocarcinoma in PSC. However, at present, the predictive values of the different methods including imaging are quite low, and the detection of early-stage cholangiocarcinoma remains difficult. Therefore, large prospective studies will be required in the future to determine the utility of novel diagnostic tools for clinical practice.

Hov and Kummen (pp. 85–92) present an overview of recent studies on the intestinal microbiota in human and experimental PSC. Although heterogeneous, these studies provide strong evidence that PSC is associated with an altered gut microbiota, characterized by low diversity and changes in multiple bacterial taxa. In experimental models of PSC, rederivation of animals into germ-free facilities may either aggravate or attenuate the disease,

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depending on the mechanistic model and on host genes.

Chung and Hirschfield (pp. 93–98) summarize the genetics of PSC associated with IBD, highlighting 23 susceptibility loci for PSC–IBD, identified by genome-wide studies. Less than half of the risk loci overlap with IBD, consistent with clinical data suggesting that PSC–IBD is distinct from IBD. The vast majority of these loci relate to immunity, in particular to the human leukocyte antigen complex. Importantly, genetic determinants account for less than 10% of total disease liability in PSC–IBD, emphasizing the predominant role of environmental factors. As outlined by the authors, it remains to be determined if dysbiosis in PSC–IBD is caused by genetic or nongenetic determinants such as diet.

Altogether, these reviews demonstrate that recent work provided significant progress in the field of PSC. They also stress the need for more efforts to transfer improvements into clinical practice.

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