Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Update on primary sclerosing cholangitis

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Summary

Primary sclerosing cholangitis (PSC) remains one of the most challenging conditions of clinical hepatology. There has been a steady growth in research to overcome this fact and the present review aims at summarizing the most recently published literature. The main emphasis will be put on the link of recent pathogenetic insights to clinical characteristics and patient management. With regard to pathogenesis, there is no consensus yet as to whether immune mediated injury or factors related to bile acid physiology are the most important. It also remains to be clarified whether PSC is a mixed bag of various secondary etiologies yet to be defined, or a disease entity predominantly represented by sclerosing cholangitis in the context of inflammatory bowel disease. Most important, there is no available medical therapy with proven influence on clinical end points, and timing of liver transplantation and patient follow-up are challenging due to the unpredictable and high risk of cholangiocarcinoma.

Introduction

To our knowledge, sclerosing cholangitis was introduced as a medical term in 1867 by Hoffman [1]. In the mid 1960s several case series were reviewed, establishing the link to inflammatory bowel disease (IBD) and describing several other clinical characteristics of a primary form of sclerosing cholangitis (PSC). The introduction of endoscopic retrograde cholangiography (ERC) throughout the 1970s greatly facilitated diagnosis, and the clinical, radiological and histopathological criteria for PSC were stated by three publications in 1980 from the US (Rochester), UK (London), and Norway (Oslo). Later, magnetic resonance cholangiography (MRC) has been recommended as the primary diagnostic modality in suspected cases of PSC (Clinical Points 1). There has been a steady growth in research activity around the many clinical challenges associated with PSC (Fig. 1), including the founding of an international PSC study group (www.ipscsg.org) in 2010. The aim of the present article is to summarize insights provided by the most recent research (published since our previous update [2]).

Clinical Points 1. Diagnosis of primary sclerosing cholangitis (PSC) [114, 117]

- In patients with a cholestatic biochemical profile not otherwise explained and where causes of secondary sclerosing cholangitis have been excluded, a diagnosis of PSC is made when magnetic resonance cholangiography (MRC) shows typical findings
- Endoscopic retrograde cholangiography (ERC) can be considered if high-quality MRC is uncertain and in patients with inflammatory bowel disease with normal high-quality MRC but high suspicion of PSC
- A liver biopsy is not necessary for the diagnosis of PSC in patients with typical cholangiographic findings
- A liver biopsy is recommended to diagnose small duct PSC if high-quality MRC (or ERC) is normal and in patients with disproportionally elevated aminotransferases to identify additional or alternative disease processes

The principle challenges in PSC all derive from the fact that etiology and pathogenesis are still largely unknown. Since the development of sclerosing cholangitis represents a "final common pathway" for multiple underlying mechanisms of bile duct injury, *in vivo* data in patients with established PSC do not necessarily reflect etiology. The first part of this review elaborates on recent insights into the pathogenesis of PSC, with a particular emphasis on research of relevance to novel treatment strategies currently in the testing phase. An update on aspects relevant to diagnosis of PSC will also be given, with a particular emphasis

Keywords: Primary sclerosing cholangitis; Inflammatory bowel disease; Cholangiocarcinoma.
Received 4 February 2013; received in revised form 12 March 2013; accepted 14 March 2013
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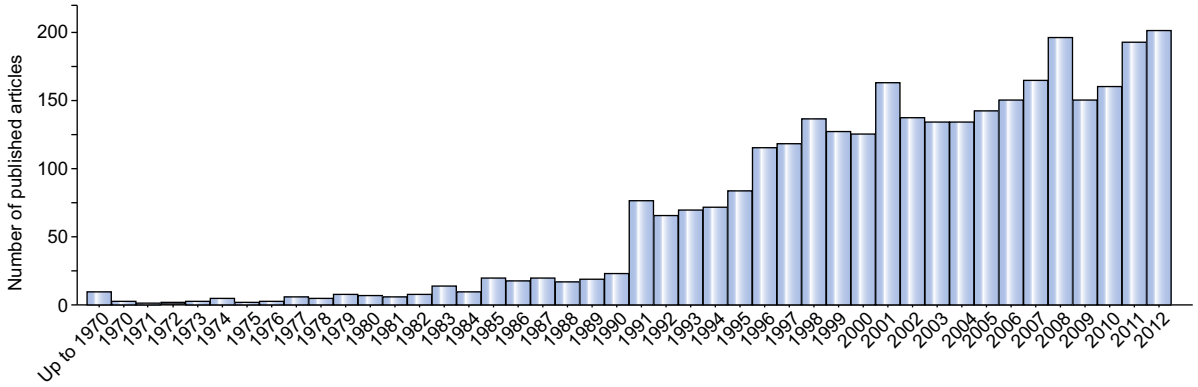

Fig. 1. Published articles reporting the search term "primary sclerosing cholangitis" (http://www.ncbi.nlm.nih.gov/pubmed/). The present review will focus on articles published from 2010 to 2012.

on the recent insights into PSC associated clinical aspects, including elevated levels of serum IgG4, IBD, cholangiocarcinoma, pruritus, and concurrent autoimmune hepatitis. Finally, we will summarize the updates regarding treatment and cancer surveillance of PSC patients.

Pathogenesis of PSC – toxicity or immunology?

There is no universally accepted explanation for the bile duct injury in PSC. Mechanistic aspects of the development of similar bile duct lesions are under intense study both in human conditions and rodent models, nurturing an ongoing discussion as to whether the primary injury is caused by immune mediated mechanisms or biochemical aspects related to bile physiology and how these two aspects can potentially be integrated in one model. The definition of a subgroup of PSC patients characterized by high serum levels of IgG4 in 2006 [3] was in support of the possibility that the PSC patient population may be heterogeneous, and that one pathogenetic mechanism cannot be expected to account for all cases. Nevertheless, from a clinical perspective in Northern Europe and the US, a relatively demarcated "syndrome" of concurrent bile duct fibrosis, predominant right-sided colitis and a neoplastic propensity at both these sites, seems to comprise 70–80% of the PSC patient population. For this group of patients, it is not unreasonable to expect a relatively uniform pathogenesis.

Genetic association studies

The genetic susceptibility to PSC aligns with prototypical autoimmune diseases as much as with IBD (Fig. 2). Indeed, the hallmark of an "autoimmune" susceptibility at a genetic level; i.e., a predominant HLA association, also accounts for the overall genetic architecture of PSC (Table 1). As for most HLA associated diseases (celiac disease being a notable exception), the immunological implications of PSC associated HLA variants are unknown. Several review articles have assessed the theoretical knowledge associated with each non-HLA susceptibility locus (Table 1) [4–7]. Only speculations are possible for the potential disease mechanisms represented by these loci, since most of the functional studies that serve as the basis of these review articles were performed prior to, and independently from the knowledge of genetic associations in PSC. Furthermore, the "pool" of risk loci is incompletely defined (for reasons discussed elsewhere [8]). Importantly, in our opinion, there is also a risk of oversimplifying implications from genetic association study outcomes if too wide assumptions are formed on the basis of each individual locus (as would only be appropriate in a monogenous trait).

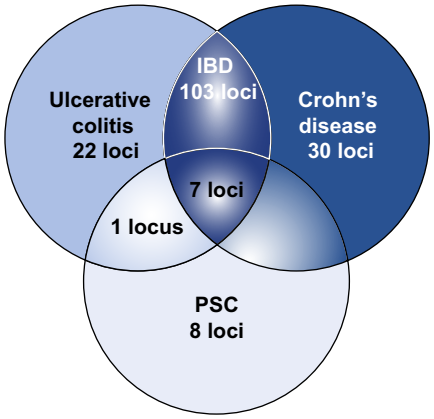

Fig. 2. Venn diagram illustrating the genetic overlap between primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD). A total of 163 IBD susceptibility loci and 16 PSC susceptibility loci were included in the plot [9,158]. The major histocompatibility complex (MHC) associations in PSC include several independent association signals and are counted as one PSC specific locus.

Despite these limitations, the largest genetic study in PSC warrants specific mentioning [9]. The study represents a major accomplishment by multiple centers within the international PSC study group. Genetic risk for PSC was assessed by means of case-control association analysis of a total of 3789 PSC cases to 25,079 controls across 130,422 single-nucleotide polymorphisms (SNPs) genotyped using the Immunochip [10]. The Immunochip is a targeted genotyping array covering 186 known disease loci from various immune-mediated diseases. Outside of these 186 loci, Immunochip also assays thousands of SNPs of intermediate significance from previous studies in these other diseases. A total of 9 novel risk loci for PSC were detected in the analysis. Furthermore, by taking *a priori* knowledge on genetic associations in other diseases into account (Crohn's disease, celiac disease, psoriasis, rheumatoid arthritis, sarcoidosis, type 1 diabetes, and ulcerative colitis), there was *a posteriori* evidence for another 33