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REVIEW

Variant and Specific Forms of Autoimmune Cholestatic Liver Diseases

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Abstract
Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are the main autoimmune cholestatic liver diseases. IgG4-associated sclerosing cholangitis is another distinct immune-mediated cholestatic disorder of unknown aetiology that is frequently associated with autoimmune pancreatitis or other IgG4-related diseases. Although the majority of PBC and PSC patients have a typical presentation, there are common and uncommon important variants or specific subgroups that observed in everyday routine clinical practice. In this updated review, we summarize the published data giving also our own experience on the variants and specific groups of autoimmune cholestatic liver diseases. Actually, we give in detail the underlining difficulties and the rising dilemmas concerning the diagnosis and management of these special conditions in the clinical spectrum of autoimmune cholestatic liver diseases including the IgG4-associated sclerosing cholangitis highlighting also the uncertainties and the potential new eras of the research agenda.

Keywords Primary biliary cholangitis · Primary sclerosing cholangitis · Antimitochondrial antibodies · Autoimmune hepatitis · Autoimmune liver diseases · Variant syndromes

Introduction

Primary biliary cholangitis (PBC)—previous nomenclature primary biliary cirrhosis—and primary sclerosing cholangitis (PSC) are the main autoimmune cholestatic liver diseases. PBC is characterized by a progressive destruction and loss of the small intrahepatic bile ducts (Carey et al. 2015; European Association for the Study of the Liver 2017a; Hirschfield et al. 2018). PSC is characterized by inflammation, scarring and fibrosis of the intrahepatic and extrahepatic bile ducts leading to multifocal strictures of the biliary tree (Karlsen et al. 2017; Lazaridis and LaRusso 2016; Lindor et al. 2015). Both diseases result in the development of significant cholestasis that may lead to liver cirrhosis with portal hypertension and end-stage liver disease.

PBC affects mainly middle-aged females between 50 and 60 years (female/male ratio: 8–10:1). However, recently it became apparent that younger patients may also be affected (Carey et al. 2015; European Association for the Study of the Liver 2017a; Gatselis et al. 2017; Hirschfield et al. 2018). From a clinical point of view, PBC diagnosis at early stages seems crucial as treatment with ursodeoxycholic acid (UDCA) can delay disease progression and improve survival (Floreani et al. 2011; Gatselis et al. 2017; Harms et al. 2018; Lammers et al. 2015; Murillo Perez et al. 2018). The diagnosis of PBC is based on the presence of at least two out of the three following criteria (European Association for the Study of the Liver 2017a; Gatselis and Dalekos 2016; Hirschfield et al. 2018; Rigopoulou and Dalekos 2008): (a) presence of antimitochondrial antibodies (AMA; positive in approximately 90–95% of PBC patients) or specific antinuclear antibodies (ANA; main antigenic targets against sp100 or gp210 proteins; detection in about 30% of PBC patients) (Gatselis et al. 2013; Granito et al. 2012; Rigopoulou et al. 2005), (b) elevated cholestatic enzymes (alkaline phosphatase and/or γ-glutamyl transpeptidase) and (c) liver biopsy indicating florid duct lesions (lymphocytic cholangitis affecting septal or interlobular bile ducts). Of note, most PBC patients with typical presentation have elevated serum levels of IgM.

In the clinical spectrum of the disease apart from the typical cases of PBC, there are also some common and uncommon important variants and specific groups of patients with

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PBC. In this context, the common variant and specific forms of PBC include the AMA-negative PBC, the isolated AMA positivity, the AMA positivity in patients with well-established autoimmune hepatitis (AIH), the PBC patients also suffering from other(s) extrahepatic autoimmune diseases and the PBC with characteristics of AIH (PBC–AIH variant) (Dalekos et al. 2019; European Association for the Study of the Liver 2015, 2017a; Hirschfield et al. 2018; Zachou et al. 2013). The less frequent PBC variant and specific forms include the premature ductopenic PBC variant, the non-cirrhotic PBC patients with portal hypertension, the PBC patients with concurrent viral hepatitis B or C and the PBC–PSC or PBC–IgG4 sclerosing cholangitis variant.

On the other hand, PSC is a rare, but serious cholestatic liver disease for which so far, no real effective therapy exists to tackle disease progression. Therefore, in most patients, liver transplantation is needed although the disease may recur after transplantation (Lazaridis and LaRusso 2016). Inflammatory bowel disease (IBD) is present in about two-thirds of PSC patients from North Europe and United States and there is a high risk for development of cholangiocarcinoma and colorectal cancer (Boonstra et al. 2013; Karlsen et al. 2017; Lindor et al. 2015; Ponsioen et al. 2016). In contrast, PSC affects approximately only 8% of IBD patients. Of interest, despite previous assumptions for a male predominance among PSC patients, recent studies have confirmed that the disease occurs as commonly in females as in males. However, PSC seems to run a subclinical and more favourable course in female patients as attested recently by a large multicentre study of the International PSC Study Group including above of 7.000 patients (Lunder et al. 2016; Weismuller et al. 2017). A similar favourable outcome of PSC has also been found in younger patients and those with Crohn's disease or without concurrent IBD (Halliday et al. 2012; Weismuller et al. 2017). The diagnosis of PSC is based on the setting of elevated cholestatic enzymes, particularly of alkaline phosphatase, although it is important to know that its serum levels are naturally fluctuating in PSC patients, along with cholangiographic evidence of strictures of intrahepatic or extrahepatic bile ducts or both by magnetic resonance cholangiopancreatography (MRCP). Indeed, MRCP is now the preferred technique of choice for PSC diagnosis, as it bears very good sensitivity and specificity (0.86 and 0.94, respectively) (Karlsen et al. 2017; Lazaridis and LaRusso 2016; Lindor et al. 2015; Schramm et al. 2017). Liver biopsy is rarely needed to establish PSC diagnosis, as the pathognomonic "onion-skin" fibrosis lesions are found very infrequently. It is obvious that several other causes of secondary sclerosing cholangitis should be excluded for a firm PSC diagnosis (Table 1). Endoscopic retrograde cholangiopancreatography (ERCP) can be performed if MRCP with or without liver biopsy is puzzling or contraindicated and there is serious suspicion of PSC presence. However, the risks of ERCP should always be weighed against the potential benefits (Aabakken et al. 2017; Lindor et al. 2015).

Table 1 Causes of secondary sclerosing cholangitis which should be excluded for a firm diagnosis of primary sclerosing cholangitis

Choledocholithiasis
Recurrent pyogenic cholangitis
Traumatic or ischemic biliary injury
HIV infection
Papillary stenosis
Pancreatic cancer or cancer of the ampulla
Chronic pancreatitis
Choledochal cysts, biliary atresia
Chronic biliary infestation
Ischemic cholangiopathy
Sarcoidosis
IgG4-associated sclerosing cholangitis (see also Table 5)

HIV human immunodeficiency virus

As for PBC, the vast majority of PSC patients have a typical presentation. However, there are also some common important variants in routine clinical practice that need attention namely, the small duct PSC and the PSC–AIH variant including autoimmune sclerosing cholangitis which is a distinct clinical phenotype in children (Dalekos et al. 2019; European Association for the Study of the Liver 2015; Gatselis et al. 2015; Gregorio et al. 2001; Karlsen et al. 2017; Lindor et al. 2015).

Finally, IgG4-associated sclerosing cholangitis is a distinct immune-mediated cholestatic disorder of unknown aetiology which is not a real subtype of PSC but is frequently associated with autoimmune pancreatitis or other IgG4-related diseases. Contrary to PSC, this clinical entity responds dramatically to steroid therapy while it appears to be less likely to associated with concurrent IBD (Kamisawa et al. 2019; Karlsen et al. 2017; Lazaridis and LaRusso 2016; Lindor et al. 2015).

In this review, we summarize the published data giving also our own experience on the variant and specific forms of PBC and PSC by underlining the difficulties and the rising dilemmas concerning their diagnosis and management. In addition, a special reference to the distinct clinical condition of IgG4-associated sclerosing cholangitis is given in a separate chapter as its differential diagnosis from PSC is of major clinical importance.

Common Variants and Specific Forms of PBC

AMA-Negative PBC

According to the assays employed at the initial screening, about 5% of patients with PBC are negative for AMA

(European Association for the Study of the Liver 2015; Gatselis and Dalekos 2016; Rigopoulou and Dalekos 2008; Zachou et al. 2013) (Table 2). It should be noted however, that investigation for AMA should be done according to recent guidelines to minimize false negative results. In brief, the indirect immunofluorescent assay, which is considered the gold standard for initial routine screening, should be performed using preferably en block fresh frozen cryostat sections of rat kidney, stomach and liver tissues as substrate. In addition, the sectioning of the kidney should be performed very carefully with appropriate orientation, because the latter sectioning is mandatory in an attempt to fix both proximal and distal renal tubules on cryostat sections (Gatselis and Dalekos 2016; Rigopoulou and Dalekos 2008). The use of equivalent commercial sections is of variable quality because, to extend the expiry date, fixatives are added, which may result in limitations of interpretation of fluorescence patterns because of enhanced background staining. Last but not least, as AMA include all immunoglobulin isotypes (IgG, IgA and IgM), it is rational to use antihuman polyvalent immunoglobulin as secondary antibody in indirect immunofluorescence assay instead of only the IgG compartment (Gatselis and Dalekos 2016; Rigopoulou and Dalekos 2008).

Additional testing is recommended if the initial routine testing by indirect immunofluorescence is negative in an

Table 2 Variant and specific syndromes of primary biliary cholangitis (PBC)

Common
AMA-negative PBC
About 5% of PBC patients depending on the assays performed; liver biopsy is needed for the establishment of diagnosis
ANA specific for PBC (anti-sp100 and anti-gp210) may help; clinical features, course of the disease and treatment response seem identical to AMA-positive patients
Isolated AMA seropositivity
About 0.5% of healthy population have AMA; no treatment is required; development of PBC in 16% of individuals over 5 years of follow-up; monitoring of cholestatic enzymes seems rational (every 6–12 months?)
AMA positivity in AIH patients
Depending on the assays performed 5–35% of AIH patients have AMA; no association with cholestatic biochemistry, cholestatic histological findings in follow-up biopsies or response to immunosuppressive treatment
Ongoing multicenter study on this topic is underway from the IAIHG
PBC accompanied by other(s) extrahepatic autoimmune diseases
See Table 3
PBC–AIH variant
Terminology varies; there is no internationally accepted consensus for its definition
The Paris criteria are still in use but are largely different from the criteria for the diagnosis of PBC and AIH
Interface hepatitis at the histological level is needed for the diagnosis of this variant
There are no randomized clinical trials for its treatment; however, treatment with combination of immunosuppression with UDCA is recommended
Uncommon
Premature ductopenic PBC variant
Very rare but severe PBC variant; no response to UDCA; liver transplantation is usually required
Non-cirrhotic PBC variant with portal hypertension
Unique manifestation of PBC (contrary to any other liver diseases); development of oesophageal varices in 5–6% of patients; careful assessment of all PBC patients at baseline and during follow-up is strongly advised
Underlying pathogenetic mechanisms obscure
Screening for varices in this variant form of PBC is recommended (particularly when platelets < 140.000 or 200.000/μl)
Prophylaxis and management approaches are similar with every other chronic liver disease; same risk for developing pulmonary hypertension as in other cirrhotic patients with portal hypertension
PBC with concurrent viral hepatitis B or C
PBC diagnosis in HBV or HCV patients is very difficult and usually delayed
It might have clinical implications as advanced liver disease at diagnosis was recorded in patients with this specific form of PBC; therefore, the presence of biochemical indices of cholestasis should prompt physicians to seek for AMA and PBC-specific ANA in an attempt to achieve a timely diagnosis of concurrent PBC
HCV-associated PBC cases seem to present worse outcome compared to those with concurrent HBV infection probably because of the old therapies with IFNs
Management is identical to the clinical practice guidelines of HBV, HCV and PBC
PBC–PSC or PBC-IgG4 sclerosing cholangitis variants
Extremely rare; No clear-cut conclusions can be given

AMA antimitochondrial antibodies, *ANA* antinuclear antibodies, *AIH* autoimmune hepatitis, *IAIHG* international autoimmune hepatitis group, *UDCA* ursodeoxycholic acid, *PBC* primary biliary cholangitis, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *IFNs* interferons, *IgG4* immunoglobulin G4 subclass, *PSC* primary sclerosing cholangitis

attempt to overcome a probable false diagnosis of AMA-negative PBC. This should be done by means of molecular-based assays such as enzyme-linked immunosorbent assays (ELISA) and immunoblot which use the major target autoantigens of AMA that have been identified and cloned since 1987 such as the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2), E2 subunit of the branched-chain 2-oxoacid dehydrogenase complex (BCOADC-E2) and E2 subunit of the 2-oxoglutarate dehydrogenase complex (OGDC-E2) (Fussey et al. 1988; Gershwin et al. 1987). This approach is of paramount importance, as indirect immunofluorescence bears several limitations (Bizzaro et al. 2012; Gabeta et al. 2007; Gatselis and Dalekos 2016; Liu et al. 2010; Rigopoulou and Dalekos 2008). Indeed, indirect immunofluorescence is labour intensive, time consuming, and not fully automated assay depending on a subjective interpretation of the observer.

Furthermore, evaluation for the detection of PBC-specific ANA such as, anti-sp100 and anti-gp210 antibodies either by indirect immunofluorescence on Hep2 cells or more preferably by ELISA and immunoblotting is very helpful, as they can establish the diagnosis of PBC when AMA are not detected (Gatselis et al. 2013; Gatselis and Dalekos 2016; Granito et al. 2012; Rigopoulou et al. 2005; Rigopoulou and Dalekos 2008). The diagnostic accuracy of PBC-specific ANA for the diagnosis of PBC seems equal to AMA detection and therefore, in AMA-negative patients with PBC-specific ANA positivity there is no need of liver biopsy to establish diagnosis. However, if both AMA and PBC-specific ANA tested negative, a liver biopsy is necessary for diagnosis (Carey et al. 2015; European Association for the Study of the Liver 2017a; Hirschfield et al. 2018). The clinical features, course and outcome along with response to treatment with UDCA seem similar to the AMA-positive patients (Carey et al. 2015; European Association for the Study of the Liver 2017a; Hirschfield and Heathcote 2008; Hirschfield et al. 2018; Mendes and Lindor 2008), although there is conflicting data concerning the progression and severity of PBC for those AMA-negative patients who have reactivity against the PBC-specific ANA (in particular against the gp210 autoantigen) (Bogdanos et al. 2007; Gatselis et al. 2013; Gatselis and Dalekos 2016; Granito et al. 2012; Invernizzi et al. 2001; Nakamura et al. 2007; Rigopoulou and Dalekos 2004, 2008; Rigopoulou et al. 2005).

Isolated AMA Positivity

AMA detection in an otherwise healthy population is not uncommon as about 0.5% of these subjects may have AMA reactivity without any symptoms or abnormal cholestatic enzymes (Mattalia et al. 1998; Shibata et al. 2004; Turchany et al. 1997) (Table 2). Older studies in AMA-positive asymptomatic individuals with normal liver enzymes showed histological lesions of PBC in about 40%, whereas PBC was developed in most of them during follow-up (Metcalf et al. 1996; Mitchison et al. 1986). However, the course of the disease in this setting was favourable, as none of the patients progressed to cirrhosis, needed a liver transplant or died due to PBC after 18 years of follow-up (Metcalf et al. 1996). Furthermore, a recent prospective study from France including AMA-positive healthy subjects revealed that only 16.7% of them developed PBC after 5 years of follow-up (Dahlqvist et al. 2017). However, in the same study, an unexpected higher overall mortality rate was recorded in these subjects compared to age- and sex-matched controls (Dahlqvist et al. 2017).

In summary, all international associations for the study of the liver agree that treatment initiation with UDCA is not needed for individuals with isolated AMA positivity. However, a yearly periodic routine screening of liver enzymes might be required in these subjects in an attempt to uncover the potential development of biochemical abnormality. If such an abnormality is found during monitoring, then initiation of treatment should be similar as for typical PBC cases (European Association for the Study of the Liver 2017a; Hirschfield et al. 2018).

AMA Positivity in Patients with Well-Established AIH

AMA, which are the serological hallmark for the diagnosis of PBC, can also be detected in patients with other liver disorders, including AIH which is an acute or chronic liver disease of unknown aetiology characterized by absence of viral hepatitis B and C markers, hypergammaglobulinaemia, circulating autoantibodies and interface hepatitis on liver biopsy (Dalekos et al. 2019; European Association for the Study of the Liver 2015) (Table 2). However, the clinical importance of AMA detection in this setting is not clear. A recent review of our group found that AMA can be detected in 5–35% of patients with well-established AIH with the highest prevalence being recorded mainly in some Japanese studies (Gatselis and Dalekos 2016). At present, most studies have shown that this finding does not bear any direct clinical significance, although it should be noted that there are many limitations such as short monitoring of the patients, infrequent sequential liver biopsies and investigation of small number of patients.

In more detail, a study from the Mayo Clinic, USA found AMA in 18% of AIH patients, but this finding was not associated with clinical and histological manifestations of PBC at diagnosis, histological features of cholestasis at repeat liver biopsies, while response to immunosuppressive treatment was similar between AMA-positive and AMA-negative AIH patients (Montano-Loza et al. 2008). Our group and a Canadian group have also reported similar findings (Liaskos et al. 2007; O'Brien et al. 2008). In the Canadian study, a

follow-up of 27 years has been reported in 15 AMA-positive AIH patients. No characteristic cholestatic lesions of PBC were found on initial or repeat liver biopsies, whereas a typical predominant course of AIH was recorded with almost identical treatment response compared to AMA-negative AIH patients (O'Brien et al. 2008).

However recently, another observational study from Canada reported three AIH patients with persistently detectable AMA who developed typical PBC over time (Dinani et al. 2012). Interestingly, one of them was already included in the first Canadian cohort published in 2008 (O'Brien et al. 2008), suggesting that probably longer than 27 years follow-up is needed for the late PBC development among AMA-positive patients with AIH. Another multicentre study comparing 264 AMA-negative and 47 AMA-positive cases of AIH showed eventually in the multivariate logistic regression analysis using AMA as a dependent variable, that AMA reactivity did not reveal any specific subgroup of AIH patients or the development of any sign of PBC characteristics after a short monitoring of 4 years (Muratori et al. 2017). Another point that the clinician should be aware is that the AMA titres seem to be lower in AMA-positive AIH patients compared to those usually detected in the PBC cases, although these findings have been reported in studies with a small number of patients (Tomizawa et al. 2015). In summary, at present, AMA-positive AIH patients should be managed as for AMA-negative cases taking into account the published guidelines for AIH diagnosis and treatment (Dalekos et al. 2019; European Association for the Study of the Liver 2015; Gatselis et al. 2015; Zachou et al. 2013).

Because of these uncertainties, a large multicentre retrospective study from the international autoimmune hepatitis group (IAIHG) using prospectively collected data on AMA reactivity in AIH patients is currently underway. The aim of this study is to address several unresolved problems such as the AMA prevalence at first diagnosis and during follow-up in patients with well-established AIH, the clinical significance—if any—of AMA reactivity in these patients regarding their demographic, clinical, serological, biochemical and histological characteristics at baseline and during follow-up along with their long-term prognosis and response to immunosuppression compared to an age- and sex-matched AMA-negative population with AIH (Dyson et al. 2019).

PBC Accompanied by Other Extrahepatic Autoimmune Diseases

Almost half of PBC patients and their families suffer from another concurrent autoimmune disease suggesting shared genetic predisposition (Table 3) (Carey et al. 2015; European Association for the Study of the Liver 2017a; Gatselis et al. 2017; Hirschfield et al. 2018; Zografos et al. 2012). Among these conditions, autoimmune Hashimoto's thyroiditis, Sjogren's syndrome—although most patients have 'Sicca complex' (dry mouth, dry eyes) rather than primary Sjogren's syndrome—and Raynaud's disease are strongly associated with PBC (Carey et al. 2015; Corpechot et al. 2010; Floreani et al. 2015a; Gatselis et al. 2017; Gershwin et al. 2005; Hatzis et al. 2008; Hirschfield et al. 2018). Therefore, the European and British clinical practice guidelines for the diagnosis and management of PBC recommend baseline screening of all PBC patients for the abovementioned common disorders (European Association for the Study of the Liver 2017a; Hirschfield et al. 2018). During follow-up, PBC patients should be monitored clinically and testing for these conditions is suggested according to the clinical needs.

Other extrahepatic autoimmune diseases that have been associated with PBC are shown in Table 3 (Corpechot et al. 2010; Dalekos et al. 1995; Floreani et al. 2015a; Gatselis et al. 2007, 2010a, 2017; Gershwin et al. 2005; Huang 2016; Liaskos et al. 2010; Zachou et al. 2006). Of note, in our series of 482 PBC patients, the predominant autoimmune disease was Hashimoto thyroiditis, there was no statistically significant difference between female and male patients regarding the prevalence of concurrent autoimmune diseases (29.5% vs. 21.5%, respectively), while 6.6% of patients suffered from more than one autoimmune disease (Gatselis

Table 3 Extrahepatic autoimmune diseases that associated with primary biliary cholangitis

Most common
Hashimoto's thyroiditis, Sicca complex (dry mouth, dry eyes) rather than primary Sjogren's syndrome and Raynaud's disease
Other extrahepatic autoimmune diseases
Autoimmune rheumatic diseases *(*rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome, scleroderma or CREST syndrome, giant cell arteritis, polymyositis or dermatomyositis and adult Still's disease*)*
Haematological (Biermer's anaemia, Henoch-Schonlein purpura, idiopathic autoimmune thrombocytopenia, autoimmune haemolytic anaemia)
Dermatological (psoriasis, vitiligo, erythema nodosum)
Gastrointestinal (celiac disease, inflammatory bowel disease)
Miscellaneous (type-1 diabetes mellitus, multiple sclerosis, interstitial lung disease)

CREST calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia

et al. 2017). Sometimes the concurrence of autoimmune diseases may result in difficulties for establishing a prompt and timely PBC diagnosis. Indeed, physicians should keep in mind this possibility in cases with various autoimmunity and elevated cholestatic enzymes. In such cases, recommendation of a reliable serologic testing for AMA and PBC-specific ANA seems very helpful (Gatselis and Dalekos 2016; Rigopoulou and Dalekos 2008).

The management of the symptoms of the associated autoimmune disorders seems very important in an attempt to control the overall symptom burden in PBC and improve the quality of life of the patients (Mells et al. 2013). However, the behaviour of this specific PBC group in terms of liver disease appears to be not different from those without concomitant autoimmune diseases, as the overall survival of patients and response to treatment with UDCA are not reduced (Carey et al. 2015; Floreani et al. 2015a; Gatselis et al. 2017). Nonetheless, real-world data targeting the specific questions on the outcome, response to treatment and quality of life of PBC patients with concurrent extrahepatic autoimmune diseases are missing.

PBC–AIH Variant

Diagnosis

A proportion of PBC patients (approximately 10–20%) may have also either simultaneously or consecutively, characteristics of AIH, while some patients with well-established AIH may also develop features of PBC during follow-up (Dalekos et al. 2019; European Association for the Study of the Liver 2015, 2017a; Gatselis et al. 2015; Hirschfield et al. 2018; Zachou et al. 2013) (Table 2). So far, many terms have been used for the description of this condition like "PBC–AIH overlap syndromes", "PBC with secondary AIH" and "hepatitic form of PBC" (Boberg et al. 2011; Dalekos et al. 2018; Lohse et al. 1999). However, the "overlap" terminology which was used for many years in the past to describe these patients suggests the concurrence of two different chronic liver diseases at the same time, which may be a misnomer as it is not the case for all patients (Boberg et al. 2011; Dalekos et al. 2019; European Association for the Study of the Liver 2015; Haldar and Hirschfield 2014; Trivedi and Hirschfield 2012). For these reasons, the term "variant" has been proposed instead, which is believed more proper to describe these conditions (Boberg et al. 2011; Dalekos et al. 2019; European Association for the Study of the Liver 2015).

The diagnosis of PBC–AIH variant in everyday clinical practice is difficult as there are no consensus criteria for its definition. Nevertheless, the "Paris criteria" published 20 years ago are still in use (Table 4; Chazouilleres et al. 1998), as some studies have shown very good sensitivity and specificity of these criteria for diagnosing patients with PBC–AIH variant (92% and 97%, respectively; Kuiper et al. 2010). However, the general impression is that the "Paris criteria" are very strict as from our experience only 50% or lower of patients with well-established AIH may fulfil these criteria. In addition, it should be kept in mind that the "Paris criteria" are largely different from the separate diagnostic criteria of each disease (Dalekos et al. 2019; European Association for the Study of the Liver 2015, 2017a; Hirschfield et al. 2018). In line with the above concerns, a recent Chinese study showed that patients with this variant may be identified more frequently and very easily using the "Paris criteria", when lowering the IgG cutoff to 1.3 times the upper limit of normal (ULN) instead of 2.0 times of the original criteria further supporting the potential underestimation of PBC–AIH diagnosis (Wang et al. 2013). Of interest, both the revised (Alvarez et al. 1999) and the simplified score (Hennes et al. 2008) for AIH diagnosis should not be used in clinical practice for the diagnosis of PBC–AIH variants, as they lack diagnostic accuracy (Boberg et al. 2011; Dalekos et al. 2019; European Association for the Study of the Liver 2015, 2017a; Gatselis et al. 2010b, 2015; Hirschfield et al. 2018; Papamichalis et al. 2007; Zachou et al. 2013). Investigation for autoantibodies against soluble liver antigen/liver pancreas (anti-SLA/LP) by specific ELISA or immunoblot with or without anti-Ro52 antibodies seems logical in the laboratory workup of patients with PBC and suspected AIH, as these antibodies have been detected in PBC–AIH variants (Eyraud et al. 2009; Kanzler et al. 2001; Muratori et al. 2009; Zachou et al. 2015).

The recent European and British clinical practice guidelines on PBC (European Association for the Study of the Liver 2017a; Hirschfield et al. 2018) as well as the European and Hellenic guidelines for AIH (Dalekos et al. 2019; European Association for the Study of the Liver 2015) recommend biopsy as an important and fundamental tool for

Table 4 Paris criteria for the diagnosis of PBC–AIH variant (adapted from Chazouilleres et al. 1998)

PBC
ALP ≥ 2 × ULN or γ-GT ≥ 5 × ULN
Detection of AMA by indirect immunofluorescence (cut-off titer: ≥ 1:40)
Florid duct lesions on liver biopsy
AIH
ALT ≥ 5 × ULN
IgG levels ≥ 2 × ULN or detection of SMA
Moderate or severe periportal or periseptal lymphocytic piecemeal necrosis (interface hepatitis) at the histological level

At least two out of three key criteria for each disease are needed for a firm diagnosis

PBC primary biliary cirrhosis, *AIH* autoimmune hepatitis, *ALP* alkaline phosphatase, *ULN* upper limit of normal, *γ-GT* gamma-glutamyl transpeptidase, *AMA* antimitochondrial antibodies, *ALT* alanine aminotransferase, *IgG* immunoglobulin G, *SMA* smooth muscle antibodies

the diagnosis of this variant form of PBC. In addition, an assessment by expert liver immunopathologist is strongly recommended because of potential therapeutic implications in PBC cases who do not respond to UDCA while in parallel they present disproportional increase of alanine aminotransferase (ALT) and/or IgG levels.

Conclusively, physicians should keep in mind that PBC–AIH variants should not be overdiagnosed in an attempt to avoid the development of side effects of immunosuppression in the PBC patients, but on the other hand, they should also be aware that it is largely questionable if the strict cutoffs of the "Paris criteria" are potentially adequate to identify all PBC patients with the PBC–AIH variant that would benefit from immunosuppressive treatment. Therefore, according to a position paper of the IAIHG, each patient with liver autoimmunity is better to be diagnosed first as an AIH, PBC, or PSC case, in keeping with the predominant features and this with additional manifestations should not be considered as suffering from a distinct clinical condition (Boberg et al. 2011; Dalekos et al. 2019; European Association for the Study of the Liver 2015; Gatselis et al. 2015; Haldar and Hirschfield 2014; Trivedi and Hirschfield 2012; Zachou et al. 2013).

Outcome and Treatment

As a firm definition of the PBC–AIH variant does not exist, controlled trials regarding the management of this condition are missing. An old but very well-designed German study compared 20 patients with overlapping characteristics with 2 groups of 20 patients each suffering from classical AIH and PBC (Lohse et al. 1999). They found that the overlap group had indeed characteristics of both AIH patients with considerable increase of ALT and IgG levels, but also typical PBC features (elevation of cholestatic enzymes and IgM levels). In more detail, the overlap patients fell between the two groups with ALT levels similarly as high as the AIH group, but most of them also with significant elevation of alkaline phosphatase levels. In addition, their genetic, serological and histological profiles were of interest. Actually, all overlap patients had at least either bile duct destruction at the histological level or detection of AMA, while in the vast majority of patients, the histocompatibility leukocyte antigens haplotype was characteristic of that reported in AIH suggesting the hypothesis that all of these overlap patients were primarily suffering from PBC and because of an AIH-related genetic susceptibility, developed a more hepatitic picture during the course of the disease (Lohse et al. 1999). Response to immunosuppression with corticosteroids alone or in combination with azathioprine in this study was excellent and comparable to AIH patients.

Regarding the natural history, most studies have shown a more severe course of patients with PBC–AIH variant compared to patients with PBC alone as attested by the earlier development of portal hypertension, liver decompensation and liver-related death or liver transplantation (Al-Chalabi et al. 2008; Chazouilleres et al. 2006; Heurgue et al. 2007; Levy et al. 2014; Ozaslan et al. 2014; Poupon et al. 2006; Silveira et al. 2007; Yang et al. 2016). However, the retrospective design of these studies along with the small number of patients included cannot result in safe conclusions. Therefore, it seems rational to treat both disease elements with a combination of UDCA and immunosuppression, as according to recent meta-analyses, combination therapy proved more effective than UDCA alone (Ozaslan et al. 2014; Zhang et al. 2015) (Table 2).

In parallel, the recent European and British clinical practice guidelines for PBC have suggested the addition of immunosuppressive therapy (either corticosteroids alone or in combination with azathioprine) to UDCA in PBC cases if at least moderate necroinflammatory activity (interface hepatitis) is present on liver histology (European Association for the Study of the Liver 2017a; Hirschfield et al. 2018). However, the recent European and Hellenic clinical practice guidelines for AIH recommend initiation of treatment at lower cutoffs of ALT or IgG compared to the "Paris criteria" and optionally even for milder AIH cases with histological activity index less or equal to four and mild or absence of fibrosis indicating further adversities in the management of patients with PBC–AIH variant (Dalekos et al. 2019; European Association for the Study of the Liver 2015). Alternatively, in patients with predominant AIH manifestations, initiation with immunosuppression only has also been suggested and the addition of UDCA is then recommended if the response is not sufficient (Dalekos et al. 2019; European Association for the Study of the Liver 2015).

Interestingly, patients with the PBC–AIH variant seem to respond to less immunosuppressive treatment and maintain remission after stopping treatment at higher rates than AIH patients (Chazouilleres et al. 2006; Ozaslan et al. 2014). Alternative agents such as mycophenolate mofetil, ciclosporin or tacrolimus can be used in non-responders (Dalekos et al. 2019; Gatselis et al. 2015; Ozaslan et al. 2014; Zachou et al. 2011, 2013, 2016). In AIH patients who develop PBC features during follow-up, the addition of UDCA seems reasonable in protecting—in particular in young patients—from the development of ductopenia and biliary cirrhosis, but definite data on this management are missing.

Uncommon Variants and Specific Forms of PBC

Premature Ductopenic Variant of PBC

A rare PBC variant was described in 1980s, which is characterized by serious protracted pruritus associated with

progressive cholestasis and jaundice (Nakanuma et al. 1988; Vleggaar et al. 2001) (Table 2). Unfortunately, UDCA treatment is not efficient in this variant form of PBC. There is extensive bile duct loss in the absence of significant fibrosis or cirrhosis at the histological level and therefore, these patients should be referred to expert centres as usually there is a need for liver transplantation because of severe and persistent itching or deep jaundice (Nakanuma et al. 1988; Vleggaar et al. 2001). Pregnancy in women with already established premature ductopenic PBC variant could be deleterious, as it may add cholestasis during the last trimester and/or post-partum.

Non-Cirrhotic PBC Variant with Portal Hypertension

Because of an increase in routine testing of liver function tests along with liver autoimmune serology testing in recent decades, the PBC pattern at presentation has changed and a reduced disease severity has now been observed (Gatselis et al. 2017; Murillo Perez et al. 2018). However, in contrast with other liver diseases, portal hypertension can occur in PBC even before the onset of cirrhosis at the early stages leading to the development of oesophageal varices in approximately 5–6% of patients (Ali et al. 2011; Ikeda et al. 2012) (Table 2). Therefore, clinical and laboratory signs of portal hypertension should be carefully investigated in all PBC patients at initial evaluation and during follow-up. The underlying pathogenetic mechanisms of portal hypertension in these cases are still unclear although a sinusoidal blockage and angiogenetic and/or fibrotic responses potentially induced by aquaporin-1 resulting in an enhanced perfusion of arterial blood flow to the sinusoids have been implicated (Iguchi et al. 2014; Maruyama et al. 2015).

Screening for varices in this variant form of PBC is recommended and in particular if platelets are less than 140.000 or 200.000/μl, Mayo risk score ≥ 4.5, albumin < 4 g/dl and/or bilirubin > 1.2 mg/dl (Bressler et al. 2005; Levy et al. 2007). Prophylaxis and management approaches should be the same as in every other chronic liver disease according to the Baveno-VI guidelines (de Franchis 2015). However, PBC patients suffering already from fatigue may experience deterioration of their symptoms by the addition of non-selective β-blockers. As the other PBC patients with cirrhosis and portal hypertension, patients with this variant form are at risk for developing pulmonary hypertension which in general is more frequent than was thought previously in PBC patients with portal hypertension while it bears poor prognosis (Shen et al. 2009).

PBC with Concurrent Viral Hepatitis B or C

The presence of chronic viral infections in patients with PBC or vice versa the presence of PBC in patients with chronic hepatitis B or C is often very difficult to be recognized taking into account the heterogeneity of liver diseases, the absence of awareness of this possibility and the shortfall of many centres outside reference centres to use reliable tests for the detection of AMA and/or PBC-specific ANA (Gatselis and Dalekos 2016; Rigopoulou and Dalekos 2008). Therefore, a considerable delay in diagnosis of this subgroup of PBC patients is characteristic (Rigopoulou et al. 2013) (Table 2). Of interest, a recent review of 1842 liver biopsies from patients with chronic hepatitis B or C from Canada showed characteristics of other liver diseases in more than 20% of them including three cases with concomitant PBC (Nair et al. 2010). On the other hand, AMA detection in patients with hepatitis C was shown to be more frequent than previously thought, reaching up to 8% of the hepatitis C population in a multicenter study from Spain and South America (Ramos-Casals et al. 2005), while in an Italian study, 8% of 170 PBC patients also suffered from hepatitis C (Floreani et al. 2003). This coexistence might have clinical implications as an accelerated development of cirrhosis and/or hepatocellular carcinoma was recorded in this specific group of PBC patients (Floreani et al. 2003; Ramos-Casals et al. 2005). The latter has also been shown in a recent study from Taiwan where 9 out of 76 PBC patients proved to carry HCV infection characterized by significant advanced liver disease (Chen et al. 2013).

From our recent retrospective analysis in 1493 hepatitis B virus (HBV) and 526 hepatitis C virus (HCV) patients, we found 17 confirmed PBC cases (8 with HCV and 9 with HBV infections) (Rigopoulou et al. 2013). In the majority of patients, the diagnosis of viral hepatitis preceded that of PBC by many years. The PBC diagnosis was based on AMA presence and elevated cholestatic enzymes in all 17 patients, while one-third experienced severe pruritus many years before diagnosis. Patients with PBC and HBV were significantly younger at PBC diagnosis compared to those with PBC and HCV. Of note, at initial assessment, 60% of patients had already established cirrhosis with the group of PBC and HCV carrying the highest frequency (87.5% vs. 33.3% in PBC and HBV; $P < 0.05$) suggesting that a prompt and timely diagnosis of this specific subgroup of PBC is of major importance (Rigopoulou et al. 2013). The PBC patients with HBV seem to have better outcome compared to those with HCV, as none of the six non-cirrhotic patients with HBV and PBC developed cirrhosis during follow-up. However, this finding could be due to the treatment options that were available for the management of HBV and HCV infections during those days (interferon-α-based therapies for HCV infection and not the current very efficient treatments with direct acting antivirals). Indeed, it is well-known that the use of nucleos(t)

ide analogues contrary to the interferon-α-based treatments in HCV can control HBV replication with no adjacent effect, related to exacerbation of autoimmune phenomena. Although there is no specific data, treatment strategies for this group of patients should follow the current practice guidelines for the management of HBV, HCV and PBC (European Association for the Study of the Liver 2017a, 2017b, 2018).

PBC–PSC and PBC–IgG4 Sclerosing Cholangitis Variants

PBC–PSC variant syndrome demonstrating the clinical and laboratory characteristics of both PBC and PSC including its variant form of small duct PSC is an exceptionally uncommon disorder (Table 2). Less than ten patients have been reported so far in the literature and therefore, general conclusions and guidelines cannot be drawn for this controversial entity (Floreani et al. 2015b; Sundaram et al. 2018). In parallel, the coexistence of IgG4-sclerosing cholangitis and PBC is also an extremely rare condition that has been reported in very few cases (Takemoto et al. 2014) (Table 2). As about 90% of IgG4-sclerosing cholangitis patients also have autoimmune pancreatitis (Huang 2016; Kamisawa et al. 2019), investigation of serum IgG4 levels along with abdominal imaging could be rational in an attempt to identify PBC patients not responding to routine treatment with UDCA but clear-cut guidelines cannot be given.

PSC Variants

Small Duct PSC Variant

The diagnosis of this variant form of PSC is made at the histological level as cholangiography even after high-quality MRCP is normal (Bjornsson 2009; Karlsen et al. 2017; Lindor et al. 2015; Schramm et al. 2017) (Table 5). Small duct PSC is found in 3–5% of PSC patients, but it is not clear if this variant represents an early stage of PSC, a real variant of PSC or a separate distinct disease compared to the classic large duct PSC (Karlsen et al. 2017; Lazaridis and LaRusso 2016; Lindor et al. 2015; Weismuller et al. 2017). Of note, there is a risk of progression to classic large duct PSC during follow-up, but the precise risk is largely unknown (Angulo et al. 2002; Bjornsson et al. 2002, 2008).

Small duct PSC is associated with better prognosis as attested recently in a recent large retrospective multicenter analysis from the International PSC study group (Weismuller et al. 2017). Actually, the latter study showed in the multivariable analysis that small duct PSC was associated with significantly lower risk of liver transplantation or death and development of hepatobiliary malignancy in both sexes compared to the classic PSC phenotype. As for classic PSC, UDCA at doses > 28 mg/kg/day should not be administered for the management of small duct PSC patients (Lindor

Table 5 Variants of primary sclerosing cholangitis (PSC) and the distinct syndrome of IgG4-associated sclerosing cholangitis

Small duct PSC variant
3–5% of PSC patients; liver biopsy is needed for diagnosis as MRCP is normal
Risk of progression to classic PSC is practically unknown
It is associated with better prognosis (lower risk of liver transplantation or death and development of hepatobiliary malignancy compared to the classic PSC)
PSC–AIH variant
Observed in 7–14% of mainly young PSC patients; ulcerative colitis is less common compared to classic PSC
Less well-defined diagnostic criteria than PBC–AIH variant; diagnosis is based on typical cholangiographic or histologic characteristics of PSC in combination with AIH features
A specific and unique variant in children and adolescents with AIH characterized by both AIH and sclerosing cholangitis manifestations (autoimmune sclerosing cholangitis)
MRCP is recommended for all children and adolescents with an initial AIH diagnosis—MRCP screening is not justified in adults
Data on the outcome are scarce and conflicting; a recent large study of the international PSC study group has shown a similar risk of liver disease progression compared to classic PSC but the development of hepatobiliary malignancy is significantly lower
Combination of immunosuppression and UDCA is suggested although biliary lesions can progress
IgG4-associated sclerosing cholangitis
Not a real PSC variant but a distinct immune-mediated cholestatic disorder of unknown aetiology; frequently associated with autoimmune pancreatitis or other IgG4-related diseases
Contrary to PSC it responds very well to steroids and it is less likely to have concurrent IBD; also it is not a risk factor for cholangiocarcinoma
Its diagnosis is based on: characteristic biliary findings on imaging, increased IgG4, coexistence of IgG4-related diseases (autoimmune pancreatitis, dacryoadenitis/sialadenitis or IgG4-related retroperitoneal fibrosis) and characteristic histopathology
Assessment of the efficacy of a trial of corticosteroids could be an optional extra diagnostic criterion
Diagnostic accuracy of serum IgG4 is not sufficient (no reliable cutoffs) while 10–20% of PSC patients have increased IgG4 levels
Outcome is favourable as remission is achieved by steroids treatment in most patients (prednisolone 0.6 mg/kg/day for initial induction therapy following by maintenance therapy with 5–10 mg/day for at least 3 years)

MRCP magnetic resonance cholangiopancreatography, *IgG4* immunoglobulin G4 subclass, *IBD* inflammatory bowel disease, *AIH* autoimmune hepatitis, *UDCA* ursodeoxycholic acid

et al. 2015). However, there is not sufficient data to argue against prescription of low-dose UDCA (13–17 mg/kg/day), as several recent studies have shown that PSC patients who normalize cholestatic enzymes have a better prognosis (Al Mamari et al. 2013; Lindstrom et al. 2013; Stanich et al. 2011).

PSC–AIH Variant

Diagnosis

As for PBC–AIH variant, the term "overlap" has been used previously for PSC patients with biochemical, serological and histological features of AIH. However, currently it has been shown that this variant form of PSC cannot be considered as a separate clinical entity and the term "overlap" should be abandoned, as actually it reflects a PSC subphenotype during a continuous clinical spectrum of the disease (Boberg et al. 2011; Deneau et al. 2017). The PSC–AIH variant is observed in 7–14% of mainly young PSC patients (Boberg et al. 2011; Deneau et al. 2017; Floreani et al. 2005; Lazaridis and LaRusso 2016; Lindor et al. 2015)—6.6% in the recent large multicenter study from the international PSC study group including 7121 PSC patients (Weismuller et al. 2017). These patients appear to have less common concurrent ulcerative colitis compared to patients with classic PSC (Weismuller et al. 2017) (Table 5).

The diagnostic criteria for patients with the PSC–AIH variant are even less well defined than those used for the diagnosis of PBC–AIH variant, while the diagnostic scoring systems of the IAIHG for the diagnosis of AIH are not useful (Dalekos et al. 2018, 2019; European Association for the Study of the Liver 2015; Gatselis et al. 2010b; Karlsen et al. 2017; Papamichalis et al. 2007). In everyday practice, PSC–AIH diagnosis is based on typical cholangiographic or histologic characteristics of PSC in combination with AIH features (Karlsen et al. 2017; Lazaridis and LaRusso 2016; Lindor et al. 2015; Luth et al. 2009) (Table 5). Of note, a specific and unique variant has been reported in almost 50% of children and adolescents suffering from well-established AIH characterized by both AIH and sclerosing cholangitis manifestations (Gregorio et al. 2001; Rojas et al. 2014). This variant form called "autoimmune sclerosing cholangitis" and recent guidelines for its diagnosis and management have been published by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Mieli-Vergani et al. 2018). Taking together, it is reasonable to recommend further testing for AIH including liver histology among PSC patients with high aminotransferases (usually > 5×ULN) and/or IgG levels. Similarly, MRCP screening is advised for all children and adolescents with an initial AIH diagnosis (Dalekos et al. 2019; European Association for the Study of the Liver 2015; Mieli-Vergani et al. 2018), while it is not justified in adults as this entity seems exceptionally rare in adults with AIH (Lewin et al. 2009).

Outcome and Treatment

Available data on the outcome of this peculiar and infrequent variant form of PSC are scarce and conflicting. Indeed, previous small case studies have shown a better outcome of patients with PSC–AIH variant compared to classic PSC probably because of the use of combination treatments (immunosuppression plus UDCA) (Floreani et al. 2005; Zenouzi and Lohse 2014) although others found opposite results (Al-Chalabi et al. 2008; Luth et al. 2009) (Table 5). In the recent large study of the international PSC study group, it has been shown that patients with PSC–AIH variant had a similar risk of liver disease progression compared to those with the classic PSC although, the development of hepatobiliary malignancy was significantly lower (Weismuller et al. 2017).

As for the PBC–AIH variant, there are no randomized controlled trials for patients with PSC–AIH variant to draw any firm conclusions for its management (Boberg et al. 2011). Nevertheless, the combination of immunosuppressive therapy and UDCA has been proposed and response criteria have been reported recently for autoimmune sclerosing cholangitis, the paediatric form of the variant (Mieli-Vergani et al. 2018). However, although the biochemical and histologic indices may improve, the biliary lesions can progress and therefore, the outcome of these patients seems worse compared to patients suffering only from AIH (Gregorio et al. 2001; Rojas et al. 2014). The European and the Hellenic clinical practice guidelines (Dalekos et al. 2019; European Association for the Study of the Liver 2015) have also suggested the combination of UDCA and prednisolone plus azathioprine, although the literature regarding treatment outcome is scarce and response rates are less striking than in AIH without PSC. Therefore, large multicenter controlled trials are needed for this infrequent variant form of PSC.

IgG4-Associated Sclerosing Cholangitis IgG4-associated sclerosing cholangitis is usually confused by unfamiliar practitioners as a subtype of PSC. Therefore, its distinction from classic PSC with high IgG4 levels is important, because the cholangiographic lesions of IgG4-associated sclerosing cholangitis may resolve completely after corticosteroid treatment (Table 5). In addition, contrary to PSC, IgG4-associated sclerosing cholangitis is not considered a risk factor for the development of cholangiocarcinoma. Its diagnosis is based on the following two or more criteria: characteristic biliary findings on imaging, increased serum levels of IgG4, coexistence of IgG4-related diseases (apart from the involvement of the biliary tract) such as autoimmune pancreatitis, dacryoadenitis/sialadenitis or

IgG4-related retroperitoneal fibrosis and characteristic histopathologic features on bile duct or ampullary biopsy showing marked lymphoplasmacytic infiltration with more than ten IgG4-positive plasma cells/high power field, storiform fibrosis and obliterative phlebitis with the last two being the most important histological findings (Kamisawa et al. 2019; Ohara et al. 2012). However, as sometimes it is difficult to obtain sufficient specimens, many centres particularly in Europe and USA are reluctant to do biopsies of the bile duct or the ampulla taking also into account the perceived risk of pancreatitis or cholangitis. In these cases, the assessment of the efficacy of a trial of corticosteroids could be an optional extra diagnostic criterion to confirm an IgG4-associated sclerosing cholangitis diagnosis (Table 5).

The diagnostic accuracy of serum IgG4 determination is not sufficient while reliable cutoffs have not been established. On the other hand, slight increase of serum IgG4 levels has also been reported in 10–20% of PSC patients not fulfilling the criteria of IgG4-associated sclerosing cholangitis (Benito de Valle et al. 2014; Berntsen et al. 2015; Boonstra et al. 2014; Karlsen et al. 2017; Ohara et al. 2013; Tanaka et al. 2014, 2017). Therefore, additional investigation of IgG4/IgG1 ratio (> 0.24 suggestive of IgG4-associated sclerosing cholangitis) and blood IgG4/IgG RNA ratio by real-time PCR which is high in IgG4-associated sclerosing cholangitis have been proposed in an attempt to improve the diagnostic algorithm (Boonstra et al. 2014; Doorenspleet et al. 2016). Nevertheless, an IgG4 cutoff of ≥ 117 mg/dl has been reported to bear 92% sensitivity and 88% specificity for the diagnosis of IgG4-associated sclerosing cholangitis, while that of ≥ 140 mg/dl or ≥ 280 mg/dl, 90% and 85% or 70% and 98%, respectively (Ohara et al. 2013).

Although there is not sufficient data on the long-term prognosis, the outcome appears favourable as steroids treatment is very efficient in the majority of patients with IgG4-associated sclerosing cholangitis. Oral prednisolone at 0.6 mg/kg/day has been recommended for initial induction treatment, following by gradual reduction depending on the response to a maintenance dose of 5–10 mg/day after 2–3 months (Table 5). Maintenance therapy should be continued for at least 3 years (Kamisawa et al. 2019). In case of relapse, re-administration of steroids at increased dose with or without immunomodulatory drugs (azathioprine, mycophenolate mofetil, etc.) or rituximab is recommended (Hart et al. 2013; Kamisawa et al. 2019).

Conclusions and Research Agenda

Apart from the typical presentation of PBC and PSC patients, there are important variant and specific syndromes in everyday clinical practice that need attention (Tables 2, 5). In addition, IgG4-associated sclerosing cholangitis is nowadays recognized as a specific immune-mediated cholestatic liver disease which is largely different from PSC (Table 5). Because of their relative rarity, these variant and specific forms of autoimmune cholestatic liver diseases suffer from several inherent difficulties in definition, diagnosis, investigation of pathogenesis and management. Some of these uncertainties are summarized below which may help scientists to design well-organized, concentrated and pioneer multicenter, research collaborations that can guide to better understanding of their pathogenesis and treatment options.

- Which is the laboratory consensus algorithm of investigation for AMA detection to minimize the AMA-negative PBC cases?
- Do we need liver biopsy for PBC diagnosis in AMA-negative PBC patients in the presence of PBC-specific ANA?
- Do we need long-term prospective studies on the significance and outcome of subjects with isolated AMA seropositivity?
- Do we need long-term prospective studies on the significance and outcome of patients with AIH and AMA seropositivity?
- What is the real impact of the presence of other extrahepatic autoimmune diseases on the outcome, response to treatment and quality of life in PBC patients?
- Do we need new criteria apart from the Paris criteria with "lower cutoffs" of IgG and ALT to proceed to liver biopsy in a PBC patient with suspicion of the presence of PBC–AIH variant?
- Which PBC patient will benefit from immunosuppressive treatment? (grade of necroinflammatory activity—investigation for other markers, e.g., anti-SLA/LP antibodies?)
- Validation of the old criteria and the unmet need for a specific diagnostic scoring system for the diagnosis of PBC–AIH variants.
- Which is the degree of histological bile duct injury that denotes PBC in patients with already established AIH? Do these patients require additional treatment with UDCA?
- Do we need randomized controlled trials for the management of PBC–AIH variants?
- Who is the candidate to develop the uncommon variants of PBC?
- Is testing for serological markers of HBV and HCV infections of any significance in PBC patients?
- Which is the real long-term prognosis and outcome of small duct variant form of PSC?
- Do we need the establishment of precise and reliable criteria for the diagnosis of PSC–AIH variant?

- Which PSC patient will benefit from the addition of immunosuppression? And do we need randomized controlled trials for the management of PSC–AIH variants?
- What are the similarities and differences between PSC and autoimmune sclerosing cholangitis?
- Do we need the establishment of a precise and reliable cutoff for IgG4 serum levels?
- What is the natural history and long-term prognosis of patients with IgG4-associated sclerosing cholangitis and what are the similarities with and differences to classic PSC?
- Do we need randomized controlled trials for the management of patients with IgG4-associated sclerosing cholangitis?

Compliance with ethical standards

Conflict of interest Authors have nothing to declare.

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