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Autoimmune Hepatitis-Primary Biliary Cirrhosis Overlap Syndrome: Current Trends in Diagnosis and Treatment

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Abstract

Primary Biliary Cirrhosis (PBC) and Autoimmune Hepatitis (AIH) are the two main immune-mediated liver diseases. Under normal conditions, they are generally differentiated easily on the basis of clinical, biochemical, serological, and histological findings. However, a small subgroup of patients may simultaneously present with features of both diseases, designated as AIH-PBC overlap syndrome, making its diagnosis even more difficult. Currently, the pathogenesis of AIH-PBC overlap syndrome is still debated and it remains unclear whether the syndrome forms a distinct entity or a variant of PBC or AIH. Nevertheless, identifying patients with overlap syndrome has important therapeutic management and prognostic implication. Moreover, their treatment is largely empirical and extrapolated from the primary diseases. Patients with AIH-PBC overlap may benefit from immunosuppressive treatment with or without Ursodeoxycholic Acid (UDCA), which may also have immuno modulatory action. Therefore, it emphasizes the importance of establishing criteria to make a clear diagnostic distinction. Since there is no current consensus on defining the overlap conditions, estimating the prevalence, diagnosis, and treatment of the AIH-PBC overlap syndrome remains a clinical one challenge. In this review, we will focus on the current perspective and progress in diagnosis and treatment of this disease.

Keywords: Autoimmune hepatitis; Primary biliary cirrhosis; Overlap syndrome; Diagnosis; Treatment

Abbreviations

AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cholangitis/Cirrhosis; AILDs: Autoimmune Liver Diseases; AMA: Antimitochondrial Auto antibodies; Ig: Immunoglobulin; UDCA: Ursodeoxycholic Acid (UDCA); ANA: Antinuclear Antibody; SMA: Anti-Smooth Muscle Antibody; Anti-LKM1: Liver-Kidney Microsomal Antibody 1; Anti-LC1: Anti-Liver Cytosol Antibody Type 1; PSC: Primary Sclerosing Cholangitis; IAIHG: International Autoimmune Hepatitis Group; pANCA: Perinuclear Anti-Neutrophil Cytoplasmic Antibody; Anti-SLA/LP: Antibody to Soluble Liver/Pancreas Antigen; Anti-SLA: Anti-Soluble Liver Antigen Antibodies; ULN: Upper Limit of Normal; HLA: Human Leukocyte Antigen; RDC: Revised Diagnostic Criteria; SDC: Simplified Diagnostic Criteria; EASL: European Association for the Study of Liver Diseases; ALP: Alkaline Phosphatase; GGT: Gamma-Glutamyltranspeptidase.

Introduction

Autoimmune Hepatitis (AIH) and Primary Biliary Cirrhosis (PBC) are the two main Autoimmune Liver Diseases (AILDs) [1]. It's well known that PBC, currently called primary biliary cholangitis, is a chronic cholestatic liver disease of unknown etiology characterized by the presence of highly specific Anti-Mitochondrial Autoantibody (AMA) and an autoimmune-mediated destruction of small intrahepatic bile ducts, resulting in portal inflammation and fibrosis which can lead to cirrhosis and ultimately, liver failure [2,3]. On the other hand, AIH is a chronic and progressive liver disease of unknown etiology, characterized by continuing hepatocellular inflammation and necrosis and tending to progress to cirrhosis [4,5]. Immune serum markers are present frequently, including autoantibodies against liver-specific and non-liver-specific antigens and elevated levels of Immunoglobulin (Ig) G [4,5]. From a practical standpoint, AIH has been broadly categorized into two distinct disease subtypes on the basis of autoantibody profiles: type 1, which is associated with either Anti-Nuclear Antibodies (ANA) or Anti-Smooth Muscle Antibodies (SMA) in serum; and type 2, which is much less common than type 1 and is associated with the presence of either Liver-Kidney Microsomal Antibody Type 1 (anti-LKM1) or Anti-Liver Cytosol Antibody Type 1 (anti-LC1) [4-6]. Most PBC and AIH patients are generally differentiated easily on the basis of clinical, biochemical, serological, and histological findings (Table 1) [6-8]. However, AIH and PBC may simultaneously coexist in some patients, designated as AIH-PBC overlap syndrome [2-8]. The diagnosis of this overlap syndrome becomes more difficult to interpret, as there is not a discriminative diagnostic index that can draw the boundaries between AIH and PBC. Since there is no current consensus on diagnostic criteria, the prevalence of PBC-AIH overlap syndrome varies among medical centres [9,10]. It has been reported in previous publications that 2.1% to 19.3% of patients with the typical hallmarks for PBC also have features of AIH [11-20]. Such a broad variation in this prevalence may owe partly to the difficulty of diagnosing two distinct autoimmune liver diseases in the same patients. Since no randomized controlled therapeutic trials have been carried out so far, therapy for AIH-PBC overlap syndrome is empiric and extrapolated from data derived from the treatment of the two primary disorders and retrospective small patient series of AIH-PBC overlap conditions.

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Table 1: Main features of Autoimmune Hepatitis (AIH) and Primary Biliary Cirrhosis (PBC).

Feature	AIH	PBC
Femal-male ratio	3.6:1	9:1
Age at diagnosis	Any age	Middle-aged (30-65 years)
Aminotransferases	Often 3-10-fold ULN	Normal or slightly elevated (<2-fold ULN)
Alkaline phosphatase	Normal or slightly elevated (<2-fold ULN)	Evalated (≥2-fold ULN)
Billirum	Elevated in later stages	Normal or slightly elevated
Immunoglobulins	IgG>1.5-fold ULN	IgM increased in most patients
Antoantibodies		
AMA	Low titre in ~5-10%	AMA in 90-95%
ANA	Significant titres	30-50%
SMA	Often present	May be present
Anti-LKM1	3-4%	Rarely
Anti-SLA/LP	10-30%	May be present
pANCA	50-95%	Rarely
HLA association	A3, B8, DR3, DR4	DR8
Liver biopsy		
Interface hepatitis	Typical finding	Variably present
Portal inflammation	Lymphoplasmacytic infiltration	Lymphocytic infiltration
Biliary changes	Rarely	Typical
Granulomas	No or Atypical	Characteristic
Coexisting IBD	Rarely associated with AIH	Not characteristic
First line medical therapy	Corticosteroids with or without azathioprine	UDCA

Notes: AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cirrhosis; AMA: Anti-mitochondrial Antibody; ANA: Antinuclear Antibody; SMA: Anti-Smooth Muscle Antibody; IBD: Inflammatory Bowel Disease; Anti-LKM1: Liver-Kidney Microsomal Antibody Type 1; pANCA: Perinuclear Anti-Neutrophil Cytoplasmic Antibody; Anti-SLA/LP: Antibody to Soluble Liver/Pancreas Antigen; UDCA: Ursodeoxycholic Acid; ULN: Upper Limit of Normal; HLA: Human Leukocyte Antigen.

In this review, we will focus on the current perspective and advances in the diagnosis and management of AIH-PBC overlap syndrome.

Is PBC-AIH Overlap Syndrome A Distinct Entity?

The term "overlap syndromes" has been introduced to the field of hepatology to describe variant forms of AIH which present with characteristics of AIH and PBC or Primary Sclerosing Cholangitis (PSC) [2-8,11-17]. Patients with overlap syndromes present with both hepatitis and cholestatic serum liver tests and have histological features of both AIH and PBC or PSC [4-9]. In particular, AIH-PBC overlap syndrome is the most common form of overlap syndromes and may be associated with a poor prognosis, with earlier onset of portal hypertension and need for liver transplantation [2,8,12]. The first cases of AIH-PBC overlap syndrome were reported in the 1970s [21,22], but this entity was assumed to be rare. Indeed, lack of universal agreement on what defines the AIH-PBC overlap syndrome has generated considerable confusion in the literature [23]. For example, this syndrome has also been named "hepatic variant of PBC", "PBC hepatic form", "variant syndromes" or "autoimmune cholangitis (synonymous with AMA-negative PBC)" [4-7,10,12]. But, there is disagreement as to the variant most commonly called AMA-negative PBC [2,5,11]. Some authors think AIH-PBC overlap syndrome patients had marked piecemeal necrosis or high transaminases, which differed from that of autoimmune cholangitis [11]. AMA-negative PBC shares many features with PBC, and is not regarded as an overlap syndrome but as a variant of PBC [2,11]. As this term is misleading, some authors suggested that the term "variant syndrome" might be more appropriate [24].

Since there is currently no known etiopathogenetic basis for the distinction of overlap from the classical disorders, it remains unclear whether PBC-AIH overlap syndrome forms a distinct entity or is a variant of PBC or AIH [8,10,23]. There is no internationally agreed criteria for diagnosis of "overlap syndromes", and several definitions have been used in various reports [4,7-14]. Patients with overlapping features between PBC and AIH most frequently present concomitantly, but there have been some reports of patients with the typical features of PBC or AIH who switched from one disease to another during the long-term course [25,26]. So, the latest guidance from the International Autoimmune Hepatitis Group (IAIHG) clearly indicated that the definition of diagnostic criteria for overlap conditions could only be arbitrary, and patients with overlapping features were not to be regarded as separate entities [7].

However, since the term is still widely used in clinical practice, identification of the so-called overlap syndrome appears to be somewhat clinical importance in the management and prognosis of these particular patients. Previous studies have shown that AIH-PBC overlap syndrome might have worse clinical outcomes compared to patients with PBC alone, with earlier onset of portal hypertension and need for liver transplantation [12,27,28]. A study from the Mayo clinic in 2007 reported that over an average 5.75-year follow-up, more

Table 2: The frequencies of PBC-AIH overlap syndrome according to published data.

Author/year	PBC (No. of patient)	AIH (No. of patient)	AIH-PBC overlap (No. of patient)/(Frequency)
Chazouillères et al./1998 [11]	130	-	12/9.2%
Silveira et al./2007[12]	135	-	26/19.3%
Neuhauser et al./2010 [13]	368	-	43(12%) [†] 23(6%) [†]
Heurgué et al./2007 [14]	52	48	13/11.3%
Muratori et al./2002 [15]	142	-	3/2.1%
Joshi et al./2002 [16]	331	-	16/4.8%
Czaja. /1998 [17]	37	162	15/7.5%
Yamamoto et al./2003 [18]	134	48	22/12.1%
Suzuki et al./2004 [19]	156	52	19/8.4%
Park Y/2015 [36]	81	61	9 (6.3%)
Yoshioka Y/2014 [37]	280	-	28(10%)

Notes: †The differences in incidence are associated with the applied criteria. Using the IAIHG revised criteria for AIH and simplified criteria, the incidence is 12% and 6%, respectively.

patients with AIH-PBC overlap developed portal hypertension (54% *vs.* 28%; P < 0.01), features of decompensate disease and progressed to transplantation or death (38% *vs.*19%; P < 0.05) compared to patients with AIH alone [12]. Moreover, patients with AIH-PBC overlap syndrome may benefit from immunosuppressive treatment with or without Ursodeoxycholic Acid (UDCA), while PBC does not response well to immunosuppressive agent [4-8,11]. Since most patients of AIH-PBC overlap syndrome required additional treatment with an immunosuppressive regimen in addition to UDCA [7,8,11], emphasizing that distinct of this overlap condition should neither be delayed nor missed.

Frequencies of AIH-PBC Overlap Syndrome

AIH occurs worldwide and its incidence varies geographically. The annual incidence of AIH among Europeans is 0.8-1.9 cases per 100,000 individuals, and its point prevalence is 11.6-16.9 cases per 100,000 persons per year and appears to be similar to that of PBC [29-31]. In Asia-Pacific area, New Zealand demonstrated a high prevalence of 24.5 per 100 000 people while other countries owned comparatively low prevalence [10,32]. In Asia most reports come from Japan; and the reported prevalence in Japan is only 0.08-0.015 cases per 100,000 persons [33]. There are no robust epidemiological data on AIH in China [32,34]. As a consequence of the lack of pathognomonic features and the difficulties this creates in making a diagnosis, published data are likely to underestimate the true incidence and prevalence of the disease.

The AIH-PBC overlap syndrome is the most common form in patients with young age and inflammatory bowel disease [8]. But estimating the true frequency of this overlap syndrome poses problems, as its low frequency and the lack of standardized criteria [7,9,35]. Nevertheless, the incidence of the AIH-PBC overlap syndrome reported in the literature has ranged from 2.1% to 19.3% (Table 2) [11-20,35-37]. The prevalence of this overlap syndrome varies among medical centres, depending on the diagnostic criteria for AIH used in different studies. Chazouillères et al. [11] proposed diagnostic criterion for AIH-PBC overlap syndrome and found that 12 (9.2%) of 130 patients with PBC satisfied these strict criteria. By applying the same set of criteria to a group of 331 patients included in a clinical trial, Joshi et al. [16] concluded that the prevalence of patients overlapping AIH was 4.8%. Two extended analyses provided evidence for AIH-PBC overlap in 7.5% of 199 patients with AIH (n = 162) or PBC (n = 37) and in 12.1% of 182 patients with PBC (n = 134) or AIH (n = 48) [17,18]. In an Italian group of patients with a diagnosis of PBC, the occurrence of AIH-PBC overlap was only 3 (2.1%) among 142 cases [15], while 26 (19.3%) among 135 PBC patients in the study by Silveira et al. [12] could be classified as an AIH-PBC overlap. Using the revised criteria for AIH, Neuhauser et al. [13] found that approximately 12% of unselected PBC patients had probable PBC-AIH overlap whereas, using only the simplified criteria, 6% of PBC patients met criteria for overlap. Of the 227 patients with autoimmune liver disease in Japan, 19 (8.4%) were diagnosed with the AIH-PBC syndrome [19]. This data is similar to another Japanese study, which reported 28 (10%) overlap syndrome out of 280 PBC [37]. In a recent study in China, the prevalence of AIH-PBC overlap is 9% among the PBC patients [38]. Therefore, the prevalence of the AIH-PBC overlap syndrome varies among medical centres based on the different diagnostic criteria they used. In addition, evidence of a significantly increased prevalence of AIH-PBC overlap syndrome in Hispanic compared with non-Hispanic PBC patients (31% *vs.* 13%, P=0.002) suggested genetic predisposition [28].

Diagnosis

Diagnosing AIH-PBC overlap syndrome remains a challenge, especially because there is still no consensus on the most appropriate diagnostic criteria [7-10]. In general, differential diagnosis of PBC and AIH is not problematic, and is easily performed by biochemical findings, autoantibody profiles and liver histology as shown in Table 1 [6-8]. However, standardization of diagnostic criteria for AIH-PBC overlap syndrome has not been achieved, and it is very difficult in diagnosing patients with possible overlap syndromes [7-10].

Diagnostic criteria for AIH

Classically, the diagnosis of AIH is based on histological abnormalities, characteristic clinical and laboratory features, abnormal levels of serum globulins, and the presence of one or more characteristic auto antibodies [4-6,39-41]. Auto antibodies are one of the distinguished features of AIH [4-6]; and the detection

Table 3: Revised diagnosis criteria for the diagnosis of Autoimmune Hepatitis (AIH) [40].

Category	Factor	Score	Category	Factor	Score
Gender	Female	+2	Concurrent immune disease	Any nonhepatic disease of an immune nature	+2
ALP:AST (or ALT)	<1.5	+2	Other autoantibodies	Anti-SLA/LPA, actin, anti-LC1, pANCA	+2
	1.5-3.0	0	Liver histology	Interface hepatitis	+3
	>3.0	-2		Predominantly lymphoplasmacytic infiltrate	+1
γ-globulin or IgG (times above ULN)	>2.0	+3		Rosetting of liver cells	+1
	1.5-2.0	+2		None of the above	-5
	1.0-1.5	+1		Biliary changes	-3
	<1.0	0		Atypical features	-3
ANA, SMA, or Anti-LKM-1 titer	>1:80	+3	HLA	DR3 or DR4	+1
	1:80	+2	Treatment response	Remission alone	+2
	1:40	+1		Remission with relapse	+3
AMA	Positive	-4	**Pre-treatment score**		>15
Hepatic viral markers	Positive	-3	Define AIH		10-15
	Negative	+3	Probable AIH		
Hepatotoxic drugs	Yes	-4	**Post-treatment scores**		
	No	+1	Define AIH		>17
Average alcoholic intake	<25 g/d	+2	Probable AIH		12-17
	>60g /d	-2			

Abbreviations: AMA: Antimitochondrial Antibodies; ANA: Antinuclear Antibodies; anti-LC1: Antibodies to Liver Cytosol Type 1; Anti-LKM1: Antibodies to Liver-Kidney Microsome Type 1; anti-SLA: Antibodies to Soluble Liver Antigen; ALP: Alkaline Phosphatase; AST: Serum Aspartate Aminotransferase; ALT: Alanine Aminotransferase; HLA: Human Leukocyte Antigen; IgG: Immunoglobulin G; pANCA: Perinuclear Anti-Neutrophil Cytoplasmic Antibodies; SMA: Anti-Smooth Muscle Antibody; HLA: Human Leukocyte Antigen; ULN: Upper Limit of Normal.

Table 4: Simplified scoring system for diagnosis of autoimmune hepatitis (AIH) [42].

Feature/parameter	Variable	Score
Autoantibodies[†]		
ANA or SMA	1:40	+1*
	≥1:80	+2*
anti-LKM-1	≥1:40	+2
anti-SLA	Positive	+2
Immunoglobulin Level		
IgG	>1-fold ULN	+1
	>1.1-fold ULN	+2
Histologic Findings		
Morphologic features	Compatible with autoimmune hepatitis	+1
	Typical of autoimmune hepatitis	+2
Viral Disease		
Absence of viral hepatitis	No viral markers	+2
Pretreatment Aggregate Score		
Definite diagnosis		≥7
Probable diagnosis		6

Notes: †Autoantibody titers as determined by indirect immunofluorescence. *Addition of points achieved for all antibodies (maximum 2 points).
Abbreviations: ANA: Antinuclear Antibodies; SMA: Anti-Smooth Muscle Antibody; anti-LKM-1: Antibodies to Liver-Kidney Microsome Type 1; anti-SLA: Antibodies to Soluble Liver Antigen; ULN: Upper Limit of Normal; IgG: Immunoglobulin G.

of autoantibody assists in the diagnosis and allows differentiation of two subtypes of AIH [4,5,10]. The characteristic circulating auto antibodies seen in AIH include ANA, SMA, anti-LKM1, anti-LC1, atypical Perinuclear Anti-Neutrophil Cytoplasmic Antibodies (pANCA), and Anti-Soluble Liver Antigen (SLA) antibodies [4-6,20,41]. However, not all patients display these immunological features. Liver biopsy is usually required to confidently confirm the diagnosis of AIH [4-6,40,41]. Histologically, AIH is characterized by interface hepatitis, with a plasma cell and lymphocyte predominance [4-6,40]. The histology findings, however, are not specific for the diagnosis of AIH and IAIHG states that a diagnosis of AIH should not be made when definite bile duct pathology or granulomas are present [1,40,42].

The IAIHG scoring system, organically published in 1993 [39] and revised in 1999 [40], was designed to improve the accuracy of diagnosis in AIH (Table 3). Although initially intended for research purposes, allowing comparison of patients in clinical trials, these criteria have been adapted widely for routine clinical practice. Despite a high degree of sensitivity (95%) and specificity (97%), the Revised Diagnostic Criteria (RDC) has proven cumbersome in daily clinical practice. In 2008, the IAIHG have published Simplified Diagnostic Criteria (SDC), evaluating just four parameters [43]. These parameters and the cumulative scores necessary for a diagnosis of probable or definite AIH are represented in Table 4. To be noted, the SDC are well-suited for assessment of typical patients [41]. Liver histology plays a major role in clinical diagnostic scoring systems and is important to confirm or support the clinical diagnosis AIH [10,39-42]. Although these criteria are available, the diagnosis of atypical

Table 5: Diagnosis of AIH-PBC overlap syndrome according to Chazouilleres et al. criteria [11].

	Criteria
PBC	ALP > 2-fold ULN or GGT > 5-fold ULN
	AMA positive
	florid bile duct lesions
AIH	ALT > 5-fold ULN
	IgG >2-fold ULN or SMA positive
	Moderate or severe periportal or periseptal lymphocytic piecemeal necrosis.

Notes: (1) AIH-PBC overlap syndrome was accepted when 2 or 3 criteria for PBC and AIH were fulfilled; (2) Histologic evidence of moderate to severe lymphocytic piecemeal necrosis (interface hepatitis) is mandatory for the diagnosis.

Abbreviations: ALP: Alkaline Phosphatase; AST: Serum Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma-Glutamyltranspeptidase; ALT: Alanine Aminotransferase; ULN: Upper Limit of Normal; AMA: Antimitochondrial Antibodies; IgG: Immunoglobulin G; SMA: Anti-Smooth Muscle Antibody.

AIH remains a clinical challenge [4-6,39-42].

Diagnostic criteria for AIH-PBC overlap syndrome

In relation to clinical practice, AIH-PBC overlap syndrome should be considered when a patient with autoimmune liver disease deviates from the normal clinical phenotype [5,23]. For instance, the presence of AMA seropositivity and cholestatic clinical, laboratory, and/or histological features in patients with AIH indicates the overlap syndrome of AIH and PBC [4-7,10,41]. Moreover, when the therapeutic response did not reach the excepted one, the presence of an overlap syndrome should also be suspected [43]. But extensively validated, stringent criteria for diagnosis of AIH-PBC overlap syndrome are lacking [7,10,41]. Chazouillères and colleagues [11] in Paris proposed the diagnostic criterion for AIH-PBC overlap syndrome, later called the "Paris criteria" [2,10,23,26,41,44], which provide an objective basis for making the diagnosis of the overlap syndrome. These require the presence of at least 2 of 3 accepted criteria for diagnosis of PBC and AIH as shown in Table 5 [11]. These criteria were incorporated in the recent European Association for the Study of the Liver (EASL) guidelines for management of cholestatic liver diseases [7], but with the emphasis that histological evidence of interface hepatitis is mandatory for the diagnosis of AIH-PBC overlap [5,41]. Liver biopsies showed interface hepatitis in 86% and lymphocytic cholangitis in 93% of the patients with AIH-PBC overlap syndrome [14]. Furthermore, these criteria recently were validated by Kuiper et al. [44] in a retrospective analysis of 134 PBC, AIH, and overlap syndrome patients followed up at a Dutch referral centre for liver disease and transplantation, the sensitivity and specificity of the Paris criteria for diagnosing the overlap syndrome were 92% and 97%, respectively.

Although this Paris criteria remains the most commonly used tool for diagnosing AIH-PBC overlap [2,10], and patients outside the Paris criteria should not be excluded from the diagnosis; those patients may have less severe forms of the AIH-PBC overlap syndrome [45,46]. Therefore, some clinicians established more 'flexible' criteria for diagnosing AIH-PBC overlap, such as an improvement in liver biochemistry whilst on immunosuppression in patients already diagnosed with PBC. For example, Bonder et al. [35] reviewed data from all patients with PBC (n = 609) and/or AIH (n = 15) examined at the Tufts Medical Center (Boston, MA) from January 1, 2000, to June 20, 2006; they found that only six (1%) patients with PBC met the Paris criteria for the overlap syndrome. In one study, the strict Paris criteria were slightly modified by Poupon et al. [25]; and the diagnostic criteria for PBC are as follows: (i) Alkaline Phosphatase (ALP) > 2-fold the Upper Limit of Normal (ULN) or Gamma-Glutamyltranspeptidase (GGT) >5-fold ULN; (ii) positive test for AMA (>1:80); and (iii) a liver biopsy specimen showing florid bile duct lesions; as well as AIH criteria: (i) ALT>5-fold ULN; (ii) IgG>1.5-fold ULN or a positive test for SMA (>1/80e); and (iii) a liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis. In another study in Japan, Yamamoto et al. [18] have also adopted the Paris criteria with slight modification as following. PBC factor included: (i) ALP>1.5-fold ULN or GGT>3-fold ULN; (ii) Positivity for AMA; and (iii) histological findings such as chronic nonsuppurative destructive cholangitis or bile ductopenia. AIH factor included: (i) elevated ALT>3-fold ULN; (ii) IgG>1.5-fold ULN; and (iii) histological findings of interface hepatitis. Those modifications indicated that clinical manifestation may vary by radical group, geographical region, and genetic predisposition.

On the other hand, several modified scoring systems have been described for identifying coexistent cases of AIH with PBC as an overlap syndrome [12-15,17,27,34,44,47,48]. In one study by Czaja et al. [17,47] the designation of AIH-PBC overlap syndrome was made in all patients originally diagnosed as having type 1 AIH or PBC who had aggregate RDC scores of 10 or greater and seropositivity for AMA. In another study by Silveira et al. [12], AIH overlap among PBC subjects was observed with use of their revised IAIHG scoring system relative to the original criteria. However, the applicability of the RDC for the diagnosis of the overlap syndrome remains questionable, because nearly 20% of PBC patients would be classified as probable AIH overlap [48]. Several previous studies have been shown that the simplified scoring system could be used for the diagnosis of AIH-PBC overlap syndrome [12,20,34,42,44]. But, one study results suggested that the Paris criteria may be superior to RDC and also the SDC for recognizing patients with AIH-PBC overlap syndrome [44].

In relation to the serologic profile of AIH-PBC overlap syndrome, Muratori et al. [49] compared 240 patients (120 with pure PBC and 120 with pure AIH) with 15 patients that had AIH-PBC overlap according to the Paris criteria and found that the concomitant presence of AMA and ANA was a highly specific pattern for AIH-PBC overlap. Moreover, this report also suggested that anti-dsDNA antibodies may be acted as a potential serological marker for AIH-PBC overlap syndrome, but this needs further validation in large-scale studies. Additionally, the presence of human leukocyte antigen (HLA)-DR7 or immunostaining of liver biopsies for IgG or IgM plasma cells has also been proposed as a surrogate marker in the diagnosis of AIH-PBC overlap [50].

Therefore, for future studies, a new category needs to be established to distinguish between conventional PBC and AIH; and establishing consensus diagnostic criteria for AIH-PBC overlap syndrome is the requisite step before launching treatment trials developing confident management algorithms.

Treatments and Outcomes

Pharmacological treatment

Therapeutic management of PBC and AIH as individual entities

is quite different. UDCA at 13-15 mg/kg/day is currently the only approved therapy for PBC [1-3]. Several studies have shown that UDCA is associated with improved serum hepatic biochemistries, delayed histological progression, and delayed the development of oesophageal varices and liver failure [1-3]. Furthermore, UDCA improves transplant-free survival [1-3]. As regards primary therapy in AIH, it has been established that corticosteroid therapy is effective for all forms of AIH, prednisone (or prednisolone) alone or a lower dose in combination with azathioprine ameliorates symptoms and improves the laboratory and histologic manifestations of liver inflammation in most patients [4-6,10,29].

The low prevalence of the overlap syndrome has made it impracticable to do large-scale, randomized controlled therapeutic trials. Therefore, current therapy for AIH-PBC overlap syndrome is empiric and extrapolated from data derived from the treatment of the two primary disorders and retrospective small patient series of AIH-PBC overlap conditions. Usually, recommendations for treating AIH-PBC overlap syndrome are based on the methods used to treat the two main autoimmune liver diseases separately [9,10,24]. Most studies, therefore, suggest that combination therapy of UDCA and immunosuppression may be the best therapeutic option for AIH-PBC overlap syndrome [11,24,27,37,41,49,51-55]. A Japanese study suggested that treatment guidelines or rationales for corticosteroids use in AIH-PBC overlap are absolutely required in the clinical setting, although the position statement remarked that combination therapy UDCA and immunosuppressive drugs was not evidence-based [27]. Despite the lack of controlled trails, the European Association for the Study of Liver Diseases (EASL) and the IAIHG practice guidelines recommend a combination of UDCA and corticosteroids (with or without azathioprine) as the first-line therapy in patients with AIH-PBC overlap syndrome [10,46].

Most of the published studies have shown that patients with PBC who have additional features of AIH will benefit from combination therapy with corticosteroids and UDCA [11,27,37,39,51,52]. In a study including 20 cases of an AIH-PBC overlap condition, 16 (80%) were treated with UDCA and steroids, and 8 of those received additional azathioprine. Transaminase levels fell below twice ULN in all 16 patients. In 14 among the 16 cases, both AST and ALT normalized; ALP levels normalized in the majority of patients and stayed above 1.5-fold ULN in only three cases [51]. A retrospective study in Japan reported that 16 cases of PBC-AIH overlap, 13 patients treated with both UDCA and immunosuppressive therapy responded well, with normal ALT and ALP levels. The remaining 3 patients treated with either prednisolone or UDCA alone developed cirrhosis and its complication, or died of liver-related causes [52]. Similarly, when steroids were added to UDCA in 20 of 28 Japanese PBC patients with suspected AIH overlap, 15 (75%) of the 20 responded [37]. Moreover, in the largest long-term follow-up study, 17 strictly defined patients received initial therapy with UDCA alone (n=11) or UDCA in combination with immunosuppressant (n=6) and were followed for 7.5 years. Three of the UDCA-treated patients were considered responders, with complete biochemical response in terms of AIH features (ALT <2-fold ULN and IgG <16 g/L) and decreased or stable fibrosis. The remaining 8 patients were non-responders with increased fibrosis in 4 [53]. Overall, fibrosis progression in non-cirrhotic patients occurred more frequently under UDCA monotherapy (4/8) than under combined therapy (0/6) (P= 0.04) [53]. Taken together, these data supported the practice to treat AIH-PBC overlap patients with a combination of UDCA and immunosuppressant [10,51-53]. A matter of concern, in those patients it is usually sufficient to treat with doses of steroids lower than in classical AIH, and many patients can be kept very successfully on low dose azathioprine in the long term, not requiring corticosteroids [23, 43,54, 56].

The aim of immunosuppressive treatment should be a normalization of transaminase levels and IgG, whereas parameters of cholestasis usually respond well to UDCA [24]. Monitoring of treatment response should follow the guidelines for AIH [10]. A study by Muratori et al. [49] showed that patients with AIH-PBC overlap syndrome had a greater likelihood of also being anti-dsDNA positive as well as AMA positive when compared to AMA positive PBC and also responds to the combination of UDCA and steroids.

However, under UDCA therapy, Joshi et al. [16] described biochemical response at 24 months and survival in one cohort of 12 strictly defined PBC-AIH overlap syndrome patients were similar to 159 patients with PBC alone. It's appropriate to start treatment with UDCA (13-15 mg/kg daily). However, if this therapy does not induce an adequate biochemical response in an appropriate time span (e.g. 3 months) or in patients with predominantly hepatitis serum liver tests, a corticosteroid should be added [46,57]. Prednisone has been used at an initial dose of 0.5 mg/kg daily and should be progressively tapered once ALT levels show a response [53]. But, the limitations of using liver biochemistry as a surrogate of treatment success in overlap must be recognized. Ozaslan et al. [56] studies suggested that patients with high AIH score and negative AMA should be treated with combined therapy of corticosteroids and UDCA. However, patients with low AIH score and positive AMA should use UDCA firstly, if no response, the addition of corticosteroids should be considered with close monitoring. Interesting, the simplified AIH scoring system could predict patients who needed corticosteroids with a higher specificity [27].

Moreover, several studies show that treatment of the AIH component of overlapping syndromes is important to avoid progression to cirrhosis [12,26,53,58]. The role of others immunosuppressant (azathioprine) in the long-term management of patients with AIH-PBC overlap syndrome is unclear, but it's an alternative to corticosteroids for long-term immunosuppressive therapy [54]. Budesonide is considered an alternative therapy in non-cirrhotic AIH patients who experience significant steroid induced side effects since it lacks the systemic side effects due to high first-pass liver metabolism [40,59,60]. The recent interest in budesonide for AIH will likely result in its use for AIH-PBC overlap syndrome [59], yet its efficacy for this condition is waited to further evaluation. Although, a recent meta-analysis found that combination therapy with UDCA and budesonide was more effective than UDCA monotherapy for AIH-PBC overlap syndrome [61]. Moreover, compared to prednisone, budesonide has fewer side effects [61]. Corticosteroid-resistance patients with AIH-PBC overlap syndrome may exist, and other alternative treatment strategies such as cyclosporine A, infliximab and mycophenolate mofetil has been considered [40,62,63], but use of these currently lacks sufficient data. Further studies are needed to determine its exact place in therapy for AIH-PBC overlap syndrome in the future.

Liver transplantation

Liver transplantation (LT) is indicated for patients with overlap syndrome who have end-stage liver disease. A retrospective study has shown that patients with a Model for End-stage Liver Disease Score ≥ 8 had a significantly higher risk to undergo LT or liver-related death [64]. Overall, AILDs account for approximately 24% of LT procedures performed in Europe and United State, with a 5-year post-LT survival rate exceeding 80% [65]. However, the major challenges facing individual cases include the optimal indication and timing for LT, and postoperative management. Patients transplanted for AILDs are more likely to experience acute rejection compared to those transplanted for non-AILDs, and the reason behind this observation is unclear [66]. Moreover, PBC-AIH overlap patients tend to have a higher rate and aggressive disease recurrence when compared with patients with single autoimmune liver disorders after LT, but the overall survival seems comparable [23,66]. AIH is reported to recur in 17% to 33% of transplanted recipients. Recurrence can be indolent and detected only by surveillance laboratory testing and liver biopsy assessments [66].

Conclusions

In summary, diagnosis and treatment of AIH-PBC overlap syndrome continue to be a major challenge. Currently, the "Paris criteria" are the most commonly used tool for diagnosing AIH-PBC overlap syndrome. There is no evidence-based recommendation for the treatment of this overlap syndrome owing to the low prevalence of these AILDs. Notably, most studies suggest that combination therapy of UDCA and immunosuppression may be the best therapeutic option for AIH-PBC overlap syndrome. It is important to keep in mind that treatment decisions should be response-guided and tailored; Liver transplantation is an excellent treatment for patients with life-threatening complication of the end-stage of liver disease.

Further studies are needed to determine diagnosis and optimal therapeutic strategies of this overlap syndrome. The clinical relevance of diagnosing the syndrome i.e. it identifies which patients might benefit from combination therapy of UDCA and corticosteroids; management those patients identified as non-responder to the UDCA and corticosteroids treatment, intolerance of the drug or drug side-effects may present a problem. Moreover, clinical studies will be needed to assess the targeted therapeutic potential of chemokine/chemokine receptor antagonists, which reduce T cell liver infiltration, in AIH-PBC overlap syndrome [1,5,67]. Perhaps, a collaborative network of clinical investigators should be encouraged to pool experiences with theses uncommon entities, describe the outer limits of acceptable finding for each classical disease.

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