International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Autoimmune Hepatitis: An Overview with Emphasis on Pharmaceutical Care

Sahitya Uppada[*1], Daisy Samitha K[1], Bhavya Sri N[1], Sadasiva Rao G[2]
[1] *PharmD Intern, Department of Pharmacy Practice, Hindu College of Pharmacy, Amaravathi Road, Guntur-522002, AP, India.*
[2] *Head of the Department, Department of Pharmacy Practice, Hindu College of Pharmacy, Amaravathi Road, Guntur-522002, AP, India.*
Corresponding Author: Sahitya Uppada

Date of Submission: 25-09-2020 Date of Acceptance: 06-10-2020

ABSTRACT: Autoimmune Hepatitis (AIH) is a non-resolving chronic liver disease that is characterized by circulating auto-antibodies and elevated serum globulin levels. The disease may start as acute hepatitis and progress to chronic liver disease and cirrhosis.AIH-1 accounts for about 80% of all cases with AIH. The detection of ANA and/or SMA is almost exclusively requisite for an AIH-1 diagnosis. Less than 10%-15% of AIH cases in Europe and North America have the AIH-2 subtype. Anti-LKM1 antibodies show a diffuse cytoplasmic staining of liver lobules and exclusively of the P3 portion of the proximal renal tubules. AIH is a disease that affects all age groups, occurs in all ethnicities and geographic regions but affects the female gender disproportionately. The etiology of AIH is still unknown.Consequently, autoimmune hepatitis has a spectrum of clinical presentations.Among drugs still widely used, nitrofurantoin and minocycline are well defined examples of drug-induced AIH. Within the clinical spectrum of AIH there are some patients who manifest clinical characteristics of either PBC or PSC. Treatment with glucocorticoids is life-saving in autoimmune hepatitis. Autoimmune hepatitis can improve during pregnancy and this improvement may allow reductions in immunosuppressive therapy during pregnancy. Treatment is continued until the disease is in remission, the treatment fails, or the person develops severe side effects from treatment. Proper education regarding the severity, treatment and lifestyle modifications may help the patient to understand more about the condition and act appropriately.

Key words: ANA(Anti-Nuclear Antibody), SMA(Smooth Muscle Antibody), Anti-LKM1(Liver Kidney Microsomal Type-1 Antibody), PBC (Primary Biliary Cirrhosis), PSC(Primary Sclerosing Cholangitis).

I. INTRODUCTION

The liver is the largest solid organ in the human body, which regulates most chemical levels in the blood. Unlike most organs, the liver has two major sources of blood. The portal vein brings in nutrient-rich blood from the digestive system, and the hepatic artery carries oxygenated blood from the heart.The blood vessels divide into small capillaries, with each ending in a lobule. Lobules are the functional units of the liver and consist of millions of cells called hepatocytes. Blood is removed from the liver through three hepatic veins. The major functions of liver include: bile production; absorbing and metabolizing bilirubin; supporting blood clot formation; metabolism of biomolecules; vitamin and mineral storage; blood filtration and purification; immune activity; production of albumin and synthesis of angiotensinogen. Liver is the only visceral organ that can regenerate. Some of the most important compounds that help liver in the process of regeneration are: Hepatocyte Growth Factor, Insulin, Transforming Growth Factor- alpha (TGF-α), Epidermal Growth Factor (EGF), Interleukin-6 (IL-6) and Norepinephrine. A healthy liver functions very efficiently. However, in a diseased or malfunctioning liver, the consequences can be dangerous or even fatal.

Autoimmune Hepatitis (AIH) is a non-resolving chronic liver disease that is characterized by circulating auto-antibodies and elevated serum globulin levels. The disease may start as acute hepatitis and progress to chronic liver disease and cirrhosis. Consequently, autoimmune hepatitis has a spectrum of clinical presentations. According to the pattern of auto-antibodies detected, a sub-classification of the disease into the following 2 main subtypes has been proposed[1-7].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

- AIH1 is characterized by the presence of Antinuclear Antibodies (ANAs) and/or Smooth Muscle Antibodies (SMAs).
- AIH2 is characterized by the detection of specific anti-liver/kidney microsomal antibody type-1 (anti-LKM1) or infrequently anti-LKM 3 or antibodies against liver cytosol type 1 antigen (anti-LC1).

EPIDEMIOLOGY

AIH is a disease that affects all age groups, occurs in all ethnicities and geographic regions but affects the female gender disproportionately[8-11]. In the United States, women are affected 3.5 times more than men, and 76% of patients in a Swedish study were women[12]. Previously considered to be a disease of the young, a recent large Danish nationwide population-based study demonstrated the peak age of incidence at more than 60 years for both men and women[13,14]. It also showed that both the incidence and prevalence of AIH is rising. Although it is still considered a rare disease, as its prevalence ranges from 16 to 18 cases per 100000 persons in Europe. In Europe and the United States, it accounts for 2% to 3% of the pediatric and 4% to 6% of the adult liver transplantations[15-17]. The occurrence and clinical course appear to vary according to ethnicity. The disease appears to be more common and more severe in the North American aboriginals compared to the Caucasian population; African-Americans are more likely to present with cirrhosis; patients with Asian or other non-European Caucasoid background have poor outcomes[18-21]. These diverse clinical outcomes between different ethnic groups, within and between countries may reflect differences in genetic predisposition, environmental stimuli as well as complex socio economic reasons such as delivery of healthcare.

ETIOPATHOGENESIS

The etiology of AIH is still unknown. However, remarkable progress in understanding the pathogenesis of the disease had been made. A prevalent assumption suggests that the occurrence of AIH is a result of genetic predisposition in susceptible individuals, after their exposure to triggering factors like microbes and certain xenobiotics which may induce liver disease. Later, the autoimmune attack against the liver is continued, potentially through "molecular mimicry" mechanisms which is further promoted by diminished control of regulatory T-cells (T_{reg})[22].

The identity of susceptibility genes related to AIH is mostly unknown. The strongest association is with genes located within the HLA region on the short arm of chromosome 6, particularly those encoding the HLA class II DRB1 alleles[23,27]. These molecules, naturally exposed on the surface of antigen-presenting cells, are essential in the presentation of the peptide antigens to CD4 T cells. DRB1*0301 and DRB1*0401 confer susceptibility to AIH-1 in European and North American patients and their possession increases the score of the revised diagnostic criteria issued by the IAIHG. DRB1*0405 and DRB1*0404 confer susceptibility to AIH in Japanese, Argentinian and Mexican patients, whereas DRB1*1301 confers susceptibility in Argentineans[24-26]. In this context, a recent genome-wide association study in the Netherlands confirmed the association of HLA-DRB1*0301 and HLA-DRB1*0401 alleles with AIH-1 and identified variants of SH2B3 and CARD10 as likely risk factors for the disease. On the other hand, DRB1*0701 and DRB1*0301 confer susceptibility to AIH-2. There are also some other studies concerning susceptibility to AIH, indicating an association with polymorphisms in genes located outside of the major histocompatibility complex (MHC), like the cytotoxic T lymphocyte antigen-4, the gene promoter of tumor necrosis factor-alpha (TNF-α) and Fas[28-35].

Molecular mimicry stems from the premise that self-antigens may share sequence homologies with proteins of external agents such as viruses and for this reason, after a first exposure and sensitization to foreign antigens, the immune system would react against self-proteins, perpetuating the chronic damage[36,37].

Anti-LKM1 antibodies are the best example of molecular mimicry in AIH. The major target autoantigen of anti-LKM1 antibodies in AIH-2 has been identified as the cytochrome P450 2D6 (CYP2D6)[38-40].A prerequisite for anti-LKM-1 production and the activation of pathogenetic mechanisms is the expression of CYP2D6 on the surface of liver cells. Although this localization is controversial, recent data indicates that CYP2D6 is exposed on the plasma membrane of hepatocytes, suggesting that either auto antibody-dependent cytotoxicity or direct lysis of liver cells due to a direct antibody-antigen binding could be operative in perpetuating the autoimmune attack against liver cells[41-47].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

However, apart from molecular mimicry, epitope spreading or exposure to previously hidden autoantigens revealed because of hepatocellular injury have been suggested as alternative pathogenetic mechanisms in the development of AIH[48]. Indeed, hepatocellular damage can begin after the presentation of an autoantigen by professional antigen presenting cells via MHC and co-stimulatory molecules. Thereafter, several cytokines can drive the differentiation of uncommitted CD4 T-helper cells (Th0) to Th1-cells secreting interferon-γ (IFN-γ), pathogenic Th17-cells that secrete the proinflammatory cytokine interleukin-17 (IL-17), or Th2-cells which secrete IL-13, IL-4 and IL-10, indicating that multiple effector cells are involved in AIH pathogenesis probably be cause of defective immunoregulatory mechanisms[49-53](Figure-1).
The mechanisms underlying the breaking of immune tolerance in AIH have not yet been completely clarified. The malfunction of regulatory T-cells, particularly of CD4+CD25+FOXP3+ T-cells, could be an explanation. In contrast with healthy subjects, CD4+CD25+ regulatory T-cells are decreased in number and functionally impaired at diagnosis, whereas an increase is recorded during effective treatment[54,55].

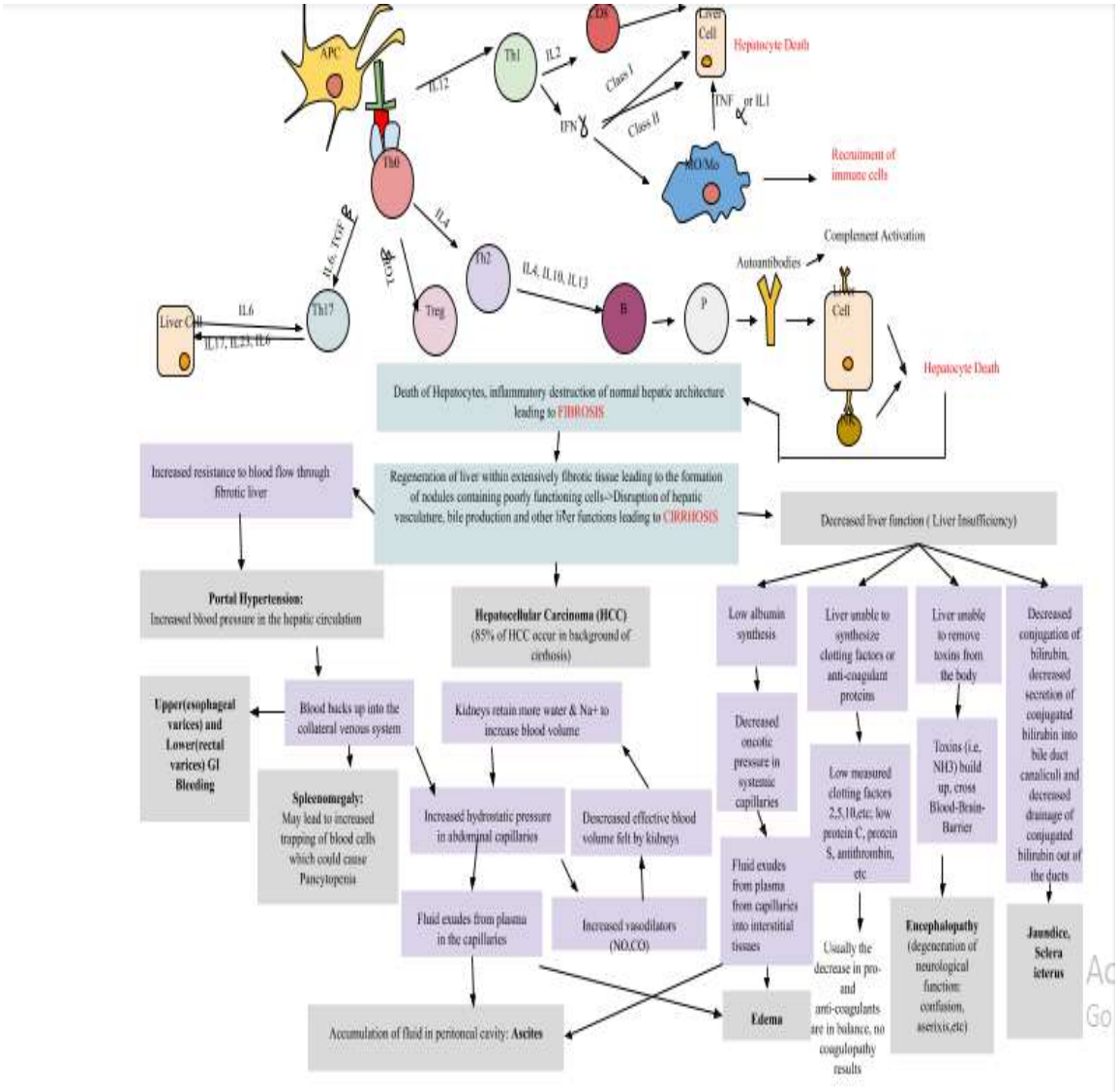

Figure-1: Depiction of Immunopathogenesis of Autoimmune hepatitis and its complications.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Recently, the interaction between the IL-4 receptor, namely the CD124 molecule and circulating autoantibodies against it, has been described in AIH[56-60]. These autoantibodies inhibit STAT6 phosphorylation, resulting finally in a neutralizing effect on the cytokine and subsequently in uncontrolled inflammatory reactions[61-64].

CLINICAL PRESENTATION

Clinical features of AIH

For many years, AIH was classically related to a typical clinical phenotype of a young female patient with endocrine abnormalities and severe hepatitis[65]. However, it is now well-established that AIH has a global distribution, can also affect males (almost 25%-30% of the patients) and can present at any age and in all ethnic groups. The disease is usually characterized by a bimodal age pattern at onset with one peak in children and teens and a second in middle age (fourth to sixth decades and especially in women after menopause), although a considerably increasing number of patients are even older than 65-70 years[66-68](Table-1).

Table-1:Clinical Features of Autoimmune Hepatitis

Characteristic	Comments
Age at presentation	Any age of both sexes and all ethnic groups; bimodal distribution usually with peaks around puberty and >40yrs of age.
Types of disease onset	Broad range from asymptomatic to acute/severe or even fulminant hepatitis. Most common clinical phenotype of the disease is characterized by an insidious onset with nonspecific symptoms such as fatigue, right upper quadrant pain, lethargy, malaise, anorexia, nausea, pruritus, fluctuating jaundice and polyarthralgia without arthritis. Acute onset of does exist and contains two different clinical entities (the acute exacerbation of chronic AIH and the true acute AIH without histological findings of chronic liver disease). One-third of patients at diagnosis have already developed cirrhosis irrespective of the presence or absence of symptoms, leading to delay in diagnosis.
Physical Findings	Depends on the clinical status of the disease, ranging from completely normal to signs and symptoms of chronic liver disease and/or portal hypertension.
Special Conditions	Presentation of AIH during pregnancy or more frequently after delivery. Development of AIH after liver transplantation for other liver diseases (de novo AIH or post transplant plasma cell hepatitis). Development of AIH after usage of drugs, supplements or herbs (drug-induced AIH, nitrofurantoin and minocycline implicated in 90% of cases.
Specific Characteristics	Frequent presence of other auto-immune or immune-mediated diseases like Hashimoto thyroiditis, Grave's disease, Vitiligo, Alopecia, Rheumatoid arthritis, Type-1 Diabetes mellitus, Inflammatory bowel disease, Psoriasis, Systemic lupus erythematosus, Sjőgren's syndrome and celiac disease in patient or his/her first degree relatives. An unusual form of AIH has been reported in 10%-18% of patients

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

	with APECED, also known as APS-1.
Complications	HCC development in AIH is less common than other liver diseases but it does exist and is associated with cirrhosis, drug-related complications are also significant in 10%-25% of patients; these complications are most commonly related to long-term corticosteroid use or azathioprine toxicity/intolerance.

AIH is characterized by fluctuation of disease activity and therefore its clinical spectrum ranges from no obvious signs or symptoms of liver disease to a severe, acute or even fulminant hepatitis(69). Indeed, acute AIH presents in approximately 25% of cases with identical signs and symptoms as patients suffering from acute viral or toxic hepatitis(Table-2). However, the clinical phenotype of acute AIH at presentation may actually be due to either an exacerbation of already established AIH that has been undiagnosed or misdiagnosed or to a true acute AIH without histological lesions of chronicity in liver biopsy(71,72). Of note, in some of these patients, serum IgG is normal and ANA at first screening may be negative and thus the clinician may not consider AIH, although a more appropriate autoimmune liver serology test could be contributory. Progression to acute liver failure is not frequent but in these exceptional cases, the prompt and timely diagnosis of AIH is of utmost importance as delay in diagnosis and starting of immunosuppressive treatment result in poor prognosis, while administration of therapy might avoid the need for liver transplantation(73).

Table-2: Occurrence of Various Clinical Features in Autoimmune Hepatitis

Symptoms		**Laboratory Findings**	
Clinical Features	**Occurrence (%)**	**Clinical Features**	**Occurrence (%)**
Fatigue Jaundice Upper abdominal discomfort Pruritus Anorexia Myalgias Diarrhoea Cushingoid features Fever (≤40℃) None at presentation	86% 77% 48% 36% 30% 30% 29% 19% 18% 25-34%	Elevated AST Hypergammaglobulinemia Elevated IgG Hyperbilirubinemia ALP >2 fold normal	100% 92% 91% 83% 33%
Signs and/or Complications		**Immuno Serological markers**	
Clinical Features	**Occurrence (%)**	**Clinical Features**	**Occurrence**

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

			(%)
Hepatomegaly Spider angioma Concurrent immune disease Splenomegaly Ascites Encephalopathy None	78% 58% <38% >32% 20% 14% <25%	SMA, ANA or Anti-LKM1 Atypical p-ANCA Anti sialoglycoprotein receptor Anti actin Anti-LC1 Anti-SLA	100% 92% (Type-1 AIH only) 82% 74% 32% (Type-2 AIH only) 11-17%
AST: Aspartate Transaminase; IgG: ImmunoglobulinG; ALP: Alkaline Phosphatase; SMA: Smooth Muscle Antibody; ANA: Anti-Nuclear Antibodies; Anti-LKM1: Liver Kidney Microsomal Type-1 Antibody; Anti-LC1: Liver Cytosol specific Antibody Type-1; Anti-SLA: Antibody against Soluble Liver Antigen			

Commonly, the clinical presentation is not peculiar and is characterized by several nonspecific findings of various intensity. Amenorrhea is also frequent but epidermal rashes and low-grade fever are rare conditions. The initial clinical evaluation is either completely normal or when frank cirrhosis has developed, typical signs and symptoms of chronic liver disease, like hepatomegaly, splenomegaly, palmar erythema and spider nevi, are present. In advanced disease, the development of ascites, esophageal varices and portal gastropathy, along with cytopenias due to hypersplenism and/or hepatic encephalopathy, are common. Approximately 12%-35% of patients are asymptomatic at diagnosis and in such cases AIH is usually documented during a random investigation for elevated transaminases which has been done for different reasons (e.g., annual check-up for insurance, investigation for other pathological entities, etc.). However, 30% of patients have already developed advanced disease at diagnosis, which is associated with lower overall survival and may indicate a delay in diagnosis. In fact, this is a challenge for a timely and prompt diagnosis of AIH as the initiation of symptoms usually present after a subclinical course of the disease lasting back for months or years, while subclinical disease of various duration can also be observed after the first clinical expression of the disease[Table-2].

Table-3: Differential Diagnosis of Autoimmune Hepatitis

Other autoimmune liver diseases
Primary Biliary Cirrhosis
Primary sclerosing Cholangitis (including small duct sclerosing cholangitis)
Variant Syndrome
Chronic Viral Hepatitis
Cholangiopathy due to Human Immunodeficiency Virus (HIV) Infection
Alcoholic Liver Disease
Drug Induced Hepatitis
Granulomatous Hepatitis
Hemochromatosis
Non-Alcoholic Steatohepatitis
α_1-Antitrypsin Deficiency
Wilson's Disease

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Systemic Lupus Erythematosus Celiac Disease

Studies conducted more than 40 years ago have shown that the disease is catastrophic without treatment as the 5 and 10 year survival rates were as low as 50% and 10% respectively, whereas a significant survival benefit has been recorded in patients treated with corticosteroids. Indeed, after immunosuppression, the 10 year overall survival rate of AIH patients has now significantly improved (80%-95%). For these reasons, the objective is still to spread knowledge regarding the diagnosis of AIH and adopt a more liberal attitude towards testing for autoantibodies in patients with elevated serum liver enzymes as effective treatment for the disease is available[74].

Special characteristics of AIH

The diagnosis of AIH can be done for the first time in pregnancy or more frequently soon after delivery. Although AIH concurrent with pregnancy is a rare event, relapse of the disease may occur in patients who are in remission during pregnancy. Therefore, this possibility should be strongly taken into account if elevation of transaminases, especially in association with hypergammaglobulinemia with selective IgG increase, is observed during pregnancy or more frequently in the postpartum period. Of note, the introduction of immunosuppression has likely enabled the occurrence of pregnancy in young females with AIH[75].

In susceptible individuals, the disease can present after the use of many drugs. Reactive metabolites may act as neoantigens, triggering the immune cells to an unwanted reaction, although the precise underlying mechanisms have been elucidated only for some drugs able to induce AIH but not currently in use, such as tienilic acid and dihydralazine. Indeed, anti-LKM type 2 antibodies (anti-LKM2) have been found in hepatitis cases induced by tienilic acid (major target autoantigen of anti-LKM2: CYP2C9), whereas in dihydralazine-induced hepatitis, a typical LKM staining pattern of the liver with predominant staining of the perivenous liver cells in the absence of kidney staining was observed (liver microsomal antibodies: anti-LM). The major target autoantigen of anti-LM antibodies has been documented as the CYP1A2. Of interest, anti-LM antibodies directed against the same autoantigen (CYP1A2) have also been reported in a specific and unusual form of AIH which develops in individuals with a rare autosomal recessive disease, the autoimmune polyendocrinopathy-candidiasis ectodermal dystrophy syndrome (APECED)[87].

Among drugs still widely used, nitrofurantoin, which is widely prescribed for urinary tract infections, and minocycline, a treatment for acne, are well defined examples of drug-induced AIH. Of interest, these two agents are implicated in 90% of cases of drug-induced AIH worldwide. Furthermore, recently it has been shown that patients with drug-induced AIH had similar clinical and histological characteristics compared to patients with “pure” AIH, although the latter had higher histological activity and there was a need for long-term immunosuppressive therapy. Nevertheless, drug-induced AIH is an intriguing and complex disorder which could present clinically in different phenotypes across the spectrum of disease. Indeed, at least three clinical scenarios have been proposed that refer to drug-induced autoimmune liver disease, namely AIH with drug-induced liver injury, real drug induced-AIH and immune mediated drug-induced liver injury. Histologically, distinguishing drug-induced liver injury from AIH remains a challenge, although a recent study has suggested that sufficient differences exist so that pathologists can use the pattern of injury to suggest the correct diagnosis[78-82].

Other drugs and herbal agents, like oxyphenisatin, ornidazole, methyldopa, diclofenac, IFN-α or IFN-γ, atorvastatin, liraglutide, antiretroviral agents for human immunodeficiency

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

virus and TNF-α blocking agents, have also been suggested in the induction of AIH development[83-85].

AIH has also been recorded after viral infections from hepatitis A virus, Epstein-Barr virus (EBV), human herpesvirus 6 and measles. In this context, the development of AIH-1 has been reported in 2/7 susceptible adults that had been previously infected by the EBV. In addition, recently Cabibi and Zellos et al reported two more cases of AIH after EBV infection (1 with AIH-1 and for the first time 1 with AIH-2). The development of AIH-2 has been reported in some patients with HCV after treatment with IFN-α but also rarely after acute HCV infection even after viral clearance. From the clinical perspective, these findings suggest that AIH should be taken seriously into account as an alternative "emerging" diagnosis in patients diseased in the past from a viral infection if they still suffer from unexplained and prolonged hepatitis. In such conditions, liver biopsy seems mandatory in an attempt to achieve a correct and timely diagnosis of a potentially catastrophic liver disease such as AIH[86].

In some circumstances, AIH may develop after orthotopic liver transplantation which was performed for other reasons. This situation has been called de novo AIH after liver transplantation, although alternative definitions like "post-transplant immune hepatitis", "graft dysfunction mimicking AIH" or "post-transplant plasma cell hepatitis" could be more rational. Nevertheless, a rapid diagnosis of de novo AIH after liver transplantation may avoid rejection and subsequently a second liver transplantation, while improving long-term survival[87].

AIH is associated with various autoimmune diseases, either in the index patient or the first-degree relatives, commonly Hashimoto thyroiditis, Grave's disease, vitiligo, alopecia, rheumatoid arthritis, diabetes mellitus type-1, inflammatory bowel disease, psoriasis, systemic lupus erythematosus (SLE), Sjögren's syndrome and celiac disease. In this context, an unusual form of AIH has been reported in approximately 10%-18% of patients with APECED[88], also known as autoimmune polyendocrinopathy syndrome-type 1. This syndrome is characterized by chronic mucocutaneous candidiasis, ectodermal dystrophy and autoimmune destruction of several endocrine organs, leading mainly to hypoparathyroidism, adrenocortical failure and gonadal failure in females. Mutations in the autoimmune regulator gene (AIRE) have been documented as the etiological basis of the syndrome. As noted above, AIH as a component of APECED is characterized by the presence of anti-LM antibodies which are typically absent in those APECED patients who do not suffer from AIH. Of interest, in AIH patients without APECED, mutations of the AIRE gene are not found, indicating that they are genetically distinct from patients with AIH as a component of APECED[89].

Rarely, AIH can concur with other frequent non-autoimmune liver disorders like chronic viral hepatitis B, C or D, non-alcoholic fatty liver disease and alcoholic liver disease. Taken together, the above associations of AIH with other non-liver autoimmune diseases as well as non-autoimmune liver diseases may further explain the delay in diagnosis as the first physician dealing with the patient (e.g., rheumatologist, endocrinologist, etc.) may not be so familiar with the vast heterogeneity of the clinical manifestations of the disease.

Complications

As a chronic liver disease, AIH has similar complications. Indeed, at first evaluation, cirrhosis developed in almost 33% of affected subjects. Unfortunately, this finding has been shown to negatively affect the 5 and 10 year survival. Therefore, a timely and correct diagnosis seems mandatory in an attempt to stop the progression of chronic hepatitis to cirrhosis, decompensated disease and the development of portal hypertension and ultimately hepatocellular carcinoma (HCC)[90]. The prevalence of HCC in AIH-induced cirrhosis is lower compared to that recorded in patients with cirrhosis due to other etiologies, such as chronic viral hepatitis, alcohol or hemochromatosis. On the contrary, recently a study from New Zealand reported an increased risk of either liver or extrahepatic malignancy in patients with AIH, while reports from the United Kingdom, Denmark, United States and Japan found male gender and cirrhosis in AIH as the most important triggering factors for the development of HCC, which finally occurs with a frequency of 1.1% per year. Thus, although the incidence of HCC is less common than in other chronic liver diseases, the risk remains sufficient to implicate at least 6 monthly surveillance in all AIH patients with cirrhosis[91].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

DIAGNOSIS OF AUTOIMMUNE HEPATITIS

Biochemical findings

The typical serum biochemical profile shows a predominantly hepatitic pattern. Of note, the levels of bilirubin and transaminases vary from just above the normal to more than 50 times these concentrations, while the cholestatic enzymes are within normal limits or moderately increased. However, it should be noted that biochemical activity does not correlate with the severity of AIH in liver biopsy. In addition, it has been shown recently that along with transaminases elevation, γ-glutamyl-transpeptidase (γ-GT) levels but not alkaline phosphatase (ALP) can also be high in AIH and moreover, it could be helpful in an independent manner for the prediction of treatment response. In keeping with the fluctuating nature of the disease, the aminotransferases and γ-GT may spontaneously normalize, despite continuing activity at the histological level[92]. This is another important topic that can result in delay and/or underestimation of AIH diagnosis as the second hit may become apparent after several months or years and could present even without any symptoms, explaining at least partially the presence of established cirrhosis in almost one third of patients at the time of diagnosis.

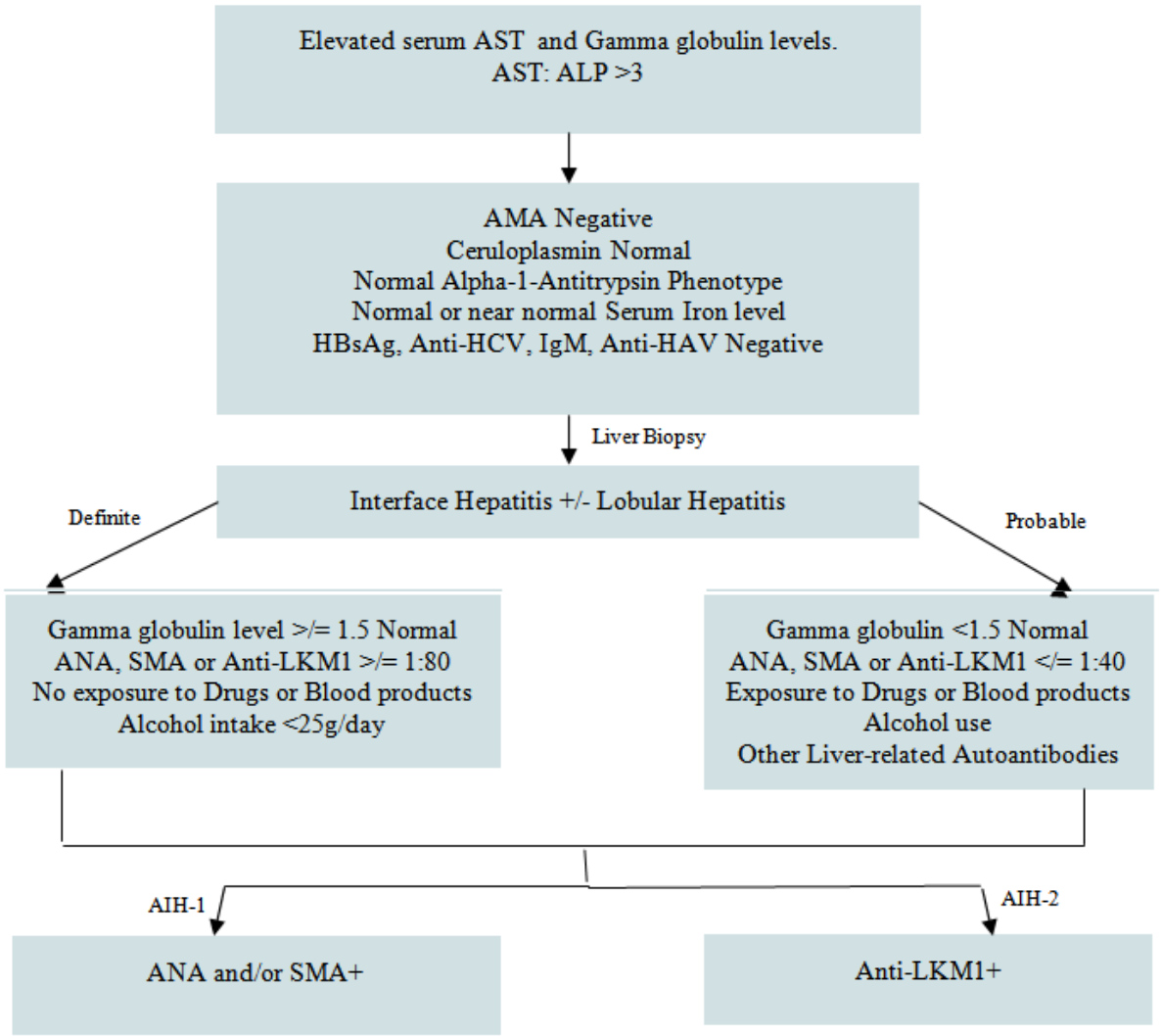

Figure-2: Diagnostic Algorithm for Autoimmune Hepatitis

In the majority of patients, a polyclonal hypergammaglobulinemia with selective increase of IgG is observed. It should be emphasized that in every day practice, IgG determination is usually

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

not performed in the laboratory assessment of an index patient with unexplained acute or chronic elevation of aminotransferases, leading to further underestimation of the disease accompanied by significant delay in prompt diagnosis[94-95]. Elevation of serum IgA suggests steatohepatitis (alcoholic or non-alcoholic) or drug-induced liver injury rather than AIH, whereas an increase in IgM levels is more characteristic of autoimmune cholestatic liver diseases. However, it should be kept in mind that the frequency of cases with increased IgG serum levels tends to decrease in children, elderly patients and those with an acute onset of the disease as almost a third of these patients may have normal IgG levels at first assessment[96]. For these reasons, AIH should never be excluded in an index patient only because IgG levels were found within normal limits. Additionally, the responsible clinician should know that low transaminases, bilirubin or IgG values do not by definition correspond to mild or inactive disease nor exclude AIH.

A marker that could have clinical significance as it might potentially contribute to AIH diagnosis, particularly in patients who present without the conventional antibodies, is complement component C4 which is characteristically low in these patients[97-99].

Table-4:Simplified Criteria for the Diagnosis of Autoimmune Hepatitis

Feature/ Parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1[1]
ANA or SMA+	≥1:80	+2[1]
Or LKM+	≥1:40	+2[1]
Or SLA/ LP+	Any titre	+2[1]
IgG or ɣ-globulin level	> upper limit of normal	+1
	>1.1xupper limit	+2
Liver histology	Compatible with AIH	+1
	Typical of AIH	+2
	Atypical	0
Absence of Viral Hepatitis	No	0
	Yes	+2

Definite autoimmune hepatitis: ≥ 7; Probable autoimmune hepatitis: ≥ 6. Typical liver histology for autoimmune hepatitis = each of the following features had to be present, namely interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell) and hepatic rosette formation. Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical = showing signs of another diagnosis, like steatohepatitis. ANA: Antinuclear antibodies; SMA: Smooth muscle autoantibodies; LKM: Liver/kidney microsomal; SLA/LP: Soluble liver antigen or liver pancreas; AIH: Autoimmune hepatitis.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Variant forms of AIH

Within the clinical spectrum of AIH there are some patients who manifest clinical characteristics of either PBC or primary sclerosing cholangitis (PSC)[100]. Although we have long known about the existence of these conditions, there is no well-defined consensus concerning the classification of these disorders and therefore so far several terms have been used, such as "overlap syndrome", "the hepatic form of PBC", "autoimmune cholangitis", "autoimmune sclerosing cholangitis" or "combined hepatitis/cholestatic syndrome", to report patients with characteristics of both AIH and PBC or PSC[101-103]. In this context, it should be noted that in children with AIH, a specific entity has been described in almost half of patients characterized by lesions of both AIH and sclerosing cholangitis[104]. Thus, the term "autoimmune sclerosing cholangitis" was introduced by Gregorio et al, also suggesting the need of an investigation of the biliary tree at least with magnetic resonance cholangiopancreatography (MRCP) in all children with a diagnosis of AIH[105]. So far, this variant seems to be unique for children with AIH as a prospective study in adults with AIH was negative and therefore, in the absence of cholestatic presentation, MRCP screening does not seem justified in adult-onset AIH[106,107].

Table-5: Variant forms of Autoimmune Hepatitis and their features

Variant forms	Features
AIH+PBC	-Presence of AMA -Presence of Histological features of Cholangitis and Bile duct loss -Treatment with Prednisone is done if ALP level is ≤2 x ULN -Treatment with Prednisone and Ursodeoxycholic acid is done if ALP level is > 2 x ULN
AIH+PSC	-Abnormal Cholangiographic features -Presence of IBD -Absence of AMA -Histological features of Cholangitis and Cholestasis may be present -Treatment includes Prednisone and Ursodeoxycholic acid
AIH+ Cholestatic features	-Presence of ANA or Anti-SMA -Histological features of Cholangitis and Cholestasis are present -Absence of IBD -Absence of AMA and Cholangiographic changes -Treatment with Prednisone and Ursodeoxycholic acid
Autoantibody Negative AIH	-13% of patients with Chronic Hepatitis of unknown cause satisfy criteria for AIH but lack the characteristic autoantibodies -Commonly called CRYPTOGENIC CHRONIC HEPATITIS. -Age, Female predominance, Frequency of Immunologic diseases, Histologic features and Lab findings are similar with classic AIH -Associated with HLA-B8-DR3 -Respond to treatment with Glucocorticoids

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; AMA: Anti-Mitochondrial Antibodies; ALP: Alkaline Phosphatase; IBD: Inflammatory Bowel Disease; ANA: Anti-Nuclear Antibodies; Anti-SMA: Anti-Smooth Muscle Antibodies; HLA-B8-DR3: Human Leukocyte Antigen haplotypes between B8 to DR3.

However, as criteria for the definition of ‘‘overlaps’’ do not exist, their diagnosis is problematic, while because of lack of standardization and instability of the study populations, the characteristics of “overlap syndromes” vary among trials[108]. Recently, it has been reported that in documented clinical cases of variant forms of AIH, the available scoring systems carry low sensitivity for the diagnosis of AIH. These findings are in accordance with the results of previous reports[109-111]. Their findings of low utility of the simplified scoring for the diagnosis of AIH in variant forms of AIH are in contrast with the conclusion of another study. Indeed, after the use of the latest score in 368 patients with PBC, only 6% could be classified as having AIH-PBC “overlaps’’, compared to 12% found by using the revised score, indicating by this how the prevalence of “overlap or variant conditions” is dependent on the definitions of these syndromes[112].

As the etiopathogenesis of AIH, PBC and PSC is still unknown, definition of criteria for these “variant forms” of AIH seems difficult and arbitrary and for these reasons, the IAIHG do not support the concept of “overlap or variant syndromes” as new and distinct disorders[113]. However, recently it has been reported that the Chazouillères et al criteria had higher sensitivity (92%) and specificity (97%) for identifying patients with AIH-PBC ‘‘overlap syndrome’’ compared to the revised and the simplified scores. Nevertheless, again these criteria do not have international consensus[114].

From the laboratory perspective, the concurrent detection of AMA and anti-dsDNA is associated with the presence of AIH-PBC “overlap syndrome”. Additionally, either HLA-DR7 or IgG or IgM plasma cells in liver biopsies have been considered as surrogate markers for AIH-PBC “variants”. However, neither IgG or IgM staining pattern of plasmacytic infiltrates was specific for AIH-PBC “overlap cases”, although an IgG/IgM ratio of less than 1 was present only in PBC, with all “overlap patients” having a respective ratio above 1[115].

Taking into account the several autoimmune or immune-mediated diseases that have been associated with IgG4, a potential involvement of this IgG subclass in autoimmune liver diseases and in particular in AIH was investigated as well. Indeed, it was found that IgG4-related AIH is present in almost a third of AIH patients and furthermore, this AIH variant is characterized, apart from the high IgG4 levels, by intense periportal infiltrate and a more favorable response to corticosteroid administration compared to IgG4-negative AIH patients. As this IgG subclass expresses poor binding, activity to complement its involvement in cell-mediated lysis is obscure and therefore its pathogenetic connection to the liver damage in AIH patients seems unlikely. IgG4 is probably the final result and not the cause of a response to abnormal immunological environments that underlie the pathogenesis of the liver damage seen in AIH. Nevertheless, it is obvious that we need more data in order to confirm, extend and define more precisely these findings along with their potential clinical significance in AIH cases[116,117].

In summary, we think that the IAIHG is right to emphasize that, due to the low frequency of “overlap syndromes or variants of AIH”, patients should be categorized as AIH, PBC and PSC based on the predominant disorder and those with “overlapping features” should not be considered as having new distinct diseases. In addition, the IAIHG scores should not be used in patients with “overlapping features”. However, specific management may be required in PBC or PSC patients who also have features of AIH.

AIH-1

AIH-1 accounts for about 80% of all cases with AIH. The detection of ANA and/or SMA is almost exclusively requisite for an AIH-1 diagnosis[118]. In most instances, the staining pattern of ANA by indirect immunofluorescence (IIF) on tissue sections or isolated immobilized cells like HEp2 cells show a homogeneous diffuse pattern, but speckled patterns are not rare. ANA are directed against single or double stranded DNA, tRNA, SSA-Ro, snRNPs, laminins A and C, cyclin

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

A or histones[119-121]. So far however, a liver-specific nuclear antigen has not been identified in AIH-1, whereas different staining patterns of ANA appear to carry limited clinical implications and diagnostic relevance in routine clinical practice and therefore, the use of HEp2 cells in the diagnostic work-up of AIH is not recommended[122].

SMA are detected by IIF on rodent liver, kidney and stomach sections; they are directed against cytoskeleton structures like filamentous actin (F-actin, the predominant autoantigen of SMA in AIH-1), troponin, tubulin, vimentin and tropomyosin[123,124]. However, reliance only on anti-actin antibodies for AIH-1 diagnosis could lead to approximately a 20% decline of diagnosed patients as F-actin is a likely but not exclusive target autoantigen of SMA[125].

Titers of at least > 1:20 in adults and > 1:10 in children should be considered positive[126]. However, titration of antibody positive sera in AIH can be helpful as a very high titer of homogeneously reactive ANA or anti F-actin is far more meaningful than a low albeit positive titer of ANA and/or SMA that may usually be detected in patients with hepatitis B or C[126-128]. In the majority of AIH-1 patients, disappearance of ANA and/or SMA is observed during immunosuppression[129]. However, autoantibody status is not related to the outcome of patients after withdrawal of corticosteroids. In addition, neither autoantibody titers at diagnosis nor autoantibody behavior in the course of the disease are prognostic markers for AIH-1. Moreover, pre-transplant ANA and SMA levels in AIH patients do not seem to affect recurrence or outcome following liver transplantation. These findings indicate that detection of ANA and SMA is more of diagnostic than prognostic value[130,131].

Of interest, 15%-30% of patients with AIH-1 have autoantibodies directed against soluble liver antigen or liver pancreas (anti-SLA/LP). This autoantibody is the most specific antibody ever identified in AIH-1, is associated with a more severe disease course and has a global distribution[132]. A recent meta-analysis showed that the diagnostic accuracy of anti-SLA/LP in AIH was very high. Therefore, from the clinical point of view, anti-SLA/LP can be used as a significant surrogate marker for the diagnosis of AIH-1, while it may also lead to a considerable decline of cases with cryptogenic hepatitis or autoantibody-negative AIH. Anti-SLA/LP antibodies target a synthase (S) converting O-phosphoseryl-tRNA (Sep) to selenocysteine-tRNA (Sec), giving a label of SepSecS. Subsequently, molecular based assays like ELISAs, immunoblot and radioligand assays have been developed for the detection of these antibodies[133].

The reason for anti-SLA/LP association with severe disease, protracted treatment and relapse after cessation of therapy in AIH patients is not known but we were the first to report that antibodies against ribonucleoprotein/Sjögren's syndrome A antigen (anti-Ro/SSA) and particularly to Ro52 antigen (anti-Ro52) are detected in 98% of patients with AIH-1 who have concurrent detection of anti-SLA/LP[134]. This concomitant detection of both autoantibodies was not because of cross-reactivity and was reported later in 77% of European and 96% of North American anti-SLA/LP positive patients. Of note, anti-Ro52 antibodies either alone or in combination with anti-SLA/LP were associated with the worst outcome of patients, as attested by an increased frequency of progression to cirrhosis and liver-related deaths[135]. Accordingly, it was suggested that the associations previously described for anti-SLA/LP antibodies may be due to their concurrence with anti-Ro52 antibodies.

However, contrary to the generally accepted assumption that anti-SLA/LP either alone or in combination with anti-Ro52 antibodies are indicators of worse prognosis and treatment outcome, a very recent study from Greece demonstrated that anti-SLA/LP positivity was not associated with the clinical, laboratory or histological characteristics of AIH patients[136]. In addition, in that study, treatment response, corticosteroid withdrawal, relapse after stopping treatment and outcome were not associated with the presence of anti-SLA/LP, anti-Ro52 or double reactivity to both autoantibodies. Moreover, Ro52 epitope mapping for the first time revealed new epitopes unique for AIH (other than those reported in Sjogren's syndrome) and independent from anti-SLA/LP positivity. Of course these novel findings need further investigation and external validation[137].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Table-6:Classification of Autoimmune Hepatitis based on autoantibodies detected	
Types of AIH	**Characteristic Autoantibodies**
AIH-1	ANA, SMA, p-ANCA (p-ANNA), anti-ASGP-R, anti-SLA/LP (specific antibody; molecular target: SepSecS)
AIH-2	Anti-LKM1 (molecular target: CYP2D6), anti-LKM 3 (molecular target: UGT1), anti-LC1 (liver specific antibody, molecular target: FTCD), anti-ASGP-R
AIH as component of APECED	ANA, anti-LC (molecular target: unknown), anti-LKM (molecular target: CYP2A6, CYP1A1, CYP2B6), anti-LM (liver specific antibody; molecular target: CYP1A2)
AIH-1: Autoimmune hepatitis type 1; AIH-2: Autoimmune hepatitis type 2; APECED: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; ANA: Antinuclear antibodies; SMA: Smooth muscle antibodies; p-ANCA: Perinuclear antineutrophil cytoplasmic antibodies; p-ANNA: Peripheral antineutrophil nuclear antibodies; Anti-ASGP-R: Antibodies against asialoglycoprotein receptor; Anti-SLA/LP: Antibodies against soluble liver antigen/liver pancreas; SepSecS: Synthase-converting O-phosphoseryl-tRNA to selenocysteine-tRNA; anti-LKM1: Anti-liver kidney microsomal antibodies type 1; CYP2D6: Cytochrome P450 2D6; Anti-LKM 3: Anti-liver kidney microsomal antibodies type 3; UGT1: UDP-glucuronosyltransferases; Anti-LC1: Anti-liver cytosol antibodies type 1; FTCD: Formiminotransferase cyclodeaminase; CYP2A6: Cytochrome P450 2A6; CYP1A1: Cytochrome P450 1A1; CYP2B6: Cytochrome P450 2B6; Anti-LM: Antibodies against liver membrane; CYP1A2: Cytochrome P450 1A2.	

AIH-2

Less than 10%-15% of AIH cases in Europe and North America have the AIH-2 subtype. Anti-LKM1 antibodies show a diffuse cytoplasmic staining of liver lobules and exclusively of the P3 portion of the proximal renal tubules[138,139]. Therefore, anti-LKM1 can be easily distinguished from AMA, which stain the proximal and distal renal tubules. Anti-LKM1 auto antibodies mainly target several epitopes of drug metabolizing enzymes of phase 1, namely CYP2D6 (molecular weight of 50 kDa)[140]. Of note, 0-10% of HCV patients independently of the genotype of HCV develop anti-LKM1 auto antibodies which are directed against the same autoantigen recognized by anti-LKM1 in AIH-2, indicating underlying cross reactivity mechanisms, although the autoantibody response to immunodominant epitopes differs[141-144]. In Italian patients with chronic hepatitis C, a genetic predisposition like HLA DR7 positivity has been suggested as a triggering factor for the development of anti-LKM1. From the clinical perspective, investigation for anti-LKM is recommended by the IAIHG in HCV patients under IFN-α-based therapies and, in cases of positive results, careful monitoring should be performed because occasionally IFN-α may unmask or induce AIH[145].

Anti-LKM 3 autoantibodies, either alone or in conjunction with anti-LKM1, are also detected in approximately 5%-10% of patients with AIH-2. In addition to signals obtained from liver and kidney tissues, anti-LKM3 may present with fluorescence signals from the pancreas, adrenal gland, thyroid and stomach. Anti-LKM 3 autoantibodies were first reported in 13%-15% of patients with chronic hepatitis D and only occasionally in HCV patients, supporting further the concept of HCV-induced autoimmunity[146]. The main autoantigen of anti-LKM 3 has been identified as the family 1 of UDP-glucuronosyl-transferases (UGT1, molecular weight of 55 kDa) both in AIH-2 and in chronic hepatitis D[147,148].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Approximately a third of patients with AIH-2, anti-LC1 autoantibodies are detected, in half of whom anti-LKM1 reactivity is also present. This autoantibody is organ-specific but not species-specific and is characterized by a cytoplasmic staining of the periportal hepatocytes. It is of interest that no staining is found around the central veins. In 10% of AIH patients this autoantibody is detected as the only one autoantibody[149-154]. It recognizes FTCD, a metabolic enzyme involved in metabolism of folate (molecular weight of 58-62 kDa). Multiple regions of FTCD trigger the LC1 autoimmune response and LC1 reactivity is predominantly directed to the FT region of FTCD[155,156]. Additional techniques like the Ouchterlony double diffusion, ELISA, immunoblot or counter-immunoelectrophoresis are usually required for anti-LC1 detection as its common concurrence with anti-LKM1 makes anti-LC1 detection by IIF difficult[157]. Titers of > 1:20 in adults and > 1:5 in children are considered positive for both anti-LKM and anti-LC1[158,159].

Detection of autoantibodies in AIH as a component of APECED (APS-1)

Hepatitis in APECED is associated with autoantibodies directed against the CYP450 complex. Indeed, CYP1A1, CYP1A2, CYP2A6 and CYP2B6 have been identified as autoantigens in APECED patients. CYP1A1, CYP2A6 and CYP2B6 are expressed in the liver and kidney, giving rise to LKM staining, while CYP1A2 is expressed only in the kidney, leading to a LM staining[160].

The highest prevalence of anti-CYP2A6 antibodies was found in a Finnish group of APECED patients (15.6%), whereas anti-CYP1A2 were detected in only 6.3%. Of interest, anti-CYP2A6 detection in this group of patients was not associated with the presence of hepatitis, whereas anti-CYP1A2 were found only in APECED patients with hepatitis. Therefore, anti-CYP1A2 could be used as a specific marker for AIH as part of APECED, albeit with its low sensitivity. Anti-CYP2A6 might be used as a surrogate marker for APECED if it is detected in a patient with AIH. In addition, using IIF, anti-LKM/LM antibodies were found in about 50% of patients with AIH as a component of APECED and in only 11% of APECED patients without hepatitis[161].

ANA are detected in almost a quarter of APECED patients, irrespective of the presence or absence of hepatitis. For this reason, ANA are not useful laboratory indicators for AIH diagnosis in APECED. So far, anti-SLA/LP, anti-LKM1 or anti-LC1 autoantibodies have not been reported in patients with AIH as part of APECED. In addition, CYP1A2 and CYP2A6 have not been identified as hepatic autoantigens in AIH patients or in patients with other autoimmune diseases. These findings suggest that AIH-1 or AIH-2 and AIH in APECED are characterized by different molecular targets of autoimmunity which do not overlap. In this context, AIH and hepatitis as an APECED component may be distinguished on the basis of a different autoantibody profile[162].

It is not known whether in APECED patients a close monitoring of anti-LM may lead to early, or even prophylactic, treatment of AIH as a new part of the disease. Evidence that autoantibodies may be detected before the clinical manifestation of a new disease component in APECED comes from adrenal and ovarian insufficiencies, where the respective autoantibodies are detected 2-3 years before the clinical presentation of the autoimmune components. The aromatic-L-amino acid decarboxylase (AADC) is another hepatic autoantigen in APECED which is expressed in the liver cytosol and was originally described as a β-cell autoantigen. Of note, the prevalence of anti-AADC autoantibodies is significantly increased in APECED patients with vitiligo (88%) and hepatitis (92%).

Challenges and unmet needs in autoantibody testing

In 2004, the serology subcommittee of the IAIHG published detailed guidelines on how to test for autoantibodies relevant to AIH, including the preparation of substrates, application of serum samples, optimal dilution, fluorochrome-labeled revealing agents, selection of controls and diagnostically relevant staining patterns. Ideally, the preferred first-line screening for ANA, SMA, LMK1, LKM3, LC1 and AMA should be the IIF on fresh frozen sections (4-8 wk stored at -20 °C) of a multi-organ substrate (liver, kidney and stomach), especially from rats. The use of HEp2 cells only for ANA, SMA and AMA detection should be avoided because of an increased frequency of false-positive results[1].

However, the development of locally validated sections for IIF is not feasible under real life conditions. Furthermore, sections of commercial origin are of variable quality as they are usually treated with fixatives to lengthen shelf-life, which may result in enhanced background staining and potentially to several difficulties in the

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

interpretation of IIF patterns. Therefore, some centers, especially in the US, for antibody testing use assays based on recombinant or purified antigens like ELISAs or immunoblot, particularly for ANA, SMA (F-actin), anti-LKM1, anti-LC1, AMA and anti-SLA/LP detection. However, from the diagnostic point of view, this approach is very questionable for the index patient with unexplained elevation of transaminases and potential underestimation is not unusual[1,2].

Regarding the levels of autoantibody titers, it should be noted that they may vary and therefore it is clear that low titers do not exclude AIH diagnosis, nor do high titers establish the diagnosis. Furthermore, repeated tests may be necessary to allow autoantibody detection and a correct diagnosis. A significant level of positivity would start at 1/40 dilution. However, for patients up to 18 years, any level of autoantibody reactivity is not frequent and therefore seropositivity at 1/20 dilution for ANA and SMA and even 1/10 for anti-LKM and anti-LC1 may be clinically important. Thus, the laboratory should give any level of positivity from 1/10 and then the interpretation of the results should be done within the clinical context and patient's age. Unfortunately, several laboratories ignore the recommended cut-off points and by using their own (1/80 or even 1/160) expand the proportion of "negatives", thus contributing further to the potential underestimation of the disease[1-3].

As autoantibody detection is very important for AIH diagnosis, both laboratory personnel and clinicians need to become more familiar with AIH manifestations and interpretation of liver autoimmune serology in order to derive maximum benefit for the affected patient. In this context, the end-user, the clinician, must order tests advisedly with good clinical data and interpret these in the light of the clinical information to make wise evidence-based decisions in an attempt to minimize the problem of underestimation of AIH diagnosis[3].

Non-conventional autoantibodies in AIH

The detection of several autoantibodies with limited or obscure clinical importance has been published in patients with AIH. These include antibodies to single and double-stranded DNA, phospholipids, histones, cyclic citrullinated peptide, asialoglycoprotein receptor (anti-ASGP-R), chromatin, centromere, Ro52, alpha-actinin (α-actinin), Saccharomyces cerevisiae, celiac disease-related autoantibodies, AMA, lactoferrin and p53 protein[163-169].

From this repertoire of autoantibodies, we shall discuss three briefly, namely AMA, antibodies to α-actinin and anti-ASGP-R antibodies, as they appear to have some significance in patients with AIH[170,171]. Although AMA remains the serological hallmark for PBC diagnosis, they can also be detected in otherwise typical cases of AIH. Indeed, frequencies between 3.6% to as high as 34% have been found for AMA presence in AIH cases[172]. The latter highest frequency was reported in Japanese patients. At present, most researchers agree that the presence of AMA in AIH does not identify a subgroup of patients requiring different therapeutic options or that leads quickly into PBC development[173]. In addition, a long-term Canadian trial has shown that corticosteroid administration in patients with classical AIH who were AMA-positive over a follow-up of up to 27 years had neither clinical nor histological indices of PBC during that period. In contrast, a small case-study recently reported three AMA-positive AIH patients in whom specific PBC manifestations overlapped in time, indicating the potential need of longer follow-up in an attempt to unmask late PBC development in these patients[174-176]. Taking together the above mentioned data, we believe that in order to define whether or not the presence of AMA in AIH is an incidental finding due to collateral bile duct injury or conceals subclinical autoimmune cholestatic liver disease and therefore can predict the future development of cholestatic pathology and the clinical onset of PBC needs to be determined in future multicenter prospective studies[177].

α-actinin is a ubiquitous cytoskeletal protein which belongs to the superfamily of F-actin crosslinking proteins, together with spectrin, dystrophin and their homologues and isoforms[178]. This fundamental cell molecule has recently gained attention as a dominant autoantigen in autoimmune diseases, like SLE and AIH-1. Indeed, it has been shown in murine models as well as in humans that anti-dsDNA antibodies may contribute to the pathogenesis of SLE-related glomerulonephritis by cross-reacting with α-actinin[179,180]. Furthermore, anti-α-actinin antibodies in combination with anti-F-actin antibodies have been detected in the sera of AIH patients, identifying a subset of patients with a clinically and histologically severe form of the disease. This double reactivity against F-actin and

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

α-actinin was not due to cross-reactivity and it was highly specific only for AIH-1 patients. In addition, we showed recently that the baseline detection of anti-α-actinin antibodies could predict treatment response in a large cohort of AIH-1 patients and for these reasons, these autoantibodies can be used as reliable markers for monitoring treatment outcome of patients. Of interest, anti-F-actin antibodies target an epitope located at positions 350-375 of the C terminus of human F-actin which actually corresponds to the α-actinin binding domain. All these findings make the hypothesis of α-actinin involvement into AIH pathogenesis very attractive and indicate the need for considerable attention and further investigations[181].

The ASGP-R is a liver-specific glycoprotein of the cell membrane. The internalization of sialoglycoproteins by binding a terminal galactose residue to coated pits is the predominant function of this receptor. Of interest, ASGP-R is expressed mainly on the surface of hepatocytes at the periportal areas where interface hepatitis is found as a marker of severe inflammatory activity in AIH patients. Therefore, a possible implication of anti-ASGP-R autoantibodies in AIH pathogenesis has been suggested. The general presumption is that the target of potentially tissue-damaging auto-reactions in AIH must be liver-specific and available to the immune system in vivo. So far, ASGP-R is the only autoantigen that fulfills these criteria. Additional support to this revealed from the common detection of anti-ASGPR autoantibodies in AIH patients (detection in 88% of patients), which was associated with the inflammatory activity of the disease and also by the fact that anti-ASGP-R titers decreased significantly during remission, while they reappear in disease exacerbations[182,183]. Therefore, anti-ASGP-R autoantibodies may be diagnostically helpful when AIH is suspected but the conventional autoantibodies are not detected. However, they are frequently detected in PBC, alcoholic cirrhosis and chronic hepatitis B or C, resulting in low disease specificity although the specificity of the respective assay for their determination has recently been improved because of the characterization of the major epitopes of ASGP-R. Nevertheless, routine determination of these antibodies is not generally recommended since standardized and easily accessible assays are still awaited.

Liver Histology in AIH

In all patients with suspected AIH, a liver biopsy should be performed, including those with acute/severe or even fulminant hepatitis. In fact, liver histology is a prerequisite for the diagnosis of AIH, as has been suggested by both diagnostic criteria of the IAIHG. It should be stated however, that although certain histological changes are characteristic, no findings are specific for AIH diagnosis. Therefore, a different view of the importance of liver histology in the diagnosis of AIH has recently been reported. In this report, the authors concluded that most patients with multiple features of AIH based on biochemical analyses and autoantibody testing did not need a biopsy as patients with atypical (5%) or compatible (95%) liver histology for AIH had similar biochemical features of the disease. We agree with aspects of the investigators, that it is possible to initiate immunosuppression in patients with the typical serological and biochemical profile of AIH. However, we also believe that histological confirmation of the diagnosis of AIH prior to therapy will facilitate treatment decisions and that liver biopsy should be performed whenever possible. This is supported by all international liver authorities, including IAIHG. Nevertheless, we need further multicenter studies in order to validate these findings because liver biopsy is not performed only for diagnosis but also for the definition of grade and stage of the disease and therefore the prognosis of AIH.

A typical feature of AIH is the presence of interface hepatitis, also called piecemeal necrosis, which denotes inflammation of hepatocytes at the junction of the portal tract and hepatic parenchyma. In general, the inflammation spares the biliary system, consists of lymphocytes and “clustered” plasma cells and usually extends into the lobules (progression to lobular hepatitis). However, a small subset of patients may show small duct injury but lack PBC features and respond similarly to corticosteroid therapy as patients with classical AIH do.

The degree of plasmacytosis can be helpful in discriminating against AIH from viral hepatitis cases. Indeed, there are rare cases of HBV infection with comparable portal plasmacytosis, while intense plasmacytosis can also be seen in hepatitis A. In addition, plasmacytosis of the portal tract might have a prognostic implication as its presence while on immunosuppression is associated with relapse after drug withdrawal. However, about 33% of AIH patients have few or

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

no plasma cells in the portal tract and, for this reason, the absence of plasma cell infiltration cannot exclude AIH diagnosis by itself. According to the simplified criteria for AIH diagnosis, emperipolesis and hepatocellular rosette formation are also "typical" histological characteristics of AIH. Of note, the origin of "emperipolesis" is derived from two Greek words (en meaning inside and peripolos meaning patrol) describing by this way the active penetration by one cell into and through a larger cell. Eosinophils can be found in AIH, making the differential diagnosis between AIH and drug-induced AIH more problematic. Parenchymal collapse, also known as multi acinar necrosis, in the appropriate clinical and serological setting could also be useful in supporting AIH diagnosis. Apart from the mildest or earliest cases of AIH, fibrosis is present in almost all patients. In untreated disease, the fibrosis may be extensive with typical cirrhotic findings. It should be noted that the necroinflammatory activity and severity of AIH at the histological level are not in accordance with the biochemical activity of the disease. Therefore, it is clear that liver biopsy provides invaluable information on outcome because almost one-third of patients have cirrhosis or bridging necrosis at presentation, carrying a poorer prognosis than those without.

Liver histology in patients with acute to fulminant AIH is different compared to that found in AIH patients with an insidious onset. In addition, recently the US NIH Acute Liver Failure Study Group suggested a set of criteria for autoimmune acute liver failure. As in the revised and simplified criteria for AIH diagnosis, liver biopsy is also mandatory for the diagnostic criteria of autoimmune acute liver failure. In particular, the following features suggestive of an autoimmune pathogenesis were found. There are two distinctive patterns of massive hepatic necrosis. The first consists of a severe form of the so-called centrilobular form of AIH with panlobular necrosis, while in the second, a typical AIH with massive hepatic necrosis accompanied in some circumstances with centrilobular involvement is found. Additional characteristics in cases of acute liver failure due to AIH include portal lymphoid follicles, a plasma cell-enriched infiltrate and central perivenulitis[184,185].

CURRENT TREATMENT APPROACHES TO AIH

There are certain guidelines(USA, EUROPE) for treating AIH. The selective treatment is given when the transaminases or AST is more than 10 times upper limit of normal ie severe hepatitis biochemically go ahead and treat if the AST is moderately or modestly increased more than 5 times the upper limit of normal and the IgG levels also increased, this is a protein that is produced in response to inflammation particularly in setting of autoimmune hepatitis and there is another indicator of disease activity so this combination would also indicate treatment and also liver bites even in the absence of liver enzymes or IgG elevation if it shows severe injury particularly with a type of autoimmune hepatitis where there is massive necrosis(cell death in liver)when we look at the biopsy it is also a very strong indication as well as when the symptoms of the hepatitis are quite incapacitating . Relative indication to treat is really anything sort of mild or quiescent disease or severe disease and it typically leads into some abnormalities in the liver enzymes and some symptoms like inflammation particularly interphase hepatitis, this requires liver biopsy[186,187].

No immediate treatment is necessary when the enzymes are normal, the IgG is normal or near-normal and the liver biopsy shows inactive disease whether there is cirrhosis or not.

Table-7: Indications for the treatment of Autoimmune Hepatitis

Absolute Indication	Not Indicated
AST >10 * ULN	AST <3 * ULN
AST>5 * ULN and IgG >2 * ULN	AST <3 *ULN
Severe liver injury with massive necrosis	Bland liver biopsy in cirrhosis, mild histology
Incapacitating symptoms	No symptoms

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Treatment with glucocorticoids is life-saving in autoimmune hepatitis, particularly during exacerbations of active and symptomatic disease; initially, prednisolone(40mg/day)is given orally; the dose is then gradually reduced as the patient and LFTs improve. Maintenance therapy should only be instituted once LFTs are normal(as well as IgG if elevated). Approaches to maintenance immunosuppressive agents in patients with low activity disease, newer agents, such as mycophenolate mofetil (MMF), are increasingly being used but formal evidence to inform practice in this area is lacking. Patients should be monitored for acute exacerbations(LFT and IgG screening with patients altered to the possible symptoms) and such exacerbations should be treated with glucocorticoids. Although treatment can significantly reduce the rate of progression to cirrhosis, end stage disease can be seen in patients despite treatment. [188]

Table-8: standard therapy for newly diagnosed AIH patients

Week	Budesonide+ Azathioprine	Prednisolone + Azathioprine (mg/dl)	Prednisolone + Azathioprine	Prednisolone+ Azathioprine
1	3 mg tid/50	60	30/50	40
2	3 mg tid/50	40	20/50	40
3	3 mg tid/50	30	15/50	30/50
4	2-3 mg tid/50	20	10/50	20/50
5	3 mg bid/50	15	10/50	15/50
6	3 mg bid/50	15	5/50	15 or 10/50

Table-9: Second line therapy for Azathioprine failures

6-mercaptopurine, mycophenolate mofetil 500-1000mg bid, cyclosporine 50-100 mg bid, tacrolimus 1-5 mg bid (level 4-8 ng/ml), budesonide
Sirolimus, everolimus, thioguanine nucleotides, rituximab, cyclophosphamide, methotrexate, IV Ig, CTLA4

Table-10: Second line therapy for AIH

Drug	Dose	Response
Mycophenolate mofetil	500-3000 mg/d	Naive -88%, refractory/intolerant -12 to 58%
Cyclosporine	2-5 mg/kg/d	Steroid failure - 93%
Tacrolimus	0.5-3 mg/bd	Steroid failure -98%

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

AIH and PREGNANCY

Autoimmune hepatitis can improve during pregnancy and this improvement may allow reductions in immunosuppressive therapy during pregnancy.Preconceptional counselling is advised and termination of immunosuppressive therapy should be attempted where possible.Patients must be counselled regarding the uncertain risk of azathioprine (CAT D) in pregnancy, and azathioprine should be discontinued, if possible, in patients during pregnancy.Post partum exacerbation of AIH must be anticipated by resuming standard therapy 2 weeks prior to anticipated delivery and by closely monitoring serum AST or ALT levels at 3 week intervals for at least 3 months after delivery.Contraception should be advised in women with advanced liver disease and features of portal hypertension because they are at risk for variceal hemorrhage during pregnancy.

MANAGEMENT OF COMPLICATIONS

Complications may include the following: Cirrhosis and complications of cirrhosis(eg, ascites, coagulopathy, hepatic coma), portal hypertension, esophageal varices, encephalopathy, renal failure, sepsis, variceal bleeding.

Acute variceal bleeding

- ABC, iv access, resuscitate-restore circulation with blood and plasma.
- Urgent endoscopy, even in known case; 20% may not be varices but other lesions-acute gastric erosions
- Local measures used to control acute variceal bleeding:
- Endoscopic band ligation or sclerotherapy is the most widely used initial therapy that stops variceal bleeding in 80% of the patients.
- Balloon tamponade, esophageal transection and pharmacological treatment, this included the use of terlipressin, the current drug of choice it releases the vasoconstrictor, vasopressin, over several hours in amounts sufficient to reduce the portal hypertension without producing the systemic effects.
- Terlipressin 2mg, iv, 6 hourly until bleeding stops, then 1 mg, 6hrly for further 24 hours.
- Octreotide , the synthetic form of somatostatin, 50 micrograms iv was given followed by an infusion of 50 micrograms, hourly.
- TIPSS(transjugular intrahepatic portosystemic stent shunting), used for acute bleeding when the patient is not responding to the sclerotherapy or banding.

Prevention of recurrent bleeding:

- Recurrent bleeding is the rule rather than the exception in patients who have previously bled from esophageal varices, and treatment to prevent this is needed.
- Band Ligation: varices occluded with a tight rubber band, the occluded varix subsequently sloughs with variceal obliteration this is repeated every 1-2 weeks until the varices are obliterated. Regular follow-up endoscopy is required to identify and treat any recurrence of varices. Generally this technique is more effective than sclerotherapy, has fewer side effects and is now the treatment of choice.
- Sclerotherapy: varices are injected with a sclerosing agent, being largely abandoned in preference to band ligation. Transient chest or abdominal pain, fever, dysphagia, occasionally esophageal perforation, esophageal strictures may also develop.
- TIPSS(Transjugular intrahepatic portosystemic shunt): Stent placed between the portal vein and hepatic vein in the liver to provide a portosystemic shunt and therefore reduce portal pressure.
- Propranolol (80-160mg/day) or nadolol, these drugs reduce portal venous pressure in portal hypertension and have been used to prevent recurrent variceal bleeding.[189,190]

Ascites

Portal hypertension results in an increase in hydrostatic pressure within the splanchnic bed. Decreased oncotic pressure caused by decreased protein synthesis may contribute to the condition. Salt restriction and use of diuretics is necessary to treat ascites, a combination of spironolactone and a loop diuretic, unless the serum sodium level is less than 125 mEq per L. patients with new onset ascites should have diagnostic paracentesis performed, consisting of cell count, total protein test, albumin level, and bacterial culture and sensitivity. Serum ascites albumin gradient is 1.1g per dl or greater, the diagnosis of portal hypertension(cirrhotic) ascites or heart failure-associated ascites is confirmed. However, a serum ascites albumin gradient less than 1.1 g per dl is suggestive of another cause of ascites, such as peritoneal carcinomatosis or nephrogenic ascites.[191]

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

Hepatic Encephalopathy

Hepatic encephalopathy is thought to be related to toxic compounds generated by gut bacteria, such as ammonia, mercaptans, and short-chain fatty acids and phenols. These compounds are transported by the portal vein to the liver, where most are normally metabolized or excreted immediately. In patients with cirrhosis, damaged hepatocytes are unable to metabolize these waste products, and portal venous blood can bypass the liver through collateral circulation (such as varices) or a medically constructed shunt.

In patients with active encephalopathy, reversible factors should be sought and managed, including constipation, noncompliance with medical therapy, infection (i.e., spontaneous bacterial peritonitis), electrolyte imbalances, gastrointestinal bleeding, and use of benzodiazepines. Paracentesis should be performed to rule out peritonitis as a cause of encephalopathy. The paracentesis should be performed during the hospitalization in which the encephalopathy is diagnosed. If encephalopathy persists, then the patient should be treated with disaccharides or rifaximin, Lactulose is a nonabsorbable disaccharide that is believed to induce an absorption of nitrogen into the bacteria of the fecal flora, making it less available to generate absorbable ammonia. Rifaximin is a non absorbable antibiotic that decreases the intestinal load of ammonia-producing bacteria. [192]

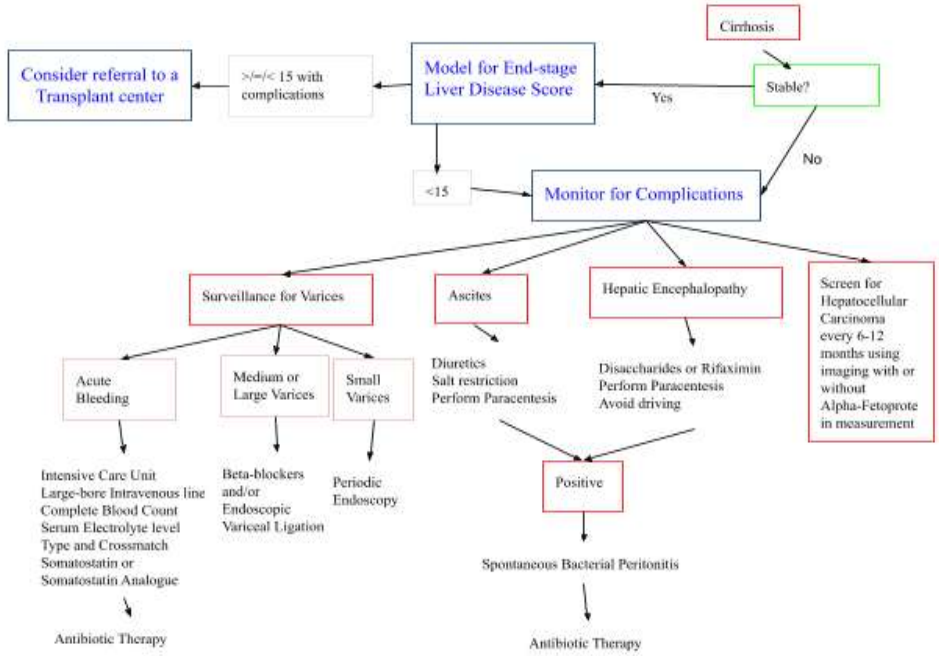

Figure-3 : Algorithm for the Management of complications of liver cirrhosis

Immunosuppressive treatment should not be instituted in patients with minimal or no disease activity or inactive cirrhosis, but these patients must continue to be followed closely, i.e. 3-6 months.Apart from alcoholic hepatitis (DF>32), it is the only hepatitis for which steroids should be given.AIH must always be suspected because early treatment can reduce the mortality and progression to cirrhosis significantly.Suspect AIH as a cause of acute or chronic hepatitis when other causes such as viral, hereditary, metabolic, cholestatic, and drug induced diseases, have been excluded.Two types based on the presence of ANA and SMA(type 1 AIH) or anti LC-1 (type 2 AIH).Immunosuppressive treatment should be instituted in patients with serum AST or ALT levels greater than 10 fold ULN, at least five fold ULN in conjunction with a serum gamma globulin level at least 2 fold ULN, and/or histological features of bridging necrosis or multi-lobular necrosis.[193]

PATIENT EDUCATION

About Medication

Glucocorticoids – Glucocorticoids such as prednisone control the inflammation in the liver,

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

thereby preventing further scarring. The main drawback of prednisone is side effects, which can include weight gain, acne, bone loss, elevated blood glucose levels (potentially leading to diabetes), an increased risk of infections, cataracts, high blood pressure, and mood and sleep disturbance, among others. People who require long-term prednisone are monitored carefully for these side effects. To minimize the risks of side effects, the lowest possible dose of prednisone is used.

Budesonide – Budesonide, another medication that may be substituted for prednisone, continues to be studied, and is increasingly used in Europe. Budesonide should only be used in patients who do not have cirrhosis.

Monitoring corticosteroid side effects:

- Cosmetic changes, including facial rounding, dorsal hump formation.
- Striae , weight gain, acne, alopecia and facial hirsutism, occur in 80% of patients after 2 years of corticosteroid treatment regardless of the regimen.
- Severe side effects include osteopenia with vertebral compression, brittle diabetes, psychosis, pancreatitis, opportunistic infection, labile hypertension and malignancy.
- Regular weight bearing exercise program, vitamin D and calcium supplementation and administration of bisphosphonates whenever needed.
- Patients on long term corticosteroid treatment should be monitored for bone disease by baseline and annual bone mineral densitometry of the lumbar spine and hip.
- Pre treatment vaccination against HAV and HBV should be performed if there has been no previous addiction.

Azathioprine or 6-mercaptopurine – A second medication, such as azathioprine {Azasan; Imuran} or 6-mercaptopurine (Purinethol) and, less commonly, methotrexate or mycophenolate mofetil, may be recommended in addition to prednisone. The benefit of adding a second medication is that it may be possible to reduce or eliminate prednisone, helping to minimize the potential side effects of prednisone.

Azathioprine and 6-mercaptopurine can also cause side effects, including allergic reactions, a low white blood cell count, inflammation of the pancreas, nausea, and abnormal liver blood tests (which can sometimes cause confusion as to whether the abnormal results are from the autoimmune hepatitis or the drugs used to treat it). There may be a small increased risk of certain types of cancer (such as lymphoma). Blood tests to monitor for these conditions are performed regularly while taking these medications.[194,195]

Mycophenolate has several potential risks, including an increased risk of developing infections or cancers. Mycophenolate can cause birth defects and should not be taken during pregnancy. Men and women who use mycophenolate must use two effective methods to prevent pregnancy (eg, condoms and a birth control pill).[196]

Duration of treatment

As a general rule, treatment is continued until the disease is in remission, the treatment fails, or the person develops severe side effects from treatment.

Remission is defined as a lack of symptoms, normal or near normal levels of liver blood tests, and improvement in the appearance of liver tissue (based upon a biopsy). The initial period of remission generally occurs 12 or more months after treatment begins. The majority of patients achieve remission by 18 months to three years of treatment.

Approximately 50 percent of patients remain in remission or have only mild disease activity for months to years after treatment is stopped. However, most patients must eventually restart treatment because the disease becomes active again (relapse). Relapse typically occurs within the first 15 to 20 months after treatment is stopped. Relapse is more likely in those who have cirrhosis on the initial liver biopsy.[197,198]

When to consider stopping therapy

Normal aminotransferases for 2 years, normal IgG, resolution of inflammation on repeat liver biopsy.

If medications are not used

Close follow-up is recommended for people who are not initially treated with medications. Follow-up generally includes a physical examination and blood tests every few months, and a liver biopsy is usually repeated at least every two years.

Prognosis

- 40% of all patients develop cirrhosis
- 54% develop esophageal varices in 2 years
- Poor prognosis if ascites or hepatic encephalopathy present
- 13 to 20% can have spontaneous resolution

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 1, pp: 57-90 www.ijprajournal.com ISSN: 2249-7781

- Of patients who survive the early and active stage of disease, approximately 41% of them develop inactive cirrhosis
- Of patients who have severe initial disease and survive the first two years, typically survive long term.

Lifestyle Modifications

- Taking medication and seeing a healthcare provider on a regular basis can help to ensure that the liver remains as healthy as possible.
- No specific diet has been shown to improve the outcome in patients with autoimmune hepatitis. The best advice is to eat a normal, healthy and balanced diet and to avoid becoming obese; obesity can increase the risk of fatty liver disease and may complicate autoimmune hepatitis.
- Alcohol should be avoided since it can cause fatty liver and other liver damage. All types of alcoholic beverages can be harmful to the liver, including beer, wine, and liquor. Patients with liver disease may worsen with even small amounts of alcohol.
- Exercise is good for overall health and is encouraged, but it has no specific benefit for people with autoimmune hepatitis.
- Many drugs are broken down by the liver. Thus, it is always best to check with a healthcare provider or pharmacist before starting a new prescription. Unless the liver is already scarred, most drugs are safe. Some people with active liver disease will be advised to take a smaller dose of medication.
- An important exception is acetaminophen (Tylenol), commonly used for headaches, other aches and pains, and fever. In people with any type of liver disease, the maximum recommended dose of acetaminophen is no more than 2000 mg (in divided doses) per 24 hours. Thus, it is reasonable to take 500 mg every four to six hours, although this should not be repeated more than four times in one day.
- There are a number of claims, particularly on the internet, that herbal medications can improve liver health. However, no single or combination of herbs has been proven to improve outcomes in patients with autoimmune hepatitis. Some herbs can cause serious liver damage, and some have been implicated in triggering autoimmune hepatitis. For this reason, we do not currently recommend any herbal treatment for liver disease.
- Do not underestimate the value of sharing your concerns with other people with autoimmune hepatitis. Ask your healthcare provider about support groups or other patients who may be willing to discuss their experiences with autoimmune hepatitis.

II. CONCLUSION

Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease with a female predominance occurring in all ages and races that may start with an episode of acute hepatitis and may lead to liver cirrhosis, liver cancer, liver transplantation or death.Over the last decades molecular targets of the most relevant disease associated autoantibodies were identified and characterized. Recent investigations on immunopathogenesis concentrated on regulatory T cells and the complex genetic background of AIH via GWAS analyses.Immunosuppressive therapy in severe cases of AIH prolongs survival. Standard of care includes corticosteroids alone or in combination with azathioprine to achieve normalization of transaminases and immunoglobulin G levels in serum. The topical steroid budesonide can be used in non-cirrhotic patients instead of predniso(lo)ne to reduce steroid specific side effects.In treatment failures mycophenolate mofetil, cyclosporine A, tacrolimus and lately anti-TNF or anti-CD20 monoclonal antibodies can be used as second-line treatment based on a careful individual risk evaluation and should be done in experienced centers. Proper education regarding the severity, treatment and lifestyle modifications may help the patient to understand more about the condition and act appropriately.

REFERENCES

[1]. Zachou K, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, Dalekos GN, Muratori L. Review article: autoimmune hepatitis -- current management and challenges. Aliment Pharmacol Ther. 2013;38:887–913.

[2]. Dalekos GN, Zachou K, Liaskos C, Gatselis N. Autoantibodies and defined target autoantigens in autoimmune hepatitis: an overview. Eur J Intern Med. 2002;13:293–303.

[3]. Czaja AJ. Autoantibodies in autoimmune liver disease. Adv Clin Chem. 2005;40:127–164.

[4]. Krawitt EL. Can you recognize autoimmune hepatitis? Postgrad Med. 1998;104:145–149, 152.
[5]. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. Hepatology. 1993;18:998–1005.
[6]. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31:929–938.
[7]. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48:169–176.
[8]. Vergani D, Alvarez F, Bianchi FB, Cançado EL, Mackay IR, Manns MP, Nishioka M, Penner E. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. J Hepatol. 2004;41:677–683.
[9]. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, Poupon R, Darnis F, Lévy VG, Grippon P. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. Hepatology. 1987;7:1333–1339.
[10]. Fabien N, Desbos A, Bienvenu J, Magdalou J. Autoantibodies directed against the UDP-glucuronosyltransferases in human autoimmune hepatitis. Autoimmun Rev. 2004;3:1–9.
[11]. Martini E, Abuaf N, Cavalli F, Durand V, Johanet C, Homberg JC. Antibody to liver cytosol (anti-LC1) in patients with autoimmune chronic active hepatitis type 2. Hepatology. 1988;8:1662–1666.
[12]. Liberal R, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: a comprehensive review. J Autoimmun. 2013;41:126–139.
[13]. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol. 1998;33:99–103.
[14]. Berdal JE, Ebbesen J, Rydning A. [Incidence and prevalence of autoimmune liver diseases] Tidsskr Nor Laegeforen. 1998;118:4517–4519.
[15]. Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. Clin Liver Dis. 2002;6:635–647.
[16]. Feld JJ, Heathcote EJ. Epidemiology of autoimmune liver disease. J Gastroenterol Hepatol. 2003;18:1118–1128.
[17]. Werner M, Prytz H, Ohlsson B, Almer S, Björnsson E, Bergquist A, Wallerstedt S, Sandberg-Gertzén H, Hultcrantz R, Sangfelt P, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol. 2008;43:1232–1240.
[18]. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol. 2002;97:2402–2407.
[19]. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, Stedman CA. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol. 2010;25:1681–1686.
[20]. Lim KN, Casanova RL, Boyer TD, Bruno CJ. Autoimmune hepatitis in African Americans: presenting features and response to therapy. Am J Gastroenterol. 2001;96:3390–3394.
[21]. Wong RJ, Gish R, Frederick T, Bzowej N, Frenette C. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J Clin Gastroenterol. 2012;46:155–161.
[22]. Muratori L, Longhi MS. The interplay between regulatory and effector T cells in autoimmune hepatitis: Implications for innovative treatment strategies. J Autoimmun. 2013;46:74–80.
[23]. Czaja AJ, Doherty DG, Donaldson PT. Genetic bases of autoimmune hepatitis. Dig Dis Sci. 2002;47:2139–2150.
[24]. Muratori P, Czaja AJ, Muratori L, Pappas G, Maccariello S, Cassani F, Granito A, Ferrari R, Mantovani V, Lenzi M, et al. Genetic distinctions between autoimmune hepatitis in Italy and North America. World J Gastroenterol. 2005;11:1862–1866.
[25]. Czaja AJ, Donaldson PT. Genetic susceptibilities for immune expression and

liver cell injury in autoimmune hepatitis. Immunol Rev. 2000;174:250–259.

[26]. Pando M, Larriba J, Fernandez GC, Fainboim H, Ciocca M, Ramonet M, Badia I, Daruich J, Findor J, Tanno H, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. Hepatology. 1999;30:1374–1380.

[27]. Czaja AJ, Souto EO, Bittencourt PL, Cancado EL, Porta G, Goldberg AC, Donaldson PT. Clinical distinctions and pathogenic implications of type 1 autoimmune hepatitis in Brazil and the United States. J Hepatol. 2002;37:302–308.

[28]. de Boer YS, van Gerven NM, Zwiers A, Verwer BJ, van Hoek B, van Erpecum KJ, Beuers U, van Buuren HR, Drenth JP, den Ouden JW, et al. Genome-wide association study identifies variants associated with autoimmune hepatitis type 1. Gastroenterology. 2014;147:443–452.e5.

[29]. Ma Y, Bogdanos DP, Hussain MJ, Underhill J, Bansal S, Longhi MS, Cheeseman P, Mieli-Vergani G, Vergani D. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastroenterology. 2006;130:868–882.

[30]. Agarwal K, Czaja AJ, Jones DE, Donaldson PT. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphisms and susceptibility to type 1 autoimmune hepatitis. Hepatology. 2000;31:49–53.

[31]. Cookson S, Constantini PK, Clare M, Underhill JA, Bernal W, Czaja AJ, Donaldson PT. Frequency and nature of cytokine gene polymorphisms in type 1 autoimmune hepatitis. Hepatology. 1999;30:851–856.

[32]. Agarwal K, Czaja AJ, Donaldson PT. A functional Fas promoter polymorphism is associated with a severe phenotype in type 1 autoimmune hepatitis characterized by early development of cirrhosis. Tissue Antigens. 2007;69:227–235.

[33]. Bogdanos DP, Lenzi M, Okamoto M, Rigopoulou EI, Muratori P, Ma Y, Muratori L, Tsantoulas D, Mieli- Vergani G, Bianchi FB, et al. Multiple viral/self immunological cross-reactivity in liver kidney microsomal antibody positive hepatitis C virus infected patients is associated with the possession of HLA B51. Int J Immunopathol Pharmacol. 2004;17:83–92.

[34]. Manns MP, Johnson EF, Griffin KJ, Tan EM, Sullivan KF. Major antigen of liver kidney microsomal autoantibodies in idiopathic autoimmune hepatitis is cytochrome P450db1. J Clin Invest. 1989;83:1066–1072.

[35]. Gueguen M, Yamamoto AM, Bernard O, Alvarez F. Anti-liver-kidney microsome antibody type 1 recognizes human cytochrome P450 db1. Biochem Biophys Res Commun. 1989;159:542–547.

[36]. Zanger UM, Hauri HP, Loeper J, Homberg JC, Meyer UA. Antibodies against human cytochrome P-450db1 in autoimmune hepatitis type II. Proc Natl Acad Sci USA. 1988;85:8256–8260.

[37]. Kerkar N, Choudhuri K, Ma Y, Mahmoud A, Bogdanos DP, Muratori L, Bianchi F, Williams R, Mieli-Vergani G, Vergani D. Cytochrome P4502D6(193-212): a new immunodominant epitope and target of virus/self cross-reactivity in liver kidney microsomal autoantibody type 1-positive liver disease. J Immunol. 2003;170:1481–1489.

[38]. Manns MP, Griffin KJ, Sullivan KF, Johnson EF. LKM-1 autoantibodies recognize a short linear sequence in P450IID6, a cytochrome P-450 monooxygenase. J Clin Invest. 1991;88:1370–1378.

[39]. Manns MP, Jentzsch M, Mergener K. Discordant manifestation of LKM-1 antibody positive autoimmune hepatitis in identical twins. Hepatology. 1990;12:840 [abstract].

[40]. Ma Y, Thomas MG, Okamoto M, Bogdanos DP, Nagl S, Kerkar N, Lopes AR, Muratori L, Lenzi M, Bianchi FB, et al. Key residues of a major cytochrome P4502D6 epitope are located on the surface of the molecule. J Immunol. 2002;169:277–285.

[41]. Muratori L, Parola M, Ripalti A, Robino G, Muratori P, Bellomo G, Carini R, Lenzi M, Landini MP, Albano E, et al. Liver/kidney microsomal antibody type 1 targets CYP2D6 on hepatocyte plasma membrane. Gut. 2000;46:553–561.

[42]. Loeper J, Louérat-Oriou B, Duport C, Pompon D. Yeast expressed cytochrome P450 2D6 (CYP2D6) exposed on the external face of plasma membrane is

functionally competent. Mol Pharmacol. 1998;54:8–13.
[43]. Miyara M, Gorochov G, Ehrenstein M, Musset L, Sakaguchi S, Amoura Z. Human FoxP3+ regulatory T cells in systemic autoimmune diseases. Autoimmun Rev. 2011;10:744–755.
[44]. Longhi MS, Ma Y, Bogdanos DP, Cheeseman P, Mieli-Vergani G, Vergani D. Impairment of CD4(+)CD25(+) regulatory T-cells in autoimmune liver disease. J Hepatol. 2004;41:31–37.
[45]. Longhi MS, Hussain MJ, Mitry RR, Arora SK, Mieli-Vergani G, Vergani D, Ma Y. Functional study of CD4+CD25+ regulatory T cells in health and autoimmune hepatitis. J Immunol. 2006;176:4484–4491.
[46]. Peiseler M, Sebode M, Franke B, Wortmann F, Schwinge D, Quaas A, Baron U, Olek S, Wiegard C, Lohse AW, et al. FOXP3+ regulatory T cells in autoimmune hepatitis are fully functional and not reduced in frequency. J Hepatol. 2012;57:125–132.
[47]. Taubert R, Hardtke-Wolenski M, Noyan F, Wilms A, Baumann AK, Schlue J, Olek S, Falk CS, Manns MP, Jaeckel E. Intrahepatic regulatory T cells in autoimmune hepatitis are associated with treatment response and depleted with current therapies. J Hepatol. 2014;61:1106–1114.
[48]. Sebode M, Peiseler M, Weiler-Normann C, Schramm C, Lohse AW, Herkel J. Phenotypic alterations of regulatory T cells in autoimmune hepatitis: causal or associated with treatment and remission? Hepatology. 2014:Epub ahead of print.
[49]. Zingaretti C, Arigò M, Cardaci A, Moro M, Crosti M, Sinisi A, Sugliano E, Cheroni C, Marabita F, Nogarotto R, et al. Identification of new autoantigens by protein array indicates a role for IL4 neutralization in autoimmune hepatitis. Mol Cell Proteomics. 2012;11:1885–1897.
[50]. Lohse AW, Manns M, Dienes HP, Meyer zum Büschenfelde KH, Cohen IR. Experimental autoimmune hepatitis: disease induction, time course and T-cell reactivity. Hepatology. 1990;11:24–30.
[51]. Voehringer D, Blaser C, Grawitz AB, Chisari FV, Buerki K, Pircher H. Break of T cell ignorance to a viral antigen in the liver induces hepatitis. J Immunol. 2000;165:2415–2422.
[52]. Djilali-Saiah I, Lapierre P, Vittozi S, Alvarez F. DNA vaccination breaks tolerance for a neo-self antigen in liver: a transgenic murine model of autoimmune hepatitis. J Immunol. 2002;169:4889–4896.
[53]. Derkow K, Loddenkemper C, Mintern J, Kruse N, Klugewitz K, Berg T, Wiedenmann B, Ploegh HL, Schott E. Differential priming of CD8 and CD4 T-cells in animal models of autoimmune hepatitis and cholangitis. Hepatology. 2007;46:1155–1165.
[54]. Zierden M, Kühnen E, Odenthal M, Dienes HP. Effects and regulation of autoreactive CD8+ T cells in a transgenic mouse model of autoimmune hepatitis. Gastroenterology. 2010;139:975–986, 986.e1-3.
[55]. Hintermann E, Ehser J, Christen U. The CYP2D6 animal model: how to induce autoimmune hepatitis in mice. J Vis Exp. 2012;(60):3644.
[56]. Lapierre P, Djilali-Saiah I, Vitozzi S, Alvarez F. A murine model of type 2 autoimmune hepatitis: Xenoimmunization with human antigens. Hepatology. 2004;39:1066–1074.
[57]. Lapierre P, Béland K, Djilali-Saiah I, Alvarez F. Type 2 autoimmune hepatitis murine model: the influence of genetic background in disease development. J Autoimmun. 2006;26:82–89.
[58]. Lapierre P, Béland K, Martin C, Alvarez F, Alvarez F. Forkhead box p3+ regulatory T cell underlies male resistance to experimental type 2 autoimmune hepatitis. Hepatology. 2010;51:1789–1798.
[59]. Lapierre P, Béland K, Yang R, Alvarez F. Adoptive transfer of ex vivo expanded regulatory T cells in an autoimmune hepatitis murine model restores peripheral tolerance. Hepatology. 2013;57:217–227.
[60]. Ehser J, Holdener M, Christen S, Bayer M, Pfeilschifter JM, Hintermann E, Bogdanos D, Christen U. Molecular mimicry rather than identity breaks T-cell tolerance in the CYP2D6 mouse model for human autoimmune hepatitis. J Autoimmun. 2013;42:39–49.
[61]. Holdener M, Hintermann E, Bayer M, Rhode A, Rodrigo E, Hintereder G, Johnson EF, Gonzalez FJ, Pfeilschifter J, Manns MP, et al. Breaking tolerance to the natural human liver autoantigen cytochrome P450

2D6 by virus infection. J Exp Med. 2008;205:1409–1422.
[62]. Iwamoto S, Kido M, Aoki N, Nishiura H, Maruoka R, Ikeda A, Okazaki T, Chiba T, Watanabe N. TNF-α is essential in the induction of fatal autoimmune hepatitis in mice through upregulation of hepatic CCL20 expression. Clin Immunol. 2013;146:15–25.
[63]. Kido M, Watanabe N, Okazaki T, Akamatsu T, Tanaka J, Saga K, Nishio A, Honjo T, Chiba T. Fatal autoimmune hepatitis induced by concurrent loss of naturally arising regulatory T cells and PD-1-mediated signaling. Gastroenterology. 2008;135:1333–1343.
[64]. Aoki N, Kido M, Iwamoto S, Nishiura H, Maruoka R, Tanaka J, Watanabe T, Tanaka Y, Okazaki T, Chiba T, et al. Dysregulated generation of follicular helper T cells in the spleen triggers fatal autoimmune hepatitis in mice. Gastroenterology. 2011;140:1322–1333.e1-5.
[65]. Schramm C, Kanzler S, zum Büschenfelde KH, Galle PR, Lohse AW. Autoimmune hepatitis in the elderly. Am J Gastroenterol. 2001;96:1587–1591.
[66]. Peng M, Li Y, Zhang M, Jiang Y, Xu Y, Tian Y, Peng F, Gong G. Clinical features in different age groups of patients with autoimmune hepatitis. Exp Ther Med. 2014;7:145–148.
[67]. Grønbæk L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol. 2014;60:612–617.
[68]. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. Aliment Pharmacol Ther. 2014;39:117–124.
[69]. Granito A, Muratori L, Pappas G, Muratori P, Ferri S, Cassani F, Lenzi M, Bianchi FB. Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. Aliment Pharmacol Ther. 2005;21:1273–1277.
[70]. Al-Chalabi T, Boccato S, Portmann BC, McFarlane IG, Heneghan MA. Autoimmune hepatitis (AIH) in the elderly: a systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. J Hepatol. 2006;45:575–583.
[71]. Stravitz RT, Lefkowitch JH, Fontana RJ, Gershwin ME, Leung PS, Sterling RK, Manns MP, Norman GL, Lee WM. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology. 2011;53:517–526.
[72]. Takahashi H, Zeniya M. Acute presentation of autoimmune hepatitis: Does it exist? A published work review. Hepatol Res. 2011;41:498–504.
[73]. Ferrari R, Pappas G, Agostinelli D, Muratori P, Muratori L, Lenzi M, Verucchi G, Cassani F, Chiodo F, Bianchi FB. Type 1 autoimmune hepatitis: patterns of clinical presentation and differential diagnosis of the 'acute' type. QJM. 2004;97:407–412.
[74]. Miyake Y, Iwasaki Y, Terada R, Onishi T, Okamoto R, Sakai N, Sakaguchi K, Shiratori Y. Clinical characteristics of fulminant-type autoimmune hepatitis: an analysis of eleven cases. Aliment Pharmacol Ther. 2006;23:1347–1353.
[75]. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, Heathcote EJ. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology. 2005;42:53–62.
[76]. Landeira G, Morise S, Fassio E, Ramonet M, Alvarez E, Caglio P, Longo C, Domínguez N. Effect of cirrhosis at baseline on the outcome of type 1 autoimmune hepatitis. Ann Hepatol. 2012;11:100–106.
[77]. Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, Lindor K. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology. 2010;51:2040–2048.
[78]. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, Lucena MI, Castiella A, Lindor K, Björnsson E. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology. 2011;54:931–939.
[79]. Lisotti A, Azzaroli F, Brillanti S, Mazzella G. Severe acute autoimmune hepatitis after natalizumab treatment. Dig Liver Dis. 2012;44:356–357.
[80]. Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. Eur J Clin Pharmacol. 2012;68:895–898.

[81]. van Casteren-Messidoro C, Prins G, van Tilburg A, Zelinkova Z, Schouten J, de Man R. Autoimmune hepatitis following treatment with infliximab for inflammatory bowel disease. J Crohns Colitis. 2012;6:630–631.
[82]. O'Leary JG, Zachary K, Misdraji J, Chung RT. De novo autoimmune hepatitis during immune reconstitution in an HIV-infected patient receiving highly active antiretroviral therapy. Clin Infect Dis. 2008;46:e12–e14.
[83]. Saitis A, Gatselis N, Zachou K, Dalekos GN. Use of TNFα antagonists in refractory AIH: revealing the unforeseen. J Hepatol. 2013;59:197–198.
[84]. Borman MA, Urbanski S, Swain MG. Anti-TNF-induced autoimmune hepatitis. J Hepatol. 2014;61:169–170.
[85]. Kern E, VanWagner LB, Yang GY, Rinella ME. Liraglutide-induced autoimmune hepatitis. JAMA Intern Med. 2014;174:984–987.
[86]. Vento S, Guella L, Mirandola F, Cainelli F, Di Perri G, Solbiati M, Ferraro T, Concia E. Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. Lancet. 1995;346:608–609.
[87]. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet. 1997;17:399–403.
[88]. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, et al. Positional cloning of the APECED gene. Nat Genet. 1997;17:393–398.
[89]. Ahonen P, Myllärniemi S, Sipilä I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med. 1990;322:1829–1836.
[90]. Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnićk GL, Elveback IR, Schoenfield LJ. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology. 1972;63:820–833.
[91]. Brissos J, Carrusca C, Correia M, Cabral J. Autoimmune hepatitis: trust in transaminases. BMJ Case Rep. 2014;2014
[92]. Obermayer-Straub P, Perheentupa J, Braun S, Kayser A, Barut A, Loges S, Harms A, Dalekos G, Strassburg CP, Manns MP. Hepatic autoantigens in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Gastroenterology. 2001;121:668–677.
[93]. Appleyard S, Saraswati R, Gorard DA. Autoimmune hepatitis triggered by nitrofurantoin: a case series. J Med Case Rep. 2010;4:311.
[94]. Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, Lindor K. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology. 2010;51:2040–2048.
[95]. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, Lucena MI, Castiella A, Lindor K, Björnsson E. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology. 2011;54:931–939.
[96]. Gatselis NK, Zachou K, Papamichalis P, Koukoulis GK, Gabeta S, Dalekos GN, Rigopoulou EI. Comparison of simplified score with the revised original score for the diagnosis of autoimmune hepatitis: a new or a complementary diagnostic score? Dig Liver Dis. 2010;42:807–812.
[97]. Azhar A, Niazi MA, Tufail K, Malek AH, Balasubramanian M, Araya V. A new approach for treatment of hepatitis C in hepatitis C-autoimmune hepatitis overlap syndrome. Gastroenterol Hepatol (N Y) 2010;6:233–236.
[98]. Rigopoulou EI, Zachou K, Gatselis N, Koukoulis GK, Dalekos GN. Autoimmune hepatitis in patients with chronic HBV and HCV infections: patterns of clinical characteristics, disease progression and outcome. Ann Hepatol. 2013;13:127–135.
[99]. Teufel A, Weinmann A, Centner C, Piendl A, Lohse AW, Galle PR, Kanzler S. Hepatocellular carcinoma in patients with autoimmune hepatitis. World J Gastroenterol. 2009;15:578–582.
[100]. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, Bomford A, O'Grady JG, Harrison PM, Heneghan MA. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for

follow-up and screening. Hepatology. 2008;48:863–870.
[101]. Ngu JH, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. Hepatology. 2012;55:522–529.
[102]. Migita K, Watanabe Y, Jiuchi Y, Nakamura Y, Saito A, Yagura M, Ohta H, Shimada M, Mita E, Hijioka T, et al. Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization-autoimmune hepatitis prospective study) Liver Int. 2012;32:837–844.
[103]. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol. 2008;103:1944–1951.
[104]. Liberal R, Grant CR, Longhi MS, Mieli-Vergani G, Vergani D. Diagnostic criteria of autoimmune hepatitis. Autoimmun Rev. 2014;13:435–440.
[105]. Rust C, Beuers U. Overlap syndromes among autoimmune liver diseases. World J Gastroenterol. 2008; 14:3368–3373.
[106]. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, Mieli-Vergani G. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001; 33:544–553.
[107]. Levy C, Naik J, Giordano C, Mandalia A, O'Brien C, Bhamidimarri KR, Schiff ER, Martin P. Hispanics with primary biliary cirrhosis are more likely to have features of autoimmune hepatitis and reduced response to ursodeoxycholic acid than non-Hispanics. Clin Gastroenterol Hepatol. 2014;12:1398–1405.
[108]. Rojas CP, Bodicharla R, Campuzano-Zuluaga G, Hernandez L, Rodriguez MM. Autoimmune hepatitis and primary sclerosing cholangitis in children and adolescents. Fetal Pediatr Pathol. 2014;33:202–209.
[109]. Lewin M, Vilgrain V, Ozenne V, Lemoine M, Wendum D, Paradis V, Ziol M, Arrivé L, Beaugrand M, Poupon R, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. Hepatology. 2009;50:528–537.
[110]. Muratori P, Granito A, Pappas G, Pendino GM, Quarneti C, Cicola R, Menichella R, Ferri S, Cassani F, Bianchi FB, et al. The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. Am J Gastroenterol. 2009;104:1420–1425.
[111]. Coss Adame E, Granados J, Uribe M, Torre A. Does HLA-DR7 differentiate the overlap syndrome of auto-immune hepatitis-primary biliary cirrhosis (AIH-PBC) from those with auto-immune hepatitis type 1? Ann Hepatol. 2011;10:28–32.
[112]. Lee H, Stapp RT, Ormsby AH, Shah VV. The usefulness of IgG and IgM immunostaining of periportal inflammatory cells (plasma cells and lymphocytes) for the distinction of autoimmune hepatitis and primary biliary cirrhosis and their staining pattern in autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. Am J Clin Pathol. 2010;133:430–437.
[113]. Abe K, Takahashi A, Nozawa Y, Imaizumi H, Hayashi M, Okai K, Kanno Y, Watanabe H, Ohira H. The utility of IgG, IgM, and CD138 immunohistochemistry in the evaluation of autoimmune liver diseases. Med Mol Morphol. 2014;47:162–168.
[114]. Trivedi PJ, Hirschfield GM. Review article: overlap syndromes and autoimmune liver disease. Aliment Pharmacol Ther. 2012;36:517–533.
[115]. Granito A, Muratori L, Muratori P, Pappas G, Guidi M, Cassani F, Volta U, Ferri A, Lenzi M, Bianchi FB. Antibodies to filamentous actin (F-actin) in type 1 autoimmune hepatitis. J Clin Pathol. 2006;59:280–284.
[116]. Czaja AJ. Behavior and significance of autoantibodies in type 1 autoimmune hepatitis. J Hepatol. 1999;30:394–401.
[117]. Dbouk N, Parekh S. Impact of pretransplant antinuclear antibody and antismooth muscle antibody titers on disease recurrence and graft survival following liver transplantation in autoimmune hepatitis patients. J Gastroenterol Hepatol. 2013;28:537–542.
[118]. Wies I, Brunner S, Henninger J, Herkel J, Kanzler S, Meyer zum Büschenfelde KH, Lohse AW. Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis. Lancet. 2000; 355:1510–1515.
[119]. Herkel J, Heidrich B, Nieraad N, Wies I, Rother M, Lohse AW. Fine specificity of

autoantibodies to soluble liver antigen and liver/pancreas. Hepatology. 2002;35:403–408.

[120]. Kanzler S, Weidemann C, Gerken G, Löhr HF, Galle PR, Meyer zum Büschenfelde KH, Lohse AW. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. J Hepatol. 1999; 31:635–640.

[121]. Ballot E, Homberg JC, Johanet C. Antibodies to soluble liver antigen: an additional marker in type 1 auto-immune hepatitis. J Hepatol. 2000;33:208–215.

[122]. Baeres M, Herkel J, Czaja AJ, Wies I, Kanzler S, Cancado EL, Porta G, Nishioka M, Simon T, Daehnrich C, et al. Establishment of standardised SLA/LP immunoassays: specificity for autoimmune hepatitis, worldwide occurrence, and clinical characteristics. Gut. 2002;51:259–264.

[123]. Ma Y, Okamoto M, Thomas MG, Bogdanos DP, Lopes AR, Portmann B, Underhill J, Dürr R, Mieli-Vergani G, Vergani D. Antibodies to conformational epitopes of soluble liver antigen define a severe form of autoimmune liver disease. Hepatology. 2002;35:658–664.

[124]. Czaja AJ, Donaldson PT, Lohse AW. Antibodies to soluble liver antigen/liver pancreas and HLA risk factors for type 1 autoimmune hepatitis. Am J Gastroenterol. 2002;97:413–419.

[125]. Efe C, Ozaslan E, Wahlin S, Purnak T, Muratori L, Quarneti C, Yüksel O, Muratori P. Antibodies to soluble liver antigen in patients with various liver diseases: a multicentre study. Liver Int. 2013;33:190–196.

[126]. Zhang WC, Zhao FR, Chen J, Chen WX. Meta-analysis: diagnostic accuracy of antinuclear antibodies, smooth muscle antibodies and antibodies to a soluble liver antigen/liver pancreas in autoimmune hepatitis. PLoS One. 2014;9:e92267.

[127]. Czaja AJ. Autoantibody-negative autoimmune hepatitis. Dig Dis Sci. 2012;57:610–624.

[128]. Yuan J, Palioura S, Salazar JC, Su D, O'Donoghue P, Hohn MJ, Cardoso AM, Whitman WB, Söll D. RNA-dependent conversion of phosphoserine forms selenocysteine in eukaryotes and archaea. Proc Natl Acad Sci USA. 2006; 103:18923–18927.

[129]. Palioura S, Sherrer RL, Steitz TA, Söll D, Simonovic M. The human SepSecS-tRNASec complex reveals the mechanism of selenocysteine formation. Science. 2009;325:321–325.

[130]. Liaskos C, Bogdanos DP, Rigopoulou EI, Norman GL, Shurns Z, Al-Chalabi T, Krawitt EL, Mieli-Vergani G, Czaja AJ, Vergani D, et al. Antibody responses specific for soluble liver antigen co-occur with Ro-52 autoantibodies in patients with autoimmune hepatitis. J Hepatol. 2007;46(Suppl 1):S250 (abstract).

[131]. Eyraud V, Chazouilleres O, Ballot E, Corpechot C, Poupon R, Johanet C. Significance of antibodies to soluble liver antigen/liver pancreas: a large French study. Liver Int. 2009;29:857–864.

[132]. Montano-Loza AJ, Shums Z, Norman GL, Czaja AJ. Prognostic implications of antibodies to Ro/SSA and soluble liver antigen in type 1 autoimmune hepatitis. Liver Int. 2012;32:85–92.

[133]. Zachou K, Gampeta S, Gatselis NK, Oikonomou K, Goulis J, Manoussakis MN, Renaudineau Y, Bogdanos DP, Dalekos GN. Anti-SLA/LP alone or in combination with anti-Ro52 and fine specificity of anti-Ro52 antibodies in patients with autoimmune hepatitis. Liver Int. 2014:Epub ahead of print.

[134]. Bridoux-Henno L, Maggiore G, Johanet C, Fabre M, Vajro P, Dommergues JP, Reinert P, Bernard O. Features and outcome of autoimmune hepatitis type 2 presenting with isolated positivity for anti-liver cytosol antibody. Clin Gastroenterol Hepatol. 2004;2:825–830.

[135]. Yamamoto AM, Cresteil D, Boniface O, Clerc FF, Alvarez F. Identification and analysis of cytochrome P450IID6 antigenic sites recognized by anti-liver-kidney microsome type-1 antibodies (LKM1) Eur J Immunol. 1993;23:1105–1111.

[136]. Klein R, Zanger UM, Berg T, Hopf U, Berg PA. Overlapping but distinct specificities of anti-liver-kidney microsome antibodies in autoimmune hepatitis type II and hepatitis C revealed by recombinant native CYP2D6 and novel peptide epitopes. Clin Exp Immunol. 1999;118:290–297.

[137]. Duclos-Vallée JC, Hajoui O, Yamamoto AM, Jacz-Aigrain E, Alvarez F. Conformational epitopes on CYP2D6 are

recognized by liver/kidney microsomal antibodies. Gastroenterology. 1995;108:470–476.
[138]. Muratori L, Lenzi M, Ma Y, Cataleta M, Mieli-Vergani G, Vergani D, Bianchi FB. Heterogeneity of liver/kidney microsomal antibody type 1 in autoimmune hepatitis and hepatitis C virus related liver disease. Gut. 1995; 37:406–412.
[139]. Dalekos GN, Makri E, Loges S, Obermayer-Straub P, Zachou K, Tsikrikas T, Schmidt E, Papadamou G, Manns MP. Increased incidence of anti-LKM autoantibodies in a consecutive cohort of hepatitis C patients from central Greece. Eur J Gastroenterol Hepatol. 2002;14:35–42.
[140]. Gatselis NK, Georgiadou SP, Koukoulis GK, Tassopoulos N, Zachou K, Liaskos C, Hatzakis A, Dalekos GN. Clinical significance of organ- and non-organ-specific autoantibodies on the response to anti-viral treatment of patients with chronic hepatitis C. Aliment Pharmacol Ther. 2006;24:1563–1573.
[141]. Ferri S, Muratori L, Quarneti C, Muratori P, Menichella R, Pappas G, Granito A, Ballardini G, Bianchi FB, Lenzi M. Clinical features and effect of antiviral therapy on anti-liver/kidney microsomal antibody type 1 positive chronic hepatitis C. J Hepatol. 2009;50:1093–1101.
[142]. Sugimura T, Obermayer-Straub P, Kayser A, Braun S, Loges S, Alex B, Lüttig B, Johnson EF, Manns MP, Strassburg CP. A major CYP2D6 autoepitope in autoimmune hepatitis type 2 and chronic hepatitis C is a three-dimensional structure homologous to other cytochrome P450 autoantigens. Autoimmunity. 2002; 35:501–513.
[143]. Dalekos GN, Obermayer-Straub P, Bartels M, Maeda T, Kayser A, Braun S, Loges S, Schmidt E, Gershwin ME, Manns MP. Cytochrome P450 2A6: a new hepatic autoantigen in patients with chronic hepatitis C virus infection. J Hepatol. 2003;39:800–806.
[144]. Ma Y, Peakman M, Lobo-Yeo A, Wen L, Lenzi M, Gäken J, Farzaneh F, Mieli-Vergani G, Bianchi FB, Vergani D. Differences in immune recognition of cytochrome P4502D6 by liver kidney microsomal (LKM) antibody in autoimmune hepatitis and chronic hepatitis C virus infection. Clin Exp Immunol. 1994;97:94–99.
[145]. Durazzo M, Philipp T, Van Pelt FN, Lüttig B, Borghesio E, Michel G, Schmidt E, Loges S, Rizzetto M, Manns MP. Heterogeneity of liver-kidney microsomal autoantibodies in chronic hepatitis C and D virus infection. Gastroenterology. 1995;108:455–462.
[146]. Clemente MG, Obermayer-Straub P, Meloni A, Strassburg CP, Arangino V, Tukey RH, De Virgiliis S, Manns MP. Cytochrome P450 1A2 is a hepatic autoantigen in autoimmune polyglandular syndrome type 1. J Clin Endocrinol Metab. 1997;82:1353–1361.
[147]. Clemente MG, Meloni A, Obermayer-Straub P, Frau F, Manns MP, De Virgiliis S. Two cytochromes P450 are major hepatocellular autoantigens in autoimmune polyglandular syndrome type 1. Gastroenterology. 1998;114:324–328.
[148]. Gebre-Medhin G, Husebye ES, Gustafsson J, Winqvist O, Goksøyr A, Rorsman F, Kämpe O. Cytochrome P450IA2 and aromatic L-amino acid decarboxylase are hepatic autoantigens in autoimmune polyendocrine syndrome type I. FEBS Lett. 1997;412:439–445.
[149]. Renaudineau Y, Dalekos GN, Guéguen P, Zachou K, Youinou P. Anti-alpha-actinin antibodies cross-react with anti-ssDNA antibodies in active autoimmune hepatitis. Clin Rev Allergy Immunol. 2008;34:321–325.
[150]. Liaskos C, Rigopoulou E, Zachou K, Georgiadou S, Gatselis N, Papamihali R, Dalekos GN. Prevalence and clinical significance of anticardiolipin antibodies in patients with type 1 autoimmune hepatitis. J Autoimmun. 2005;24:251–260.
[151]. Gabeta S, Norman GL, Gatselis N, Liaskos C, Papamichalis PA, Garagounis A, Zachou K, Rigopoulou EI, Dalekos GN. IgA anti-b2GPI antibodies in patients with autoimmune liver diseases. J Clin Immunol. 2008;28:501–511.
[152]. Chen M, Shirai M, Czaja AJ, Kurokohchi K, Arichi T, Arima K, Kodama T, Nishioka M. Characterization of anti-histone antibodies in patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol. 1998; 13:483–489.
[153]. Montano-Loza A, Czaja AJ, Carpenter HA, Piette A, Murphy D, Shums Z, Burlingame

R, Norman GL. Frequency and significance of antibodies to cyclic citrullinated peptide in type 1 autoimmune hepatitis. Autoimmunity. 2006;39:341–348.

[154]. Fusconi M, Vannini A, Dall'Aglio AC, Pappas G, Cassani F, Ballardini G, Frisoni M, Grassi A, Bianchi FB, Zauli D. Anti-cyclic citrullinated peptide antibodies in type 1 autoimmune hepatitis. Aliment Pharmacol Ther. 2005;22:951–955.

[155]. Hausdorf G, Roggenbuck D, Feist E, Büttner T, Jungblut PR, Conrad K, Berg C, Klein R. Autoantibodies to asialoglycoprotein receptor (ASGPR) measured by a novel ELISA--revival of a disease-activity marker in autoimmune hepatitis. Clin Chim Acta. 2009;408:19–24.

[156]. Czaja AJ, Shums Z, Binder WL, Lewis SJ, Nelson VJ, Norman GL. Frequency and significance of antibodies to chromatin in autoimmune hepatitis. Dig Dis Sci. 2003;48:1658–1664.

[157]. Guéguen P, Dalekos G, Nousbaum JB, Zachou K, Putterman C, Youinou P, Renaudineau Y. Double reactivity against actin and alpha-actinin defines a severe form of autoimmune hepatitis type 1. J Clin Immunol. 2006;26:495–505.

[158]. Oikonomou KG, Zachou K, Dalekos GN. Alpha-actinin: a multidisciplinary protein with important role in B-cell driven autoimmunity. Autoimmun Rev. 2011;10:389–396.

[159]. Zachou K, Oikonomou K, Renaudineau Y, Chauveau A, Gatselis N, Youinou P, Dalekos GN. Anti-α actinin antibodies as new predictors of response to treatment in autoimmune hepatitis type 1. Aliment Pharmacol Ther. 2012;35:116–125.

[160]. Czaja AJ, Shums Z, Donaldson PT, Norman GL. Frequency and significance of antibodies to Saccharomyces cerevisiae in autoimmune hepatitis. Dig Dis Sci. 2004;49:611–618.

[161]. Yiannaki EE, Zintzaras E, Analatos A, Theodoridou C, Dalekos GN, Germenis AE. Evaluation of a microsphere-based flow cytometric assay for diagnosis of celiac disease. J Immunoassay Immunochem. 2004;25:345–357.

[162]. Germenis AE, Yiannaki EE, Zachou K, Roka V, Barbanis S, Liaskos C, Adam K, Kapsoritakis AN, Potamianos S, Dalekos GN. Prevalence and clinical significance of immunoglobulin A antibodies against tissue transglutaminase in patients with diverse chronic liver diseases. Clin Diagn Lab Immunol. 2005;12:941–948.

[163]. Dalekos GN, Bogdanos DP, Neuberger J. Celiac disease-related autoantibodies in end-stage autoimmune liver diseases: what is the message? Liver Int. 2008;28:426–428.

[164]. Nezu S, Tanaka A, Yasui H, Imamura M, Nakajima H, Ishida H, Takahashi S. Presence of antimitochondrial autoantibodies in patients with autoimmune hepatitis. J Gastroenterol Hepatol. 2006;21:1448–1454.

[165]. Rigopoulou EI, Dalekos GN. Molecular diagnostics of primary biliary cirrhosis. Expert Opin Med Diagn. 2008;2:621–634.

[166]. Liaskos C, Bogdanos DP, Rigopoulou EI, Dalekos GN. Development of antimitochondrial antibodies in patients with autoimmune hepatitis: art of facts or an artifact? J Gastroenterol Hepatol. 2007;22:454–455.

[167]. Montano-Loza AJ, Carpenter HA, Czaja AJ. Frequency, behavior, and prognostic implications of antimitochondrial antibodies in type 1 autoimmune hepatitis. J Clin Gastroenterol. 2008;42:1047–1053.

[168]. O'Brien C, Joshi S, Feld JJ, Guindi M, Dienes HP, Heathcote EJ. Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology. 2008;48:550–556.

[169]. Dinani AM, Fischer SE, Mosko J, Guindi M, Hirschfield GM. Patients with autoimmune hepatitis who have antimitochondrial antibodies need long-term follow-up to detect late development of primary biliary cirrhosis. Clin Gastroenterol Hepatol. 2012;10:682–684.

[170]. Schiano TD, Fiel MI. To Biopsy or not to Biopsy … Clin Gastroenterol Hepatol. 2011;9:3–4.

[171]. Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. Liver Int. 2004;24:322–329.

[172]. Muratori L, Muratori P, Zauli D, Grassi A, Pappas G, Rodrigo L, Cassani F, Lenzi M, Bianchi FB. Antilactoferrin antibodies in autoimmune liver disease. Clin Exp Immunol. 2001;124:470–473.

[173]. Himoto T, Yoneyama H, Kurokohchi K, Inukai M, Masugata H, Goda F, Haba R, Watanabe S, Senda S, Masaki T. Clinical significance of autoantibodies to p53 protein in patients with autoimmune liver diseases. Can J Gastroenterol. 2012;26:125–129.
[174]. Muratori P, Muratori L, Gershwin ME, Czaja AJ, Pappas G, MacCariello S, Granito A, Cassani F, Loria P, Lenzi M, et al. 'True' antimitochondrial antibody-negative primary biliary cirrhosis, low sensitivity of the routine assays, or both? Clin Exp Immunol. 2004;135:154–158.
[175]. Renaudineau Y, Croquefer S, Jousse S, Renaudineau E, Devauchelle V, Guéguen P, Hanrotel C, Gilburd B, Saraux A, Shoenfeld Y, et al. Association of alpha-actinin-binding anti-double-stranded DNA antibodies with lupus nephritis. Arthritis Rheum. 2006;54:2523–2532.
[176]. Renaudineau Y, Deocharan B, Jousse S, Renaudineau E, Putterman C, Youinou P. Anti-alpha-actinin antibodies: a new marker of lupus nephritis. Autoimmun Rev. 2007;6:464–468.
[177]. McFarlane BM, Sipos J, Gove CD, McFarlane IG, Williams R. Antibodies against the hepatic asialoglycoprotein receptor perfused in situ preferentially attach to periportal liver cells in the rat. Hepatology. 1990;11:408–415.
[178]. Treichel U, Gerken G, Rossol S, Rotthauwe HW, Meyer zum Büschenfelde KH, Poralla T. Autoantibodies against the human asialoglycoprotein receptor: effects of therapy in autoimmune and virus-induced chronic active hepatitis. J Hepatol. 1993;19:55–63.
[179]. Czaja AJ, Pfeifer KD, Decker RH, Vallari AS. Frequency and significance of antibodies to asialoglycoprotein receptor in type 1 autoimmune hepatitis. Dig Dis Sci. 1996;41:1733–1740.
[180]. Yoshioka M, Mizuno M, Morisue Y, Shimada M, Hirai M, Nasu J, Okada H, Sakaguchi K, Yamamoto K, Tsuji T. Anti-asialoglycoprotein receptor autoantibodies, detected by a capture-immunoassay, are associated with autoimmune liver diseases. Acta Med Okayama. 2002;56:99–105.
[181]. Hilgard P, Schreiter T, Stockert RJ, Gerken G, Treichel U. Asialoglycoprotein receptor facilitates hemolysis in patients with alcoholic liver cirrhosis. Hepatology. 2004;39:1398–1407.
[182]. Husa P, Chalupa P, Stroblová H, Husová L, Slesinger P, Zajíc J. Autoantibodies to asialoglycoprotein receptor in chronic hepatitis C patients. Acta Virol. 2001;45:7–11.
[183]. Björnsson E, Talwalkar J, Treeprasertsuk S, Neuhauser M, Lindor K. Patients with typical laboratory features of autoimmune hepatitis rarely need a liver biopsy for diagnosis. Clin Gastroenterol Hepatol. 2011;9:57–63.
[184]. Te HS, Koukoulis G, Ganger DR. Autoimmune hepatitis: a histological variant associated with prominent centrilobular necrosis. Gut. 1997;41:269–271.
[185]. Fujiwara K, Fukuda Y, Yokosuka O. Precise histological evaluation of liver biopsy specimen is indispensable for diagnosis and treatment of acute-onset autoimmune hepatitis. J Gastroenterol. 2008;43:951–958.
[186]. Garcia-tsao G, pagliaro L. natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies j. Hepatol. 2006; 44:217-31.
[187]. Thomas MB, jaffe D, choti MM, et al. hepatocellular carcinoma : consensus recommendations of the national cancer institute clinical trails planning meeting . J clin oncol. 2010;28(25);3994-4005.
[188]. Taha HA, waked IA. Liver disease on the nile; an association since millennia. Nile liver journal. 2007:80.
[189]. Abstracts of the biennial meeting of the international association for the study of the liver, april 15-16, 2002 and the 37th annual meeting of the european association for the study of the liver, april 18-21, 2002.madriad, spain. J hepatol. 2002; 36.
[190]. Heidelbaugh JJ, Bruderly M. Cirrhosis and chronic liver failure: part 1 diagnosis and evaluation . Am Fam physician . 2006;74(54):756-762.
[191]. Kanwal PS, Wiesner RH, Malinhoc M, et al. a model to predict survival in patients with end stage liver disease. Hepatology . 2001,33(2):464-470.
[192]. Bass NM, Mullen KD, sanyal A et al. Rifaximin treatment in hepatic encephalopathy . N engl J Med.2010;362(12);1071-1081.
[193]. Gluud LL, Klingenberg S, Nikolova D, Gluud C blanding ligation versus beta

blockers as primary prophylaxis in esophageal varices: systematic review of randomized traila. Am J Gastroenterol . 2007;102(12:)2842-2848.

[194]. Garcia- agan JC, Caca K, bureau C, et al; early TIPS cooperative study group. Early use of TIPS in patients with cirrhosis and variceal bleeding . N Engl J med. 2010;36209(25)2370-2379.

[195]. Flamm SL, Parker RA, Chopra A risk factors associated with chronic hepatitis C virus infection: limited frequency of an unidentified source of transmission. Am J Gastroenterol 1999;93(38):597-600.

[196]. Chavez - tapia, NC, barrientos- Gutierrez T, Tellez-Avila FI, Soares- Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane database syst rev.2010;(9):CD002907.

[197]. Garcia- Tsao G, Lim JK. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the department of veterans affairs hepatitis C resource center program and national hepatitis C program Am J gastroenterol. 20090000;10409700;18940].

[198]. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guide-lines for management of autoimmune hepatitis. Gut 2011;60:1611-1629.