Autoimmune hepatitis

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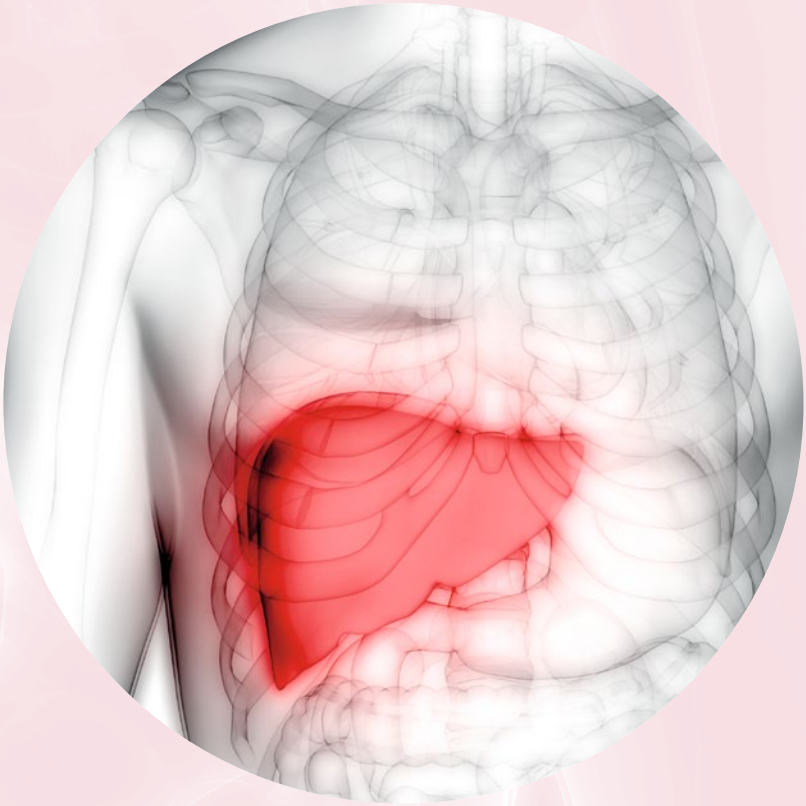

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Contents

1 Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that is associated with serological findings of certain autoantibodies and elevated gamma globulin levels. Its prevalence in Europe is around 15–25 per 100,000 inhabitants.[1,2] AIH affects about three times as many women as men and can occur at any age.[1–4] In 4–14% of cases, AIH presents concurrently with primary biliary cholangitis (PBC) and in 2–8% of cases, it presents concurrently with primary sclerosing cholangitis (PSC).[5–8] In about 40% of cases, AIH is associated with extrahepatic autoimmune diseases or phenomena, most commonly with autoimmune thyroiditis[9,10] (Table 1).

Prevalence of AIH in males versus females

Extrahepatic diseases associated with AIH	**Prevalence [reference values]**
Autoimmune thyroiditis	10–23%[9–11]
Ulcerative colitis	1–8%[9–11]
Rheumatoid arthritis	2–8%[9,10,12]
Sjögren syndrome	1–15%[9,10,12]
Celiac disease	1–2%[9,10,12]
Systemic lupus erythematosus	1–13%[9–12]
Type 1 diabetes	1–9%[9–11]
Multiple sclerosis	0.4–1%[9,10,12]
Vitiligo	1–2%[9,10]
Polymyalgia rheumatica	1%[10]
Psoriasis	3%[10,11]
Mixed connective tissue disease	2.5%[10]
Raynaud's disease	1.6%[9]
Alopecia areata	1%[9]

Table 1: Extrahepatic, immune-mediated diseases/phenomena that may occur in association with AIH

2 Clinical presentation and natural course

AIH is characterized by loss of immunological tolerance to hepatocytes in genetically predisposed patients leading to inflammatory liver injuries which can result in the development of liver fibrosis and ultimately in liver cirrhosis. Approximately 30% of patients are asymptomatic at the time of diagnosis.[2,4,11,12] In these cases, AIH is often diagnosed during investigation for unexplained elevated liver enzymes on routine testing or testing performed for other reasons. Frequently, clinical presentation of this disease is non-specific and characterized by symptoms such as reduced physical performance, fatigue, pain in the upper right region of the abdomen, and/or arthralgia. In approximately 30% of adult AIH patients, liver cirrhosis is already present at the time of diagnosis.[2,4,11–15] In these patients, typical skin symptoms (such as spider naevi or palmar erythema) may be detected, as well as in later stages symptoms of liver dysfunction and portal hypertension, such as hepatic encephalopathy, ascites, and esophageal varices (Fig. 1). Approximately 25% of patients initially exhibit an acute hepatitis with jaundice, which in rare cases can progress to fulminant or even acute liver failure.[2,16–18]

Autoimmune polyglandular syndrome type 1 (APS-1) is a form of AIH which is found in about 10–18% of patients. APS-1 is characterized by chronic mucocutaneous candidiasis, ectodermal dystrophies, and immune-mediated tissue destruction of endocrine organs (hypoparathyroidism, adrenal insufficiency, and hypogonadism).[9,19] In 22% of patients with APS-1 and AIH, antinuclear antibodies (ANA) are detectable, but other autoantibodies that can be found in AIH patients are not detected.[9,20]

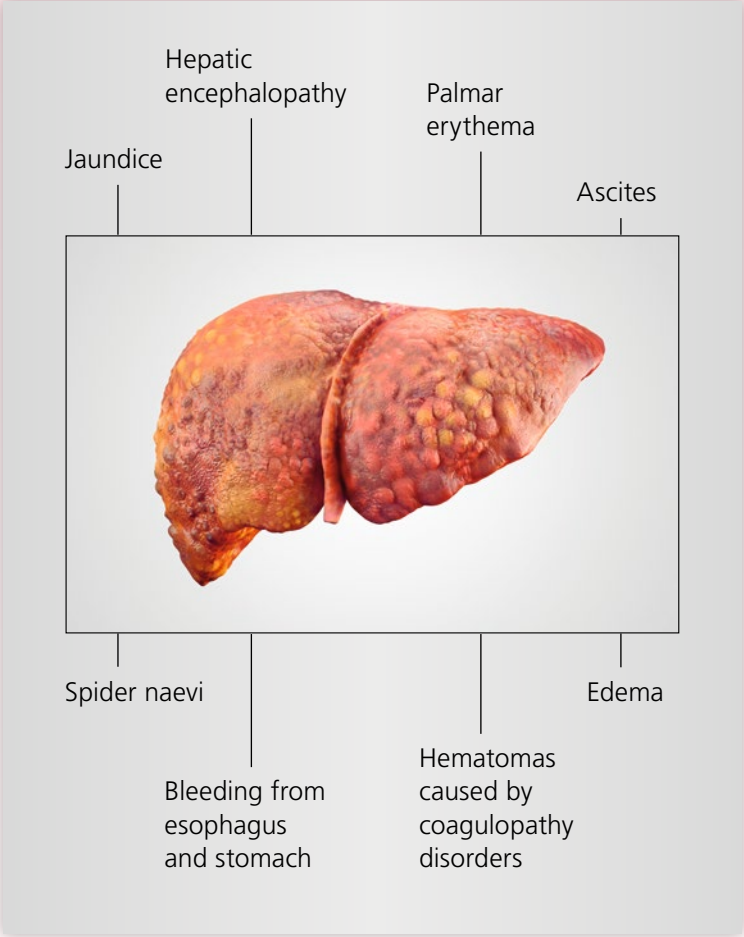

Fig. 1: Possible symptoms of liver cirrhosis

3 Diagnosis

The diagnostic criteria for AIH include the detection of certain autoantibodies, elevated immunoglobulin G (IgG) levels, a corresponding liver histology, and the exclusion of viral hepatitis. In routine laboratory diagnostics, increased transaminase levels are usually observed, with alanine aminotransferase (ALT) levels being higher than aspartate aminotransferase (AST) levels in the absence of advanced fibrosis/cirrhosis (AST:ALT < 1). If cirrhosis is present, the ratio may reverse and a De Ritis ratio of > 1 (AST:ALT > 1) may be observed. Furthermore, elevated total gamma globulin levels may be detected in the serum electrophoresis.

Additional verification of the AIH diagnosis is achieved through quantitative measurement of IgG levels, as well as the detection of antinuclear antibodies (ANA), antibodies against smooth muscle actin (SMA), liver kidney microsome type 1 (LKM-1), and soluble liver antigen/liver-pancreas antigen (SLA/LP).[10,17] The latter are very specific for AIH and can be found in up to 30% of patients.[2,21,22] Anti-SLA/LP antibodies are more commonly observed in combination with ANA and/or SMA, and can be found without simultaneous detection of other antibodies in approximately 10% of cases.[21–23] Depending on the autoantibody profile, it is possible to distinguish between AIH type 1 (ANA, anti-SMA, and/or anti-SLA/LP antibodies) and AIH type 2 (antibodies against LKM-1 or, more rarely, against LKM-3 and/or against liver cytosol [anti-LC1]).[2,10] The majority of patients (about 75%) will have AIH type 1.[2,11] AIH type 2 generally affects younger patients and, in comparison to AIH type 1, is more frequently associated with a fulminant course of the disease.[10,24,25]

ANA (and anti-SMA) can also occur in other liver diseases, such as viral hepatitis, steatohepatitis, or drug-induced liver injury which can be explained by neoantigen expression and activation of the immune system.[10,26] Anti-LKM antibodies have also been reported in other liver diseases such as chronic hepatitis C virus infection.[27,28] However, these antibodies differ from the LKM-1 antibodies found in AIH in regard to their recognizing target antigens.[10,29] In the case of an acute/fulminant presentation, autoantibodies and elevated IgG levels may also be missing.[30]

If elevated cholestasis parameters are detected (alkaline phosphatase [AP], gamma-glutamyltransferase [GGT] and possibly bilirubin), it is necessary to consider liver diseases such as PBC, PSC or IgG4-cholangiopathy, as well as the possibility of drug-induced liver injury – for instance cholestatic hepatitis caused by azathioprine.

A liver biopsy should be performed to confirm the diagnosis, and to exclude other or clarify coexisting liver diseases (e.g. PBC). Although there are no pathognomonic histological criteria for AIH, typical histological changes may be detected. These include lymphocytic or lymphoplasmacellular infiltrates at the portal-parenchymal interface (interface activity). However, the absence of plasma cells (in about a third of cases) does not exclude AIH.[31] Liver histology may also show necroses and regeneration phenomena such as rosette formation (several hepatocytes surrounding a bile canaliculus) and the presence of neoductuli (Fig. 2).[10]

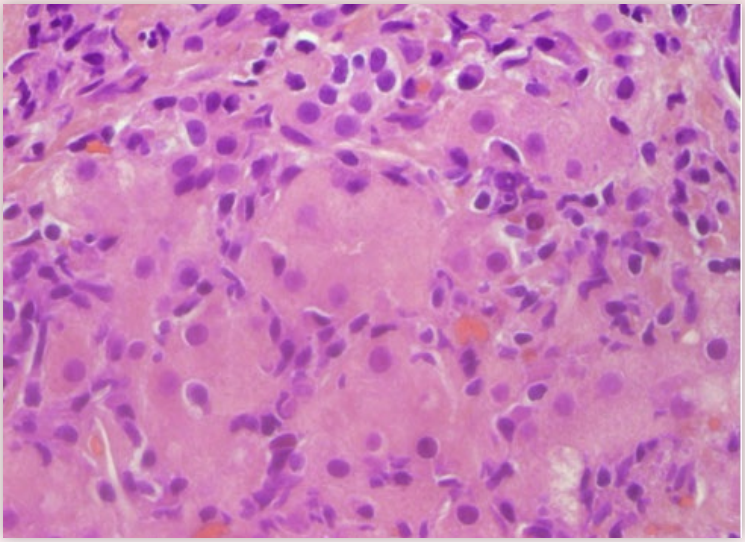

Fig. 2: Microscopic image of a liver biopsy from a patient with AIH, depicting elevated numbers of plasma cells and rosette formation, 400-fold magnification

The diagnosis "autoimmune hepatitis" is always an exclusion diagnosis. It is based on clinical, histological and serological findings. Diagnostic scores can be helpful in verifying the AIH diagnosis.[10] A diagnostic scoring system for assessing the likelihood of AIH was created and later revised by the International Autoimmune Hepatitis Group (IAHG). This scoring system uses the following diagnostic criteria: sex, ratio of alkaline phosphatase to transaminases, IgG/gamma globulin, autoantibodies, viral hepatitis markers, medications, drug abuse, alcohol consumption, genetic factors, other autoimmune diseases, liver histology, and response to immunosuppressive treatment.[25] A simplified scoring system based on the detection of autoantibodies, IgG elevation, liver histology, and the exclusion of viral hepatitis is considered comparable to the IAHG scoring system (Table 2).[32] This less complex system can be used to verify AIH diagnosis in a clinical setting.

Variable	Limit value	Points
ANA or SMA*	≥ 1:40 ≥ 1:80	1 2
or LKM antibodies*	≥ 1:40	2
or SLA/LP antibodies*	Positive	2
IgG	> upper normal limit > 1.1 × upper limit of normal	1 2
Liver histology	Consistent with AIH Typical of AIH	1 2
No viral hepatitis	Yes	2

*Maximum number of points for all antibodies:	2
Score ≥ 6:	Probable AIH
Score ≥ 7:	Definite AIH

Table 2: Simplified score for determining the likelihood of AIH[32,33]

4 Drug treatment

Immunosuppressive treatment prolongs the survival of patients with AIH.[34] AIH patients with moderate or severe inflammatory activity, or patients with mild inflammatory activity and symptoms or risk factors such as relevant fibrosis/cirrhosis, should therefore receive treatment.[2,10] From a histological perspective, clinically relevant inflammatory activity is present in case of a modified hepatitis activity index according to Ishak (mHAI) of ≥ 4–6/18 points.[2,10,35] Elevated transaminase and IgG levels are surrogate markers for inflammatory activity. It remains unclear whether patients with low activity and no risk factors benefit from immunosuppressive treatment.[2,10] An argument for immunosuppressive treatment in this situation may be that the natural course of AIH is generally progressive.[36] In addition, fluctuating transaminase levels may lead to underestimation of inflammatory activity.[37] Therefore, immunosuppressive treatment can be considered even in the case of lower disease activity, in order to prevent AIH flares and thus possible fibrosis progression, until the dynamics of the disease can be assessed over time.[10]

The aim of the treatment is to induce and maintain complete biochemical remission (normalization of transaminase levels and IgG) and histological remission (mHAI ≤ 3/18 points), preventing progression towards liver cirrhosis and associated complications.[1,2,10] Histological remission generally lags behind biochemical remission by several months, and biochemical remission does not always occur in conjunction with complete histological remission.[36,38,39]

4.1 Therapies for remission induction and maintenance

Prednisone/prednisolone should be used for the induction of remission. In patients without advanced fibrosis/cirrhosis, treatment with budesonide can be used instead (see below).

Prednisone/prednisolone treatment can be performed as monotherapy (60 mg/day or 0.5–1 mg/kg bw/day), or as a combination therapy of prednisone/prednisolone (30 mg/day) and azathioprine (50 mg/day).[2,10,17] For remission induction, monotherapy with azathioprine alone is not sufficiently effective.[34] After beginning the prednisone/prednisolone treatment, azathioprine at an initial dose of 50 mg/day should be added in timely manner. The azathioprine treatment should then be increased to 1–2 mg/kg bw/day according to treatment response and possible side effects.[10] Compared to prednisone/prednisolone monotherapy, fewer steroid-specific side effects can be expected with the combination therapy, which is based on a lower initial prednisone/prednisolone dose, while its efficacy is comparable. However, higher prednisone/prednisolone doses (up to 1 mg/kg bw/day), which should lead to a faster remission induction, may also be justified in combination therapy.[10] During steroid therapy, osteoporosis prophylaxis is recommended.[10]

In patients without advanced fibrosis/cirrhosis, and particularly in patients with an increased risk profile for steroid-related side effects – such as diabetes or osteoporosis – budesonide (3 × 3 mg/day) in combination with azathioprine (1–2 mg/kg bw/day) can be used instead of prednisone/prednisolone for remission induction.[10,40] Budesonide has a more favorable side effect profile than prednisone/prednisolone, which can be attributed to its high first-pass effect in the liver and the associated lower systemic steroid level. In a multicenter, phase 2b study coordinated in Germany, the efficacy and incidence of side effects of budesonide (initial dose: 3 × 3 mg/day) in combination with azathioprine (1–2 mg/kg bw/day) were compared with prednisone (initial dose: 40 mg/day) in combination with azathioprine

(1–2 mg/kg bw/day).[40] The primary end point – complete biochemical remission without steroid-related side effects – was more frequently achieved in the budesonide group (47%) than in the prednisone group (18.4%). After 6 months of treatment, there was an option to switch from prednisone to budesonide, which significantly reduced prednisone-related side effects from 44.8% to 26.4% after an overall treatment period of 12 months (Fig. 3).[40] This study demonstrates that budesonide in combination with azathioprine is suitable for the induction and maintenance of remission, and is associated with fewer steroid-related side effects. However, budesonide should not be used for patients with advanced fibrosis/cirrhosis, because of an enhanced risk of reduced hepatic metabolism and increased toxicity as well as reports of portal vein thrombosis and other complications.[41,42]

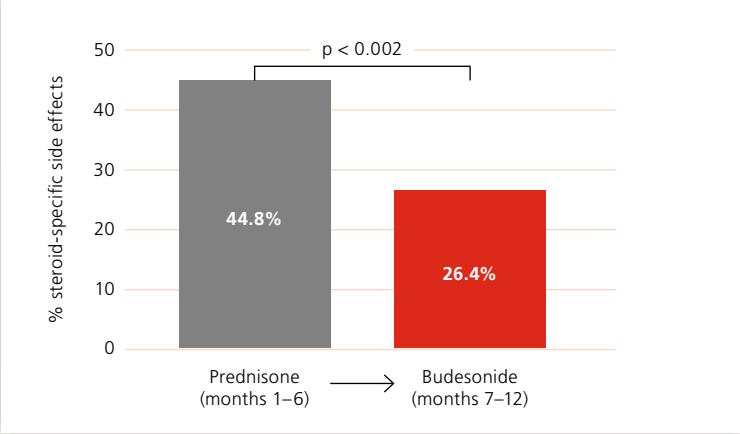

Fig. 3: Patients who received a 6-month combination therapy with prednisone (40 mg/day with subsequent gradual dose reduction to 10 mg/day) and azathioprine (1–2 mg/kg bw/day) showed a significant reduction in steroid-specific side effects 6 months after switching to a combination therapy with budesonide (3 × 3 mg/day, after remission: reduction to 2 × 3 mg/day) and azathioprine (1–2 mg/kg bw/day).[40]

When azathioprine is used, potential side effects such as blood count changes and hepatotoxicity, as well as the occurrence of pancreatitis, must be considered (Table 3). If azathioprine is not tolerated due to side effects (which is the case for approx. 10% of patients), therapy can be switched to mycophenolate mofetil (up to 2 g/day).[2,10,43] Alternatively, treatment with 6-mercaptopurine (active metabolite of azathioprine) can also be attempted, as some patients tolerate this substance despite azathioprine intolerance.[2,10,44,45]

In the case of a fulminant course of the disease, short duration treatment with high-dose intravenous steroids can be attempted, but the risk of infections has to be weighed. When AIH occurs as acute liver failure, a liver transplantation center must be immediately contacted.[10]

Therapeutic response is assessed by monitoring aminotransferase and IgG serum levels. The prednisone/prednisolone dose is gradually reduced depending on the treatment response. The aim is to taper prednisone/prednisolone after biochemical remission is achieved and to maintain remission with azathioprine (up to 2 mg/kg bw/day) alone or in combination with the lowest required dose of prednisone/prednisolone. As an alternative for patients without liver cirrhosis, and especially in cases where the risk of steroid-related side effects (Table 3) should be avoided, budesonide (2 × 3 mg/day) can be combined with azathioprine for remission maintenance.[10,40] For patients with azathioprine intolerance and low disease activity, low-dose prednisone/prednisolone monotherapy can be considered.[2]

Potential side effects of AIH treatment	
Prednisone/prednisolone	**Azathioprine**
Cushing's syndrome	Leukopenia, thrombocytopenia
Osteoporosis/osteopenia	Anemia
Diabetes mellitus	Nausea, vomiting
Weight gain, edema	Diarrhea
Liver steatosis	Pancreatitis
Glaucoma, cataract	Liver damage

Table 3: Possible side effects of prednisone/prednisolone or azathioprine treatment

Discontinuation of maintenance treatment should be attempted, at the earliest, two years after complete biochemical remission has been achieved (preferably with monotherapy).[2,10] Performing a liver biopsy prior to treatment withdrawal can help to determine the risk of relapse. Patients with persistent histological inflammatory activity are at high risk of relapsing after discontinuation of treatment and should therefore continue treatment.[2,10,46] A liver biopsy prior to treatment discontinuation is particularly advisable for patients who have lower tolerance to a repeated remission induction therapy following a relapse.[2] A relapse is possible even years after treatment discontinuation and successful remission; regular laboratory monitoring is therefore required for the rest of the patient's life.[10,47]

4.2 Management of patients with inadequate response or non-response to standard therapy

Approximately 10% of patients exhibit no response to the standard immunosuppressive treatment.[2,10] In the case of treatment failure, compliance should be verified and the presence of co-existing liver diseases should be clarified. In patients with no response, or sub-optimal response, longer treatment (at least 4 weeks) with higher doses of prednisone/prednisolone (60 mg/day) and azathioprine (up to 2 mg/kg bw/day, if tolerated) can be performed or alternative immunosuppressive drugs can be used.[2,10] Patients who do not respond sufficiently to initial budesonide treatment should be switched to prednisone/prednisolone treatment.[2,10]

The use of alternative immunosuppressive drugs, such as calcineurin inhibitors (cyclosporine A or tacrolimus), should be discussed with a liver center.[10] These drugs are used as second-line treatment for AIH, taking into account the possible side effects such as infections, changes in blood count, metabolic disorders, renal failure, and risk of developing malignoma. Compared with calcineurin inhibitors, there is less experience with other alternative immunosuppressive medications for the treatment of AIH patients non-responding to standard therapy. There is some evidence that mTOR inhibitors such as sirolimus and everolimus may induce remission in this situation.[48,49] In particularly difficult cases, anti-TNFα antibody treatment may be considered.[50] However, it should be noted that there have also been reported cases of AIH induced by administration of infliximab.[51,52] There are also indications that anti-CD20 antibodies could be a successful rescue therapy for AIH.[53]

5 Prognosis

For the majority of AIH patients, the prognosis is good – largely dependent on a positive response to immunosuppressive treatment.[54,55] However, patients who fail to respond to long-term therapy have an increased risk of disease progression and cirrhosis development. AIH progression towards liver cirrhosis can be accelerated by co-existing liver diseases. AIH cirrhosis is associated with higher liver-related mortality and higher overall mortality.[10,13,56] The risk of developing hepatocellular carcinoma in AIH cirrhosis is 1–2% per year.[2,57,58] Monitoring of AIH cirrhosis patients by abdominal ultrasound is recommended at 6-month intervals.[2,10]

6 Summary

Autoimmune hepatitis (AIH) is a chronic, autoimmune-mediated liver disease which, if untreated, can progress to cirrhosis. It is characterized by elevated transaminase levels, elevated IgG levels, and the occurrence of typical autoantibodies and histological changes. AIH responds well to immunosuppressive treatment in the majority of cases. As with other chronic liver diseases, AIH symptoms are non-specific or may be absent.

The standard therapy is prednisone/prednisolone in combination with azathioprine. For patients without liver cirrhosis, budesonide instead of prednisone/prednisolone can be used in combination with azathioprine. The side effects of prednisone/prednisolone treatment can be reduced by switching to budesonide, due to its high first-pass effect. In patients who do not respond to standard therapy, alternative immunosuppressive agents used in rheumatology and transplantation medicine may be considered. However, these treatments have only been tested in small case series with a heterogeneous patient population, and they should therefore be used in an individually tailored manner after consultation with a liver center.

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