Autoimmune hepatitis

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Introduction

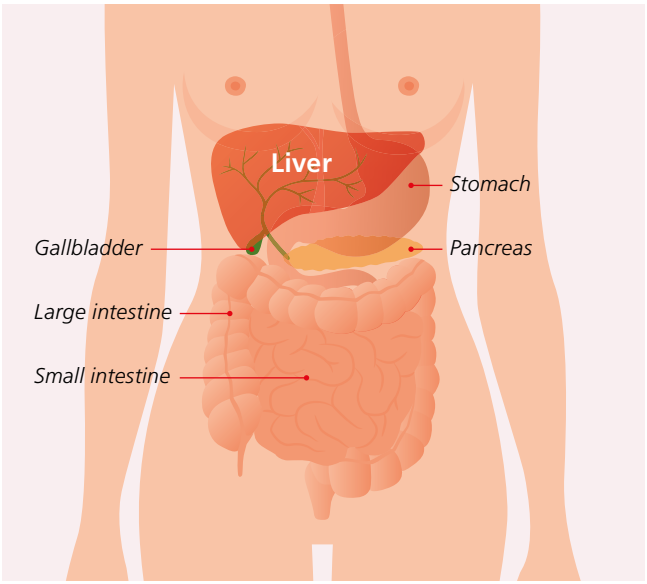
The liver

The liver is located in the right upper quadrant of the abdomen, directly below the diaphragm and the bottom of the rib cage, which makes it difficult to feel by hand. It is an organ that is surrounded by a capsule of connective tissue and is made up of four different lobes: a larger right lobe, a smaller left lobe, and 2 other small lobes (the lobus caudatus and lobus quadratus).

Structure and function

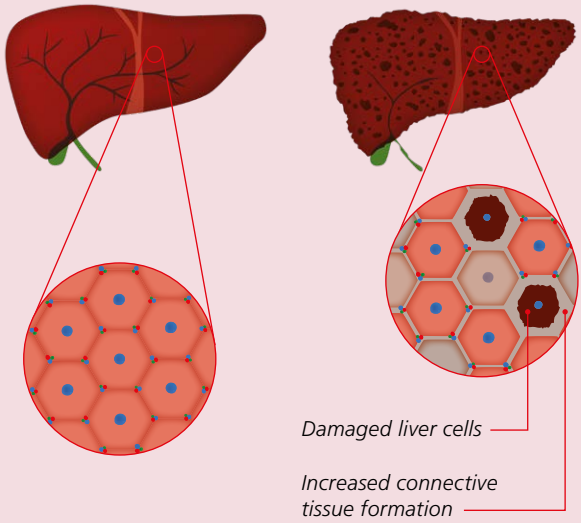
1.4 liters of blood flow through the liver each minute. It has an important filtering function and plays a role in the metabolization and degradation of drugs and toxins such as alcohol. The liver also plays an important role in the defence of infections, production of blood coagulation factors, metabolization of proteins, fats, and carbohydrates, as well as in regulation of minerals, vitamins, and hormone levels. It produces 700–1.500 ml of bile fluid each day, which is stored in the gallbladder and is released from bile ducts into the small intestine after eating. The main function of bile is to promote the digestion of fats.

Prolonged or repeated contact with toxic or infectious substances or dysregulation of the immune system can result in liver inflammation (“hepatitis”), which can cause liver damage. However, the liver has a high capacity of self-regeneration. As a result, it may take many years of ongoing liver damage before a decrease in liver function is noticed.



Healthy liver

Liver with cirrhosis



What is autoimmune hepatitis?

Autoimmune diseases are caused by an overreaction of the immune system to the body's own tissues. In autoimmune hepatitis (AIH), the immune system no longer recognizes liver cells as being its "own" but rather as being "foreign". As a result, it attacks them, leading to chronic liver inflammation. In the course, this can lead to connective tissue remodeling of the liver (fibrosis), which can result in liver cirrhosis (final stage of fibrosis).

The reasons for the reaction against own body structures in autoimmune diseases are not yet fully understood. In addition to hereditary (genetic) factors, environmental factors are also thought to play a role. It is assumed that multiple factors must come together for AIH to develop.

Autoimmune disease: An overreaction of the immune system to the body's own cells or cell components. The body's own structures are recognized as being "foreign" and are no longer tolerated, and therefore attacked by immune cells. This results in inflammatory organ damage.

Definition and incidence

How common is AIH and can it occur together with other conditions?
AIH is a rare disease. The prevalence is reported to be approximately 17 per 100.000 persons in European countries.[1] AIH predominantly affects women, but in 25–30% of all cases men are also affected.

While the disease can start at any age, most adults are first diagnosed between the ages of 40 and 70 years old.[2] AIH can occur together with other autoimmune diseases of the liver where the immune system primarily attacks the bile ducts, like primary biliary cholangitis (PBC; up to 25% overlap with AIH) and primary sclerosing cholangitis (PSC; up to 14% overlap with AIH).[1–4]

AIH may also occur in combination with other autoimmune diseases that do not affect the liver. The simultaneous occurance of AIH with other autoimmune diseases that affect the intestine (ulcerative colitis, celiac disease), thyroid gland (Hashimoto's thyroiditis), pancreas (type 1 diabetes), or joints (rheumatoid arthritis) is possible.[2]

Clinical symptoms

What are the physical signs of AIH?

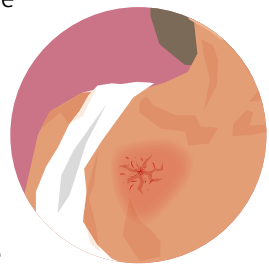
The symptoms presented by patients with AIH are not specific and do not differ from those of other inflammatory liver diseases. These include fatigue, malaise, and a right upper quadrant pain. Patients may also show yellow discoloration of the skin, mucosa, and the conjunctiva of the eyes (jaundice), which is caused by an increased concentration of the bile pigment bilirubin in the blood. Jaundice may be accompanied by itching.

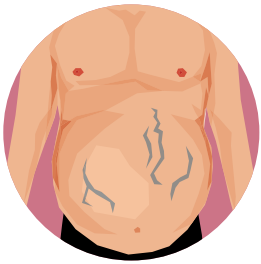
At the early stage of chronic liver inflammation, patients might not experience any symptoms at all. During this stage, AIH is often diagnosed by chance during a routine examination of elevated liver enzymes.

Course

Persistent liver inflammation can lead to liver remodeling. In this situation normal liver tissue is replaced by connective tissue (fibrosis). If AIH is not adequately treated or is diagnosed too late, the disease can result in the final stage of fibrotic remodeling, called liver cirrhosis, after several years. Cirrhosis is accompanied by a loss in liver function. This can affect many functions of the body, for example blood coagulation. As a result of this impaired blood coagulation, longer bleeding after injury and faster occurance of hematomas can be observed. Reduced protein production can result in lower leg swelling, so-called low protein edema. Muscle loss (sarcopenia) may occur over time, especially in the arms and legs. Reduced detoxification of the liver can lead to decreased concentration and memory function as well as increased fatigue and sleepiness. These symptoms are called hepatic encephalopathy.

Among the signs of liver cirrhosis are spider naevi of the skin, which represents vacular nodules with spider-like extensions that can be observed primarily on the chest. Cirrhosis may also lead to high levels of bilirubin in the blood, which can cause yellow coloring of the skin and conjunctiva of the eyes (jaundice). Fluid accumulation in the abdomen (ascites) represents another complication of cirrhosis which is associated with weight gain and increase of waist circumference. Migration of bacteria into ascites, which in part can be caused by defects of the intestinal membrane barrier, might cause inflammation of the peritoneum (sponatenous bacterial peritonitis).[5] Due to ascites and protein deficiency, kidney dysfunction (hepatorenal syndrome) can occur. The fibrotic remodeling of the liver leads to a high resistance to blood flow through the liver. As a consequence, the blood can bypass the liver by other routes, which can result in the formation of esophageal or gastric varices. Over time, these varices may lead to life-threatening bleedings characterized by vomiting of blood that can appear like coffee grounds or by black tarry stools (table 1).





Complications of cirrhosis

Blood coagulation disorders with higher risk of bleeding
Swelling in the lower legs (low protein edema)
Muscle loss in the arms and legs (sarcopenia)
Skin abnormalities caused by liver cirrhosis (spider naevi)
Yellow discoloration of the skin and conjunctiva of the eyes (jaundice)
Fluid accumulation in the abdomen (ascites), bacterial infection of the abdominal fluid (spontaneous bacterial peritonitis)
Kidney dysfunction (hepatorenal syndrome)
Decline in brain function (hepatic encephalopathy)
Greater susceptibility to infections
Varicose veins in the esophagus or stomach (esophageal/gastric varices)
Bleedings from varicose veins in the esophagus or stomach (bloody vomit/vomit looks like coffee grounds, tarry stools)

Table 1

Diagnosis

How is AIH diagnosed?

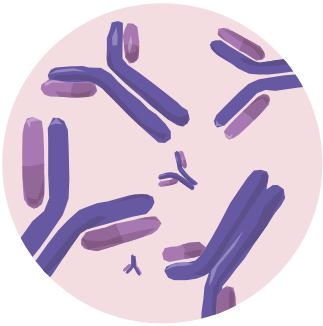
Transaminases, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are among the blood test parameters which indicate inflammation and liver damage. These enzymes are found in liver cells and their concentration in blood increases when the liver cells are damaged. Repeated detection of elevated transaminase levels is not indicative for a specific liver disease. In this situation, additional diagnostic procedures should be performed for further clarification.

In addition to elevated transglutaminase levels, AIH is characterized by certain autoantibodies. These autoantibodies target structures of the body's own tissues, such as nuclear antigen (ANA), smooth muscle antigen (SMA), liver kidney microsome (LKM-1), or the soluble liver antigen/liver-pancreas antigen (SLA/LP).[1, 2, 6–9]

Antibodies: Soluble proteins called immunoglobulins (Ig) that are produced by specialized cells of the immune system. Immunoglobulins contain binding sites that are highly specific for the components of other proteins. These components include surface structures of foreign cells, bacteria, fungi, viruses, pollen, as well as drug or food ingredients. Immunoglobulins can then trigger other processes, such as neutralization of bacteria. In rare cases, the body produces antibodies that target its own structures, so-called autoantibodies (from the Greek αὐτο- (auto-), meaning "self"). There are several different classes of immunoglobulins (such as IgG).

Detection of these autoantibodies is used to define AIH in adulthood (table 2). The ANA, SMA, and SLA/LP antibodies are definitive signs of AIH in adults (type 1 AIH), who comprise about 75% of all cases, while LKM-1 antibodies are primarily found in childhood/adolescent cases of AIH (type 2 AIH).[1, 8, 9]
However, the levels of autoantibodies in the blood are not related to the severity of AIH. For this reason, it is not necessary to measure autoantibody levels in the course of the disease.

It is important to note that autoantibodies such as ANA or LKM-1 are also found in other diseases such as viral liver diseases.[1, 2, 8] In order to confirm a diagnosis of AIH, it is therefore necessary to rule out other possible causes of the liver disease, especially viral hepatitis, using appropriate diagnostic procedures.



Increased activation of the immune system as observed in patients with AIH, is reflected by elevated levels of immunoglobulin G (IgG) in the blood. Therefore, this marker is not only used to confirm the diagnosis (see table 2) but is also used together with transaminase levels to evaluate disease activity.[1, 2, 8] Therefore, transaminase and IgG levels are repeatedly detected during the course of the disease. This also allows to evaluate the treatment response.

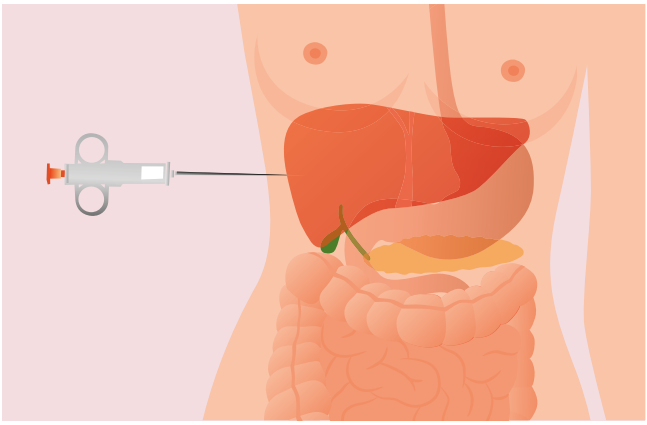


Fig. 1: Liver biopsy. A thin, hollow needle is guided by ultrasound to remove a small tissue sample from liver.

Together with the blood markers listed above, characteristic features in the liver tissue confirm the diagnosis of AIH.[1, 2, 7–9] For this reason, a liver biopsy is usually recommended. For this purpose a small tissue sample is taken from the liver by a small needle under ultrasound control (fig. 1).

The findings of this liver biopsy are not only useful for confirming the diagnosis of AIH but can also be used to rule out other liver diseases. Liver biopsy is also useful to evaluate the histological disease activity and fibrosis stage. It can also help to clarify whether additional autoimmune diseases such as primary biliary cholangitis (PBC) are present.

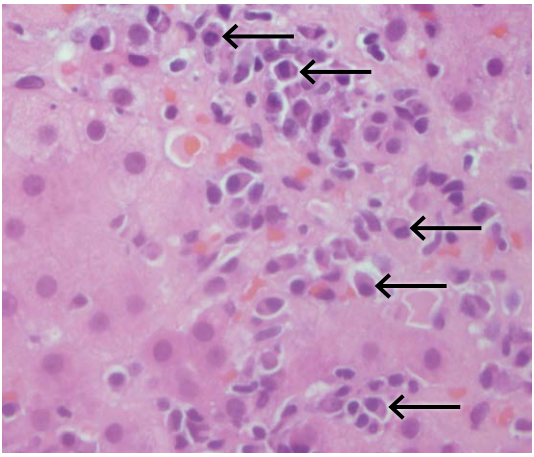


Fig. 2: Microscopic image (400-fold magnification) of a liver biopsy sample from a patient with AIH. Arrows show an increased number of plasma cells, as a sign of inflammation. (With kind permission of the Institute of Pathology, Hannover Medical School)

Diagnostic Criteria for AIH

Positive detection of autoantibodies (ANA, SMA, SLA/LP or LKM-1)
Elevated IgG levels
Typical histology for AIH
Exclusion of viral hepatitis

Table 2: Criteria used to diagnose AIH.[8]

Treatment

How is AIH treated?

The goal of AIH treatment is complete resolution of liver inflammation, which leads to the normalisation of altered blood parameters (elevated transaminase and IgG levels) and resolution of histological alterations. This goal is achieved by drugs that supresss the increased activity of the immune system and that are therefore called immunosuppressants.

Treatment is started using corticosteroids (also called just "steroids") such as prednisone or prednisolone at a dose of 0.5–1 mg/kg body weight per day.[2] A lower steroid dose (30 mg per day) can also be used if azathioprine (another immunosuppressant) is taken at the same time (usually at a dose of 50 mg per day).[2] This step can help to reduce the potential side effects associated with steroids (table 3), such as dysregulation of blood glucose or increased blood pressure, loss of bone mass (osteopenia), or increased eye pressure (glaucoma). The initial steroid dose is then gradually reduced each week according to the changes in transaminase and IgG levels. Usually, the reduction begins already in the second week of treatment. Most patients experience major improvement in their transaminase and IgG levels within the first two weeks of treatment.

Immunosuppressants: Medications that suppress the immune system and thus prevent the body's own tissue from being attacked and damaged. However, immunosuppressants may cause side effects such as infections or a (slightly) higher risk of developing cancer. This is why it is important to have regular preventive check-ups and to be vaccinated against hepatitis A and B, pneumococcal and influenza infection.[2]

A patient's response to steroid therapy is also used to confirm the diagnosis of AIH.[2, 7] Once transaminase and IgG levels have returned to normal, immunosuppressive therapy is usually maintained using azathioprine alone (up to 1–2 mg/kg body weight per day) with close monitoring for possible side effects (table 3). Regular blood count controls are especially necessary for patients taking azathioprine.

Possible side effects of the standard treatments for AIH

Prednisone/ prednisolone	Azathioprine
Moon face	Reduced white blood cell counts
Weight gain, abdominal obesity	Reduced red blood cell counts (anemia)
Fatty liver	Pancreatitis
Increase of blood glucose	Elevated liver enzymes (liver damage)
High blood pressure	Nausea, vomiting
Mental disorders	
Bone loss	
Glaucoma	
Cataract	

Table 3: Please see the package leaflet of each drug for the complete list of side effects.

To lower side effects of prednisone/prednisolone, a different steroid (= budesonide) can be used for treatment of AIH patients without cirrhosis. In contrast to prednisone/prednisolone, 90% of budesonide is directly metabolized in the liver. This means that it is highly active within the liver and that the budesonide levels in the bloodstream are lower, hence it is better tolerated (fig. 3).

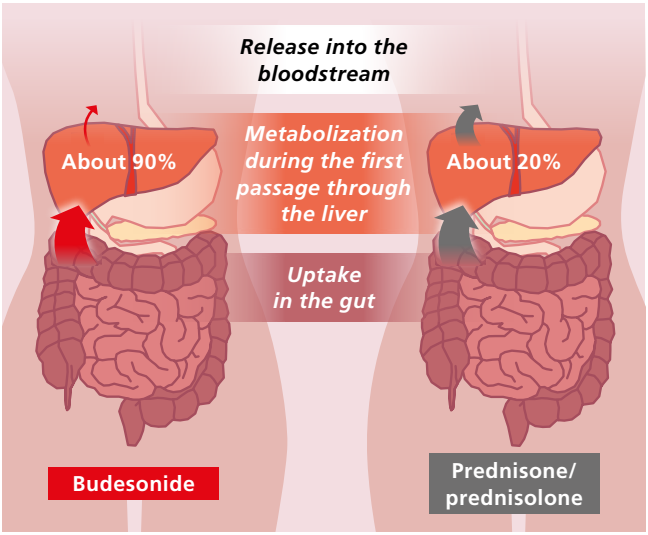


Fig. 3: Budesonide and prednisone/prednisolone are absorbed in the gut and transported in the portal vein to the liver. In contrast to prednisone/prednisolone, the majority of budesonide is metabolized during the first pass through the liver. This means that it exerts most of its effects in the liver and not in other organs. As a result, patients taking budesonide experience fewer side effects than patients taking prednisone/prednisolone.

This beneficial feature of budesonide was confirmed in a European study in patients with newly diagnosed non-cirrhotic AIH or an acute inflammatory flare of AIH without cirrhosis, who were treated with budesonide in combination with azathioprine (1–2 mg/kg body weight per day).[10] Based on these results, budesonide – which exterts its effects mainly in the liver – can be taken by AIH patients without cirrhosis as an alternative treatment to systemic steroids. However, there is much less experience with budesonide for patients with severe (fulminant) AIH or AIH with acute liver failure. In this situation, prednisone/prednisolone is still recommended.[11] Budesonide is taken three times per day in the form of a 3 mg capsule (in combination with azathioprine), and the dose is reduced based on improvements in transaminase levels. Once transaminase levels have returned to normal, budesonide can be taken at a lower dose as maintenance therapy, or the maintenance therapy can be continued with azathioprine alone (up to 1–2 mg/kg body weight per day) after budesonide has been tapered.

In patients with cirrhosis, budesonide is metabolized worse in the liver, which can result in more steroid-related side effects. Accordingly, budesonide is not recommended for treatment of patients with liver cirrhosis.

Frequently asked questions

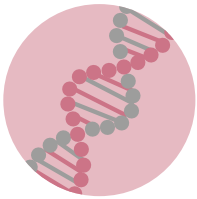
How long should AIH be treated?

Because of the individual treatment response there is no fixed treatment duration. Once transaminase levels have returned to normal, maintenance therapy should be continued for at least 2 years.[1, 2] If aminotransferase levels are repeatedly within the normal range during this time period, a liver biopsy is usually recommended before the end of immunosuppressive therapy in order to confirm that inflammation has completely resolved in the liver tissue.

If patients have no detectable inflammation in liver tissue and transaminases are within the normal range, treatment termination under close monitoring of the liver enzymes can be performed. Patients without detectable inflammation have a much lower relapse rate than patients who still have inflammation in their liver tissue.[12, 13]

An increased inflammatory activity in patients with cirrhosis can lead to a deterioration of liver function, resulting in the complications described above. Therefore, complete termination of the immunosuppressive therapy is usually not recommended for cirrhosis patients.

Is AIH genetically caused or hereditary?



AIH is not caused by a specific genetic mutation and does not have a classical hereditary pattern. However, as with many autoimmune diseases, AIH has a certain genetic predisposition that is associated with certain genetic features.[14, 15] Genetic factors may also influence the course of the disease. There are no genetic tests for the diagnosis or prediction of disease course available so far.

What are the risks for pregnant women?

Pregnancy in AIH is considered as high-risk pregnancy with a 20% risk of premature birth, although this is not higher than the risk observed with other chronic liver disease.[2, 16] Especially patients with liver cirrhosis, poor control of their disease despite therapy or without therapy should be closely monitored during and within the first 6 months after pregnancy.[2, 11] The risk of developing a disease flare after delivery is much higher without treatment and is observed in about 50% of cases.[17]

The individual course of disease should be considered for treatment of AIH in pregnancy. Therapy with prednsione/prednisolone and/or azathioprine should be continued during pregnancy at the lowest dose required to suppress inflammation in AIH.[1, 2, 11] Although an increased risk of fetal harm has been observed with azathioprine in animal studies,[18] this observation has not yet been confirmed in pregnant human women treated with azathioprine.[16, 19–21] Nonetheless, the risks and benefits should be weighed carefully.

Pregnant women with active AIH within the previous 12 months before pregnancy, or with AIH and cirrhosis have a higher risk of complications.[11] Pregnant women with cirrhosis should undergo an endoscopy after the first trimester in order to screen for varicose veins in the esophagus, which may then need to be treated by rubber band ligation.[11] Cirrhosis during pregnancy also increases the risk of complications for the child, both before and after birth.[16] Therefore, close monitoring and care at a center with the appropriate expertise is recommended for pregnant women with AIH and advanced liver disease.

Are there any alternative medications if standard therapy is not effective or is not tolerated?

If inflammation is not adequately suppressed by the treatment options described above, even after increasing the dose, other immunosuppressive drugs which are not yet approved for the treatment of AIH (called off-label use) may be an option. This is the case for about 10% of patients, while another 10–13% do not tolerate standard therapy.[2, 11, 22] Alternative drugs are available for these patients which have shown promising results in smaller studies.

These alternatives include mycophenolate mofetil,[23–28] tacrolimus,[29–32] and cyclosporine.[33–35] However, these drugs should only be used to treat AIH after consulting with a hepatology center. Patients with AIH and irreversible acute liver failure or end-stage liver disease may also be candidates for liver transplantation if there are no

other treatment options available. In this situation, it is important to contact a hepatology center as soon as possible.

Is AIH associated with a higher risk of cancer?

People with AIH-induced cirrhosis are at a higher risk of developing liver cancer (hepatocellular cancer; HCC), which is indicated with 1–2% per year.[1, 36–38] Therefore, AIH patients with cirrhosis should undergo ultrasound examinations of the liver every 6 months.[2, 11] Other factors may exacerbate AIH-related liver damage, such as alcohol, smoking, or other chronic liver diseases such as non-alcoholic fatty liver disease, and thus may increase the risk of developing cirrhosis and HCC.

Can diet or lifestyle have an effect on AIH?

A balanced diet and a healthy lifestyle with regular exercise may improve well-being and prevent nutritional deficiencies in people with chronic liver disease. Substances that are harmful for the liver – especially alcohol – should be avoided. Interestingly, recent studies implicate that coffee may have a protective effect on the liver.[39, 40] Research also shows that coffee may help to prevent liver cancer in patients with chronic liver disease.[41]

Multivitamin supplements are usually not necessary with a balanced diet. In order to counteract bone loss caused by steroids, patients taking prednisone/prednisolon should additionally take vitamin D supplements and ensure an adequate dietary calcium intake (in the absence of contraindications for these supplements such as kidney stones) depending on the prednisone/prednisolone dose and the individual risk of osteoporosis.

These supplements are also needed if osteoporosis has already been diagnosed. Bone density is measured using an X-ray technique (DEXA: dual energy X-ray absorptiometry). If bone density drops below a certain threshold (T-score), the benefit of treatment with medications that promote bone growth should be evaluated based on the patient's risk factors.[2]

Summary

- AIH is an autoimmune-mediated liver disease.
- If left untreated, AIH can result in the development of liver cirrhosis.
- AIH is characterized by elevated levels of transaminases and IgG, as well as the presence of typical autoantibodies and histological signs.
- Symptoms may be non-specific or even non-existent.
- The majority of patients respond well to immunosuppressive treatment, particularly to steroids.
- If patients do not respond to standard therapy, other immunosuppressants usually used for rheumatological diseases or in transplantation medicine are an option but require consultation with a hepatology center before start of treatment.

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