Autoimmune hepatitis:

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Abstract

Autoimmune hepatitis is made of several clinical, analytical and histological findings, significant only when considered as a whole. Because of its autoimmune etiology, the diagnosis can be confused at times with other diseases of the immune diseases. This is a medical field in constant change. The authors present a concise review of the principal characteristics of the disease, based on a review of recent literature.

Key words: autoimmune hepatitis, antibodies, genetics, immunity, treatment of autoimmune hepatitis.

Introduction

As shown in the meeting of the International Autoimmune Hepatitis Group in June 1992,[1] the definition of autoimmune hepatitis (AIH) is not linear or simple. At this meeting, the diagnostic criteria of this disease were widened to include therapeutic response. A set of clinical and laboratory criteria was established, to which a score was assigned, allowing for a diagnosis of AIH even in the presence of findings that do not match the classical concept, such as the presence of antimitochondrial antibodies, the presence of hepatitis C (HCV) or the absence of antibodies related to the liver. It is also important to highlight that there is no need to wait six months for the definition of chronicity when the acute or fulminant forms of presentation are identified.[1] Although a prospective validation has not yet been established, interest in using this scoring system was reaffirmed at a recent meeting of an international working group.[2,3]

The definition of AIH, following the recommendations of this Working Group, claims the disease is characterized by a recurrent hepatitis, predominantly periportal, usually accompanied by autoantibodies and hypergammaglobulinaemia, and responds to immunosuppressive therapy in most cases.[4]

Pathogenesis

Etiopathogenesis

The mechanisms of autoimmunity in the pathogenesis of this disease are currently known, but complete scientific evidence is lacking. Moreover, it is thought there may be environmental factors that trigger immune responses in patients who are genetically predisposed. Among these factors, the most commonly investigated is viruses, and among these, the hepatitis C virus (HCV). Before the development of the current diagnostic techniques, there is no doubt that the strong relationship between the two diseases was due to false positives, probably by cross-reactivity (for structural similarities between human proteins and proteins encoded by the HCV genome), by the hyperglobulinaemia in AIH, or because of the nonspecific immune response.[5]

In addition, the detection of HCV has been a routine practice for only a relatively short time – previously, serums were not processed quickly enough, which led to false results due to the degradation of the serum proteins. However, more recent detection tests, namely polymerase chain reaction (PCR), have confirmed the presence of the virus in some patients. In this case, one of four scenarios may exist:

1 - The virus causes the production of endogenous interferon that triggers an autoimmune response in susceptible individuals,[3] as occurs in exogenous administration;[6] 2 - HCV and low-titer SMA and/or ANA: the antibodies are considered as a non-specific phenomenon, and the disease should be considered

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as a predominant viral hepatitis;[3,5,7] 3 - HCV and high--titer SMA and/or ANA: cases like this are rare and the treatment approach is not yet well defined, neither is its classification as AIH, and these are currently considered "overlap cases"; 4 - HCV and anti-LKM1. The classification of the disease still raises doubts; some authors advocate that it is an AIH and others consider it to be a predominantly viral hepatitis. The former viewpoint is explained by the similarity between two sequences of the protein P450II D6 and one sequence of the proteins produced by the HCV, which can cause cross-reactivity.[3,8] However, various publications have suggested that these amino acid sequences are different in the case of AIH and the hepatitis C virus.[3,6,7,9] This may be the distinguishing point of the two diseases. But as will be addressed later in this review, histological data also exist that distinguish between the two clinical entities. Moreover, in the case of hepatitis C, anti-GOR antibodies (peptide) are found that are not present in AIH.[10] Whatever the case, for most authors this entity is part of AIH.

The diagnosis of AIH is also documented after infection by the hepatitis A virus,[3,11,12] Epstein-Barr virus[13] and acute infection by the hepatitis B virus.[12] In relation to the measles virus, its genome has often been found in the lymphocytes of patients with AIH and with systemic lupus erythematosus, rheumatoid arthritis and cryptogenic cirrhosis; therefore rather than a single cause, it is a common epiphenomenon, reflecting its high prevalence in the general population. As for the Delta virus, its relation to AIH has not yet been demonstrated.[3]

Other possible triggers include certain drugs, such as alpha-methyldopa, oxyphenisatin, nitrofurantoin and halothane. However, a favorable genetic configuration is necessary for the induction of autoimmunity that these drugs can cause to be perpetuated, as generally, the symptoms and the presence of antibodies disappear after the treatment is discontinued.

In conclusion, based on present knowledge, AIH is generally considered an idiopathic disease.[5]

Autoantibodies

These are what traditionally characterize the disease. However, its pathogenicity has not been proven and its production does not appear to be associated with specific immunogenic stimuli[3,5] with the exception of the LKM and ASGPR types (see below).

Smooth muscle antibody (SMA): appears to reflect mainly the existence of anti-F-actin antibodies, anti-F being a cytoskeletal protein. The association with HLA-DR4 is significant in low titers, but is lost in higher titers, therefore it may not be consistent. Typically, its titer is greater than 1:80[14] and appears in association with ANA; nevertheless, it appears as a single antibody in about 26% of cases.[3] The simultaneous presence of ANA and SMA is rare in an HCV infection, therefore it can serve as an additional differential diagnosis in this condition.

Antinuclear antibody (ANA): is associated with the haplotype DR4. The positivity for this autoantibody is associated with titers greater than 1:80, which may be considered the minimum "valorization" value. However, this value provokes no unanimity, since a value greater than 1:40 can sometimes be reported.[14] There are several patterns found by indirect immunofluorescence, the most common in AIH being the homogeneous and the speckled patterns. The latter seems to be associated with the onset of the disease at younger ages and with a higher transaminase count, reflecting a more severe disease.[3] Nevertheless, the response to the therapy does not appear to depend on the type of pattern, so its characterization does not offer advantages. Typically, it is associated with the smooth muscle antibody (SMA).

Anti-actin antibodies: not routinely tested for. However, when the SMA titer is higher than 1:320, their presence is strongly suggested.[15]

Antimitochondrial antibodies (AMA): develop in about 20% of cases, usually with titers lower than 1:160. In this case, the histology is that of AIH, the hepatic copper is low, and the response to the therapy with corticosteroids is good. If the titers are high, an overlap syndrome or primary biliary cirrhosis can be considered.[3,5,7,15]

Liver/kidney microsomal antibodies type 1 (anti--LKM1): these are part of a broad group that recognizes microsomal constituents. There are also type 2 antibodies, associated with a lesion of the liver produced by ticrynafen, and type 3 antibodies, associated with a Delta virus infection.[5,15,16] The LKM1 antibodies develop in AIH, and are mutually exclusive to SMA and/or ANA. They react with cytochrome P450IID6 in 90% of patients. In the remaining 10%, these antibodies react with another microsomal enzyme (P450IA2), responsible for the metabolism of phenacetin. One possible hypothesis is that the latter constitutes another subgroup of patients within type 2 AIH.[3]

The liver/pancreas antibody (anti-LP), the antigen of which appears to be a protein of the Hepatocyte cytosol, develops as a single antigen in about 30% of patients. Together with the anti-soluble liver antigen (anti-SLA, which recognizes cytokeratins 8 and 18 of the hepatocyte cytoskeleton as antigens), a third type of AIH can be defined.[3]

Other antibodies can be found: anti-liver cytosol type I (anti-LCI), anti-asialoglycoprotein receptor antibody (anti-ASGPR) and anti-neutrophil cytoplasmic antibody (ANCA). These are, however, the subject of research and still do not have clearly-established practical significance, therefore, they will not be presented in depth here. But although its relationship with AIH has yet to be confirmed, its presence can lead to the diagnosis of cases that have thus far been considered idiopathic.[3,17,18,19,20]

Autoantigens

Despite all the antibodies described above, the identification of the liver constituents capable of triggering immune responses and causing subsequent hepatic lesion is not yet complete. To date, the two most likely candidates are cytochrome P450IID6 and hepatic lectin ASGPR.[3,21]

Genetics and AIH

As in other diseases, the major histocompatibility complex, found on the chromosome[6] is examined in the search the genetic predisposition for this disease. It is known that susceptibility to the development of AIH is associated with certain phenotypes of HLA (human leukocyte antigen) groups, particularly class II HLA-DR3 and-DR4 (the latter being predominant in Asian patients).[3,5,21] DR3 is associated with HLA-B8 in 94% of Caucasians.

Pathophysiology

Hepatic lesion in this disease is caused by a phenomenon of autoimmunity. In regards to the mechanisms of humoral immunity, the theory is defended that the unmodulated production of antibodies by clones of B lymphocytes, probably against the target proteins P450IID6 and ASGPR, leads to the formation of antigen-antibody complexes and the activation of natural killer T lymphocytes. Based on this theory, the functional change occurs in the cells that control the activity of the B lymphocytes, possibly the non-antigen specific suppressor T lymphocytes.[20,23] It is probably transmitted by the genes that express HLA (mainly HLA-B8-DR3).[3,23] However, these events only occur when the disease is active, and are reversible with the use of corticosteroids, therefore this theory does not explain the mechanism of self-perpetuation of the hepatic lesion. But if the defect is in the suppressor T lymphocytes that are specific to a particular antigen, the antigen will not be eliminated with therapy, which may explain the recurrences. The importance of these disorders in the pathogenesis of AIH remains unclear.[3] The mechanisms of immune-mediated lesions can be explained by an abnormal activity of the class II MHC antigens on the surface of the hepatocyte. Thus, P450IID6 and ASGPR are presented as antigens of T helper cells (CD4). These end up activating cytotoxic T lymphocytes (CD8), the most probable effector cell. Histology seems to confirm this hypothesis.[3] A third possibility is that self-reactive clones remain, which should have been eliminated during ontogenesis, but for some reason were not, triggering autoimmune responses at a later stage in life.

Histopathology

The classic histological appearance is that of a mononuclear infiltrate in the portal spaces, sometimes passing into the inner lobes of the liver (piecemeal necrosis), but typically sparing the biliary structures. A pattern of already-established bridging necrosis or cirrhosis can be observed.

Although not pathognomonic, certain histological patterns are known to occur more frequently in certain types of liver disease, from which a notion of specificity and predictive value in relation to its evolution can be drawn. The presence of moderate to severe piecemeal necrosis, with lobular hepatitis and plasma cell infiltration of the portal spaces without steatosis or lymphoid clusters, has specificity of 81% and a positive predictive value of 68% in the diagnosis of AIH. However, using these rather strict criteria, sensitivity is lost (40%).[7,24]

Classification

The importance of classifying AIH into subtypes is that diagnosis, treatment and assessment of prognosis are made easier, as it decreases the variability and heterogeneity,[23] allowing the "compartmentalization" of patients. Currently, it is possible to classify two, or maybe even three[7] types based on the presence of

TABLE I

Types of AIH

Types	Antibody	Characteristics
1	SMA and/or ANA	>young women
2		
A	Anti-LKM 1 (anti-P450DII6)	>young women, HCV-
B	Anti-LKM 1 (anti-P450DII6)	Older age group, no sex predominance, HCV+
	Anti-LKM 1 (anti-P450IA2)?	(debatable)

different circulating autoantibodies.

Type 1 is characterized by the presence of SMA and/or ANA, and approximately 70% of patients are women aged under 40 years. It is associated with other autoimmune diseases in 17% of patients. At the time of diagnosis, 25% of the patients have cirrhosis, which corresponds to an inert and subclinical evolution.[3,5,7]

Type 2 has circulating anti-LKM1, which are mutually exclusive to SMA and/or ANA. These patients are typically younger (children between 2 and 14 years) and the disease has a much more rapid and severe evolution, and may be fulminant. It is also more often associated with other autoimmune diseases. Hepatitis C is involved in the type 2 genesis, which led to its sub classification. Although controversial, since opinions are not unanimous,[25] this sub-classification consists of subtype 2a, which resembles classical AIH, and subtype 2b, which affects older patients, with a less marked predominance of females and lower titers of anti-LKM1, as well as positivity to HCV. As mentioned earlier, in about 10% of the patients, the anti-LKM1 recognizes not the P450IID6, but the P450IA2, for which reason a third subtype was proposed.[3]

Type 3, the most recent subtype, is not yet fully defined or accepted. It will be characterized by the presence of anti-SLA and/or anti-LP.[7] Although these patients do not have anti-LKM, they can have ANA or SMA, for which reasons, there are those who consider it as part of type 1. Perhaps the importance of these antibodies is the fact that they may serve to reclassify some patients with liver disease thus far considered cryptogenic. *Table I* shows the "classic" types of AIH.

This classification is not complete, since it does not include patients without circulating antibodies, but whose diagnostic score classifies their disease as AIH. It should also be noted that AIH may be associated with signs of viral infection or other autoimmune liver diseases, constituting the overlap cases discussed later.

Clinical presentation and evolution

The clinical presentation of this disease is extremely diverse, ranging from an insidious onset with few, nonspecific manifestations to an abrupt form with rapid evolution to fulminant hepatitis. Generally, the insidious forms have few clinical manifestations, consisting of constitutional symptoms such as asthenia and anorexia. The diagnosis is often reached after the onset of decompensated cirrhosis thus far undiagnosed, with ascites or gastrointestinal bleeding due to a rupture of esophageal varices. On the other hand, the presentation may be typical of an acute hepatitis, with fever, discomfort in the right hypochondriac, and jaundice.

Because AIH is related to other autoimmune diseases, it is not uncommon for signs and symptoms to exist in these conditions, such as changes in the thyroid function (for Hashimoto's or Basedow's disease), Sjogren's syndrome, kidney changes due to glomerulonephritis or renal tubular acidosis, hemolytic anemia, lupus erythematosus, vitiligo, painful red eye and decreased visual acuity due to previous uveitis, scleroderma, diabetes, and rheumatoid polyarthritis, among others.

The evolution of patients with AIH is variable and depends, for example, on the severity of the lesion found in the liver biopsy, the patient's phenotype, the therapy and the response to it. In untreated patients, the evolution is very variable and unpredictable, and can range from progressive evolution of the liver disease through to alternating periods of active disease, with lengthy or less lengthy periods of remission, until it reaches a stage of fulminant hepatic failure. On average, more than half of the untreated patients die within three to five years of diagnosis. In terms of histology, the abundant infiltration of mononuclear cells in the portal spaces, and the presence of bridging necrosis, reflect a more aggressive evolution to cirrhosis. It appears that the degree of piecemeal necrosis has no prognostic value. The therapy causes a substantial improvement in prognosis: mean survival increases to twelve years, and even for those who

do not go into remission after three years of therapy, cirrhosis occurs only in 37% patients within five years and in 47% within ten years. When cirrhosis is already developed, the presence of prolonged jaundice, ascites or repeated episodes of encephalopathy give a poor prognosis.[14] Although of little practical interest, we claim that patients with HLA-DR3 or -B8 tend to have a more aggressive disease, with more rapid progression to cirrhosis.[3,5,14]

Overall, AIH is a rare cause of chronic hepatitis (about 5% of the cases), predominantly affecting women and presenting two peaks of maximum incidence between 13 and 30 years of age and between 40 and 60 years of age. However, the diagnosis can be made at any age in both men and women, and should always be considered in the differential diagnosis of all liver diseases.

Laboratory tests

Blood count may show nonspecific changes due to hypersplenism secondary to cirrhosis (low platelet and leukocyte count) suggestive of normocytic normochromic anemia, which is characteristic of chronic diseases. In general, the presence of more severe anemia is associated with autoimmune haemolysis and is rare.

The liver tests are typically altered, particularly with elevated ALT (usually four to six times the normal values). There may be an increase in the bilirubin and alkaline phosphatase counts, but this increase is typically unimportant. The liver function (seen in albumin count and coagulation status) will depend on the degree of evolution of the disease.

Normally, there is a global hypergammaglobulinaemia or an increase in IgG. An increase in serum ferritin or transferrin saturation can be observed. Finally, circulating autoantibodies can also be observed.

Diagnosis and differential diagnosis

According to the recommendations of the International Autoimmune Hepatitis Group, the diagnosis should be considered in any patient, especially females, where there is unexplained acute or chronic hepatitis or changes in liver tests in the absence of clinical symptoms, particularly if the patient or close relatives have a history of other autoimmune changes.

The diagnosis, as stated above, may be definitive or probable, depending on various criteria shown in *Table II*. Because AIH is a complex syndrome with many components that by themselves, do not suggest the diagnosis, the score proposed by the International Autoimmune Hepatitis Group is useful, as it theoretically allows the combination of the isolated findings, giving them a certain score. Also, it takes into account the response to immunosuppression therapy. This score is shown in *Table III*.

As for the differential diagnosis, other recognized causes of liver disease should be excluded such as viral hepatitis (A, B, C, Epstein-Barr, cytomegalovirus, herpes simplex), Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis (PBC), alcoholic liver disease, nonalcoholic steatohepatitis and toxic liver disease, among others. For the differential diagnoses, appropriate tests for each of the previous cases should be requested, and a careful histological evaluation of the liver biopsy conducted, possibly calculating the hepatic iron index.

In some cases, after evaluating the patient, there can be situations where the data are sufficient to confirm the existence of AIH, unless it is associated with a viral infection (patients with associated hepatitis C, with positive PCR and high titers of SMA and/or ANA), or with an autoimmune cholangiopathy (primary biliary cirrhosis and primary sclerosing cholangitis). In these cases, the predominant disease should be established, and treated accordingly.

Our intention here is merely to give a brief introduction to the associations between AIH and autoimmune cholangiopathy. These are the so-called overlap cases. The manifestations of AIH in some patients are associated with characteristic findings of primary biliary cirrhosis or primary sclerosing cholangitis (PSC). In the first case, however, there is rarely room for diagnostic doubt, since antimitochondrial antibody levels are low and with little clinical significance.[7] The association between AIH and PSC may be explained by the similarity of the HLA haplotypes, which may determine similar pathological mechanisms between them. However, it was suggested[26] that these situations are only forms of autoimmune hepatitis with marked lesions of the biliary tracts.

Treatment

Despite the heterogeneity of this disease and incomplete understanding of the underlying pathogenic mechanisms, AIH is considered to respond well to corticosteroids (CC), therefore these are still the basic treatment, as monotherapy or in combination with

TABLE II

Diagnostic criteria for autoimmune hepatitis

Parameters	Definitive	Probable
Histology	Periportal hepatitis with lymphocyte and plasma cell infiltration, with or without lobular hepatitis or a bridging pattern of necrosis. No biliary lesions, granulomas, siderosis, copper deposition or steatosis, or any other changes suggestive of another etiology.	Same
Biochemical	Changes in transaminases, particularly if alkaline phosphatase levels are not very high. Alpha-1-antitrypsin, ceruloplasmin and iron levels - normal.	If ceruloplasmin and copper levels are abnormal: Wilson's disease is excluded by ophthalmoscopy and copper urinary excretion is excluded after test with D-penicillamine. If iron levels are abnormal, hemochromatosis is excluded after identifying the iron content by biopsy.
Ig	Elevated total globulins, gamma globulin or IgG 1.5 times the normal values.	Any elevation of globulins, gamma globulins or Ig G levels
Autoantibodies	High titers of ANA, SMA or anti-LKM (above 1:80 in adults or 1:20 in children)	ANA, SMA or anti-LKM titers above 1:40 in adults. In children, ANA or anti-LKM titers above 1:10 or SMA above 1:20. Patients who do not have these antibodies, but who have other liver antibodies, might be included.
Viral markers	Negativity for HAV-IgM, HBsAg, HBc-IgM and anti-HCV, and others (EBV, CMV;...) No history of parenteral exposure to blood or derivatives	The chance that individuals with HCV may be included is forewarned.
Other Etiologies	Alcohol consumption <35g/day for men and <25g/day for women with no recent history of use of known hepatotoxic drugs	Alcohol consumption <50g/day for men and < 40g/day for women with no recent history of use of known hepatotoxic drugs. Although these criteria are not met, patients with hepatic lesion still may be included despite abstinence from alcohol or drug withdrawal.

Adapted from the recommendations of the International Autoimmune Hepatitis Group, Hepatology 1993; 18:998.

azathioprine.

There is still no consensus that this treatment is appropriate for all patients. Although CC have proven effectiveness in patients with initial liver biopsy showing bridging necrosis, multilobular necrosis or cirrhosis, in mild cases their usefulness has not been sufficiently demonstrated.[7] On the other hand, their use causes adverse effects, which can sometimes be severe, so an alternative approach for patients with mild disease may be careful clinical and laboratory monitoring. But bearing in mind that evolution can be insidious, with development of subclinical cirrhosis, in addition to clinical and laboratory monitoring, liver histology with serial biopsies is necessary. Liver biopsy is an invasive method that carries inherent risks, so the monitoring strategy for patients with mild disease must be carefully considered.

Despite what was mentioned in the previous paragraph, there are a number of absolute indications to start the treatment:[7] the presence of incapacitating symptoms attributed to the liver disease, histology indicating bridging necrosis or multilobular collapse, and important and sustained elevations in ALT (> 10 times the normal level) and immunoglobulins (≥ 2 the normal level). If untreated, the three-year mortality rate is 50% and the ten-year mortality rate is 90%. In contrast, if treated, the five-year survival rate is over 90% and the ten-year survival rate is 65% when

TABLE III

Diagnosis scoring system for autoimmune hepatitis

Parameters	Score	Parameters	Score
Gender		Hepatotoxic drugs/ transfusions	
Male	0	Yes	- 2
Female	+2	No	+ 1
Alk.Ph.:transaminase ratio		Alcohol (g/day)	
≥3	-2	Male	
<3	+2	<35	+2
globulins, g-globulins or IgG (x normal)		35-50	0
>2	+3	50-80	- 1
1,5-2	+2	>80	-2
1-1,5	+1	Female	
<1	0	<25	+2
ANA titers. SMA or LKM		25-40	0
Adults		40-60	- 1
>1:80	+3	>60	- 2
1:80	+2	Histology:	
1:40	+1	inflammation/periportal necrosis	
<1:40	0	with lobular involvement	+3
Children		without lobular involvement	+2
ANA or Anti-LKM >1:20	+2	rosette formation	+1
>1:10 and <1:20	-2	predominant plasma cell infiltration	+1
<1:10	0	lesions of the biliary tract	- 1
SMA		data compatible with the other diagnosis	
>1:20	+3	(granuloma, siderosis, copper deposition, steatosis,...)	- 3
1:20	+2	Genetic factors:	
<1:20	0	concurrent autoimmune diseases (patient or close relatives)	+ 1
other hepatic auto-Ac	+2	HLA-B8-DR3 or -DR4	+1
antimitochondrial	- 2	Response to the therapy:	
Present	0	full response	+2
Absent		partial response	0
IgM-anti HAV; AgHBs; IgM-anti HBc or HCV-RNA	- 3	treatment failure	0
Anti-HCV + (ELISA, RIBA, PCR)	- 3	no response	
other markers of acute viral infection	- 3	(disease still active)	- 2
absence of viral markers	+3	recurrence during/after treatment	+3
		with initial full response	+1

Note:
If before the therapy the score is > 15 and after the treatment it is > 17, the diagnosis is "Definitive"
If before the therapy the score is between 10 and 15, and after between 12 and 17, the diagnosis is "Probable"
Lower values are considered inconclusive.
(Adapted from the recommendations of the International Autoimmune Hepatitis Group, Hepatology 1993; 18:998)

cirrhosis is present at the time of diagnosis, and 80% when it is not.[7]

The objective of the therapy is complete clinical, biochemical and histological remission. The treatment starts with monotherapy with CC or CC in combination with azathioprine. As azathioprine takes several weeks to reach therapeutic levels, its use should begin as soon as the diagnosis is made. Remission occurs in about 60%-80% of patients after a initial therapeutic approach. When complete remission occurs, treatment should be continued with low doses of corticosteroids associated with azathioprine or azathioprine alone (2 mg/kg/day), which according to some researchers, has better results than monotherapy.[27,28,29] This treatment should be used for a long period of time (two years) and only then should a gradual withdrawal of the therapy be attempted.

If gastrointestinal effects, fever and arthralgia due to the azathioprine limit its use, or if no response to this drug is observed, the use of its analog 6-mercaptopurine can be attempted. Although their mechanisms of action are the same, a difference in side effects is observed, which may be related to individual differences in metabolism. Cyclophosphamide can also be used as a substitute for azathioprine.[28] Cyclosporine may also be useful in this disease, in cases of resistance to corticosteroid. It works in a reversible manner, inhibiting the release of lymphokines and preventing the expansion of cytotoxic T lymphocytes. However, it can cause adverse effects that may be severe (renal insufficiency, high blood pressure and risk of oncogenesis).

As mentioned above, the basic treatment is corticosteroids. Nevertheless, its efficacy is not universal: about 9% of patients do not respond to therapy, 13% respond only partially, and in 13% the side effects mean the treatment has to be discontinued. Finally, approximately 70% of patients experience recurrence when the therapy is discontinued.[7] If patients do not respond to the treatment, i.e. if clinical biochemical and histological deterioration are observed despite the treatment, the doses of prednisolone may be increased, or cyclosporine may be used instead, as mentioned above, or preferably, a liver transplant may be performed. In case of incomplete response, which corresponds to no remission in three years of continuous treatment, therapy with low doses of prednisone can be empirically attempted for an indefinite period of time, with transplant being indicated at the first sign of decompensation (e.g., ascites). If the side effects of the corticosteroids become unbearable, the dose should be reduced to a minimum, seeking to find a balance between control of the hepatopathy and the level of side effects. The first recurrence should be treated as relapse AIH, with the same doses. If multiple recurrences occur after discontinuing the corticosteroids, permanent maintenance therapy with low doses of corticosteroids associated with azathioprine should be considered, or azathioprine alone.

Many immunosuppressants have been studied; these are currently mostly used to prevent rejection after transplantation, but are now starting to be used as immunosuppressants in AIH.[3,7] One of these is FK506 (tacrolimus), a fungal derivative with the same mechanism of action as that of cyclosporine, but apparently with fewer side effects and greater immunosuppression power.

Liver transplantation should be further considered when the initial manifestation of the disease is characterized by acute hepatitis with fulminant liver failure. ■

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