Update on autoimmune hepatitis

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Abstract
Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown etiology that occurs in children and adults of all ages. Characteristics are its autoimmune features, hyperglobulinemia (IgG), and the presence of circulating autoantibodies, as well as a response to immunosuppressant drugs. Current treatment consists of prednisone and azathioprine and in most patients this disease has become very treatable. Over the past 2 years, a couple of new insights into the genetic aspects, clinical course and treatment of AIH have been reported, which will be the focus of this review. In particular, we concentrate on genome-wide microsatellite analysis, a novel mouse model of AIH, the evaluation of a large AIH cohort for overlap syndromes, suggested novel criteria for the diagnosis of AIH, and the latest studies on treatment of AIH with budesonide and mycophenolate mofetil.

Key words: Autoimmune hepatitis; Autoimmune liver disease; Budesonide; Genetics; Mycophenolate mofetil; Overlap syndromes

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INTRODUCTION
Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown etiology that occurs in children and adults of all ages[1]. Most patients are female. Characteristics of the disease are a fluctuating spontaneous course of activity, hyperglobulinemia (IgG), and the presence of circulating autoantibodies, as well as a response to immunosuppressant drugs. However, AIH shows considerable heterogeneity[2]. No single clinical or biochemical test proves the presence of AIH. An exception may be the presence of soluble liver antigen/liver-pancreas (SLA/LP) autoantibodies. In 1992, the International Autoimmune Hepatitis Group recommended a scoring system for the diagnosis of AIH to allow reliable diagnosis of the disease, and this was further updated in 1999[3]. The sensitivity of the scoring system for AIH ranges from 97% to 100%, and its specificity for excluding chronic hepatitis C ranges from 66% to 92%(4). Besides, variant, overlapping, or mixed forms of AIH, it shares common features with other putative autoimmune liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis[5]. Although some patients do present with acute liver failure and may need liver transplantation[6], the overall prognosis of AIH is mostly determined by response to corticosteroid therapy. Overall, long-term survival and average life expectancy are excellent and estimated to be comparable with those of the normal population[7].

IMMUNOPATHOGENESIS
Although the pathogenetic mechanism of the disease is still unknown, an underlying genetic predisposition has been suggested because of the fact that patients are predominantly female and the association of the disease with certain human leucocyte antigens (HLAs). HLA genes reside in the major histocompatibility complex (MHC), which is located on the short arm of chromosome 6. The MHC is a genetic system with extensive polymorphism. Although multiple genes are probably involved, HLA genes appear to play the dominant role in predisposition to AIH[8]. Particularly, HLA B8, DR3 and DR4 are found at a significantly higher frequency
in different populations with AIH\textsuperscript{[7,8]}. The challenge is to investigate whether these findings help to better understand the etiology of AIH, predict its prognosis, or further improve its treatment.

**DIAGNOSIS**

The presentation of AIH is very heterogeneous, and may be characterized by an undulating course with periods of decreased or increased activity; thus, clinical manifestations are variable, ranging from asymptomatic disease to severe icteric hepatitis, and even fulminating hepatic failure that requires liver transplantation, depending on the intensity of the autoimmune reaction\textsuperscript{[1]}. Patients may present with non-specific symptoms of varying severity, such as fatigue, lethargy, malaise, anorexia, nausea, abdominal pain, and itching. Arthralgia of the small joints is common. Physical examination may be without pathological findings, but may also reveal hepatomegaly, splenomegaly, jaundice, and signs and symptoms of chronic liver disease\textsuperscript{[1-3]}. Many patients with acute presentation have histological evidence of chronic disease upon liver biopsy, which indicates that they probably have had subclinical disease for a long time (acute or chronic disease). Long periods of subclinical disease may also occur after presentation. In addition, diseases with an autoimmune background such as Hashimoto thyroiditis, ulcerative colitis, type 1 diabetes, rheumatoid arthritis, and celiac disease are more frequently found in patients with AIH\textsuperscript{[10]}. In general, hepatitis with elevation of aspartate aminotransferase (AST) and alanine aminotransferase leads to the diagnosis of AIH. In particular, viral and toxic hepatitis must be excluded. Some cases, however, are characterized by cholestasis, with high levels of conjugated bilirubin and alkaline phosphatase. In such circumstances, extrahepatic obstruction and cholestatic forms of viral hepatitis, drug-induced disease, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and variant syndromes must be considered.

One characteristic laboratory feature of AIH is elevation of serum globulins, in particular, gamma globulin, with a selective increase in IgG, which is generally 1.2-3.0 times higher than the upper level of normal. The characteristic circulating autoantibodies seen in AIH include antinuclear antibodies (ANAs), smooth-muscle antibody (SMA), SLA/LP autoantibodies, and liver-kidney microsome (LKM) autoantibodies. In addition, perinuclear antineutrophil cytoplasmic antibodies and liver-cytosol type 1 antibodies are frequently encountered in patients with AIH. Antimitochondrial antibodies are sometimes present in patients with AIH\textsuperscript{[11,12]}. In these patients, an overlap syndrome of AIH and PBC should be considered\textsuperscript{[9]}. However, it should be noted that autoantibodies are found in various liver diseases, and their presence, by itself, is not diagnostic of AIH. With respect to the pathogenesis of AIH, there is little evidence that autoantibodies play a crucial role.

Since there is no single test proving the diagnosis of AIH (an exception could be SLA/LP autoantibodies), liver histology remains of central importance. As percutaneous liver biopsy frequently suffers from a high rate of sampling error with respect to the staging of fibrosis and cirrhosis\textsuperscript{[13,14]}, we frequently perform (mini)laparoscopy-guided liver biopsy in AIH patients, particularly at initial diagnosis.

The histological appearance of AIH is the same as that of chronic hepatitis of other etiologies, and although certain changes are characteristic, no findings are specific for AIH. AIH is generally characterized by a mononuclear-cell infiltrate that invades the limiting plate (peripoortal infiltrate, also called piecemeal necrosis or interface hepatitis that progresses to lobular hepatitis). There may be an abundance of plasma cells, a finding that in the past has led to the use of the term “plasma-cell hepatitis”. Eosinophils are frequently present. The portal lesion generally spares the biliary tree. Fibrosis is present in all but the mildest forms of AIH. In advanced disease, fibrosis is extensive, and with the distortion of the hepatic lobule and the appearance of regenerative nodules, it results in cirrhosis\textsuperscript{[14]}.  

**TREATMENT**

If untreated, severe AIH has a very high mortality rate of up to 50% after 3-5 years of diagnosis\textsuperscript{[15]}. Immunosuppressive therapy with corticosteroids, usually in combination with azathioprine is considered the gold standard to induce and maintain remission. Moreover, response to immunosuppressive therapy confirms the diagnosis of AIH\textsuperscript{[10]}. The therapeutic goal should be complete normalization of transaminases because progression to liver cirrhosis may occur in patients with residual inflammatory activity within the liver. However, side effects of therapy must be taken into consideration. The magnitude of aminotransferase and gamma globulin elevations does not necessarily correlate with the histological extent of injury and provides little help with respect to the initiation of treatment.

Under immunosuppression, the vast majority of patients achieve complete remission\textsuperscript{[16]}. If patients not sufficiently responding to immunosuppressive therapy, the diagnosis of AIH should be thoroughly reevaluated. In some patients an overlap syndrome of AIH with PBC or PSC can be a reason for insufficient response to immunosuppression, and addition of ursodeoxycholic acid may further improve laboratory results.

Although some patients remain in remission after drug treatment is withdrawn, most require long-term maintenance therapy. Even though there is only scarce evidence for how long maintenance therapy should be given, it has been proposed that patients should be in stable remission for at least 4 years before withdrawal of immunosuppressive therapy can be considered\textsuperscript{[17]}. However, patients positive for LKM1 antibodies (type 2 AIH) should be treated with life-long immunosuppression, which can only be stopped in patients with ANA- and SMA-positive AIH (type 1 AIH). Since biochemical response and clinical remission do not necessarily mean that there is histological evidence of resolution of AIH, repeated liver biopsy should be performed, particularly if withdrawal of immunosuppressive therapy is planned.

In the very few patients that do not tolerate or have
significant side effects to standard therapy, alternative immunosuppressive therapies have been proposed, mainly on the basis of small series or case reports. Cyclosporine appeared to be effective in a group of adult patients who were corticosteroid-resistant[18]. A regimen of cyclosporine for 6 mo followed by the administration of prednisone and azathioprine was reported as successful in inducing remission in children[19]. Limited data are available concerning the use of tacrolimus[20], methotrexate[21], cyclophosphamide[22], ursodiol[23] and mycophenolate mofetil (MMF)[26]. Data on a novel large study on budesonide in combination with azathioprine are discussed below[28].

Although AIH primarily shows a chronic course with relapses under therapy (if immunosuppression is rapidly reduced), and particularly after discontinuation of immunosuppressive therapy, long-term prognosis is excellent, assuming close medical surveillance and/or treatment[1]. For some reason, the development of hepatocellular carcinoma is a very rare complication in patients with AIH, even though many patients have established liver cirrhosis at the time of diagnosis and patients are immunosuppressed. This fact might give further insight into the pathogenesis of liver carcinogenesis.

OVERLAP SYNDROMES-UPDATE

2008: SYSTEMATIC REVIEW REVEALS HIGH ASSOCIATION OF AIH WITH AUTOIMMUNE THYROIDITIS

Although the pathogenetic mechanisms of autoimmune diseases in various organs remain unresolved, an accumulation of autoimmune diseases in individual patients has been observed. An overlap of AIH and PBC or PSC has been well documented. However, overlap with autoimmune diseases other than PBC or PSC has not yet been investigated in a large cohort. In a systematic review of our cohort of 278 patients with AIH, 111 (40%) were diagnosed with additional autoimmune diseases. Besides overlap syndromes with PBC and PSC, autoimmune thyroiditis was the most common concurrent disease, and was diagnosed in 28 patients (10%). Other concurrent autoimmune diseases comprised vitiligo (five patients), rheumatoid arthritis (five patients), Sjogren’s syndrome (four patients), ulcerative colitis (four patients), conjunctivitis (four patients), celiac disease (three patients), systemic lupus erythematosus (two patients) type 1 diabetes (two patients), multiple sclerosis (two patients), polymyalgia rheumatica (two patients), and urticaria (two patients). One patient each was diagnosed with Crohn’s disease, autoimmune gastritis, collagen colitis, hypophysitis and sarcoidosis. In conclusion, overlap with other autoimmune diseases is common in patients with AIH and mirrors the full range of known autoimmune diseases. Therefore, an extended diagnostic screening for accumulating autoimmune diseases seems reasonable in patients with AIH. In particular, monitoring for autoimmune thyroiditis must be considered mandatory at 10% of our patients with AIH developed such a condition[24].

GENETIC BASIS OF AIH-UPDATE 2008: A GENOME-WIDE DNA MICROSATELLITE STUDY REVEALS MICROSATELLITE ASSOCIATIONS

Although the pathogenesis of the disease is still unknown, an underlying genetic predisposition has been suggested because of the fact that patients are predominantly female, and the well-documented association of the disease with certain HLAs. It has been suggested that multiple individual genes are involved in the development of AIH, mostly based on the identification of single nucleotide polymorphisms[27-30]. However, until recently, a genome-wide search for the underlying genetic mechanisms has not been performed.

Yokosawa et al[31] investigated 400 polymorphic microsatellite markers in 81 patients with type 1 AIH. These markers covered the complete genome, with an average spacing of 10.8 cM. Of these, two markers, on chromosome 11 and 18, D11S902 and D18S464, respectively, were demonstrated to be significantly associated with AIH. An additional seven markers (D2S367, D6S309, D9S273, D11S1320, D16S423, D17S938 and D18S68) were designated as candidate susceptibility regions. Furthermore, a total of 17 markers were suggested to be relevant for resistance towards AIH. To further narrow down the genetic basis to individual genes within these microsatellite regions, a 500-kb perimeter of the D11S902 and D18S464 regions was screened for genes with a biological function that would fit into a potential pathogenetic mechanism of autoimmune liver disease. Several candidate genes such as PIK3C2A, ABCC8, KCNJ11 and VAPA were named to be involved in diverse cell functions that need to be further evaluated and investigated by means of molecular biology[32]. The genetic data were then integrated with clinical data on the course of the disease. However, no differences were seen in the clinical courses of patients with respect to their genetic background, mirrored by means of the identified microsatellite profile. The authors pointed out, that these differences in microsatellite profile were not observed in HLA-DR4-negative patients, a finding that needs to be further investigated and confirmed[31].

MODELING AIH-UPDATE 2008: A NOVEL MOUSE MODEL OF AIH

Mouse models of human diseases are of significant help in exploring the basic principles of disease development. However, modeling AIH in mice has been challenging. Concanavalin A (Con-A)-induced acute liver injury is considered to be a model of human AIH. Major criticisms of this model are that mice stimulated with Con A do not develop autoantibodies and that a single injection of Con A may induce rapid damage of liver cells, which culminates in lethal fulminant hepatitis, in contrast to the more chronic nature of AIH.

Kido et al[33] have now presented a new mouse model...
of AIH based on an NTx- and PD-1 double knock out. By influencing the regulatory T cells (Tregs), these mice develop characteristics of AIH. Tregs are a specialized subpopulation of T cells. They function as suppressors of immune system activation, and maintain tolerance to autoantigens and immune system homeostasis. Tregs have been previously at the center of attention, as this T cell population has been demonstrated to be defective numerically and functionally in patients with AIH\cite{1}.

A recently described mouse model of AIH provides improved modeling of the disease, as the mice develop ANAs as well as CD4+ and CD8+ T-cell infiltration\cite{2}. Furthermore, on a histological level, these NTx-PD-1 double knock out mice develop a significant mononuclear cell infiltration and massive lobular necrosis, without bile duct destruction and fibrosis. This model certainly needs further evaluation, with respect to the underlying pathogenetic mechanisms, especially as it has been demonstrated that simply deleting Tregs is not sufficient for inducing AIH. Furthermore, PD-1 deficiency alone does not alter the suppressive activity of Tregs. Thus, the details of PD-1/Treg interaction may be of great interest in the further appreciation of this novel mouse model of AIH. Nevertheless, providing this novel mouse model of AIH, Kido et al\cite{3} have certainly discovered a powerful tool for genetic research on the development of AIH and additional treatment options.

### DIAGNOSIS OF AIH-UPDATE 2008:

#### SIMPLIFIED CRITERIA FOR THE EVALUATION OF AIH

Given the diverse clinical presentation of AIH, its diagnosis often remains challenging. To date, only SLA/LP autoantibodies are highly specific for the diagnosis of AIH\cite{4}. However, they are only present in about 20% of patients. Currently, the diagnosis of AIH is made using the scoring system of The International Autoimmune Hepatitis Group. The scoring system has been demonstrated to be highly sensitive with a range from 97% to 100%, and its specificity for excluding chronic hepatitis C ranges from 66% to 92%\cite{5}. However, handling of these criteria is rather laborious because they were primarily designed for scientific purposes.

Hennes et al\cite{6} have now proposed shortened, easier-to-use criteria that consist of a set of only four relevant pieces of information. These clinical criteria are IgG, autoantibodies (ANA, SMA and SLA), histology, and exclusion of viral hepatitis. The novel shortened criteria have been demonstrated to either confirm or exclude the diagnosis of AIH with both positive and negative predictive values well over 90%.

In detail, the authors have proposed the following scoring system. Patients with IgG > 16 g/L, ANA and SMA > 1:40, and a compatible histology are assigned one point for each applicable criterion. Those with IgG > 18 g/L, ANA and SMA > 1:80, the presence of SLA/LP antibodies, histology compatible/typical for AIH, and negative viral markers are assigned two points per applicable criterion. Six or more points made the diagnosis of AIH very likely, and seven or eight points confirmed the diagnosis of definite AIH.

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These novel criteria for the diagnosis of AIH provide a valuable simplification for daily clinical practice. However, they should be further investigated and confirmed by independent prospective studies\cite{7}.

### UPDATE 2008-ALTERNATIVE TREATMENT OF AIH WITH MMF

In most cases, patients with AIH can be treated successfully with prednisone, with or without azathioprine. However, a considerable number of patients with AIH, and in need of immunosuppressive treatment, tolerate azathioprine only poorly, or do not respond efficiently to treatment\cite{8}. A smaller number of patients will even fail to respond to this conventional therapy\cite{9}. As discussed above, several other therapies have been studied for their efficacy in AIH, but these studies were small or single case reports. However, MMF has demonstrated encouraging results in a few studies on small cohorts of patients with AIH. Thus, MMF has increasingly shifted into the center of attention as an alternative treatment option of AIH.

MMF inhibits purine synthesis by acting as an inhibitor of inosine monophosphate dehydrogenase. MMF treatment has been established successfully in many other conditions, such as rheumatoid arthritis or Crohn’s disease. In addition, the drug has become routinely used in immunosuppressant regimens in patients who have undergone solid organ transplantation.

Triggered by a first case report in 1998\cite{10}, several smaller studies have reported consecutively on successful treatment of AIH with MMF. Richardson et al\cite{11} have reported on successful MMF treatment of seven patients. Five of these patients had normal transaminases after 3 mo treatment, as well as a significant reduction in steroid dose and hepatic activity index\cite{12}. These findings were...
further supported by a series of five Canadian patients who also benefited from transaminase normalization, a steroid sparing effect and histological remission\[41\]. Lately, Inductivo-Yu et al\[37\] and Chatur et al\[38\] have reported on an additional 31 patients with AIH being successfully treated with MMF. In addition to the benefits observed in the earlier case report series, Inductivo-Yu et al\[37\] have also documented that the inflammatory scores and Ishak fibrosis scores were decreased. These results have been further supported by observations from patients who had received a liver transplantation for AIH and required immunosuppressant therapy after transplantation. In these patients, MMF was also demonstrated to be part of the immunosuppressant regimen\[39\].

In 2008, Hennes et al\[40\] reported the largest cohort to date of 36 patients treated with MMF. In contrast to earlier studies, they observed a much lower frequency of response to MMF treatment, as only 14 patients (39%) experienced remission, which was defined as AST less than twice the upper limit of normal. Twenty-two patients (61%) did not respond sufficiently to MMF. In a subset analysis, they further demonstrated that the response rate to MMF was dependent on the cause of treatment cessation of azathioprine. Most patients with prior non-response to azathioprine did not respond to MMF treatment either.

MMF certainly provides a valuable therapeutic option in patients with AIH. However, the latest and, so far, largest study by Hennes et al\[40\] suggests that less than half of all patients may benefit from MMF. Thus, MMF may be a valuable alternative to azathioprine but does not seem to be an option for the treatment of AIH after azathioprine non-response.

### TREATMENT OF AIH-UPDATE 2008: ESTABLISHING TREATMENT WITH BUDENOSIDE

Budesonide is a corticosteroid with the highest affinity for the glucocorticoid receptor when compared with other steroids. The drug has a high first pass metabolism, which results in a low incidence of systemic glucocorticoid-related adverse effects\[41,42\]. Budesonide has been demonstrated to be a highly efficient therapeutic option in the treatment of a wide range of diseases. Budesonide has been demonstrated to be a therapeutic option for inducing remission of Crohn’s disease. It has been demonstrated to be less effective than conventional steroids, but also exhibited fewer adverse events and lower adrenal suppression\[43\]. Furthermore, the combination of budesonide and formoterol is an efficient alternative in asthma management in patients not adequately controlled by conventional regimens with short-acting β-adrenoceptor agonists\[44\].

Given a high efficiency in several inflammatory diseases and fewer adverse effects, treatment of AIH with budesonide may highly beneficial if its efficiency were comparable to the conventional prednisolone. Over the past decade, several smaller studies have suggested the efficacy of budesonide for remission induction\[45\]. However, one study failed to demonstrate such efficacy in AIH\[46\].

Recently, Manns et al\[47\] have compared combined budesonide and azathioprine to standard prednisolone treatment of 208 patients with AIH. The primary end point of the study was complete remission without typical steroid adverse effects, defined as facial swelling, diabetes mellitus, acne, hirsutism, striae and glaucoma.

Budesonide treatment was initiated at 3 mg three times daily and was reduced to 3 mg twice daily when the patients reached clinical remission. Prednisolone was initiated at 40 mg/d and reduced to 10 mg/d in week 9. Azathioprine was administered to both groups at a dose of 1-2 mg/kg per day. In comparison between these two groups, significantly more patients in the budesonide group reached the predefined primary endpoint of biochemical remission without typical adverse effects of steroids (47% vs 18.4%, \(P < 0.00001\)). Furthermore, for secondary endpoints, especially biochemical remission, budesonide was superior to prednisolone (60% vs 38.8%, \(P = 0.00128\)). However, for the long-term results of normalization of bilirubin and IgG over a 6-mo period, budesonide was not superior to prednisolone, as 83% versus 89.3% of patients experienced normalization of bilirubin and 56.0% vs 62.1% normalization of IgG.

Although these data seemed convincing at first sight, the studies have been discussed controversially with respect to the prednisolone dose. A potentially too-low dose of prednisolone was considered to be responsible for a very low 18.6% remission rate. These results seem poor compared to the approximately 90% remission in previous studies on AIH treatment.

In this first large study, budesonide has been proven to be an efficacious alternative to prednisone, with a highly beneficial adverse effect profile in patients with AIH. However, long-term results of budesonide treatment have yet to be collected and data on longer follow-up are expected soon\[47\]. Special attention needs to be given to the question of a comparable prednisolone dosage in the (control) conventionally treated patients.

### CONCLUSION

Over the past 2 years, substantial progress has been made in evaluating alternative treatment options for AIH. With respect to the pathophysiological changes that lead to the development of AIH, microsatellite studies have identified novel genomic regions that are involved in the development of the disease. Finally, the diagnosis of the disease may become easier if the novel shortened criteria for the diagnosis of AIH prove to be accurate in further studies.

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