Current and future perspectives in autoimmune hepatitis

ABSTRACT

Autoimmune hepatitis occurs in genetically susceptible individuals as a result of loss of immunological tolerance to hepatic autoantigens that can be precipitated by environmental triggers. The clinical manifestation is usually insidious but can be also acute with liver failure. The diagnosis is made on the basis of antibody positivity, elevated immunoglobulin G levels and interface hepatitis on liver histology. Induction of remission is achieved with high-dose steroids in the majority of cases, and maintenance of remission with azathioprine. Treatment withdrawal is achievable only in a small proportion of patients. Patients with acute liver failure unresponsive to steroids or those with end-stage liver failure or hepatocellular carcinoma may require liver transplantation. Variant forms of overlapping autoimmune hepatitis with either primary biliary cholangitis or sclerosing cholangitis are associated with worse outcomes. New insights into the pathophysiology of the disease may provide novel therapeutic targets and a more individualized approach to treatment of autoimmune hepatitis.

Autoimmune hepatitis is a rare liver disease, characterized by loss of immunological tolerance to hepatic autoantigens. The prevalence and clinical course of autoimmune hepatitis varies substantially according to gender, geographical area and ethnicity. The female predominance with a female:male ratio of 4:1 is well documented. The annual incidence of autoimmune hepatitis in northern European populations is 1.07–1.9 per 100 000, and the point prevalence 16–18 per 100 000 people (Feld and Heathcote, 2003). A significantly higher prevalence has been documented in native Alaskan populations (Hurlburt et al, 2002). Initially thought to be a disease of young women, it is now recognized that autoimmune hepatitis can affect all age groups (Al-Chalabi et al, 2006). A bimodal distribution has been observed with the first peak in childhood or adolescence and the second in middle age between the 4th and 6th decade of life.

Autoimmune hepatitis is classified into two types according to the serological autoantibody pattern (Lohse and Mieli-Vergani, 2011). Type 1 disease is the most common (90% of cases), and is characterized by the detection of antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or antibodies against soluble liver antigen (anti-SLA). The age of onset, clinical presentation, severity and need for long-term immunosuppression therapy is variable in type 1 autoimmune hepatitis. Type 2 autoimmune hepatitis (10% of cases) is characterized by the presence of liver/kidney muscle antibodies type 1 (anti-LKM1) or rarely type 3 (anti-LKM3), or antibodies against liver cytosol type 1 (anti-LC1). This type has a younger age of onset, more advanced disease at diagnosis, more severe activity and very high relapse rate after treatment withdrawal.

The clinical presentation is also variable from subclinical chronic liver disease and cirrhosis with hepatocellular carcinoma, to acute icteric hepatitis or acute liver failure necessitating liver transplantation. Untreated autoimmune hepatitis is associated with high mortality and morbidity. The introduction of steroid therapy was associated with a dramatic survival benefit of >90% (Lamers et al, 2010).

This review focuses on the pathophysiology of the disease, clinical presentation, diagnosis and treatment strategies.

Pathophysiological mechanisms and triggers

The pathophysiology of autoimmune hepatitis entails a complex interplay of immunological, genetic and environmental factors (*Figure 1*). The loss of self-tolerance is the result of impaired balance between liver-specific T regulatory cells and effector cells of liver damage (CD4 and CD8 cells, B cells, natural killer cells, macrophages and monocytes) (Wen et al, 1990). Under normal circumstances T regulatory cells exert control over the proliferation, cytokine excretion and cytotoxicity of the effector cells ensuring immunotolerance. Impaired T regulatory cell control function or impaired effector cell responsiveness results in recognition of liver-specific autoantigens, enhanced cytokine release and cytotoxicity, eventually leading to liver damage (Ferri et al, 2010).

Cytochrome P450 2D6 (CYP2D6) has been recognized as the principal liver-specific autoantigen in type 2 autoimmune hepatitis, targeted by anti-LKM1 (Manns et al, 1989) and the SLA in type 1 disease (Wies et al, 2000). Human leukocyte antigen (HLA) class II molecules on hepatocytes have the ability to bind liver autoantigens and present them to effector cells. HLA genetic polymorphisms can increase or decrease susceptibility to autoimmune hepatitis (Lobo-Yeo et al, 1990; Czaja and Donaldson, 2000). HLA DR3 (DRB1*0301) and DR4 (DRB1*0401) have been linked with increased susceptibility to type 1

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Figure 1. Immunopathogenesis of autoimmune hepatitis. HLA = human leukocyte antigen.

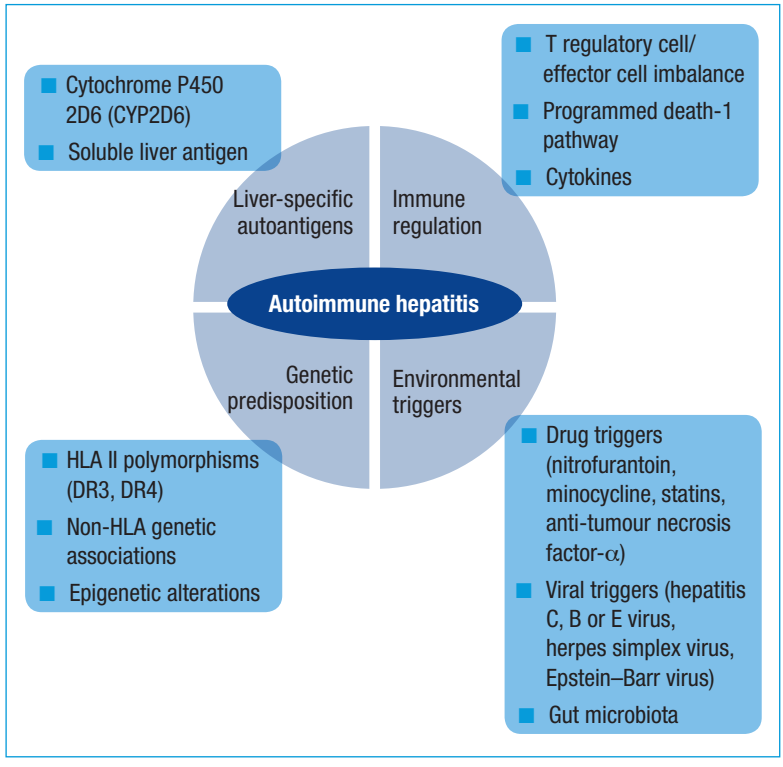


Table 1. Potential drug triggers for autoimmune hepatitis

Common	Minocycline
	Nitrofurantoin
	Interferon-α
	Infliximab
Less common	Ezetimibe
	Interferon-β
	Ornidazole
	Diclofenac
	Indomethacin
	Terbinafine
	Methyldopa
	Ranitidine
	Atorvastatin
	Fluvastatin
	Fibrates
	Adalimumab
	Daclizumab
	Hepatitis A vaccination
	Herbal medicines (dai-taiko-so or da chai hu tang)

autoimmune hepatitis in European and northern American populations (Strettell et al, 1997; de Boer et al, 2014). HLA DR3 (DRB1*0301) and DR7 (DRB1*0701) have been associated with type 2 disease in the UK and Brazil (Bittencourt et al, 1999). Allelic polymorphisms have been associated not only with disease susceptibility, but also with clinical manifestations, severity and response to therapy (van Gerven et al, 2015). There is increasing interest in non-HLA genetic associations, identified by genome-wide association studies (such as SH2B3 gene that inhibits T-cell activation), and epigenetic changes affecting gene activity (DNA demethylation, histone modifications, micro-ribonucleic acids) that can alter the risk of developing autoimmune hepatitis (Czaja, 2017).

In genetically susceptible individuals, the onset of autoimmune hepatitis can be triggered by external (viruses, drugs) or internal (gut microbiota) antigens via mechanisms of molecular mimicry and cross-reactivity. Viral antigens, such as hepatitis B, C and E, herpes simplex or Epstein–Barr virus antigens, can trigger autoimmune responses in the liver (Manns, 1997). Homology between hepatitis C virus epitopes and the P450 2D6 (CYP2D6) liver-specific autoantigen has been described along with the presence of anti-LKM1 antibodies in patients with chronic hepatitis C (Manns and Obermayer-Straub, 1997). A number of drugs can precipitate autoimmune hepatitis via the same mechanism (Björnsson et al, 2010). Nitrofurantoin and minocycline are the most commonly reported culprits, but statins and anti-tumour necrosis factor-α agents have also been implicated (*Table 1*) (Yeong et al, 2016). Drug-induced autoimmune hepatitis shares the same clinical features with classic autoimmune hepatitis, although it usually does not require long-term immunosuppressive therapy.

The role of the gut microbiome is increasingly recognized in health and disease. Gut dysbiosis, increased gut permeability and bacterial translocation have been implicated in several disease processes, including autoimmune hepatitis (Lin et al, 2015). Gut-derived antigens are believed to precipitate liver inflammation via molecular mimicry (Yuksel et al, 2015). Novel insights into the pathophysiological mechanisms of the disease, such as non-HLA genetic associations, epigenetic alterations and the role of the gut microbiome, could provide new therapeutic targets in the future (Czaja, 2017).

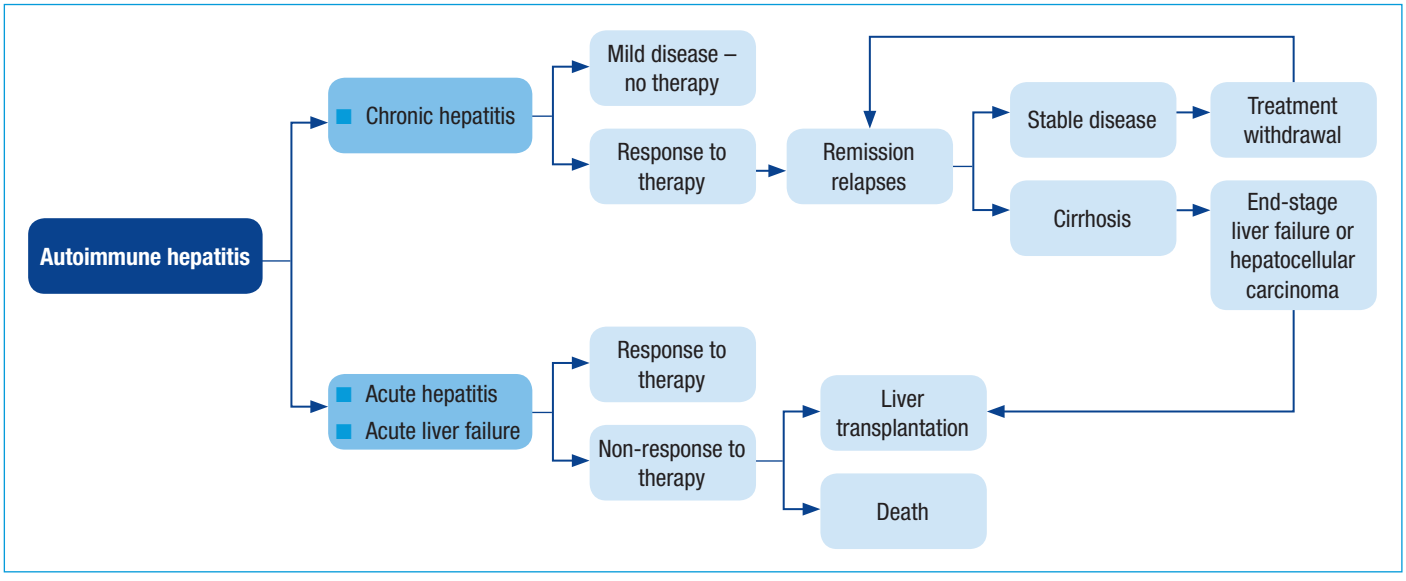
Clinical presentation and diagnosis

Clinical manifestations

The diagnosis of autoimmune hepatitis is made in cases of abnormal liver biochemistry with predominant hepatitic pattern on the basis of the presence of autoantibodies, elevated immunoglobulin G (IgG) levels and typical histological findings of interface hepatitis (Gleeson and Heneghan, 2011).

The majority of cases present, or might be incidentally diagnosed, with features of chronic liver disease that may have remained subclinical for several years (*Figure*

Figure 2. Clinical presentation and course of autoimmune hepatitis.



2). Symptoms are usually non-specific including fatigue, right upper quadrant pain or discomfort, pruritus and arthralgias. Approximately 25% of adult and 50% of paediatric cases will have established cirrhosis at diagnosis, and a proportion will present with decompensated liver disease (jaundice, ascites or variceal bleeding) (Feld et al, 2005). Patients with cirrhosis are at risk of developing hepatocellular carcinoma at estimated rates of 1% annually (Yeoman et al, 2008), and require 6-monthly surveillance according to the paradigm of other chronic liver diseases.

A smaller proportion of patients (25%) will have a severe acute presentation either with acute icteric hepatitis or less commonly with acute liver failure (Stravitz et al, 2011). This manifestation may represent a frank acute autoimmune hepatitis without histological evidence of chronic liver disease, or acute hepatitis developing on a background of previously undiagnosed autoimmune hepatitis cirrhosis (Takahashi and Zeniya, 2011). The diagnosis of autoimmune hepatitis in this setting might be problematic as typical serological indices (autoantibody positivity and elevated IgG levels) might be absent, and exclusion of other aetiologies is necessary. Response to high-dose steroid therapy might provide diagnostic clues, but can be variable.

Autoantibodies

The detection of serum autoantibodies plays a central role in the diagnosis of autoimmune hepatitis. ANA, SMA and/or anti-SLA are detected in type 1 autoimmune hepatitis. Detectable ANA or SMA titres are found in 65% of type 1 autoimmune hepatitis patients, but 20% of patients are negative for all conventional autoantibodies (Vergani et al, 2004). Anti-SLA are highly specific for the disease and have been associated with more severe disease course (Kanzler et al, 1999). Anti-LKM1, anti-LC1 and anti-LKM3 can be present in type 2 disease which is more common in children (Homberg et al, 1987). Most of these autoantibodies are not disease-specific with the exception of anti-SLA. Notably, autoantibodies may be absent in acute severe autoimmune hepatitis. Repeat testing for autoantibodies is warranted in case of strong clinical suspicion in initially negative cases, as antibody titres may exhibit temporal variability. Other autoantibodies can be detected in a small proportion of autoimmune hepatitis patients with unclear clinical significance.

Histology

A liver biopsy is mandatory at initial presentation in patients with autoimmune hepatitis to establish the diagnosis and accurately stage the disease, in terms of necroinflammatory activity and extent of hepatic fibrosis (Heneghan et al, 2013). The typical histological features of autoimmune hepatitis are lympho-plasmacytic infiltrate in the portal tract, extending into the hepatic lobule (interface hepatitis). Although interface hepatitis is typical for autoimmune hepatitis, it is not a pathognomonic finding as it can be observed in other liver disorders. Centrilobular (zone 3) changes can be also observed, more commonly in acute hepatitis. Parenchymal collapse is a frequent finding in acute severe autoimmune hepatitis or acute liver failure (Hofer et al, 2006).

A liver biopsy is particularly useful in the 20% of cases of seronegative autoimmune hepatitis to confirm the diagnosis. Histology also helps exclude other liver pathologies and/or diagnose variant syndromes such autoimmune hepatitis overlap with primary biliary cholangitis or primary sclerosing cholangitis. Repeat liver biopsy may be required to assess disease progression despite immunosuppressive treatment. When treatment withdrawal is considered in patients with biochemical remission, histology can help rule out residual significant inflammatory activity that may increase the risk of relapses. A hepatitis activity index (HAI) score >3 has been associated with increased risk of autoimmune hepatitis relapse.

There is extensive experience with the use of transient elastography (FibroScan) in chronic viral hepatitis, and liver stiffness measurement is routinely used to quantify and monitor hepatic fibrosis in this setting. However, experience with non-invasive fibrosis markers in autoimmune liver diseases is limited. Transient elastography can be used in autoimmune hepatitis beyond the acute phase (at least 6 months after the initial diagnosis) as the acute inflammatory process may account for falsely increased liver stiffness measurements. Transient elastography might be a useful modality in long-term monitoring of fibrosis progression or regression in autoimmune hepatitis, but further research is required in this direction (Hartl et al, 2017).

Diagnostic criteria

The diagnosis of autoimmune hepatitis is mainly clinical, using a combination of clinical, serological and histological parameters. The International Autoimmune Hepatitis Group developed diagnostic criteria for autoimmune hepatitis that were based on gender, presence and titre of autoantibodies, IgG concentration and histological findings, after exclusion of alcohol and other aetiologies of chronic liver disease (Johnson and McFarlane, 1993; Alvarez et al, 1999). Although these criteria can accurately classify cases as definite, probable and not probable autoimmune hepatitis, their complexity limits their use in clinical practice, albeit they remain a useful tool in the setting of clinical trials. Simplified criteria (*Table 2*) were published in 2008 (Hennes et al, 2008), and were validated in external cohorts of autoimmune hepatitis patients (Czaja, 2008; Yeoman et al, 2009). The original criteria have higher sensitivity in diagnosing less typical cases of autoimmune hepatitis, whereas the more recent simplified criteria exhibit higher specificity and are more accurate in excluding non-autoimmune hepatitis cases.

Variant and overlapping syndromes

Autoimmune hepatitis can coexist with other autoimmune liver diseases such as primary biliary cholangitis or primary sclerosing cholangitis, which can create diagnostic confusion (Heathcote, 2002). Alternatively, over time, disease may evolve from one to another. Patients with established autoimmune hepatitis can exhibit cholestatic liver biochemistry, features of cholangiopathy on biliary tract imaging or histological evidence of bile duct damage. Similarly, patients with primary sclerosing cholangitis or primary biliary cholangitis can develop serological features of autoimmune hepatitis and interface hepatitis on liver histology. In patients with primary biliary cholangitis, suboptimal response to conventional therapy with ursodeoxycholic acid should raise the possibility of a concomitant autoimmune process, potentially warranting steroid therapy. The 'Paris criteria' have been developed to diagnose primary biliary cholangitis–autoimmune hepatitis variant syndrome, and exhibit high sensitivity and specificity (Kuiper et al, 2010). Approximately half of paediatric patients with autoimmune hepatitis will have concomitant features of sclerosing cholangitis at the time of diagnosis, a syndrome defined as autoimmune sclerosing cholangitis (Gregorio et al, 2001). This disease is not generally recognized in adult patients, with the variant form of autoimmune hepatitis–primary sclerosing cholangitis developing in only a small proportion of patients. In view of the rarity of these syndromes, large prospective studies are difficult to perform and guidelines are lacking. In most cases, however, a dominant disease phenotype can be defined, and the dominant disease should be treated in order to avoid unnecessary exposure to immunosuppressive therapy.

> **"The diagnosis of autoimmune hepatitis is mainly clinical, using a combination of clinical, serological and histological parameters."**

Treatment

Aims and indications for treatment

Initial observations showed poor prognosis with untreated autoimmune hepatitis with a 5-year survival rate of 50% and 10-year survival of 10%, whereas with the introduction of immunosuppressive therapy the 10-year

Table 2. Simplified diagnostic criteria for autoimmune hepatitis

Variable	Cut-off	Points
Antinuclear antibody or anti-smooth muscle antibody	>1:40	1
Antinuclear antibody, anti-smooth muscle antibody or anti-liver/kidney muscle antibody	>1:80	2
Soluble liver antigen	Positive	2
Immunoglobulin G	>upper limit of normal	1
	>1.1 x upper limit of normal	2
Liver histology	Compatible with autoimmune hepatitis	1
	Typical autoimmune hepatitis	2

Score >6 probable autoimmune hepatitis, >7 definite autoimmune hepatitis. Adapted from Hennes et al (2008).

> Close monitoring is required in untreated patients because of the unpredictable relapsing course of the disease.

survival increased to >90% (Lamers et al, 2010). The aim of pharmacological therapy is to achieve complete remission and prevent progression to end-stage liver failure and hepatocellular carcinoma, and to salvage cases of acute severe autoimmune hepatitis without the need for liver transplantation. Complete biochemical remission is defined as normalization of both liver function tests and IgG levels. Confirmation of complete histological remission is a stronger end-point, taking into consideration that liver biochemistry does not always correlate with histological findings, but requires a repeat liver biopsy (Al-Chalabi and Heneghan, 2007).

Pharmacological therapy is indicated in all patients diagnosed with autoimmune hepatitis, but can be potentially deferred in cases with histologically proven mild disease activity (HAI <4) in which the risks associated with immunosuppression outweigh the benefits, such as elderly patients with multiple comorbidities (European Association for the Study of the Liver, 2015). The survival rate of untreated asymptomatic non-cirrhotic patients with mild disease was similar to those treated with immunosuppression (Feld et al, 2005). Close monitoring is required in untreated patients because of the unpredictable relapsing course of the disease. Treatment may also not be indicated in cases of 'burnt-out' autoimmune hepatitis cirrhosis with low inflammatory activity (European Association for the Study of the Liver, 2015).

Induction therapy

Corticosteroids are the mainstay of induction therapy in autoimmune hepatitis. Azathioprine monotherapy was less effective in inducing remission compared to steroids (Murray-Lyon et al, 1973). A steroid+azathioprine combination had similar efficacy to steroid monotherapy, but with fewer steroid-related side effects. Azathioprine should be introduced early in the course of the disease in view of its steroid-sparing effect. Azathioprine can be commenced either simultaneously with prednisolone or after transaminase levels have normalized; however, typically this is deferred until the bilirubin level is <100 µmol/litre (European Association for the Study of the Liver, 2015). The latter strategy has been proposed in an effort to avoid diagnostic confusion with rare cases of idiosyncratic azathioprine-induced hepatotoxicity. The recommended starting dose of prednisolone is either 30 mg daily reduced to 10 mg over 4 weeks (Gleeson and Heneghan, 2011), or 60 mg daily reduced to 20 mg over 4 weeks (European Association for the Study of the Liver, 2015). Higher doses of prednisolone (1 mg/kg/day) might be required in some cases, and high-dose intravenous steroids are recommended in patients with acute severe presentation. The dose of prednisolone should be tapered to a maintenance dose of 5–10 mg daily. Azathioprine can be commenced at the dose of 1 mg/kg/day, and subsequently increased to 2 mg/kg/day in an effort to achieve complete steroid withdrawal (*Table 3*) (Stellon et al, 1988).

Thiopurine methyltransferase is an enzyme involved in azathioprine metabolism. Very low thiopurine methyltransferase activity (homozygous state) is associated with high risk of azathioprine-induced myelotoxicity and severe cytopaenias; azathioprine is not indicated in this setting. Thiopurine methyltransferase heterozygosity can be associated with lower than normal enzyme activity. Azathioprine can be commenced at a lower dose in these patients with close monitoring for toxicities. Although thiopurine methyltransferase testing is not routinely performed in all centres, it can help optimize treatment strategies in autoimmune hepatitis and avoid significant toxicities (Heneghan et al, 2006). Measurement of azathioprine metabolites, in particular 6-thianoguanine nucleotides, can be used to assess adequacy of azathioprine dosing or compliance with treatment (Heneghan et al, 2006).

Corticosteroids are associated with several side effects that limit their long-term use, such as hyperglycaemia, weight gain, osteopenia and psychosis. Budesonide exhibits high first-pass hepatic metabolism and is therefore associated with fewer systemic side effects. A randomized clinical trial demonstrated that budesonide has similar efficacy with prednisolone in inducing remission, with significantly fewer side effects (Manns et al, 2010). Budesonide+azathioprine combination achieved remission without steroid-related side effects in a higher proportion of patients as opposed to the conventional prednisolone+azathioprine combination. Budesonide is therefore an alternative to prednisolone in patients without cirrhosis who are at risk of steroid-related toxicity.

Table 3. Treatment of autoimmune hepatitis

Induction therapy	Prednisolone 30–60 mg/day. Taper to 10 mg in 6–12 weeks	Budesonide 9 mg/day (non-cirrhotic patients)	High-dose intravenous steroids in severe acute autoimmune hepatitis
	Add azathioprine 1 mg/kg/day (when bilirubin <100 µmol/litre)	Mycophenolate mofetil (low thiopurine methyltransferase or intolerance to azathioprine)	Tacrolimus (non-response to conventional therapy)
Maintenance therapy	Azathioprine 2 mg/kg/day	Azathioprine 1–2 mg/kg/day	Mycophenolate mofetil or tacrolimus
	Steroid withdrawal	Prednisolone 5–10 mg/day	

Maintenance of remission

Maintenance of remission can be ideally achieved with azathioprine monotherapy (2 mg/kg/day) or with combination of azathioprine with low-dose prednisolone (typically <10 mg daily) (*Table 3*) (Johnson et al, 1995; European Association for the Study of the Liver, 2015). Low-dose prednisolone maintenance monotherapy is an alternative option in cases where long-term exposure to azathioprine is not tolerated or not desirable (Cropley and Weltman, 2017). The role of budesonide in maintenance of remission remains unclear. Budesonide, either as monotherapy or in combination with azathioprine, maintained long-term remission in 40% of patients who could not tolerate or did not respond to prednisolone (Peiseler et al, 2018). Budesonide had a favourable safety profile in terms of bone density, but 25% of patients had to be switched to prednisolone because of insufficient response or intolerance of budesonide.

Patients in remission may have a long-term uneventful clinical course, but vigilance for autoimmune hepatitis relapses is recommended. Relapses are usually treated according to their severity either with high-dose steroids, similar to the scheme used in induction therapy, or with intensification of the baseline immunosuppression. Regression of fibrosis has been demonstrated in autoimmune hepatitis, but progression can also occur despite treatment in suboptimally controlled disease (Dufour et al, 1997).

Treatment withdrawal is feasible in a small proportion of patients in long-term remission, although up to 80% of patients will relapse requiring re-introduction of immunosuppression within 1-year of treatment withdrawal (van Gerven et al, 2013). Complete biochemical remission for at least 2 years before immunosuppression withdrawal is associated with lower risk of relapse (Hartl et al, 2015). Ongoing histological activity at the time of withdrawal is associated with an increased risk of relapse (Czaja and Carpenter, 2003). Tapered withdrawal of immunosuppression can be attempted in selected patients under close monitoring of liver biochemistry.

Suboptimal response, refractory cases and drug toxicity

Biochemical remission can be achieved in 85% of patients with conventional therapy – 10–15% of cases may exhibit only partial or no response (refractory cases). In addition, a proportion of patients may not tolerate conventional therapy as a result of drug-related toxicity. Alternative strategies should be sought in those cases including mycophenolate mofetil or calcineurin inhibitors (ciclosporin or tacrolimus) (Van Thiel et al, 1995; Fernandes et al, 1999; Richardson et al, 2000). Since mycophenolate mofetil metabolism is not thiopurine methyltransferase-dependent, it can be used in patients who are intolerant of azathioprine because they have low thiopurine methyltransferase levels. Mycophenolate mofetil is generally not effective in patients who did not respond to azathioprine (Zachou et al, 2011).

“Patients in remission may have a long-term uneventful clinical course, but vigilance for autoimmune hepatitis relapses is recommended.”

Low dose tacrolimus can be an effective rescue therapy in difficult-to-treat cases.

Liver transplantation is an effective treatment in patients presenting with acute or subacute liver failure unresponsive to steroids or those who develop complications of end-stage liver failure or hepatocellular carcinoma. Liver transplantation is associated with excellent outcomes and 75% 10-year survival (Liberal et al, 2013). Autoimmune hepatitis recurrence is not uncommon in patients who underwent liver transplantation for autoimmune hepatitis (Gautam et al, 2006). Autoimmune hepatitis can also develop in patients who underwent liver transplantation for other indications (de novo autoimmune hepatitis) (Heneghan et al, 2001b; Mieli-Vergani and Vergani, 2004). The diagnosis of autoimmune hepatitis in this setting is based on the same serological and histological criteria, and management is similar to that of the original disease.

Special populations

The principles of autoimmune hepatitis management during pregnancy are similar to those in non-pregnant patients. Autoimmune hepatitis can enter a remission period during pregnancy, and relapses are more common post-partum because of the immune reconstitution. Adverse outcomes of pregnancy are associated with suboptimally controlled active disease before conception (Westbrook et al, 2012). Current first-line immunosuppressive strategies are safe during pregnancy, with the exception of mycophenolate mofetil which is contraindicated because of potential teratogenicity (Schramm et al, 2006). In patients using mycophenolate mofetil as primary or secondary immunosuppression, it should be withdrawn or substituted 3 months before an attempt at conception. Vigilance in monitoring is required in the post-partum period for the early diagnosis of relapses (Heneghan et al, 2001a).

With regards to overlap syndromes, in case a predominant disease can be identified this should be treated as a priority, and treatment for the secondary disorder can be added in case of suboptimal response. In autoimmune hepatitis–primary biliary cholangitis variant with features of both diseases, treatment should include both immunosuppression and ursodeoxycholic acid. In patients with primary sclerosing cholangitis who develop features of autoimmune hepatitis (serological indices and interface hepatitis) immunosuppressive therapy should be introduced. Patients with variant syndromes tend to have a more aggressive disease course, more rapid fibrosis progression and worse liver-related outcomes (Heathcote, 2002).

KEY POINTS

- Autoimmune hepatitis is characterized by loss of immunological self-tolerance that can be triggered by environmental factors.
- It is diagnosed on the basis of presence of autoantibodies, elevated immunoglobulin G and interface hepatitis on liver histology.
- The clinical presentation can be variable from chronic subclinical disease to acute liver failure.
- Steroids are the mainstay of induction therapy. Maintenance therapy consists of azathioprine with or without low-dose steroids.
- Variant forms of overlap with either primary biliary cholangitis or sclerosing cholangitis are rare but are associated with worse outcomes.

Future aspects

Complete biochemical remission can be achieved in 85% of patients with conventional immunosuppressive strategies. The safety and toxicity profiles of current therapies is a limitation in terms of patient tolerability and compliance. Complete histological remission is likely more challenging to achieve. Patients with persistent necroinflammatory activity despite treatment are at risk of disease progression and adverse liver-related outcomes. Novel therapeutic targets are therefore required. Genome-wide association studies have provided insight into HLA and non-HLA genetic associations, the impact of epigenetic alterations is emerging and there is more clarity with regards to T regulatory cell dysfunction and gut dysbiosis. An increasing understanding of these pathophysiological aspects could potentially provide new therapeutic targets in the future and allow for a more personalized approach to immunotherapy in autoimmune hepatitis to improve outcomes and patient tolerability. **BJHM**

Conflict of interest: none.

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