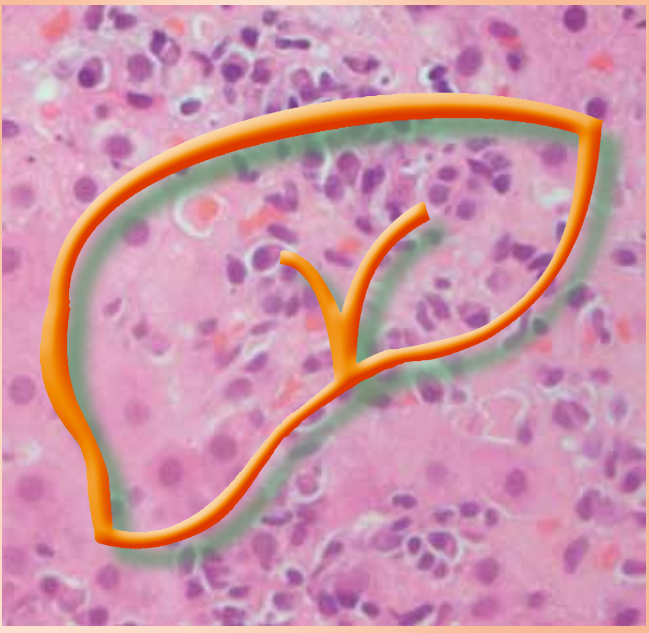
Autoimmune Hepatitis



H. Bantel
Hannover Medical School (Germany)

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H. Bantel
Hannover Medical School (Germany)

Author:

Prof. Dr. Heike Bantel
Department of Gastroenterology, Hepatology and Endocrinology
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany
E-Mail: bantel.heike@mh-hannover.de

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Introduction

Autoimmune disorders result from an exaggerated reaction of the immune system directed against the body's own tissues. In autoimmune hepatitis (AIH), the liver cells are no longer recognized as "belonging" to the organism and are therefore attacked by the immune system resulting in chronic inflammation of the liver. As a long-term consequence of chronic inflammatory liver injury the normal liver tissue is replaced by connective tissue (fibrosis), which can progress to liver cirrhosis, the final stage of fibrotic transformation.

The causes of the reaction against the body's own tissues in patients with autoimmune disorders remain largely unknown. Beside genetic factors, a number of other factors such as infections with viruses or bacteria, the dysregulation of white blood cells (lymphocytes) and certain proteins (cytokines) that affect the immune system have been suggested. It has been implicated that the development of AIH requires the interplay of many different factors.

AIH is a rare disease. In the countries of Europe, the number of new cases (incidence) ranges from 0.1 to 1.9 per 100,000 persons per year, with a disease frequency (prevalence) of 2.2 to 17 cases per 100,000 persons [1].

AIH can occur at any age. It predominantly affects women. The simultaneous occurrence of AIH with other autoimmune diseases of the liver, such as primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), in which the immune system primarily attacks bile ducts, is seen in about 6–13% of cases [2, 3].

AIH may also occur in combination with autoimmune disorders affecting organs and tissues outside of the liver. For example, AIH may occur simultaneously with autoimmune disorders of the bowel (ulcerative colitis, celiac disease), the thyroid gland (Hashimoto's thyroiditis), the pancreas (diabetes mellitus type 1) or the joints (rheumatoid arthritis) [4].

Clinical characteristics

In terms of its symptoms and clinical appearance, autoimmune hepatitis is non-specific and resembles other inflammatory liver diseases. Patients commonly report tiredness, fatigue, reduced physical performance and a feeling of pressure or pain in the right upper abdomen. In some cases, patients develop jaundice, a yellowish discoloration of the skin, mucous membranes and whites of the eyes (sclerae) due to an elevated concentration of bilirubin, a degradation product of haemoglobin, the red pigment of the blood. In some cases, the stool may be pale or clay-colored, while the urine appears very dark. The jaundice may be accompanied by generalized itching (pruritus).

If this inflammation of the liver persists, the liver tissue may enter a phase of transformation. In such cases, healthy liver tissue is gradually replaced by connective tissue in a process known as fibrosis. If AIH is diagnosed too late or inadequately treated, the process of fibrosis may, after a course of many years, result in liver cirrhosis. Liver cirrhosis is associated with a loss of liver function. For example, the coagulation of the blood is affected, resulting in prolonged bleeding or in a greater propensity for developing haematoma ("blue marks"). The liver's role in detoxification is also impacted, and patients may experience difficulties with concentration and memory, together with increasing fatigue and sleepiness.

Other signs of liver cirrhosis include reduced body hair, erythema (reddening) of the palms of the hand, yellowish discoloration of the skin and eyes, and the development of "vascular spiders", which are tiny, punctate nodules from which a network of fine vessels spreads like a spider web. A further consequence of liver cirrhosis is the accumulation of fluid in the abdomen (ascites). The abdominal membrane (peritoneum) may then become inflamed as a result of bacterial invasion (spontaneous bacterial peritonitis). Liver cirrhosis causes increasing resistance against blood flow through the liver. In an effort to find alternative routes, the blood distends other vessels, which can result in development of oesophageal varices. These varices may later become the source of life-threatening haemorrhage.

It is not uncommon for patients to be completely asymptomatic, that is, free of complaints, during the initial stages of chronic hepatitis. In this stage, AIH is often diagnosed in the course of the work-up for a coincidental finding of elevated liver enzymes during a routine check-up.

Diagnosis

Transaminases are liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) that are released from damaged liver cells into the blood as a result of inflammatory liver injury. The elevation of transaminases is not specific and does not allow to make conclusions about the cause of liver injury. If it persists, however, your physician should undertake further diagnostic testing in order to determine the type and cause of the underlying liver disorder(s).

In addition to the elevation of transaminases, increased levels of autoantibodies can be detected in the blood of AIH patients. These antibodies are directed against components of the body's own tissues, such as the antinuclear antigen (ANA), the smooth muscle antigen (SMA), the liver-kidney microsome type-1 (LKM-1), or the soluble liver antigen/liver pancreas (SLA/LP) [5-7].

Although the detection of these autoantibodies supports the diagnosis of AIH, certain autoantibodies, such as ANA or LKM-1 may be detected in other disorders, such as viral infections of the liver [7]. Moreover, the autoantibody titers do not correlate with disease activity of AIH. It is therefore not necessary to monitor autoantibody titers after the diagnosis of AIH has been established.

An increase in the activity of the immune system as it can be observed in patients with AIH is reflected in the increased concentration of immunoglobulin G (IgG) in the blood. This marker therefore not only helps to confirm the diagnosis but is, together with the transaminases, used to assess disease activity [7]. Thus, the transaminases and IgG will be monitored repeatedly during the course of the disease and are used to determine patients' response to therapy.

In addition to determining the above mentioned blood markers, a liver biopsy for histological assessment of the liver tissue is usually recommended in order to confirm the diagnosis of AIH [6, 7]. This procedure involves the sonographically-guided puncture of the liver with a hollow needle and the withdrawal of a small liver tissue specimen *(figure 1)*.

During the biopsy procedure, a fine, hollow needle is used to puncture the liver under sonographic guidance and local anesthesia. A small tissue specimen is withdrawn for microscopic analysis.

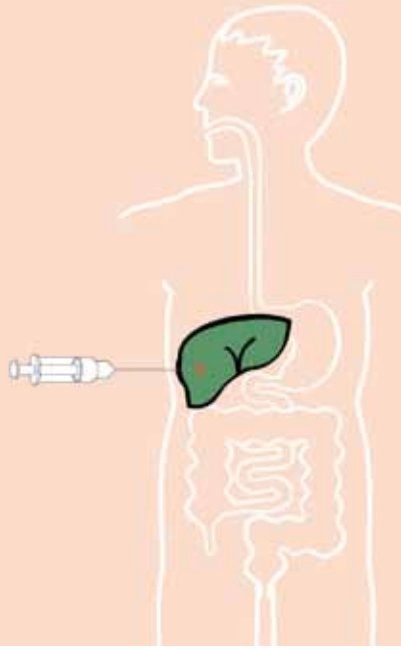

Figure 1:
Liver biopsy

The results of microscopic examination of the liver tissue do not serve only to confirm the diagnosis of autoimmune hepatitis but also help to distinguish it from other liver disorders. The histological examination of the liver tissue can also reveal other autoimmune diseases, such as primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC), which may occur simultaneously with AIH. Furthermore, the examination of the biopsy specimen provides information about the histological disease activity and the degree of liver fibrosis *(figure 2)*.

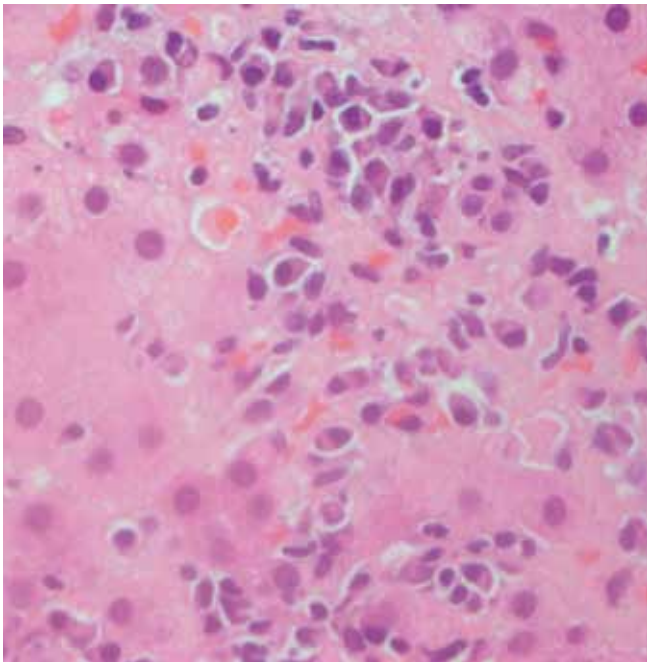

Figure 2:
Microscopic view of a specimen of liver tissue obtained from a patient with AIH (400x magnification). Note the increased number of plasma cells as a sign of inflammatory activity (provided by the Institute of Pathology, Hannover Medical School, Germany).

Confirmation of a diagnosis of AIH requires the exclusion of other causes of liver damage, especially viral hepatitis, by means of appropriate laboratory testing.

Therapy

The goal of therapy in patients with autoimmune hepatitis is to reduce liver inflammation which is reflected in a normalization of the AIH-related changes in the liver tissue and blood (elevated transaminase and IgG levels). This is achieved by means of medications that suppress the increased activity of the immune system (immunosuppressants).

Typically, therapy starts with a steroid (cortisone) preparation such as prednisone or prednisolone at a dose of 60 mg per day [7]. As an alternative, patients may receive a second immunosuppressant, azathioprine (often at a dose of 50 mg per day), which allows for a smaller steroid dose (30 mg per day) [7]. Reducing patients' exposure to steroids helps to avoid undesired side effects of cortisone therapy, such as elevations in blood sugar or blood pressure (hypertension), loss of bone mass (osteopenia or osteoporosis) or increase in intraocular pressure (glaucoma).

The cortisone dose is then reduced stepwise, week to week, with respect to the course of transaminases and IgG levels. This reduction can generally be started in the second week of therapy. A majority of patients show a significant improvement in both transaminases and IgG levels within the first two weeks. Response to cortisone therapy is considered as a further criterion confirming the diagnosis of AIH [6]. Once transaminases and IgG levels have normalized, it is usual to continue immunosuppressive maintenance therapy with azathioprine alone.

Prednisolone	**Azathioprine**
Moon face	Reduced white blood cell count (leukocytopaenia)
Obesity	Reduced haemoglobin (anaemia)
Liver steatosis	Pancreatitis
Increased blood glucose	Increased transaminases (liver toxicity)
Hypertension	Nausea, vomiting
Psychological changes	
Osteoporosis	
Increased intraocular pressure	
Cataract	

Table 1:
Potential side effects associated with standard therapy of autoimmune hepatitis

Recently, an alternative steroid – budesonide – has been approved for treatment of AIH that offers a reduced risk of cortisone-specific side effects. Unlike systemically acting steroids such as prednisone and prednisolone, more than 90% of budesonide is metabolized directly in the liver. This provides for a high local efficacy in the liver while at the same time minimizing the steroid burden on the rest of the body *(figure 3)*.

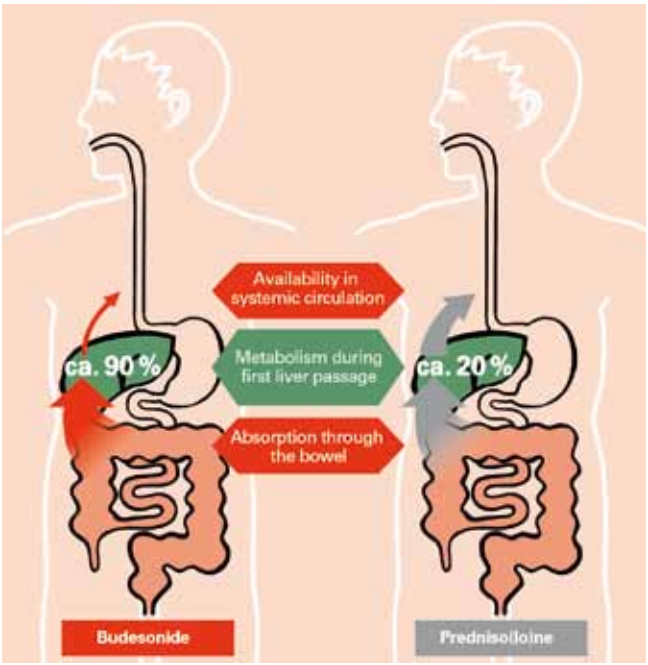

Figure 3:
Budesonide and prednisolone are absorbed through the bowel and are carried by the circulation to the liver. Unlike prednisolone, however, budesonide is mostly metabolized during its first passage through the liver ("first-pass effect"), with the result that the medication exerts its effects predominantly in the liver and to a lesser extent in other organs. Thus, compared with prednisolone, the risk of steroid-typical side effects is lower with budesonide.

As a result, budesonide causes significantly fewer side effects than do conventional cortisone preparations. This positive property has been confirmed in a Europe-wide study of over 200 patients with either newly diagnosed AIH or in an acute flare of previously confirmed AIH without liver cirrhosis [8]. Among these patients, budesonide was associated with fewer cortisone-related side effects than was prednisolone.

These findings underscore budesonide's value as a promising, locally acting alternative to conventional steroids in the treatment of acute flares of AIH in patients without cirrhosis of the liver. Budesonide is initially given three times a day in the form of a 3-mg capsule. The dose is then reduced stepwise according to patients' response to treatment as reflected in the normalization of transaminase levels.

Once transaminase levels have normalized, budesonide can be continued at a lower dose as maintenance therapy. Because the metabolism of budesonide is significantly reduced in patients with pre-existing liver cirrhosis, more of the steroid enters the systemic circulation and the risk of steroid-typical side effects increases correspondingly. Thus, administration of budesonide in patients with pre-existing cirrhosis of the liver is not recommended.

Duration of therapy

Because each patient responds differently to treatment, there is no pre-defined duration of therapy. It is recommended that, once the disease is in remission as reflected in the normalization of transaminase levels, maintenance therapy should be continued for at least two years [4, 7]. If transaminase levels repeatedly remain normal throughout this period, patients are in most cases advised to undergo liver biopsy prior to discontinuing immunosuppressive therapy in order to document the complete resolution of inflammatory activity also in the liver tissue.

If biopsy confirms the absence of inflammatory activity in the liver tissue and transaminase levels remain within normal limits, immunosuppressive therapy can be tapered followed by closely monitoring of transaminase levels. Patients with complete histological (based on biopsy findings) and biochemical (transaminase levels) remission experience a much lower relapse rate following discontinuation of immunosuppressive therapy than do patients with remaining inflammatory activity in the liver [4, 9–11].

In patients with pre-existing cirrhosis of the liver, an inflammatory flare can lead to further worsening of liver function with development of the above-described complications. The decision to discontinue immunosuppressive therapy in these patients must therefore be approached with a higher degree of caution.

Frequently asked questions

Is autoimmune hepatitis hereditary?

Are there special risks associated with pregnancy?

Are there alternatives for patients who cannot tolerate or do not respond adequately to the standard therapy?

Is autoimmune hepatitis associated with an increased risk of developing cancer?

Can diet or lifestyle affect autoimmune hepatitis?

Is autoimmune hepatitis hereditary?

Autoimmune hepatitis (AIH) is not an inherited disease in the strict sense. Nevertheless, as observed in other autoimmune disorders, there appears to be a genetic predisposition which is associated with certain genetic criteria [12]. Genetic factors also appear to affect the course of the disease.

Are there special risks associated with pregnancy?

The majority of women with AIH, including those not being treated, do not develop an acute disease flare during pregnancy. Following delivery, however, women not receiving immunosuppressive therapy have a much higher risk of an inflammatory flare, which may occur in about 50% of cases [13].

Steroid therapy (prednisolone) is considered safe during pregnancy, although it may lead to lower birth weight [14].

Azathioprine has been shown in animal experiments to be associated with an increased risk of teratogenic effects (embryo defects) [15]. This observation, however, has not been confirmed in human females treated with azathioprine during pregnancy [13, 16, 17]. A small residual risk to the unborn child cannot, however, be completely excluded when azathioprine is administered during pregnancy.

Treatment of AIH during pregnancy should take into consideration each patient's individual disease course prior to pregnancy. In every case, azathioprine and/or cortisone should be continued at the lowest dose that is effective for suppressing the inflammatory activity of AIH [18]. The rate of stillbirths and fetal abnormalities in patients with AIH does not appear to be higher than that of the general population [19].

An increased risk of complications appears to affect predominantly those women who exhibited AIH disease activity in the year prior to conception or those with pre-existing liver cirrhosis. Liver cirrhosis in expecting mothers is also associated with an increased risk to the child for complications before and after birth [20]. Pregnant women with advanced liver disease require careful monitoring in cooperation with an experienced center.

Are there alternatives for patients who cannot tolerate or do not respond adequately to the standard therapy?

If the above-described standard therapy does not, even after maximizing the dosages, result in an adequate suppression of the inflammation, patients may obtain other immunosuppressants that have not yet been approved for the treatment of AIH ("off-label use"). This affects about 5–10% of patients, while another 5% are unable to tolerate standard therapeutic agents [18, 21–23]. These patients may benefit from a number of alternative drugs, which have shown promising results in small groups of patients. These agents include mycophenolate-mofetil [24–26], cyclosporine [27–29] and tacrolimus [30, 31]. The administration of these drugs in patients with AIH should, however, be done in consultation with a Hepatology center.

Is autoimmune hepatitis associated with an increased risk of developing cancer?

Hepatocellular carcinoma (HCC, liver cancer) is one of the most feared complications of liver cirrhosis. In one study of over 240 patients with AIH, 6% developed HCC in the course of their disease. Beside a longer (at least 10 years) history of liver cirrhosis, factors that were associated with the development of HCC include male sex and lack of response to immunosuppressive therapy [32, 33]. Thus, regularly screening for HCC may be considered in patients with liver cirrhosis [18]. The risk of liver cirrhosis and, as a result, the risk of developing HCC, is further increased by the presence of other factors, such as overweight or alcohol abuse, which can aggravate the liver damage due to AIH.

Can diet or lifestyle affect autoimmune hepatitis?

A balanced diet coupled with a healthy lifestyle and regular exercise can improve general wellbeing in patients with AIH and other chronic liver diseases, and prevent nutritional deficiencies. It is crucial to reduce existing overweight and avoid underweight: A normal body-mass index (BMI) of 19 to 25 kg/m² should be the aim. The BMI is a rough guide for assessing a person's body weight in relation to his height. It is calculated by dividing the person's body weight in kilograms (kg) by the square of the height in meters (m²).

Substances, such as alcohol, that can further damage the liver should be avoided. Coffee, however, has been shown in recent studies to exert a protective effect on the liver [34, 35]. Furthermore, research findings showed that coffee can help to prevent the development of liver cancer in patients with chronic liver diseases [36].

Patients consuming a balanced diet generally do not require additional supplementation with multivitamin preparations. However, patients receiving systemic steroids such as prednisolone should supplement their diet with vitamin D and calcium in order to counteract the steroid-associated osteopenic effects.

Literature

1. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol. 1998;33(1):99–103.

2. Gheorghe L, Iacob S, Gheorghe C, Iacob R, Simionov I, Vadan R, et al. Frequency and predictive factors for overlap syndrome between autoimmune hepatitis and primary cholestatic liver disease. Eur J Gastroenterol Hepatol. 2004;16(6):585–92.

3. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology. 1998;28(2):360–5.

4. Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges. Gastroenterology. 2001;120(6):1502–17.

5. Volkmann M, Martin L, Bäurle A, Heid H, Strassburg CP, Trautwein C, et al. Soluble liver antigen: isolation of a 35-kd recombinant protein (SLA-p35) specifically recognizing sera from patients with autoimmune hepatitis. Hepatology. 2001; 33(3):591–6.

6. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol.1999;31(5):929–38.

7. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193–213.

8. Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010;139(4):1198–206.

9. Hegarty JE, Nouri Aria KT, Portmann B, Eddleston AL, Williams R. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. Hepatology. 1983;3(5):685–9.

10. Czaja AJ, Freese DK; American Association for the Study of Liver Disease. Diagnosis and treatment of autoimmune hepatitis. Hepatology. 2002;36(2):479–97.

11. Czaja AJ, Davis GL, Ludwig J, Taswell HF. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. Hepatology. 1984;4(4):622–7.

12. Donaldson PT, Doherty DG, Hayllar KM, McFarlane IG, Johnson PJ, Williams R. Susceptibility to autoimmune chronic active hepatitis: human leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. Hepatology. 1991; 13(4):701–6.

13. Schramm C, Herkel J, Beuers U, Kanzler S, Galle PR, Lohse AW. Pregnancy in autoimmune hepatitis: outcome and risk factors. Am J Gastroenterol. 2006;101(3):556–60.

14. Dotan I, Alper A, Rachmilewitz D, Israeli E, Odes S, Chermesh I, et al. Maternal inflammatory bowel disease has short and long-term effects on the health of their offspring: A multicenter study in Israel. J Crohns Colitis. 2013;7(7): 542–50.

15. Rosenkrantz JG, Githens JH, Cox SM, Kellum DL. Azathioprine (Imuran) and pregnancy. Am J Obstet Gynecol. 1967;97(3):387–94.

16. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. Gastroenterology. 2003;124(1):9–17.

17. Peyrin-Biroulet L, Oussalah A, Roblin X, Sparrow MP. The use of azathioprine in Crohn's disease during pregnancy and in the post-operative setting: a worldwide survey of experts. Aliment Pharmacol Ther. 2011;33(6):707–13.

18. Gleeson D, Heneghan MA; British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011; 60(12):1611–29.

19. Werner M, Björnsson E, Prytz H, Lindgren S, Almer S, Broomé U, et al. Autoimmune hepatitis among fertile women: strategies during pregnancy and breastfeeding? Scand J Gastroenterol. 2007;42(8):986–91.

20. Westbrook RH, Yeoman AD, Kriese S, Heneghan MA. Outcomes of pregnancy in women with autoimmune hepatitis. J Autoimmun. 2012;38(2–3):J239–44.

21. Kanzler S, Löhr H, Gerken G, Galle PR, Lohse AW. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. Z Gastroenterol. 2001;39(5): 339–41, 344–8.

22. Czaja AJ, Carpenter HA.Thiopurine methyltransferase deficiency and azathioprine intolerance in autoimmune hepatitis. Dig Dis Sci. 2006;51(5):968–75.

23. Summerskill WH, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. Gut. 1975;16(11):876–83.

24. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naïve patients. J Hepatol. 2011;55(3):636–46.

25. Aw MM, Dhawan A, Samyn M, Bargiota A, Mieli-Vergani G. Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow-up. J Hepatol. 2009;51(1):156–60.

26. Hennes EM, Oo YH, Schramm C, Denzer U, Buggisch P, Wiegard C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? Am J Gastroenterol. 2008;103(12): 3063–70.

27. Alvarez F, Ciocca M, Cañero-Velasco C, Ramonet M, de Davila MT, Cuarterolo M, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. J Hepatol. 1999;30(2):222–7.

28. Debray D, Maggiore G, Girardet JP, Mallet E, Bernard O. Efficacy of cyclosporin A in children with type 2 autoimmune hepatitis. J Pediatr. 1999;135(1):111–4.

29. Fernandes NF, Redeker AG, Vierling JM, Villamil FG, Fong TL. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. Am J Gastroenterol. 1999;94(1): 241–8.

30. Van Thiel DH, Wright H, Carroll P, Abu-Elmagd K, Rodriguez-Rilo H, McMichael J, et al. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. Am J Gastroenterol. 1995;90(5):771–6.

31. Aqel BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. J Clin Gastroenterol. 2004;38(9):805–9.

32. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. Hepatology. 2008;48(3):863–70.

33. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol. 2008;103(8):1944–51.

34. Masterton GS, Hayes PC. Coffee and the liver: a potential treatment for liver disease? Eur J Gastroenterol Hepatol. 2010; 22(11):1277–83.

35. Kalthoff S, Ehmer U, Freiberg N, Manns MP, Strassburg CP. Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach. Gastroenterology. 2010;139(5):1699–710.

36. Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. Hepatology. 2007;46(2):430–5.

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