Prediction of outcome in autoimmune hepatitis and variant syndromes

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Chapter 1

General introduction

Autoimmune hepatitis is a chronic inflammatory disease of the liver characterized by autoantibodies, raised total level of IgG and interface hepatitis. Presentation can vary from asymptomatically raised liver enzymes to jaundice and liver failure (1, 2). After randomised controlled trials beginning in the 1970s treatment of patients with AIH with corticosteroids and azathioprine became the standard. In these trials induction therapy with prednisolone decreased short-term mortality from 41-56% to 5-28% in naïve AIH patients 24-41% to 5-6% in those with a relapse of AIH, while maintenance with azathioprine enabled reduction of the dose of prednisolone to reduce side-effects (3, 4). Nowadays AIH patients without liver cirrhosis have a similar life expectancy as the general population (3). However, up to a third of patients presents with cirrhosis, not all patients reach complete remission, some patients have specials presentations like acute severe AIH or variant syndromes, and relapses can occur, all of which can have an impact on prognosis (5).

In this thesis we aimed to predict outcome of AIH using the differences in presentation - including immunological cytokines, acute severe presentation and variant syndrome - and early treatment response. Knowledge on predictors for long-term and short-term outcome can lead to further development of personalized medicine in autoimmune hepatitis. In personalized medicine immunosuppressive medication can be adjusted to individual risk factors. This adjustment may prevent undertreatment causing disease progression in some patients and overtreatment causing side-effects in other patients.

Presentation

Autoimmune hepatitis occurs more in women than in man. The disease can present at any age although there is increased incidence in the second decade and between the fourth and sixth decade (6). Presentation of autoimmune hepatitis has a wide range differing from asymptomatically raised liver enzymes to acute liver failure. Frequently reported symptoms are fatigue, arthralgia, jaundice and itching (5, 6).

At diagnosis, the aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are elevated while the cholestatic liver enzymes are normal or only slightly elevated. Total IgG level is elevated in approximately 90% of patients and is used as one of the criteria to distinguish AIH from other liver disease. A recent report showed that IgG level at diagnosis does not influence presentation or treatment response (7). Besides total IgG level, autoantibodies are another hallmark feature of AIH and these distinguish AIH type 1 from AIH type 2: AIH type 1 is the most prevalent type of AIH characterized by smooth muscle antibodies and/or antinuclear antibodies, while AIH type 2 occurs more often in children and is characterized by liver kidney microsome type 1 antibodies (LKM-1) (5).

On liver biopsy interface hepatitis is a typical histological feature. Prominent presence of plasma cells in the immune infiltrate, emperipolesis and hepatic rosetting also occur frequently (8). Bile duct injury is atypical for AIH but can be present in up to 10% of patients (8).

For the diagnosis of autoimmune hepatitis the revised or simplified criteria of the international AIH group are used (9, 10). These criteria consist of features typical of AIH including IgG level, presence of autoantibodies and histological features.

Special presentations

Presentation with acute liver failure, also called acute severe AIH (AS-AIH), is rare but poses a clinically relevant problem. AS-AIH is defined as presentation with jaundice and coagulopathy as signs of synthetic and excretory liver disfunction. Patients with AS-AIH require rapid treatment with high-dose corticosteroids to improve liver function (11). If liver function does not improve, rapid screening and listing for liver transplantation should be considered. Liver transplant free survival was between 20-90% in AS-AIH depending on the report and the used case definition (12-15).

A second rare presentation of AIH is the presence of features of both AIH and another autoimmune liver disease (primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC)) (16). This phenomenon is called AIH variant syndrome or AIH with features of PBC, PSC or vice versa. In contrast to AIH, the cholestatic diseases PBC and PSC are not treated with corticosteroids but with ursodeoxycholic acid (UDCA). Although the lack of standardized criteria makes the diagnosis of variant syndrome complicated, it is important to identify the patients who may benefit from combination therapy with UDCA and immunosuppression (16). As long-term treatment with immunosuppression has side-effects, the benefit should be balanced to the side-effects. Based on small retrospective studies, for AIH-PBC the Paris criteria were developed and guidelines advise combination therapy with UDCA and corticosteroids in patients fulfilling these criteria (5, 17). For AIH-PSC no formal criteria exist but combination therapy may also be indicated in these patients (5).

Standard treatment

Prednisolone and azathioprine have been used for treatment of autoimmune hepatitis since the 1970's and are still the backbone of current treatment (5, 18, 19). After induction treatment the dose of prednisolone can be tapered and stopped in some patients. However, in many patients long-term treatment with low-dose prednisolone is required to maintain remission. This maintenance treatment with

low-dose prednisolone can still lead to an increased risk of diabetes, cataract and bone fractures (20).

To reduce side-effects of prednisolone, treatment with budesonide can be an alternative especially in non-cirrhotic patients. Due to a large first pass effect in the liver, budesonide has less systemic side-effects than prednisolone. In a randomized controlled trial, budesonide was as effective in inducing remission with less side effects compared to prednisolone (21). Nevertheless for induction of remission most experts favor prednisolone (22).

A few weeks after start of corticosteroids azathioprine is added as maintenance treatment. Addition of azathioprine allows to reduce the dose of corticosteroids and the associated side-effects. Azathioprine can cause gastrointestinal side-effects and cytopenia as side-effects. In case these side-effects occur, 6-thioguanine and mycophenolate mofetil are possible alternatives (23, 24).

Treatment response and long-term outcome

The aim of treatment is to reach complete biochemical remission, defined as ALT, AST and IgG within the reference ranges which probably prevents progression of disease to liver cirrhosis, liver transplantation and mortality (5). Partial response or partial remission is defined as improvement of aminotransferases without normalization, while treatment failure or non-response is defined as no or minimal improvement of aminotransferases (5). As discontinuation of treatment leads to relapse in more than 90% of patients, life-long maintenance treatment is needed in the vast majority of patients (25).

With treatment autoimmune hepatitis patients in general have a good long-term survival with a 10-year survival of approximately 90%. Life expectancy of non-cirrhotic AIH patients is comparable to the general population in the Netherlands (3). Factors that have been associated with long-term outcome in univariate analysis are age at diagnosis, presence of liver cirrhosis at diagnosis, ethnicity and treatment response. Older age was found to be not only a risk factor for overall mortality but also for liver related mortality and liver transplantation (2, 26-29). Comorbidity and frailty are more often present in elderly patients. These can be independent risk factors but might also result in a more cautious treatment of elderly patients. Liver cirrhosis was present at diagnosis in 20-30% of the patients (27, 30) and has been associated with worse survival (2, 26, 29-33). Different ethnic populations appear to have different outcomes, as decreased survival has been reported in patients with Asian, African or Caribbean descent as compared to Caucasian patients (30, 34, 35).

The reason for this difference is not entirely clear. It could relate to genetic factors influencing severity of AIH or response to treatment, but could also relate to socio-economic, environmental or cultural factors, for instance influencing access or adherence to treatment.

Besides baseline variables, treatment response appears very important for long-term outcomes. Complete biochemical remission has been associated with a better long-term survival and less development of cirrhosis, while partial response and recurrent relapses were associated with the opposite (36). However the influence of mildly elevated aminotransferases or isolated elevated IgG during treatment on long-term outcome is still unknown. No multivariable analysis of all these risk factors have been performed. In addition, treatment response was studied as a baseline variable, while it occurs during follow-up leading to bias.

If the hypothesis that treatment response is an independent prognostic risk factor is true, new treatment options are needed for patients with partial response. Currently no registered second-line treatment alternatives are available for these patients. A retrospective study showed that mycophenolate mofetil led to response in 92% of patients with intolerance to azathioprine but only 34% of patients with an incomplete response. Tacrolimus was effective in 57% of patients but no prospective trials have been performed (37). For these difficult-to-treat patients new treatment options are urgently needed, with currently available drugs or new options with biologicals.

Complement and B-cell immunity

In order to develop new targeted treatment options, a better understanding of the pathophysiology of autoimmune hepatitis is necessary. The presence of autoantibodies and raised total IgG in blood and plasma cells suggests involvement of B-cell immunity and complement. It is therefore a logical first step to have a closer look at complement and B-cell immunity in AIH.

The complement system is an important part of the innate immune system providing protection against infections. The complement system can be activated via three different pathways: the classical pathway, the lectin pathway and the alternative pathway. The classical pathway of complement is activated by several ligands predominantly target bound antibodies (38). Activation of the complement system can result in formation of several inflammatory mediators such as C3b, C3a and C5a as well as the membrane attack complex. Activation of complement is beneficial in fighting infections, but it can contribute to tissue damage if activated by target bound autoantibodies in the context of autoimmune disease. The successful introduction of

C5 inhibitor eculizumab for atypical haemolytic uremic syndrome and paroxysmal nocturnal haemoglobinuria proved that the complement system can be targeted in vivo (39, 40). It is important to elucidate the role complement has in autoimmune hepatitis, to see if complement inhibitors like eculizumab could be promising new treatment options.

Besides complement, cytokines and their receptors involved in B-cell immunity could also be interesting targets for new treatment options as elevated IgG and autoantibodies are hallmarks of AIH. B-cells are the cornerstone of humoral immunity and essential for production of antibodies. B-cells develop from immature B-cells in the bone marrow to transitional cells to naïve B-cells. After activation, naïve B-cells will differentiate to (non) class switched memory B-cells or plasma cells B-cell activating factor of the tumour necrosis family (BAFF) is a cytokine necessary for survival of transitional and naïve B-cells. Overproduction of BAFF can result in survival of autoreactive B-cells (41). Interleukin 21 (IL-21), a second B-cell cytokine, stimulates differentiation of B-cells towards plasma cells and inhibits regulatory T-cells (42, 43). Interleukin 2 is a natural antagonist of IL-21. The exact role of different B-cell populations, BAFF and IL-21 in autoimmune hepatitis is still unclear. However, recent case reports described BAFF inhibition and low-dose IL-2 treatment in difficult to treat autoimmune hepatitis patients, showing that factors related to B-cell immunity may provide new treatment targets for the future (44, 45).

Using the differences in presentation, immunological markers and early treatment response we aimed in this thesis to predict long-term outcome of AIH. The results can hopefully be used to further develop personalized medicine for AIH.

Aims and outline of this thesis

Although the long-term survival of AIH patients in general is good, there is limited knowledge on factors predicting a poor outcome. Predicting outcome could lead to treatment differentiation and personalized medicine for AIH patients in the future. In some patients this could prevent undertreatment with risk of disease progression and overtreatment with risk of side-effects in other patients.

In the existing literature most risk factors were identified univariately and suboptimal methods were used for studying treatment response as a prognostic variable. Therefore the first aim of this thesis was to predict outcome of autoimmune hepatitis patients using multivariable analysis of differences in presentation and early treatment response.

It was anticipated that these studies would confirm that incomplete remission of AIH is indeed related to a worse prognosis. This emphasizes the need for new treatment options, in turn requiring better insights into pathophysiology. Therefore the second aim was to better understand the pathophysiology of AIH, as this could result in new therapeutic options for patients with a high risk of disease progression.

First we focused on the general AIH population as we developed and validated a multivariate model capable of predicting long-term survival at diagnosis, described in chapter 2 *'Development and validation of a prognostic score for long-term transplant-free survival in autoimmune hepatitis type 1'*, and the relation of age on presentation and long-term outcome was studied in chapter 3 *'Role of age in presentation, response to therapy and outcome of autoimmune hepatitis'*.

Then, in chapter 4 and 5, we focused on special presentations of autoimmune hepatitis. If patients with acute severe autoimmune hepatitis do not respond to treatment with high dose corticosteroids, liver transplantation is often necessary. We hypothesized that improvement of liver function in the first 2 weeks could predict need for liver transplantation in the first year of treatment. This was investigated in chapter 4 *'Early predictors of short-term prognosis in acute and acute severe autoimmune hepatitis'*. Presentation of AIH with features of primary biliary cholangitis can lead to difficulties in diagnosis. In chapter 5 *'Autoimmune hepatitis – primary biliary cholangitis variants are often treated outside Paris criteria with similar results'* the use of clinical criteria for the diagnosis of AIH-PBC variant syndrome in 'real-world' clinical practice was analysed. Secondary aim of this study was to compare

outcome of patients treated within and outside the clinical criteria and to compare these to the outcome of AIH and PBC patients.

Besides baseline characteristics, treatment response is an important factor determining outcome in AIH. However in previous studies, treatment response was used as a baseline variable although it occurs during follow-up. The aim of chapter 6 *'Aminotransferases during treatment predict long-term survival in patients with autoimmune hepatitis type 1: a landmark analysis'* was to analyse treatment response using landmark analysis. Secondary, the aminotransferase and IgG were studied longitudinally as continuous variables in relation to long-term outcome.

In the second part of this thesis, we focused on the pathophysiology of AIH to find new treatment options for difficult to treat patients. Due to involvement of B-cell immunity in AIH we hypothesized that complement would be an important factor in the pathophysiology of AIH and other autoimmune liver diseases. This was studied in chapter 7 *'The role of complement activation in autoimmune liver disease'*.

The presence of autoantibodies and plasma cells points to an important role for B-cells and B-cell related cytokines in the pathophysiology of AIH. Inhibition of B-cell cytokines, including BAFF and IL-21 might provide new therapeutic options for the future. BAFF and IL-21 levels may help to identify patients with the most benefit of these treatments. In chapter 8 *'B-cell marker based immunological phenotype predicts treatment response in patients with autoimmune hepatitis'* we therefore studied BAFF and IL-21 levels in AIH and their relation to presentation and treatment response.

In chapter 9 the main results of this thesis were summarized and discussed, including future perspectives.

References

1. van Gerven NM, de Boer YS, Mulder CJ, et al. Auto immune hepatitis. World J Gastroenterol 2016;22:4651-4661.
2. Feld JJ, Dinh H, Arenovich T, et al. Autoimmune hepatitis: Effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005;42:53-62.
3. van den Brand FF, van der Veen KS, de Boer YS, et al. Increased Mortality Among Patients With vs Without Cirrhosis and Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2019;17:940-947 e942.
4. Lamers MM, van Oijen MG, Pronk M, et al. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. J Hepatol 2010;53:191-198.
5. European Association for the Study of the L. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63:971-1004.
6. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. Aliment Pharmacol Ther 2014;39:117-124.
7. Hartl J, Miquel R, Zachou K, et al. Features and outcome of AIH patients without elevation of IgG. JHEP Rep 2020;2:100094.
8. Tiniakos DG, Brain JG, Bury YA. Role of Histopathology in Autoimmune Hepatitis. Dig Dis 2015;33 Suppl 2:53-64.
9. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999;31:929-938.
10. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48:169-176.
11. Rahim MN, Liberal R, Miquel R, et al. Acute Severe Autoimmune Hepatitis: Corticosteroids or Liver Transplantation? Liver Transpl 2019;25:946-959.
12. Yeoman AD, Westbrook RH, Zen Y, et al. Prognosis of acute severe autoimmune hepatitis (AS-AIH): the role of corticosteroids in modifying outcome. J Hepatol 2014;61:876-882.
13. Anand L, Choudhury A, Bihari C, et al. Flare of Autoimmune Hepatitis Causing Acute on Chronic Liver Failure: Diagnosis and Response to Corticosteroid Therapy. Hepatology 2019;70:587-596.
14. Anastasiou OE, Dogan-Cavus B, Kucukoglu O, et al. Corticosteroid Therapy Improves the Outcome of Autoimmune Hepatitis-Induced Acute Liver Failure. Digestion 2018;98:104-111.
15. Zachou K, Arvaniti P, Azariadis K, et al. Prompt initiation of high-dose i.v. corticosteroids seems to prevent progression to liver failure in patients with original acute severe autoimmune hepatitis. Hepatol Res 2019;49:96-104.
16. To U, Silveira M. Overlap Syndrome of Autoimmune Hepatitis and Primary Biliary Cholangitis. Clin Liver Dis 2018;22:603-611.
17. Chazouilleres O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998;28:296-301.
18. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 1971;40:159-185.
19. Murray-Lyon IM, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. Lancet 1973;1:735-737.

20. van den Brand FF, van der Veen KS, Lissenberg-Witte BI, et al. Adverse events related to low dose corticosteroids in autoimmune hepatitis. Aliment Pharmacol Ther 2019;50:1120-1126.
21. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139:1198-1206.
22. Liberal R, de Boer YS, Andrade RJ, et al. Expert clinical management of autoimmune hepatitis in the real world. Aliment Pharmacol Ther 2017;45:723-732.
23. van den Brand FF, van Nieuwkerk CMJ, Verwer BJ, et al. Biochemical efficacy of tioguanine in autoimmune hepatitis: a retrospective review of practice in the Netherlands. Aliment Pharmacol Ther 2018;48:761-767.
24. Baven-Pronk AMC, Coenraad MJ, van Buuren HR, et al. The role of mycophenolate mofetil in the management of autoimmune hepatitis and overlap syndromes. Alimentary Pharmacology & Therapeutics 2011;34:335-343.
25. van Gerven NM, Verwer BJ, Witte BI, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol 2013;58:141-147.
26. Werner M, Wallerstedt S, Lindgren S, et al. Characteristics and long-term outcome of patients with autoimmune hepatitis related to the initial treatment response. Scand J Gastroenterol 2010;45:457-467.
27. Baven-Pronk M, Biewenga M, van Silfhout JJ, et al. Role of age in presentation, response to therapy and outcome of autoimmune hepatitis. Clin Transl Gastroenterol 2018;9:165.
28. Ngu JH, Gearry RB, Frampton CM, et al. Predictors of poor outcome in patients w ith autoimmune hepatitis: a population-based study. Hepatology 2013;57:2399-2406.
29. Choi J, Choi GH, Lee D, et al. Long-term clinical outcomes in patients with autoimmune hepatitis according to treatment response in Asian country. Liver Int 2019;39:985-994.
30. de Boer YS, Gerussi A, van den Brand FF, et al. Association Between Black Race and Presentation and Liver-related Outcomes of Patients With Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2018.
31. Migita K, Watanabe Y, Jiuchi Y, et al. Hepatocellular carcinoma and survival in patients with autoimmune hepatitis (Japanese National Hospital Organization-autoimmune hepatitis prospective study). Liver Int 2012;32:837-844.
32. Landeira G, Morise S, Fassio E, et al. Effect of cirrhosis at baseline on the outcome of type 1 autoimmune hepatitis. Ann Hepatol 2012;11:100-106.
33. Hoeroldt B, McFarlane E, Dube A, et al. Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology 2011;140:1980-1989.
34. Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. Hepatology 2007;46:1828-1835.
35. Wong RJ, Gish R, Frederick T, et al. The impact of race/ethnicity on the clinical epidemiology of autoimmune hepatitis. J Clin Gastroenterol 2012;46:155-161.
36. Hartl J, Ehlken H, Sebode M, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2018;68:754-763.
37. Efe C, Hagstrom H, Ytting H, et al. Efficacy and Safety of Mycophenolate Mofetil and Tacrolimus as Second-line Therapy for Patients With Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2017;15:1950-1956 e1951.

38. Trouw LA, Daha MR. Role of complement in innate immunity and host defense. Immunol Lett 2011;138:35-37.
39. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 2006;355:1233-1243.
40. Legendre CM, Licht C, Loirat C. Eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med 2013;369:1379-1380.
41. Mackay F, Browning JL. BAFF: a fundamental survival factor for B cells. Nat Rev Immunol 2002;2:465-475.
42. Gensous N, Charrier M, Duluc D, et al. T Follicular Helper Cells in Autoimmune Disorders. Front Immunol 2018;9:1637.
43. Long D, Chen Y, Wu H, et al. Clinical significance and immunobiology of IL-21 in autoimmunity. J Autoimmun 2019;99:1-14.
44. Arvaniti P, Giannoulis G, Gabeta S, et al. Belimumab is a promising third-line treatment option for refractory autoimmune hepatitis. JHEP Rep 2020;2:100123.
45. Lim TY, Martinez-Llordella M, Kodela E, et al. Low-Dose Interleukin-2 for Refractory Autoimmune Hepatitis. Hepatology 2018;68:1649-1652.