Chapter 8

General discussion and future prospects
Since its first description in the 1950’s Autoimmune hepatitis has been a disorder known by variety of terms. Major advances were made in its management based on controlled trials performed in England and the USA in the 1970s and 1980s¹. Unfortunately, in recent decades there has been a dearth of controlled clinical trials and, thus, many questions remain unanswered regarding the optimal management of this disease. To this, more knowledge on the pathophysiology of AIH and translating this knowledge into new treatment options that will change clinical practice, are important steps to be taken towards reaching this ultimate goal. This thesis therefore, aimed to gain insight in some aspects of epidemiology, etiology, clinical course and treatment of AIH.

AIH is a relatively uncommon disease and only few studies have explored the prevalence of AIH. Moreover the incidence and prevalence vary quite widely between studies of specific populations. The incidence of AIH reported from different parts of the world range from 0.52 to 1.9 per 100,000 population per year, and prevalence estimates range from 4 to 42.9 per 100,000²-⁷. The wide variation may reflect differences in environmental and genetic factors, although differences in methodology have undoubtedly contributed. Since no data existed on the epidemiology of AIH in the Netherlands, we have conducted an epidemiology study in the Netherlands and found a mean annual incidence of 1.1 per 100,000 per year and a point prevalence of 18.3 per 100,000 for the Dutch population (chapter 2). These findings are comparable to studies from other European countries, including Denmark, Norway, Sweden, the United Kingdom and Spain²,⁶-⁸.

Interestingly, a significant rise in incidence was seen in our cohort during the last decade and this may indicate a true rise in incidence or, alternatively, increased awareness and diagnostic accuracy. These findings are in line with a recent observation from a single centre study in Denmark⁸. It is obvious that the reliability of epidemiological investigations depends on the correct diagnosis of the disease. No clear pathognomonic features exist for AIH and therefore the diagnosis relies on a combination of compatible biochemical, immunological and histological features together with exclusion of other liver diseases⁹. Nevertheless, the diagnosis is sometimes not straightforward and requires considerable expertise. To facilitate an uniform diagnosis, criteria for the diagnosis of AIH were defined by the international autoimmune hepatitis group (IAIHG) in 1992¹⁰, revised in 1999¹¹ and more recently simplified criteria¹² were proposed. So far no prospective studies have been conducted to validate the different diagnostic scoring systems. In our study population, 97% of patients satisfied the criteria for probable or definite AIH using the revised original criteria. The small group of patients who did not meet the criteria included a high number of PBS overlap patients. Only 75% of patients with the clinical diagnosis AIH met the criteria for probable or definite AIH using the simplified scoring system. In addition almost one-fifth of patients who could be classified as definite AIH according to the revised original criteria did not fulfill the diagnosis
according to the simplified criteria. These findings indicate that at least in this large cohort the original revised criteria appear to be superior to the simplified criteria. Prospective studies are needed to define the validity of the different scoring systems.

In all but its mildest form fibrosis is often present at diagnosis and with advanced disease bridging fibrosis and cirrhosis are often seen in AIH. A Complication common to cirrhosis is advanced stage liver disease, including hepatocellular carcinoma (HCC). The retrospective study presented in this thesis showed that more than half of the patients had fibrosis at diagnosis and in addition already 12% had cirrhosis (chapter 2). Similar or even higher cirrhosis rates have been observed in other studies, which indicates that disease has remained unrecognized for a significant period of time prior to diagnosis. HCC developed in 1% of patients after a median of 6 years following diagnosis and 3% of patients underwent liver transplantation after a median of 5 years following diagnosis. Apart from these serious complications, AIH poses a serious disease burden on patients. In our cohort as much as 47% reported persistent AIH-related symptoms including fatigue, joint pain and abdominal pain despite the instituted immunosuppressive treatment.

Associated concomitant autoimmune diseases in AIH are common in up to 40% of patients. Primary biliary cirrhosis (PBC) and Primaire Sclerosende Cholangitis (PSC) can have clinical, laboratory, histological and genetic findings that resemble those of AIH and AIH can have features that resemble each of these cholestatic syndromes. The diagnosis of AIH in the setting of PBC and PSC can be challenging and should be considered in the differential when a patient deviates from the normal clinical course and expected response to therapy. In addition to these well known associated autoimmune disorders there is evidence for the association with other (organ-specific) autoimmune diseases as well. Data from small sample sets including a maximum of 157 patients indicated that AIH patients may be at increased risk for celiac disease (CD). In these studies the prevalence varies widely, from 1.1 % to 11.5 %. In chapter 3 we have evaluated the seroprevalence of celiac disease in a large cohort of AIH patients and demonstrate that the presence of CD in AIH patients (3.5%) is more common compared to the general population (0.35%) yet not as high as reported in some of the previous studies. The occasional co-occurrence with CD is important to recognize because, as has been suggested, malabsorption of immunosuppressive medication may delay effective treatment.

Interestingly a gluten-free diet has had a beneficial effect on the outcome of the liver disease in some patients with severe liver disease of unknown cause, and these observations warrant further investigation. Whether or not the slight increase in seroprevalence of CD in AIH patients warrants mass screening in these patients is a matter of debate.
More than 20 years ago an association between certain viral infections including herpes simplex virus 1 (HSV 1) infection and autoimmune hepatitis has been described\textsuperscript{24, 25}. Other infectious agents including hepatitis C virus (HCV), cytomegalovirus, human T lymphotropic viruses 1 and 2 or salmonella typhimurum have been suggested to be capable to induce autoimmune liver disease\textsuperscript{26}.

Chronic infection with hepatitis E virus (HEV) has been described in liver and kidney transplant recipients and persistent HEV infections have been described in organ transplant recipients receiving higher doses of immunosuppressive treatment\textsuperscript{27}. HEV may present itself with histological and biochemical features of AIH and thus acute disease may be misclassified as de novo onset of AIH if HEV infection has not been excluded. To what extent Hepatitis E virus (HEV) infections may lead to chronic hepatitis in patient groups receiving immunosuppressive medication including AIH is currently unknown. To explore this question we have, in chapter 4, investigated the prevalence of HEV in AIH patients. We show that screening of AIH patients for the presence of HEV antibodies, suggesting past exposure, revealed a seroprevalence of 29.9%. This is slightly higher when compared to the prevalence of 26.7% in the Dutch population\textsuperscript{28}.

In the study presented in this thesis we have not identified chronically HEV-infected patients that were erroneously classified as AIH (chapter 4). This clinical information suggests that the risk to develop chronic hepatitis E should not be overestimated in patients with lower levels of immunosuppressive medication. However, HEV can occur and awareness of the possibility of HEV infection in AIH diagnosis and treatment should be entertained.

AIH is believed to result from a combination of genetic and environmental factors, yet the exact aetiology remains unidentified. Identifying cause and trigger of the inflammatory process would not only greatly advance our understanding, but help in the design of more specific and more effective immune interventions. Genetic factors have been shown to play an important role in many aspects of a variety of autoimmune diseases. This has let to the examination of the genetic predisposition in AIH by looking both at family disease and specific genetic markers. As noticed in this thesis (chapter 2) as well as in other studies, familial occurrence of AIH is extremely rare, however the high frequency of other autoimmune diseases, both within patients as well as in relatives of patients, strongly suggest a genetic predisposition\textsuperscript{29}.

These observations are in line with the human leukocyte antigen (HLA) class-II genotypes that were described already in the nineties in small datasets from different populations\textsuperscript{30-34}. In Caucasian populations, the $\text{HLA DRB1}^*$0301 and $\text{DRB1}^*$0401 alleles have been identified as independent determinants of susceptibility to AIH\textsuperscript{35}. However HLA alone does not explain the whole genetic predisposition to AIH and genes outside the major histocompatibility complex region were suspected to play a role in AIH susceptibility. Such genetic risk factors, usually with a limited individual relative risk, can nowadays be identified by screening large groups of
patients using genome-wide association studies. A major effort of this thesis was to pave the way for such genetic studies by identifying sufficient numbers of patients.

As a preclude for such a hypothesis-free analysis we started with a different approach by studying an association with the cytotoxic T lymphocyte antigen-4 (CTLA-4) gene, which has previously been associated with a number of autoimmune diseases, including diabetes and multiple sclerosis\textsuperscript{36, 37}.

Similarly, associations with this gene were observed in a very small population of Caucasian AIH patients\textsuperscript{38}. The study presented in this thesis did not find any significant association between the CTLA-4 gene and AIH in a large cohort of patients (chapter 6). The association between CTLA-4 and AIH was also not confirmed in subsequent Japanese, Brazilian and German study populations, suggesting a varying risk among different ethnic populations, or, more likely, a type I error\textsuperscript{39-41}.

Genome-wide association studies (GWASs) have shown to be a powerful, hypothesis-free tool for investigating the genetic architecture of complex diseases\textsuperscript{42}. Over the last decade, several GWASs in PSC and PBC have successfully identified genetic susceptibility loci in these autoimmune liver diseases\textsuperscript{43}. The work presented in this thesis paved the way for this first GWAS in AIH and this study has meanwhile been completed (addendum). This study unequivocally established AIH as a complex genetic disorder with strong involvement of the MHC region. A prominent association was found with the HLA-DRB1\textsuperscript{*0301} and HLA-DRB1\textsuperscript{*0401} genotypes in type 1 AIH patients (chapter 5). It is of interest to note that susceptibility to AIH relates to different HLA genes in different geographical regions\textsuperscript{44}. These geographical and ethnic distinctions in the genetic predisposition for the same disease may point towards region-specific etiological agents that trigger the onset of AIH. Most studies including the studies presented in this thesis have primarily included Caucasian patients. Future studies should focus on disease course and outcome in different ethnic populations in relation to differences in genetic susceptibility.

Previous studies have shown contrasting associations with disease severity and outcome in relation to the HLA-DRB1\textsuperscript{*0301} and HLA-DRB1\textsuperscript{*0401} genotype\textsuperscript{45-47}. We were able to confirm this association in our large cohort of patients (chapter 5). Our observations reaffirm the possibility that disease severity in type 1 AIH has a genetic basis and that it may be possible to define genetic indices of prognosis. In general, the success rate of translation of genome based technologies to commercially feasible products is low. Despite the ongoing progress in genetic association studies in complex diseases, there are many barriers to cross before genetic factors will be used in clinical practice. Additional studies are needed to identify those patients at greatest risk of disease progression and identify the most affective treatment regimens to achieve maintain remission.
AIH was the first chronic liver disease in which medical treatment was clearly shown to be effective, based on controlled trials. However, treatment remains largely based on these studies, which were performed several decades ago, and is, in many respects, suboptimal. So far, limited studies have determined the long-term outcome effects of these treatment regimes and there is therefore pressing need for further clinical trials in AIH.

One major unresolved dilemma in AIH treatment relates to the question whether treatment can be discontinued in patients who are in longstanding remission. Whereas former literature from the 1970s indicated a high risk of relapse after drug withdrawal, a more recent retrospective analysis from 2002 observed that long term remission after drug withdrawal occurred in 47% of patients and this study concluded that all patients should be considered as candidates for drug withdrawal. Indeed, AASLD guidelines (2010) now recommend drug withdrawal after at least 2-year treatment, when serum liver and immunoglobulin levels have been repeatedly normal. Given the controversy in the literature, we studied in our series of patients the frequency of relapse after drug withdrawal in AIH patients while being in remission for at least two years. We demonstrate that virtually all patients will eventually require retreatment after discontinuation of therapy and that this generally occurs within the first two years after drug withdrawal. Subsequent attempts to discontinue therapy were invariably associated with the re-occurrence of a relapse which led us to suggest a more reluctant attitude towards discontinuation of immunosuppressive treatment in AIH patients. In fact, the British Society of Gastroenterology have adapted our study in their guidelines (2013) leading to the recommendation of a reluctant attitude towards tapering or discontinuing of therapy. Prospective studies are warranted to substantiate these observations and it would be of interest to identify clinical and laboratory indices to predict the risk of early relapse after drug withdrawal.

This thesis has aimed to provide new insights in the field of Autoimmune hepatitis and there has been progress in understanding AIH. Important advances have been made in the epidemiology, etiology, clinical course and treatment of AIH. Future research will hopefully continue to provide new insights that will further reduce morbidity and be enable to substantiate the value of laboratory features, liver biopsy, to optimize the diagnostic criteria at diagnosis, genetics and treatment strategies.
Reference List


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