CHAPTER 1

General introduction

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INTRODUCTION

Autoimmune hepatitis (AIH) was first described by Jan Gösta Waldenström, who described a severe liver condition that mostly affected women and was characterized by an elevation in serum gammaglobulins. It is an uncommon autoimmune liver disease of unknown aetiology, with a prevalence of approximately 17 per 100,000. The term autoimmune hepatitis was first used by Mackay et al. in 1965, but before its formal acceptance of this name by an expert panel in 1993, the disease has also been described in different terms, including chronic active hepatitis. Two types of AIH are recognized, based on the presence of auto-antibodies. AIH type-1 is characterised by antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and soluble liver antigen/liver pancreas antibodies (SLA/LP) and occurs predominantly in adult women. The rarer AIH type-2 occurs predominantly in children and is characterised by the presence of liver kidney microsomal-1 antibodies (LKM-1) anti-liver cytosol type 1 antibody (anti-LC-1). AIH is a heterogeneous disease both in presentation and outcome, of which many aspects remain to be elucidated.

AETIOLOGY

The aetiology of AIH is unknown, but the inflammation in the liver parenchyma and portal areas is characterised by a mixed T-cell and B-cell response. Molecular mimicry, in which exogenous antigens trigger an immune response which is also directed at similar but endogenous antigens, has been proposed as a potential pathological mechanism in autoimmune disease development. In addition, loss of immune tolerance due to impaired function and number of regulatory T cells as well as impaired function of Th-17 cells has also been implicated in AIH. Early studies in the nineteen-nineties in small populations of AIH patients have shown that certain human leukocyte antigen (HLA) genotypes confer an increased susceptibility to AIH, suggesting that part of the disease susceptibility is genetically determined. In addition, up to 10-15% of AIH patients have a clinical overlap with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). The manifestations of these respective traits in a subgroup of AIH patients may be indicative that AIH is part of a spectrum of autoimmune liver diseases with a shared genetic risk. In the last decade, genome-wide association studies (GWAS) have emerged as a powerful and unbiased approach for the identification of new genetic susceptibility loci in autoimmune diseases. In this type of study, patients and population controls are screened for differences in a large number (100,000-1,000,000) of single nucleotide polymorphisms (SNPs).
These SNPs are common genetic variations, which are present in 1-50% of the general population and in themselves do not necessarily confer risk for disease development, but may ‘tag’ a genetic region or coding gene that is involved in disease crucial biological pathways or disease development. During this GWAS ‘era’, over 15,000 SNPs have been associated with over 1000 traits in more than 2000 studies (http://www.ebi.ac.uk/gwas/). These associated loci generally confer only a small increase in the risk to develop a condition or trait (typically with odds ratios between 1.2-1.6) and require large numbers, often several thousands, of patients and population controls to be detected. The identification of genetic susceptibility loci can help to improve the understanding of disease pathogenesis. Recent GWAS in the clinically overlapping conditions of PBC and PSC have identified several genetic risk factors underlying these traits. This technique hence is a promising tool to identify new genetic risk factors in AIH.

DIAGNOSIS

The diagnosis of AIH is hampered by the lack of a single test and is made on a combination of the above mentioned clinical characteristics and the exclusion of other liver conditions. In order to standardize the diagnostic work-up of AIH, the International Autoimmune Hepatitis Group (IAIHG) devised a diagnostic scoring system, which was revised in 1999. In 2008 the same expert group published a more comprehensive set of diagnostic criteria to aid diagnosing AIH in daily practice at the patient bedside. In both sets of diagnostic criteria histological proof of (interface) hepatitis is considered a diagnostic hallmark of AIH and therefore mandatory to make a definite diagnosis of AIH. However, there are differences between the two scoring systems with respect to other histological features, underlining the uncertainty regarding key-features that are pathognomonic. The dissimilarities between the scoring systems, as well as the lack of clear-cut definitions of the typical AIH features, may impair the adequate and timely recognition and the treatment of AIH.

DRUG-INDUCED LIVER INJURY

Drug-induced liver injury (DILI) has features similar to those of other liver diseases, including autoimmune hepatitis (AIH). Drug-induced liver injury (DILI) occurs in approximately 19 per 100,000 persons per year. Liver injury may occur due to direct toxicity but is more often idiosyncratic, due either to metabolic or immunologic factors. It is hypothesized that liver cell damage can trigger a sensitization response to nuclear and actin auto-antigens, resulting in B-cell mediated auto-antibody production and cytotoxic T-cell responses which resembles autoimmune hepatitis (AIH). The presence
of autoimmune features such as anti-nuclear antibodies (ANA), smooth muscle antibodies (SMA), elevated immunoglobulin G (IgG) levels and liver histological features of AIH are not uncommon in DILI.\textsuperscript{16, 17, 20, 21} It has been suggested that DILI can induce or unmask chronic AIH, which may be a distinct phenotype from immune mediated DILI, which resolves after cessation of the culprit drug or agent.\textsuperscript{22, 23} Nitrofurantoin, minocycline, hydralazine and methyldopa are best known to cause DILI with an autoimmune phenotype which in most cases resolves after cessation of the drug, but evidence has so far been anecdotal.\textsuperscript{20} The last decades have seen an increase in the use of herbal and dietary supplements (HDSs).\textsuperscript{24} This development has led to increase in the reports of HDS-associated liver injury, which may present with autoimmune features.\textsuperscript{25, 26} The presentation of the injury is diverse and the outcome varies from transient liver test increases to fulminant hepatic failure resulting in death or requiring liver transplant.\textsuperscript{24}

\section*{MANAGEMENT}

If AIH is left untreated, mortality is as high as 50\% at 6 months after diagnosis. Early trials in the seventies showed a clear survival benefit of steroids with and without the use of maintenance therapy with azathioprine.\textsuperscript{27-29} It appears that AIH requires life-long immunosuppressive therapy, up to 90\% of patients in remission relapse after treatment withdrawal.\textsuperscript{30} Up to 10\% of AIH patients may require liver transplantation due acute liver failure at presentation or the inability to achieve stable remission over a prolonged time.\textsuperscript{31} In part due to the low prevalence of the disease, which has hampered the design and development of new clinical trials, high quality data on therapeutic management of AIH are scarce. Hence there is no evidence for the best steroid induction dose, tapering schemes and maintenance dose of azathioprine. Similarly, second-line therapies for those 10-20\% of patients that fail to achieve remission due to non-response or side effects, remain experimental due to the lack of comparative trials.\textsuperscript{2, 32} One of the potential strategies to improve therapy outcome is thiopurine dose optimisation, but this strategy is often limited due to dose limiting side-effects.\textsuperscript{33} The recently published guidelines on the management of AIH by the AASLD, BSG and EASL are thus still expert rather than evidence-based.\textsuperscript{32} Hence there is a need for new studies looking into better treatment options in AIH.

\section*{AIMS AND OUTLINE OF THIS THESIS}

In \textbf{Chapter 2} we reviewed published results on aetiology, epidemiological and clinical characteristics as well as management of AIH.\textsuperscript{34} The aim of this thesis was to elucidate several key issues with regard to genetic risk, diagnosis and treatment of AIH:
To identify genetic risk factors of autoimmune hepatitis  
In chapter 3 we evaluated the role of the potential AIH risk factor, the CTLA-4 +49 SNP, in a large cohort of Dutch Caucasian AIH patients and controls.  
In chapter 4 we further explored the genetic epidemiology by means of the first GWAS and replication analysis in large cohort of AIH type-1 patients and population controls.  
In chapter 5 we studied the implication of the AIH associated human leukocyte antigen (HLA)-DRB1*03:01 and HLA-DRB1*04:01 genotypes in the MHC region on clinical characteristics and outcomes of AIH patients.

To evaluate the assessment of histopathological features in autoimmune hepatitis.  
In chapter 6 we evaluated the use of histological features that are considered typical in either the revised original (1999) and/or simplified (2008) criteria in the diagnosis of AIH, describing a novel, systematic approach for the assessment of these features in liver biopsies of AIH patients.

To assess the prevalence and relevance of autoimmune features in drug-induced liver injury.  
In chapter 7 we studied the clinical characteristics and the presence of autoimmune features in patients with liver injury caused by nitrofurantoin, minocycline, methyldopa, or hydralazine.  
In chapter 8, a review of literature describes the current insight into the increase in the reports of herbal and dietary supplement associated induced liver injury, which may present with autoimmune features.

To evaluate current management of autoimmune hepatitis patients  
Chapter 9 discusses the results of an online questionnaire assessment amongst international expert hepatologists, describing their practices in the management of patients with AIH.

To assess the potential of thiopurine treatment optimisation with allopurinol as a second-line treatment strategy in autoimmune hepatitis  
In chapter 10 we describe the results of this strategy in a case series of AIH patients with intolerance or nonresponse to standard therapy due to a skewed metabolism.  
Chapter 11 is a summary of the findings in this thesis, discussing the implications for the clinical management as well as further research questions in autoimmune hepatitis.
REFERENCES
