Part One

GENERAL INTRODUCTION
Part one
General introduction

Autoimmune hepatitis (AIH) is an inflammatory liver disease of unknown cause\(^1\). It is characterised by the presence of interface hepatitis and portal plasma cell infiltration on, hypergammaglobulinemia, and autoantibodies\(^2\). AIH reflects a complex interaction between triggering factors, autoantigens, genetic predisposition and immunoregulatory networks\(^3, 4\). Women are affected more frequently than men and disease can develop in all age groups. The clinical spectrum is wide, ranging from absent or mild symptoms to fulminant hepatic failure and may vary among ethnic groups\(^5\). AIH has features that resemble Primary Sclerosing Cholangitis (PSC) and Primary Biliary Cirrhosis (PBC) and overlap with these disorders are reported in 10-20% and 2-8% of cases, respectively\(^6, 7\). Associated concomitant autoimmune diseases in AIH have been reported in up to 40% of patients and may mask the underlying liver disease\(^2\). Due to the absence of a specific marker of the disease and the large heterogeneity of its clinical, laboratory and histological features, AIH has an evolving complexity that has generated multiple challenges in its diagnosis and management\(^1\). These challenges reflect difficulties in recognizing its diverse clinical phenotypes, optimizing current corticosteroid regimens, identifying problematic patients early, and incorporating new drug options into safe and effective management strategies.

The aetiology of AIH is still unknown, but genetic and environmental factors are implicated. Exogenous factors, such as concomitant autoimmune diseases, viruses and drugs, have been proposed as triggers for AIH\(^8\). On the other hand it is generally believed that AIH occurs as the consequence of an exaggerated immune response in a genetically susceptible host\(^9\). The exact relationship between the genes and autoimmune process remain largely undefined. AIH is a polygenic disorder and although the heritable component is relatively small, there is good evidence that several genes can affect the risk of developing the disease.

If left untreated, AIH usually progresses to liver failure requiring transplantation\(^10\). The goal of AIH treatment is to obtain early complete remission, to prevent disease progression, and to maintain this in the long-term on the lowest possible dose of medication\(^11\).

Knowledge about the pathophysiology, clinical features and treatment has grown over the past years, however many questions regarding AIH remain unanswered.

This thesis, aimed to gain insight in some aspects of epidemiology, etiology, clinical course and treatment of AIH.
Part one

**Thesis outline**

The first part of this thesis focuses on epidemiology, clinical features and concomitant diseases in AIH. Chapter 1 provides a review on the epidemiology, clinical course, diagnostics, complications and treatment of patients with AIH.

The aim of chapter 2 was to investigate the incidence and prevalence of AIH patients in the Netherlands with 16.7 million inhabitants. In addition the clinical spectrum and validity of diagnostic criteria was evaluated in a large AIH patient cohort.

AIH is associated with concomitant autoimmune diseases. Associations between celiac disease (CD) and AIH have been described and in chapter 3 we have evaluated the incidence of CD in AIH patients and discuss whether screening for CD in AIH patients should be considered.

Liver disease with histological and biochemical features resembling AIH may also be resulting from Hepatitis E virus (HEV) infection. HEV is a non-enveloped, positive-sense, single-stranded ribonucleic acid (RNA) virus and thus acute disease may be misclassified as de novo onset of AIH when HEV has not been excluded. To what extent HEV infections may lead to chronic hepatitis in patient groups receiving immunosuppressive medication including AIH is currently unknown. Therefore in chapter 4 we investigated the prevalence of Hepatitis E virus in AIH patients.

The second part of this thesis focuses on genetic associations in AIH. Although the exact pathogenic trigger of AIH remains unknown, it is generally believed that disease occurs as the consequence of an exaggerated immune response in a genetically susceptible host.

Indeed, several immune related genes, including human leukocyte antigen (HLA) class-II molecules and cytotoxic T lymphocyte antigen-4 (CTLA-4) gene, have been associated with the development of AIH in small study populations. Chapter 5 describes a large cohort of AIH patients and documents the presence of HLA DRB1*0301 and HLA-DRB1*0401 alleles. In addition we aimed to evaluated if HLA-DRB1*0301 and HLA-DRB1*0401 alleles influence the clinical manifestation and outcome of patients with AIH.

The strongest association between non-MHC gene and the occurrence of AIH has been described in the CTLA-4 gene. The results of the role of this polymorphism in a sufficiently large cohort of well-defined Caucasian AIH patients is described in chapter 6.

Current treatment strategies for AIH consist of an induction course with prednisone and frequently include subsequent addition of azathioprine (AZA) as steroid-sparing maintenance therapy. There is no prescribed minimum or maximum duration of treatment. The long-term treatment requirements for AIH remain unclear and decisions to treat to pre-established endpoints, withdrawal medication after prolonged inactivity on long-term maintenance schedules, or indefinitely continue therapy in some form, have not been soundly based. The third part of
this thesis, chapter 7, consist of a study performed to investigate the frequency of relapse after drug withdrawal while being in remission for at least two years.

This thesis ends with a general discussion and discusses future perspectives in Autoimmune Hepatitis research (chapter 8) and a summary of all results is presented (chapter 9). The addenda describes the identified loci in a genome-wide association study (GWAS) in a large cohort of AIH patients and controls.
Part one

Reference List


General introduction and outline