GENERAL INTRODUCTION

Inflammatory bowel disease (IBD) is an overarching term comprising (amongst others) Crohn’s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDu), all characterized by chronic idiopathic inflammation of the gastrointestinal tract with alternating periods of remission and relapses. The global incidence is rising and this is highest in Western countries ranging from 10-30 per 100,000 inhabitants (prevalence in USA approximately 1 million, in Europe approximately 2.5 million). [1] The diagnosis of IBD is primarily based on clinical, endoscopic, histological and radiological criteria. [2] The cornerstone of diagnosis remains (ileo)colonoscopy, which is an invasive procedure. [3] Over recent years, several biochemical tests have been evaluated to make the diagnosis of IBD less likely, of which the proteins from the S100 family appear to be the most sensitive and specific to date. Of these, the S100A8/A9 protein, also known as calprotectin, is currently used as a fecal biomarker in patients with a suspected intestinal inflammation, and IBD in particular, or during follow-up of previously diagnosed IBD. [4] However, there still is a great scope for improvement in non-invasive methods to diagnose and follow-up patients with IBD.

Treatment of IBD comprises amongst others the induction and maintenance of remission. Once remission is achieved by induction therapy, long-term maintenance therapy will commonly be initiated. According to the current Dutch and international IBD guidelines, a step-up regimen is applied, typically starting with less potent immunosuppressants, sometimes in accelerated fashion in severely active disease. [5-7] When maintenance therapy with immunosuppressive therapy in both CD and UC is indicated, the first choice is usually a thiopurine derivative.
Thiopurines as a pharmaceutical compound (available as the derivatives azathioprine (AZA), mercaptopurine (MP) and a less conventional derivative, thioguanine (TG)) were discovered in the 1950s by Gertrude Elion and George Hitchings. [8] Their metabolism is complex and has been partly elucidated in the past decades. By the activity of several enzymes, evolutionary developed to neutralize non-self or foreign DNA ingested by food intake, thiopurines are converted into two pharmacologically active metabolites, being 6-methylmercaptopurine (6-MMP, mainly accounting for (hepatotoxic) side-effects) and 6-thioguaninenucleotides (6-TGN), which are currently believed to be primarily responsible for the anti-inflammatory effect by the binding of the small GTPase Rac1, ultimately leading to the inhibition of anti-apoptotic effect, causing apoptosis of CD28-stimulated T-cells). [9-12]

Unfortunately, over 50% of the patients have to discontinue thiopurine therapy with AZA or MP within two years, mostly due to intolerable adverse events (39%) or ineffectiveness (16%). [13] In a proportion of these patients, especially the patients with a skewed thiopurine metabolism (i.e. the preferential formation of 6-MMP over 6-TGN), the addition of allopurinol, a xanthine oxidase inhibitor, to a reduced dose (25-33%) of the original thiopurine derivative, contributes to better tolerability and effectiveness. [14] These and potentially other patients might also benefit from a switch to TG [15, 16] or might have to switch to more potent therapy such as therapy with biologicals (e.g. infliximab, adalimumab, ustekinumab, vedolizumab or golimumab). [5, 7]
In the first part, this thesis focuses on the search for novel biomarkers in diagnosing and staging IBD. In Chapter 2, the literature is reviewed regarding the use of S100A12 as a potential biomarker for several diseases, including IBD. In Chapter 3, differences in concentrations of S100A12 measured in EDTA-plasma and serum were described, providing a warning for future biomarker studies. Chapter 4 shows the results of the usefulness of sRAGE measurement as a surrogate biomarker for IBD, as sRAGE acts as the receptor for advanced glycation end-products, such as the S100 proteins.

Part two of this thesis (Chapter 5-11) focuses on the optimization of thiopurine therapy in IBD. Chapter 5 consists of a practical review of thiopurine therapy, written based on the viewpoints of gastroenterologists from one university hospital and one large district hospital in The Netherlands. In Chapter 6, results of the optimization of thiopurine therapy in two real-life cohorts are provided. Chapter 7 provides information on the pharmacology of thiopurine therapy in IBD patients, compared with hematological and hepatic markers. In Chapter 8, results of the switch to mercaptopurine therapy in patients intolerant to azathioprine were depicted, whereas Chapter 9 reviews the literature regarding the efficacy of the third thiopurine derivative thioguanine. In Chapter 10, the tolerability and effectiveness of thioguanine and methotrexate therapy in patients with ulcerative colitis are compared in a multicenter database study of all eight academic hospitals. In Chapter 11, concentrations of xanthine oxidase activity were measured in 144 IBD patients. Since xanthine oxidase is an important enzyme in the metabolism of thiopurines, the measurement of xanthine oxidase activity might guide dosing in patients before the initiation of thiopurine therapy.
In part III of this thesis (Chapter 12-14), the focus is on complications of thiopurine therapy. Chapter 12 describes the association of myelotoxicity with (extremely) high concentrations of 6-MMP in patients receiving conventional thiopurine derivatives. Chapter 13 describes 11 cases receiving orthotopic liver transplantation due to (complications of) nodular regenerative hyperplasia, based on a nationwide cohort study amongst all liver transplantation centers in The Netherlands during the past 20 years. Lastly, in Chapter 14, the results of an international multi-center study (Amsterdam, The Netherlands and Christchurch, New Zealand) amongst IBD-patients receiving transient elastography of the liver are shown. In this study, possible factors contributing to higher stiffness of the liver are evaluated.
References