INTRODUCTION
RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by a symmetrical inflammation of the synovium, resulting in tenderness and destruction of bone and cartilage in various joints, particularly the smaller parts of the hands and feet. RA affects approximately 1.0 percent of the general population, women more often than men, and the inflammatory burden of the disease results in functional disability.(1-4) Several contributors to RA pathogenesis have been identified in recent years: genetic factors (shared epitope on locus HLA-DRB1, but also PTPN22, STAT4, 6q23 and TRAF1/C5), cigarette smoking, autoantibodies (rheumatoid factor (RF), anti-cyclic citrullinated protein antibodies (ACPA)), infectious agents, as well as nutritional and hormonal factors.(5-19) Ultimately, an interplay between these endogenous and exogenous factors has been postulated to break immunological tolerance and trigger the immunological response that manifests itself as RA. The immunological activation of RA leads to infiltration of the synovium by an orchestra of immune cells like T and B cells, macrophages, dendritic cells and fibroblast-like synoviocytes, contributing to the proliferation of cell tissue (i.e. pannus formation) and neovascularization.(20-23) These immunological processes perpetuate systemic inflammatory responses, leading to a chronic, disabling disease which results in the inability to work and an impaired quality of life.(1-4)

CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS

The manifestations of RA are not confined to symmetrical inflammation of the joints: in approximately 40% of cases, non-articular tissues and organs - like skin, eye, lung, heart, kidney, blood vessels, the nervous system or bone marrow - are involved. (24) Moreover, there is accumulating evidence for an increased risk of comorbid conditions like osteoporosis and cardiovascular disease (CVD), the leading cause of death in RA patients.(25-29) The increased CVD burden for RA patients is predominantly due to accelerated atherosclerosis.(30) Interestingly, in the last decades it has become clear that atherosclerosis can be considered an inflammatory disease and that inflammation itself drives all stages of atherosclerosis.(31-33) Nowadays, there is increasing evidence that the chronic inflammatory burden of RA induces the onset of traditional cardiovascular risk factors like insulin resistance, abdominal obesity, hypertension and dyslipidemia.(34) Co-occurrence of several of these cardiometabolic risk factors has been called the “Metabolic syndrome”,(35) which increases the development of not only CVD but also diabetes mellitus (DM).(36-42) Recently, it has become apparent that RA is associated with a higher prevalence of metabolic syndrome and, interestingly, metabolic syndrome seems related to disease activity in RA.(43-46) The inflammation in RA patients may contribute to CVD development and may exacerbate
traditional CVD risk factors like dyslipidemia in several ways. Dyslipidemia is a well-recognized risk factor for atherosclerosis and has increasingly been associated with RA, mostly in untreated RA patients. New insights in pathophysiology of lipid metabolism indicate that lipoprotein composition changes during inflammation into a more proatherogenic cholesterol particle. In this way, high-grade inflammation turns the combination of cardiovascular risk factors and the lipid metabolism, i.e. both levels and composition of lipids, into a very unfavorable cardiovascular risk profile. Hypothetically, when low disease activity or remission has been reached, pivotal anti-inflammatory treatment and immunomodulating therapy in RA may decrease the prevalence of traditional CVD risk factors and thereby beneficially influence both CVD risk and lipid metabolism.

HYPOTHYROIDISM AND RHEUMATOID ARTHRITIS

Autoimmune hypothyroidism is considered the most common autoimmune disease and its prevalence has been estimated to be up to 2%, with a higher concentration in older women. The most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto’s thyroiditis), leading to thyroid tissue destruction. Autoimmune thyroiditis is characterized by the elevated presence of antibodies against thyroid peroxidase (TPOabs), although the precise role of TPOabs in pathogenesis has not yet been established. Moreover, autoimmune thyroiditis has been associated with different genetic polymorphisms, suggesting a genetic predisposition. Traditionally, autoimmune diseases like hypothyroidism and RA were considered separate disease entities, as the manifestations are, on the one hand, more organ specific (such as Hashimoto thyroiditis), and on the other hand, more systemic (such as RA). In general, patients suffering from an autoimmune disease have a strong hereditary susceptibility for other autoimmune diseases and higher incidences of autoantibodies have been detected in their relatives. Intriguingly, different family members may develop the same disease entity in totally different organs and disease constellations. This diversity and broad spectrum of manifestation of autoimmune disorders is called the “mosaic of autoimmunity”. In this context, patients with similar genetic, immunological, hormonal and environmental risk factors may eventually evoke different autoimmune diseases. The combination of RA and autoimmune thyroiditis was already recognized half a century ago. More recently, the coexistence of RA and hypothyroidism was reassessed, but data on this relationship remains sparse. As hypothyroidism and RA are both relatively common autoimmune diseases associated with increased CVD morbidity and mortality, further research into the interaction between these two diseases is worthwhile, both from a cardiovascular and from an immunological point of view.
B CELL TARGETED THERAPY IN RHEUMATOID ARTHRITIS

Over the last decades, a shift towards more aggressive treatment has brought about significant improvements. Such strategies combine disease-modifying antirheumatic drugs (DMARDs) with methotrexate (MTX) as the anchor drug in the early stages of the disease stage.(74-76) Another breakthrough in the treatment of RA was the introduction of the group of therapeutic agents known as ‘biologicals’. These biological agents specifically target mediators in the orchestra of inflammatory responses. The first biological agents in RA were directed against the pro-inflammatory cytokine tumor necrosis factor (TNF). Advances in biotechnology led to the development of biological agents against the pro-inflammatory cytokines interleukine (IL)-1 and IL-6 for RA treatment. Recently, agents directed against (activation of) T cells (abatacept) and B cells (rituximab) have become available for clinical use. Although the importance of the autoantibody rheumatoid factor (RF) and anti-cyclic citrullinated protein antibodies (ACPA), (mainly produced by plasma cells which differentiate out of matured B cells) is well-documented, the importance of B cells was long subject of debate. This is because RA was believed to be a T cell-dependent disease. In addition to producing autoantibodies, B cells play a crucial role in ectopic lymphogenesis (with germinal center formation in synovium), antigen presentation to T cells and cytokine production, all of which perpetuate the immune response in RA.(77) Recent studies demonstrated B cell-targeted therapy to be an efficacious and safe treatment option in both anti-TNF naïve and anti-TNF refractory RA patients (78-85). Despite these revolutionary breakthroughs and the availability of a wide arsenal of therapeutic drugs, the disease is still active in the majority of RA patients. Because of the progressive damage caused by the inflammatory burden of the disease, and the high cost of treatment using biologicals, it is highly desirable to discriminate between responders and non-responders before the initiation of treatment.

GENOMICS IN RHEUMATOID ARTHRITIS

It has been widely accepted that RA is a disease with clinically different manifestations and phenotypes. This “heterogeneity” of RA is also reflected by the presence or absence of serological markers (ACPA), the spectra of histological findings of synovial tissue in active RA and the different response to therapy between patients.(86-90) Inter-individual differences in a heterogeneous disease like RA should be represented by the way genes and proteins are expressed, as gene expression profiles are the fingerprint or signature of a disease entity. In this way not only discriminating, but also unifying molecular markers may be identified, ultimately leading to a better understanding of RA pathogenesis. In fact, RA patients show different expressions of gene signatures (e.g. interferon signature) in different stages of the disease and the identification of these gene signatures underscores this heterogeneity.(91;92) Genomic profiling therefore can determine the
molecular characteristics and underlying biological processes of every individual patient in a heterogeneous group. Moreover, heterogenomics may be an elegant scientific tool to relate unifying gene expression profiles to differences in the results of treatments. In this way, urgently needed new biomarkers may be discovered, which will ultimately pave the way for the personalization of medicine in RA treatment.

OUTLINE AND AIMS OF THE THESIS

This thesis covers two main subjects. The first part describes the relationships between RA, CVD and thyroid dysfunction. The second part investigates clinical aspects of treatment of RA patients with rituximab.

SECTION 1 (CHAPTERS 1.1 – 1.4): THYROID DYSFUNCTION AND RHEUMATOID ARTHRITIS: MORE THAN COEXISTENCE

This section has three main objectives. Firstly, this section studies whether the prevalence of hypothyroidism is higher in RA patients than in the general population. Secondly, this section investigates the relationship between hypothyroidism and CVD risk in RA; do RA patients with hypothyroidism run a higher CVD risk than patients without? Finally this sections aims to explore whether the thyroid function is affected by immunomodulating therapy in RA patients.

Section 1 focuses different aspects of thyroid dysfunction related to RA, and the relationship with CVD. In chapter 1.1, the prevalence of hypothyroidism in RA patients in both the general population and in a secondary care referral center are described. Furthermore, this chapter describes the prevalence of cardiovascular diseases in RA patients with and without hypothyroidism. Chapter 1.2 compares the occurrence of metabolic syndrome, a constellation of risk factors for diabetes mellitus and cardiovascular disease, in CVD event naive RA patients with hypothyroidism to the occurrence of this syndrome in euthyroid RA patients. Moreover, 10-year cardiovascular disease risk is estimated according to the Framingham risk algorithm in both patients groups. In chapter 1.3, data about the prevalence of thyroid peroxidase (TPO) antibodies in RA patients is presented. This chapter also investigates whether TPO antibody-positive RA patients differ from TPO antibody-negative RA patients, with respect to cardiovascular risk and RA parameters. Chapter 1.4 explores how different immunomodulating therapies (anti TNF treatment and B cell depletion therapy) affect the thyroid function.
SECTION 2 (CHAPTERS 2.1 – 2.2): RITUXIMAB IN RHEUMATOID ARTHRITIS: MORE THAN B CELL DEPLETION

In this section, there are also three main objectives. We first focus on lipid metabolism during rituximab treatment, to establish whether the lipid profile improves during efficacious rituximab treatment. This section then reports on pharmacogenomic effects of rituximab treatment, providing insight into the biological basis for clinical responses to rituximab. Finally, this section investigates whether the correlation between baseline gene expression profiles and treatment outcome offers opportunities to identify new biomarkers for rituximab treatment.

Section 2 discusses different clinical aspects of B cell targeted therapy. Literature about the relationship between rituximab and lipid metabolism is sparse. However, dyslipidemia is an important mediator in CVD development in RA, and pivotal immunomodulating therapy is believed to improve lipid profiles. Chapter 2.1 therefore starts by reporting on alterations in lipid levels and HDL composition in RA patients during a six months’ rituximab treatment. We also explore whether alterations in lipid levels and HDL composition differ between responders and non-responders.

Despite rituximab depleting B cells in all patients, there is still an inter-individual difference in response to rituximab. Chapter 2.2a therefore investigates pharmacological effects on gene expression profiles in a genome-wide approach during six months of rituximab treatment, to establish whether differences in pharmacodynamics could explain differences in the outcome of treatment. Moreover, pharmacogenomics provides insight into different treatment-induced and B cell targeted pathways in relation to clinical response. Finally, Chapter 2.2b examines whether baseline gene expression profiles can predict the clinical outcome of rituximab treatment.
REFERENCES


Introduction


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