Chapter 1

General introduction
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Rheumatoid arthritis (RA) is a chronic, systemic auto-immune disorder characterized by synovial inflammation of the joints and destruction of cartilage and bone (Figure 1). The worldwide prevalence of RA is estimated to be about 0.5-1%, and the disease is about two to three times more prevalent in females than males. RA can develop at any age, but most often presents between the ages of 50 and 60. The specific cause of RA is not yet fully understood, although genetic factors and environmental factors (for example infections and smoking) play a role.  

At the onset of RA, patients often present with chronic, symmetric inflammation in the small joints of the hands and feet, and the wrists, although larger joints can be affected too. The inflamed joints are painful, swollen and stiff, and may cause movement restrictions and loss of function. Many patients experience general malaise or fever, and suffer from fatigue, even in periods with limited or no inflammation. RA is a heterogeneous disease; the course of disease and prognosis varies strongly per patient.

In RA, the chronically inflamed synovium may destroy bone, these bone destructions are also known as erosions. Furthermore, the inflamed synovium may produce enzymes that are involved in breakdown of cartilage (secondary osteoarthritis), which may cause reduced joint space width. Damage of bone, cartilage, and surrounding tissues may cause irreversible joint deformities and loss of function, which may have major impact on physical functioning in daily life.

![Figure 1. Comparison of a healthy joint and an inflamed joint](image)

Treatment of rheumatoid arthritis

The treatment of RA has undergone some major changes in the last decades due to major scientific insights. First of all, early and intensive suppression of inflammation may inhibit or delay the destruction of cartilage and bone, the so-called “window of opportunity”. Therefore, the treatment of RA should be started as soon as possible.
Second, combination therapy of disease-modifying anti-rheumatic drugs (DMARDs) proved to be more effective than monotherapy.\textsuperscript{7-12} Therefore, the majority of early RA patients, especially those who present with moderate or high disease activity, preferably starts treatment with a combination of two or three DMARDs simultaneously, almost invariably with glucocorticoids. The therapy will be tapered in a later phase of treatment, when a status of low disease activity or remission (a state of absence of disease activity) is maintained.\textsuperscript{1,4-6,13}

Third, treatment targeted to decrease disease activity, and ultimately aimed to achieve clinical remission, has been shown to maximize long-term health-related quality of life through control of symptoms, prevention of structural joint damage, normalization of daily functioning and participation in social and work-related activities. Therefore, RA patients are preferably treated according to a so-called “treat-to-target strategy”, in which disease activity is regularly monitored (every 1-3 months during active disease), and treatment is intensified if disease activity is high, or continued or tapered if disease activity is moderate or low. The ultimate aim of the treatment is to rapidly achieve remission in early RA patients. A state of low disease activity may be an acceptable alternative therapeutic goal, particularly in patients with long-standing disease.\textsuperscript{1,4-6,13-15}

Fourth, much more is known about the pathophysiology of RA nowadays, which contributed to the development of new anti-rheumatic drugs specifically targeted at immune cells (for example B- or T-cells), immune mediators (for example TNF-α and interleukins) or specific intracellular compounds (for example JAK proteins). These new drugs are called biological DMARDs (bDMARDS) and targeted synthetic DMARDs (tsDMARDs). The development of bDMARDs and tsDMARDs offers new treatment opportunities, especially for those patients who experience limited or no effect of treatment with (a combination of) traditional synthetic DMARDs. Generally, bDMARDS and tsDMARDs are started when patients do not achieve a therapeutic effect of treatment with (a combination of) traditional synthetic DMARDs.\textsuperscript{1,2,6}

**COBRA and COBRA-light combination therapy**

An example of successful combination therapy is COBRA therapy (Dutch acronym for ‘COmbinatietherapie Bij Reumatoïde Artritis’, combination therapy for rheumatoid arthritis), which combines initially high-dose prednisolone (60 mg/day), with methotrexate (MTX) and sulfasalazine (SSZ).\textsuperscript{7} Despite confirmed clinical effectiveness, safety and cost-effectiveness on the short and long term, COBRA therapy was infrequently prescribed by rheumatologists due to the complexity of the treatment schedule, the large number of pills, the possible side effects of high-dose prednisolone use, and the possible interaction between SSZ and MTX.\textsuperscript{16,17} Therefore, an attenuated combination therapy was designed, “COBRA-light”, combining a lower initial prednisolone dose (30 mg/day), with a higher dose of MTX, but no SSZ.\textsuperscript{18}
In the COBRA-light trial, COBRA-light therapy was compared with COBRA therapy in an open-label, randomized controlled, non-inferiority trial design. In brief, COBRA-light therapy (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX escalated to 25 mg/week in 8 weeks) was compared with COBRA therapy (prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and SSZ 2 g/day) on clinical and radiological outcomes in 162 early RA patients (Figure 2). A treat-to-target protocol was used, with minimal disease activity as treatment goal (Disease Activity Score in 44 joints (DAS)<1.6, at that time defined as clinical remission). In the period of 6 months to 1 year, treatment intensification of MTX (in COBRA) and addition of etanercept was mandated per protocol in patients who did not reach minimal disease activity (DAS<1.6). After 1 year, treatment was continued without protocol, and therapy was adjusted by the treating physician according to clinical judgment, preferably in a treat-to-target design. Patients were intensively monitored up to two years and visited their rheumatologist and research nurse 3, 6, 9, 12, 18 and 24 months after trial initiation.

COBRA-light therapy proved to be non-inferior to COBRA therapy in clinical and radiological efficacy and safety after 6 and 12 months. Although the results of the first year of treatment with COBRA-light therapy were favourable, long-term data were lacking. Therefore, we developed the COBRA-light extension study, in which the efficacy and safety of initial COBRA-light versus COBRA therapy after a 4-year follow-up period was studied (Chapter 2).

**Remission**

The ultimate target for treatment of RA is a state of clinical remission, defined as the absence of signs and symptoms of significant inflammatory disease activity. In the past, various definitions of remission were used interchangeably, measuring different states of disease activity. Therefore, a new, uniform, strict and easy-to-use definition of remission was developed in 2011: the ACR/EULAR remission criteria. The criteria were validated for their potential to predict good functional and radiographic outcome in future. The criteria require, intentionally, no minimum duration of remission, because it was beyond the scope of the committee to determine a minimum clinically relevant duration. However, since RA is a chronic, progressive and destructive disease, with disease activity over time as best predictor of progression and destruction, the duration of remission is a very important aspect. In addition, RA patients themselves find duration an important aspect of remission as well. Therefore, we studied whether sustained periods of remission could predict good functional and radiographic outcome in RA patients (Chapter 3).
FIGURE 2. Overview of COBRA and COBRA-light combination therapy (continues)
**FIGURE 2.** Overview of COBRA and COBRA-light combination therapy
Chapter 1

**Physical activity**

It is well-known that regular physical activity has multiple health benefits, such as decreased mortality and decreased morbidity of cancer, cardiovascular disease, and other chronic diseases. Regular physical activity might have additional health benefits for RA patients, such as positive effects on aerobic capacity, muscle strength and muscle function, without exacerbating disease activity and pain. However, it might be difficult for RA patients to perform physical activities regularly, especially during periods of high disease activity. The relation between disease activity and physical activity in RA has been described cross-sectionally, but not longitudinally. Therefore, we studied this longitudinal relation between disease activity and self-reported physical activity in COBRA-light patients during their first year of treatment (Chapter 4).

**Body composition**

Body composition describes the ratio of fat mass, lean body mass, bone mass and water in the human body. It can be estimated by relative simple methods like the assessment of body weight and height to calculate the Body Mass Index (BMI), the assessment of skin folds and circumferences, and from conductivity, which uses the resistance of an electrical flow through the body to estimate body fat (bioelectrical impedance analysis (BIA)). More complex and expensive methods are based on total body scans (e.g. dual-energy X-ray absorptiometry (DXA)), body density (e.g. underwater weighing) and body volume (e.g. air displacement plethysmography).

The chronic, systemic inflammation in RA is not only associated with destruction of cartilage and bone, but impacts body composition of RA patients as well. The underlying mechanism may be that chronic, systemic inflammation is associated with changes in levels of cytokines that cause a state of hyper-metabolism, which increases energy demands that contribute to the loss of fat-free mass (FFM). During exacerbations of disease, decreased physical activity and disuse of muscles can result in further loss of FFM. FFM is important as it contributes to multiple vital body functions. A loss of FFM may decrease functional capacity and may have serious consequences for morbidity and mortality of RA patients. Fat mass (FM), or adipose tissue, can be considered as an active, endocrine organ, secreting several pro-inflammatory cell signaling proteins, the so-called adipocytokines. Increased FM and obesity are frequently observed in RA patients, and are associated with an increased risk of the development of hypertension, diabetes mellitus and cardiovascular disease.

Prednisolone, a glucocorticoid, is well known for reducing inflammation in RA patients rapidly and effectively, and is often used in the initial treatment strategy of RA patients. Next to its anti-inflammatory properties, prednisolone may cause alterations in energy metabolism, and high doses can lead to muscle wasting, fat accumulation and fat redistribution from peripheral to central tissues. The short-term effects of prednisolone on body composition of prednisolone-naive early RA patients are unknown. Therefore,
we performed a study to investigate the effects of two different prednisolone regimens (COBRA and COBRA-light therapy) on body composition in early RA patients after 26 weeks of treatment (Chapter 5).

Rheumatoid cachexia is a condition of altered body composition, in which patients present with an involuntarily loss of FFM and a stable or increased FM. Rheumatoid cachexia probably results from the complex interplay between inflammation, physical activity, drug treatment and nutritional intake (Figure 3).31,33 The condition often remains undetected in routine clinical examination, since the loss in FFM is masked by a gain in FM, resulting in little or no weight loss.31 Still, rheumatoid cachexia can be demonstrated in 20-50% of patients with RA, depending on the definition used, and is associated with patient’s disability, increased morbidity and premature mortality.32,38-44 New consensus definitions of “pre-cachexia” and “cachexia” have been published for use in different patient populations.45,46 We studied the applicability and relevance of these new definitions in RA patients (Chapter 6).

**FIGURE 3.** Overview of potential causes and clinical manifestations of rheumatoid cachexia by Summers et al.31 Summary of current knowledge regarding the underlying mechanism and clinical manifestations of rheumatoid cachexia. The questions marks denote areas in which the current state of knowledge is still preliminary; CVD = cardiovascular disease.
Assessment of body composition

Since chronic, systematic inflammation may have impact on body composition of RA patients, careful and regular assessment of body composition is important. BMI is a simple, easy and widely used parameter to assess body composition in clinical practice, but fails to identify the changes in FFM and FM often present in (weight stable) RA patients.\textsuperscript{33,47} DXA is a valid and reliable method to assess both FFM and FM accurately, and is often used as a reference method for body composition measurement in clinical studies.\textsuperscript{48-50} However, the use of this method is expensive, patients are exposed to small amounts of radiation, the device is non-portable, and requires trained radiologists for interpretation, which makes it unsuitable for every-day use in clinical practice.

BIA might be a more suitable method to assess body composition in RA patients in clinical practice, as it is relatively cheap, simple, rapid, safe and non-invasive, uses a portable device and can be easily performed after minimal training.\textsuperscript{49-52} A limitation of BIA is that the precision and accuracy of its assessments depends on the fluid and electrolyte status of patients.\textsuperscript{48-51} Furthermore, BIA has not been sufficiently validated in RA patients. Therefore, we initiated a study to investigate the differences between the assessment of body composition by BMI and BIA in a cohort of 65 RA patients (Chapter 7). After promising results, we decided to compare BIA with two different DXA devices in a cohort of 43 RA patients (Chapter 9).
Outline of this thesis

Part I
The first part of my thesis describes outcomes of the COBRA-light trial. In chapter 2, we describe the efficacy and safety of initial COBRA-light and COBRA therapy after a 4-year follow-up period. We compare both treatment strategies on their effect on disease activity, remission, functional and radiological outcomes, and in terms of survival, comorbidities and overall medication use. In chapter 3, we present the validity of the new ACR/EULAR remission criteria for both short and sustained periods of remission in early RA patients. For this chapter, 2-year follow-up data of the COBRA-light trial was used, and the main clinical outcomes over a 2-year follow-up period are described as well. In chapter 4, we describe the longitudinal relation between disease activity and self-reported physical activity in COBRA-light patients during their first year of treatment. In chapter 5, we present the effects of two different prednisolone regimens (COBRA and COBRA-light) on body composition in prednisolone-naive RA patients after 26 weeks of treatment.

Part II
The second part of my thesis focuses on the assessment of body composition in RA patients. In chapter 6, we describe the relevance of the new “pre-cachexia” and “cachexia” definitions for RA. In chapter 7, we present the differences between the assessment of body composition by BMI and BIA in a cohort of RA patients. In chapter 8, we comment on an article published by Wolfe and Michaud, who used BMI as a measure for overweight and obesity in RA patients. In chapter 9, we present the results of a comparison study, in which BIA is compared with two DXA devices for the assessment of body composition in RA patients.

In chapter 10, the most important findings of this thesis are summarized and discussed.
Chapter 1 General introduction

References