INTRODUCTION

In the Netherlands, approximately 1% of the population suffers from the chronic disease rheumatoid arthritis (RA). The impact of this disease influences many aspects of patients’ life, such as performing daily activities. To categorize all these aspects, the World Health Organization developed a framework to assess the impact of a disease: the International Classification of Functioning, Disability and Health (the WHO ICF) framework (2001). In this framework the impact of a disease can be assessed through five components: ‘body functions and structures’, ‘activities’, ‘participation’, ‘environmental factors’ and ‘personal factors’.

The disease perspective

The treatment of RA patients has altered throughout the years. Earlier, the pyramid model was used as drugs became available: starting with non-steroidal anti-inflammatory drugs (NSAIDs); when not efficient enough, monotherapy with a disease modifying anti rheumatic drug (DMARD), such as sulfasalazine or hydroxychloroquine was added. Glucocorticoids and other immunosuppressive therapies were avoided as much as possible. In the eighties of the last century, methotrexate re-emerged, and was given in increasing doses. What we learned from this model was that DMARDs need approximately three to six months to start exerting their effect, and that damage of joints already occurred during this period. Eventually methotrexate (at doses of 20-30 mg/w) became first line therapy, and the reverse pyramid model became more and more popular, in which aggressive treatment was started, and medication was only tapered on clinical improvement. The hypothesis was that initial aggressive treatment would have a positive effect on long-term outcome, the so-called “window of opportunity”. Ultimately, this would result in less disability.

The COBRA (COmbinatietherapie Bij Reumatoïde Artritis) strategy that includes glucocorticoids is the first aggressive treatment strategy based on the reverse pyramid model; in its first application, it proved superior to sulfasalazine monotherapy, the standard of care at the time. Its efficacy was subsequently assessed in the Behandel STrategieën trial (BeSt): COBRA strategy was again superior to sequential monotherapy, step-up therapy but also as effective as infliximab treatment plus methotrexate. Although proven to be very effective in the treatment of RA, ten years after the COBRA trial, the COBRA
strategy was only in limited use in daily practice. Rheumatologists mentioned they only provide methotrexate and different dosages of prednisolone, varying from low dose to higher oral dosages, and parenteral injections: this variation is clearly suboptimal. Therefore, the COBRA-light strategy was developed as a compromise between rheumatologists. To assess if this light version was non-inferior to the original COBRA strategy, the COBRA-light trial was performed (chapters 2-4).

The functioning perspective
To apply the whole ICF framework, the components ‘activities and participation’ and environmental and personal factors’ should also be considered. These items comprise daily activities (such as performing household, self-care), relationships with others, leisure time activities, participating at work (paid and unpaid), and social network. As an initiative of the European League Against Rheumatism (EULAR), the Rheumatoid Arthritis Impact of Disease (RAID) score was developed in 2008. Aim of this initiative was to develop a score entirely based on patient-reported outcomes (PROs) which could be used in clinical trials in RA. This score combined several important outcome measures for patients (chapter 5).

One important outcome is performing paid (or unpaid) work, and all items related to performing a job. Although we are now more able to control disease activity, RA still has a major impact on work participation. Compared to the general population, patients with RA in the Netherlands have approximately 12-20% less paid jobs, experience 2-3 times more days of sick leave, and are about 7 times more work disabled. It has been proposed that early treatment with biological agents can improve work productivity, decrease sick leave and work disability, compared to standard of care. This would result in a decrease in indirect costs, compensating the high cost price of these therapies, and possibly decreasing total (societal) costs of RA. Studies of the effect of biological treatment on indirect costs are increasing, but little is known about their effects on productivity at work (presenteeism), and sick leave (absenteeism), assessed in chapter 6.

Only a few studies have assessed the effect of intensive conventional DMARD treatment (such as COBRA and COBRA-light strategy) on work outcome. Therefore, we wanted to know whether intensive treatment with combination therapy (COBRA and COBRA-light) also resulted in positive work
outcome in early RA patients, and if we were able to find associations between several disease, personal and work related factors at baseline, and eventually predict sick leave over a one-year period (chapter 7).

SECTION I  THE COBRA-LIGHT TRIAL

Chapter 2 Non-inferiority of COBRA-light after 26 weeks of treatment
In this study 164 patients were randomized to receive either COBRA or COBRA-light strategy. The COBRA strategy consisted of three-drug regimens: 7.5 mg/week methotrexate, 2 gr/day sulfasalazine and initially 60 mg/day prednisolone, tapered to 7.5 mg/day in 7 weeks. The COBRA-light schedule consists of methotrexate which increases to 25 mg/week and 30 mg/day prednisolone, tapered to 7.5 mg/day in 9 weeks. In this first chapter of this thesis, the primary outcome of the COBRA-light trial, change in disease activity score of 44 joints (DAS44), at week 26 is described. The results revealed that the DAS44 significantly decreased in both groups: in COBRA-light with –2.2 points (SD 1.1); in COBRA with –2.5 points (SD 1.2). The difference between the groups in DAS44 change was 0.3 point (95% CI: −0.0 to 0.7; p=0.08). All other outcome measures were not significantly different between both strategies. We could concluded that COBRA-light is non-inferior to standard COBRA therapy.

Chapter 3 Non-inferiority of COBRA-light after 52 weeks of treatment
In the second six months of the study, etanercept (an anti-tumour necrosis factor (anti-TNF)) was added according to protocol in both strategies at week 26 or 39 in case minimal disease activity (i.e. DAS44 lower than 1.6 points) was not reached. Clinical and radiological outcome were also assessed. To assess whether both strategies suppress radiological joint progression, data on radiology was analysed.

A stabilization in DAS44 scores was seen in the second half year of the trial. In contrast to the first 26 weeks, the confidence interval of difference in \( \Delta \text{DAS44} \) no longer included the predefined clinically relevant threshold of 0.5, strengthening the claim of non-inferiority for COBRA-light therapy. Although both strategies showed good results on DAS44 scores, 75% (n=61) in the COBRA-light group, and 59% (n=47) in the COBRA group still needed intensification of their treatment with etanercept, as this percentage of patients did not reach...
the predefined level of DAS44 < 1.6. The DAS44 decreased with approximately 0.3 points in patients who actually received and used etanercept for 6 months. In conclusion both therapies have major, comparable favourable effects on disease activity, functional ability and radiological outcome after 1 year in patients with early RA. Addition of etanercept according to protocol was often not implemented by treating rheumatologists, and patients receiving it appeared to have limited added benefit, probably because of low disease activity levels at its initiation.(3)

Chapter 4 Cost-utility of COBRA-light versus COBRA strategy
In the last chapter of section I, the cost-utility of COBRA-light strategy compared to the COBRA strategy was assessed. The economic evaluation of both strategies was performed from the societal perspective: all actual direct medical costs (e.g., laboratory measurements, x rays, medication), direct non-medical costs (e.g., over-the-counter medication, and the need for paid and unpaid household help) as well as indirect costs (costs that arise due to work related disablement) were calculated and combined into one variable: the total costs. We collected data on all costs through three-monthly cost-diaries completed by patients. Also data from medical records as well as the radiology department were collected.

To calculate the costs related to sick leave, the friction cost method was used. With this method only sick leave during a friction period (23 weeks) needed to replace a person is taken into account.(4;5) In order to perform incremental cost-utility analyses, the cumulative costs and number of quality-adjusted life years (QALYs) per patient per treatment group were calculated. For all patients cumulative costs between baseline and week 52 were calculated by summing all costs at every visit. Sensitivity analyses were performed to assess the robustness of the findings. Based on actual costs as reported by the patients, costs for etanercept were lower in the COBRA-light group, despite higher number of patients needing intensification with etanercept compared to COBRA. Due to protocol violations, less patients actually received etanercept in the COBRA-light group. Therefore, a sensitivity analysis was performed in which the cost of etanercept use was assumed to be as indicated in the protocol.

In conclusion, COBRA-light strategy did not significantly differ from COBRA therapy in cost-effectiveness when actual costs were compared. However, if the original DAS44-driven treat-to-target protocol had been fully followed, the
larger number of etanercept users in the COBRA-light arm would have made this arm significantly more expensive than the COBRA arm. Given the modest efficacy and high costs of starting etanercept in the presence of low disease activity in our trial, such a strategy needs better justification than is available now.

Section II  RHEUMATOID ARTHRITIS AND WORK

Chapter 5 Content validity of the RAID score
In the first chapter of section II, the content validity of the RAID score was assessed. In the RAID score, the most important outcome measures for patients are combined in one measure. This response index is intended to be used in clinical trials in RA to replace the use of different questionnaires per outcome without missing important information for patient. The content validity was assessed in two ways. First, focus group discussions (FGDs) with 18 patients were performed to assess which domains of patient’s life RA had impact on. Secondly, a comparison of the RAID score with the World Health Organization (WHO) comprehensive core set of International Classification of Functioning, Disability and Health (ICF) for RA was made.

After performing three FGDs, we could conclude that from the seven domains in the RAID score, five were indicated as being relevant for the study population: a) coping with the disease; b) functional disability assessment (activities performed in daily life); c) pain; d) fatigue, and e) emotional well-being. The domains sleep and physical well-being were briefly or not at all mentioned in the FGDs. The domains work, relationships with third parties and leisure time activities (not in the RAID) were also considered important. Five out of the seven items from the RAID score refer to three domains of the WHO ICF core set of RA. RAID adds two domains not covered by the WHO ICF (coping and fatigue), and omits four, of which two are outside the scope of a PRO measure (Body structures and functions).

In conclusion, the Dutch version of the RAID score has acceptable content validity. More research is needed to confirm whether the domains (paid) work, relationships with others and activities performed in spare time are important in other patient groups. If so, these should be considered in a future upgrade.
**Chapter 6 Systematic review of the impact of biological therapy on sick leave**

In this chapter, the results of a systematic review on the effect of biological treatment on work participation were described. Several studies have shown that worsening of RA might finally result in withdrawal from the labour force, either because of official work disability, early retirement or self-perceived disability. This might lead to financial problems as well as psychosocial problems for the patients. After the introduction of biological therapies in the treatment of RA, the opportunity to control disease activity, and slowing down the progression of joint damage has improved. But prices of these therapies are high which led to an increase in the total health care costs of RA. If biological therapies could result in savings in indirect costs, by decreasing sick leave and presenteeism, an offset of the drugs could occur.

The conclusion of this article was that almost all studies included in this review showed positive results of biological agents on absenteeism and presenteeism compared with start/continue usual care with DMARD, the general population or the situation before starting biological agents, although no pooled effect size could be calculated due to heterogeneity of all data. The effect on employment status was more conflicting, with only a fifth of the cohort studies reporting a positive result, as opposed to 40% of the RCTs. It seems of interest that 50% of studies that assessed early methotrexate-naive patients showed a positive result on employment status.

**Chapter 7 Prediction of sick leave and worker productivity in early rheumatoid arthritis patients**

Despite effective biological DMARD treatment in reducing levels of disease activity, sick leave for extended periods and work disability remains a major problem, as can be concluded from chapter 2.2. In comparison with studies on biological drugs, there are relatively few studies which measured the effect of conventional DMARD therapy on sick leave in RA patients. And if present, all analyses were performed on the delta change between the baseline measurement and the last visit, instead of using longitudinal data. Therefore, in the last chapter of section II, paid work as outcome in the COBRA-light trial was assessed longitudinally. First, the associations between personal-, disease-, and work related variables with sick leave were analysed. Secondly, a longitudinal prediction model to predict sustained sick leave after one year of treatment was built.
Since COBRA-light strategy proved to be non-inferior to COBRA strategy, all patients were pooled for this study. Predictors for sick leave and worker productivity were assessed through a 3-months’ time-lag multivariable logistic generalized estimating equations (GEE) model. A 3-month time-lag model relates the result of a possible predictor to being on sick leave (yes/no) in the following three months. Sick leave (yes/no) was defined as the occurrence of at least 1 day of absence from work due to illness (absenteeism) in the preceding 3 months.

In conclusion, sick leave, as well as improved worker productivity, were both mainly predicted by non-disease specific variables. Both outcomes can be predicted on a three months basis, using the outcome over the past three months for the next three months. By applying this model in daily practice, decisions for therapy change could be based not solely on disease activity, but could also take into account a possible high risk for sick leave in the upcoming three months.

**Overall discussion**

From a disease perspective, based on this thesis, it can be concluded that COBRA-light is non inferior to COBRA strategy: both effectively reduce disease activity levels, improve functional ability and slow down radiological joint progression. Secondly, in a setting of low disease activity, etanercept has limited added benefit after 6 or 9 months of treatment with intensive combination strategies including prednisolone. Thirdly, despite non-inferiority on clinical outcome measures, COBRA-light is more expensive compared to COBRA, mainly driven by costs due to a higher number of etanercept users.

From the functioning perspective, based on this thesis it can be concluded that sick leave in the COBRA trial participants was predicted by higher patient global assessment scores, having fatigue, higher disease duration and reporting sick leave at baseline. These factors, together with work-related factors need to be considered in strategies to prevent work disability. Secondly, although the RAID score offers an outcome measure solely based on patient reported outcome, patients do miss questions on work, relationships with third parties and leisure time activities. And finally, biological therapies improve work participation, but the large heterogeneity of studies on this subject in terms of population, design, analyses and most importantly in outcome measures limits interpretation of the data.