Chapter 1

General introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mostly affects peripheral joints but may have systemic manifestations, potentially resulting in irreversible joint damage.[1,2] RA may present at any age, and the disease is more common in women than in men. The global prevalence of RA is estimated to be rather stable during the past decades, ranging from 0.5-1%.[1,3] A few decades ago, many patients had prognostically unfavourable disease, were continuously suffering from pain and stiffness, and faced functional disability and progressive joint destruction. Extra-articular manifestations of the disease included involvement of internal organs, which interfered with general wellbeing and resulted in frequent hospitalisations and increased mortality.[4-6] During the last decades, major changes have impacted the global severity of RA. The disease is often recognized earlier nowadays, and effective treatment often starts before joint destruction has occurred.[7,8] In 2010 new criteria by ACR and EULAR were released, pertaining to patients with more recent RA.[9] Treatment strategies, aiming at low disease activity assessed by recently developed and validated scores, exploiting combinations of antirheumatic drugs, corticosteroids and/or biologic therapies, have together resulted in a more effective suppression of inflammation and radiographic progression. To date, RA is a far more manageable disease than decades ago, and severe damage to joints and internal organs has become rather rare. RA is to some extent comparable to other chronic conditions, such as diabetes, where patients are frequently monitored and therapy is adjusted according to laboratory tests, in order to prevent the future risk of organ damage.[10,11] As a relative novelty in the field of rheumatology, treatment decisions may now include decisions about tapering medication when the disease has been adequately suppressed, and long-term drug-free remission seems to become a feasible reality.[12-14]

THEAPIES AND TREATMENT MANAGEMENT

Rheumatologists may use three types of antirheumatic disease modifying drugs (DMARDs): 1. classical or conventional synthetic (cs) DMARDs, 2.biologic (b) DMARDs and 3. corticosteroids. Of the csDMARDs methotrexate (MTX) is most often used, and may be most effective. MTX is considered to be the ‘anchor drug’, is well tolerated but rather slow acting and may need several months to fully exert its efficacy.[15] MTX can be used as monotherapy but is claimed to be more effective in combination with other DMARDs. Up to two-third of

all RA patients does not achieve a low disease activity state with methotrexate alone and other csDMARDs such as sulfasalazine[16] and leflunomide[17,18] can be chosen as monotherapy or added to MTX.[19] Also bDMARDs and oral corticosteroids are most effective in combination with csDMARDs, preferably MTX. Several studies have shown that a bDMARD plus a csDMARD, as well as csDMARDs in combination with oral corticosteroids,[20-22] are more effective than monotherapy with csDMARDs.[23,24]

The third category of DMARDs is glucocorticoids. Glucocorticoids differ from csDMARDs in that they usually act very rapidly. Their long term use is disputed because of the fear of adverse events, and glucocorticoids are often prescribed only for short periods of time. Glucocorticoids can be used orally, but also locally in the form of intra articular injections. The main purpose of glucocorticoids is symptom relief by suppression of inflammation, but glucocorticoids have also been demonstrated to inhibit radiographic progression, which effectively makes them DMARDs.[25]

Recommendations management RA

The changes in treatments and treatment approaches during the recent years have resulted in new strategies to manage RA. In 2010 collaborating international rheumatologists have released a set of recommendations for the management of RA for patients with bDMARDs and csDMARDs, to be used in all-day clinical practice.[11] In these recommendations the values of an early diagnosis, of an early treatment start and of setting treatment goals and monitoring them meticulously, have been stipulated. Of note, a shared treatment decision between patient and physician, emphasising mutual responsibility for the treatment outcome, was considered very important. Also, stepwise algorithms have been developed for the start of medication in newly diagnosed patients, with treatment adjustments based on measured clinical responses. The procedures also include tapering of medication for patients in sustained remission or in a low disease activity state. It is recommended that DMARD medication should be intensified or changed if a predefined treatment target was not met within a time frame of 3-6 months.[10] Such a time frame was not (yet) specified for tapering medication in patients with longstanding remission, since patients may flare and therefore tapering should be performed cautiously.[11] In an attempt to further emphasize the importance of meticulous monitoring and guided decisions about treatment intensification, the treat-to-target (T2T) initiative has formulated recommendations to stimulate rheumatologists to set and aim at achieving treatment goals.[25] In 2013 the 2010 EULAR recommendations were

updated including improved treatment strategies for which scientific proof has become available.[26] The ultimate goal to achieve in an individual patient with RA is a (long-standing) state of remission. To date, a significant proportion of the patients have still not reached this target of remission or even a more lenient target of low disease activity.[11] This implies that the care for RA can still be improved. While improvement of care often has a connotation of 'developing better drugs', in the field of RA a better implementation of existing recommendations in daily practice may be similarly effective in achieving this goal.

Treat to target

As mentioned before, a treat-to-target approach has been formulated to provide guidance for the management of RA in clinical practice. It describes definitions for achieving a clinical state of remission, and the frequency (every three months in patients with active RA and every six months in patients with low disease activity or remission) of patient monitoring using validated composite measures.[25,27]

Both the EULAR and treat-to-target recommendations have been recognized by experts to be associated with better functional and radiographic outcomes.[28] Patients agree with these recommendations,[29] but may experience and interpret symptoms differently than their physicians.[30-32] Here, a trained nurse could be instrumental in helping patients understand why clinicians want to follow a treat-to-target approach.[33]

Implementation of recommendations in clinical practice

As mentioned above, better implementation of recommendations in clinical practice is important to improve care for RA. In general, increasing numbers of recommendations for clinicians have been developed during the past decade. Recommendations seek to improve the quality of care, and are thought to have an impact on patient outcomes, and there is a need to disseminate and implement them in clinical practice. Implementation of recommendations is not easy and not well understood. Strategies of dissemination are important, but previous studies have shown that it is not clear which strategy is most appropriate.[34,35]

Another factor of importance is related to how physicians interpret the content of recommendations: Physicians tend to follow recommendations according to their own interpretation, especially if the text of recommendations leaves room for alternative interpretations. Another well-known factor interfering with an appropriate implementation is the presence of significant comorbidities that may or may not interfere with a correct follow

up of recommendations (that often do not specifically include guidance about specific co-morbidities). Lack of awareness on -and agreement with- therapies are also reasons for not implementing them in clinical practice.[36-38]

CLINICAL OUTCOMES

Disease activity

Inherent to the treat-to-target strategy is the use of composite scores to evaluate disease activity and treatment success. A high score implies high disease activity and a need to intensify treatment. During the 1990s these scores have been developed, based on physicians' and patients' judgement of disease activity, primarily to study the efficacy of treatments in clinical trials,[39] and later to assess variation of disease activity over time in individual patients. The first composite score was the Disease Activity Score (DAS). This measure includes the Ritchie Articular Index (RAI) for the assessment of tenderness in 53 joints, the number of swollen joints among 44 joints, the erythrocyte sedimentation rate (ESR in mm/hr.) and the visual analogue scale (VAS) for patient's assessment of global health (ranging from 0-100 with 0=best and 100=worst). All together, these components form the following DAS formula: $0.54 * \sqrt{RAI} + 0.0065 * SJC + 0.33 * \ln(ESR) + 0.007 * VAS\text{-}GH$ (Patient's assessment of global health, or alternatively, patients' assessment of global disease activity, rated on a 100 mm visual analogue scale, with 0 mm as best and 100 mm as worst possible).[40] The regression coefficients and the mathematical transformations, which are incompletely understood and inappropriately valued by many as being too laborious, serve in reality to optimize the performance of the DAS in groups of patients and in individuals.

EULAR has formulated criteria with which patients can be classified as having high (DAS>3.7), moderate (DAS: 2.4-3.7) or low disease activity (DAS: 1.6-2.4) or remission (DAS<1.6). A clinical improvement is defined when the DAS is 0.6 points lower than at the previous visit.[41, 42] Later, modifications of the DAS have been developed, such as the DAS28 including only 28 joint counts for swelling and tenderness.[43] Another modification includes C-reactive peptide (CRP) instead of ESR. In addition, indices with a far simpler metric have been developed to measure disease activity: the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI).[44,45] Theoretically, these simplifications have gone at the cost of performance of the indices: At the group level they still work; at the individual patient level they may fall short.

Nowadays, the DAS (actually often its 28-joint modification with CRP instead of ESR) is one of the most used composite scores worldwide. In clinical trials it has been proven that adjustment of treatment intensity based on the DAS results in better clinical and radiographic outcomes.[46-48] However, in terms of implementation, a lot is still to gain: Several studies have suggested that DAS-steered therapy is not yet widely applied in clinical practice.[49-54] Among the multiple alternative explanations, the following two are relevant for the discussion here: 1. Physicians may put more value on certain components of the DAS than on the DAS itself, and use for instance ESR or swollen joint count rather than DAS to decide about treatment; and 2.[55] Differences between the patient's and the physician's perception of the level of disease activity may be at the basis of a patient's refusal to follow up a DAS-based advice by the physician.

Physical functioning

In addition to disease activity, measures for functional disability have been developed in order to score how well patients were able to perform daily activities. The most widely used measure is the Health Assessment Questionnaire (HAQ). The HAQ consists of 24 questions regarding eight distinct categories: dressing, arising, eating, walking, hygiene, reach, grip and usual activities.[56] The HAQ reflects disability in daily activities. With disability either related to actual disease activity or to damage due to previous disease activity, the HAQ can be seen as consisting of two components, the reversible and the irreversible HAQ.[57] Medication changes that suppress actual disease activity may decrease the total HAQ only to the extent where sustained damage has a permanent impact on functional ability.[57,58] Thus, to avoid irreversible disability, disease activity has to be suppressed early, in order to prevent the occurrence of joint damage.

Radiologic joint damage

Earlier treatment initiation and the use of combinations of therapies including oral corticosteroids or the newer bDMARDs have resulted in fewer patients developing severe joint damage. Ideally, clinical remission (no symptoms of RA activity) is accompanied by radiographic remission (absence of joint damage, or no progression from baseline). Joint damage can be assessed with several scoring methods.[59] For the small joints of hands and feet the modified Sharp van der Heijde Score (SHS) is often used, which scores the number and severity of erosions and the severity of joint space narrowing in 44 joints of the wrists, hands

and feet, resulting in a possible maximum score of 448.[60] The SHS is usually applied in clinical trials, because it is too comprehensive to apply in individual patients in clinical practice, and requires special training. In research, SHS is still considered very important because it may reflect the level of disease activity, both in terms of extent and duration. Often, (partially) patient-reported outcomes such as DAS and HAQ are tested against the external standard of joint damage, quantified by SHS. The Larsen score is most often used to score the severity of damage in the large joints (shoulders, elbows, wrists, hips, knees and ankles), and has a range from 0 to 5 per joint.[61]

TREAT TO TARGET: FROM TRIALS TO DAILY PRACTICE

Many trials have proven the efficacy of targeted treatment with regard to clinical outcomes. The TICORA study was the first to demonstrate that targeted treatment aiming at low disease activity results in better clinical and radiological outcomes than 'routine' interview-based care.[46] Other trials demonstrating that a treat to target approach may result in remarkable clinical and radiological improvement were FINRA-Co,[62] CAMERA,[63] and the BeSt study.[64] The BeSt study, discussed in some more detail here since data from this study will feature in this thesis, has started as a multicentre randomised clinical trial consisting of four treatment arms and aimed at effective disease suppression using principles of targeted treatment in patients with recently diagnosed active RA. Between 2000 and 2002, 508 patients were randomised to: 1) sequential monotherapy of csDMARDs, 2) step-up therapy of csDMARDs, 3) initial combination therapy of csDMARDs with tapered high-dose prednisone or 4) initial combination therapy including infliximab. In addition, intra articular corticosteroid injections were allowed at the rheumatologists' discretion. Every three months, protocolled treatment adjustments were made based on the DAS. The HAQ was also completed at each visit. The Best study was one of the trials that have shown that DAS-steered treatment may result in better long-term clinical outcome, such as functional ability,[64] and in less progression of joint damage.

METEOR and other databases

The benefits of DAS-steered therapy have been studied in clinical trials[46-48,65,66] including optimal protocols, motivated rheumatologists and nurses, and relatively healthy (trial) patients. Whether or not treat-to-target is feasible and practiced in common daily clinics,

however, was not well known. The Measurement of Efficacy of Treatment in the 'Era of Outcome' in Rheumatology (METEOR) database has been developed to help clinicians implementing strategies such as treat-to-target in their routine clinical care. The database serves as an online software tool for rheumatologists to encourage frequent monitoring, subsequent treatment adjustments, and registration of disease activity and physical functioning in patients with RA. The METEOR initiative has been started by rheumatologists and has been developed for rheumatologists worldwide. Besides composite measures and functional ability data, rheumatologists can add information on medication use and other patient- and physician- reported outcomes. METEOR can also provide benchmarks to the rheumatologist that allows him to compare his performance with that of other rheumatologists. This may lead to research comparing data of clinical outcomes in RA care within and between countries.[67] Apart from METEOR, other international initiatives (registers, databases or cohorts) promote T2T in clinical practice and advocate comparing clinical outcomes between countries.[68,69] Many of these initiatives exploit a rather small database and although they may overlap in design and registration, it appears to be difficult to combine data for integrated analyses. To improve the quality of research EULAR has published a repository of databases in which researchers can collaborate and share information on databases, which will be further discussed in this thesis.

International Recommendation Implementation Study (IRIS)

To study the incorporation of the EULAR and the treat to target recommendations for RA in clinical practice and to identify how application of these recommendations by rheumatologists could be further enhanced, the International Recommendation Implementation Study (IRIS) was started. In the IRIS a survey was established to study whether rheumatologists apply the recommendations in clinical practice. A well-recognized pitfall of surveys is that we do not know if the outcome of the survey truly reflects daily practice: responses might be influenced by 'desirable' answers that participants may give.[29,50,52,54]

For the IRIS study, rheumatologists worldwide were contacted via their national rheumatology societies and asked to participate, and 132 rheumatologists from many countries agreed. These were asked to follow an educational program, which included reading two scientific papers on treat to target therapy, and watching an educational video. Before the educational training they were asked to fill in a questionnaire on their awareness on the EULAR and treat to target recommendations. After the educational program, the participating

rheumatologists were asked to each include 5-10 newly diagnosed RA patients, which were then followed up for one or two years.

OUTLINE OF THIS THESIS

Main Aims

- Compare rheumatologists' agreement with - and their actual performance of - treat-to-target recommendations in daily clinical practice.
- Investigating (cultural) differences in perceptions of both the RA-patient and the treating physician in rating the global disease activity of the patient

The main focus of this thesis is on treat-to-target therapy and improving care in RA, in particular on rheumatologists' awareness and the implementation of treat-to-target recommendations in daily clinical practice. In **Chapter 2** we focused on existing databases in the field of rheumatoid arthritis. Here we have described the results of a systematic literature review in which we were aiming to provide an overview of the existing European (international and national) databases in RA. In four international- and 30 national databases we described characteristics, such as the aims, funding, size, year of inception, collection of clinical data and participation in the repository of databases. The latter database was set up by the EULAR to stimulate collaboration between European researchers. In the context of a DAS steered trial (the Best-trial database) we have further investigated the use and the benefits of intra articular injections on local inflammation, which includes swollen and tender joints over 3 months (short term). Over a longer period, intermediate (until 1 year after injection) and long term (until 8 years after injection) we investigated the association between intra articular injections and systemic clinical outcomes, such as the DAS and HAQ (**chapter 3**).

In **chapter 4 and 5** we focused on the patient- versus the physician-reported outcomes in RA in the METEOR database, since they may have different perceptions of patients' disease activity. We investigated differences in assessments of the patients' global disease activity by patient and physician, and explored which determinants influenced both patients' and physicians' assessments. We also investigated which determinants were associated with a difference (>20mm) in global disease activity score of the patient and the physician.

In **chapter 5** we investigate whether differences between patients' and physicians' assessment of global disease activity are dependent on the country of residence, as language, patient-

physician interaction or other cultural differences may affect how patients and physicians perceive this subjective outcome.

In **chapter 6** we focussed on whether DAS steered therapy has been applied in clinical practice. Questionnaire-based research suggests that rheumatologists apply T2T on a daily basis, while on the other hand some observational studies have suggested that DAS steered therapy is infrequently practiced. Therefore we have investigated whether - and if yes: to what extent - DAS steered therapy has been applied in a clinical practice database (METEOR). The association between level of DAS and treatment adjustments was compared in various DAS-classification groups.

In **chapter 7** we showed the first results of the IRIS study. This study compared rheumatologists' willingness to use a T2T approach, as based on the results of a questionnaire, with subsequent data from the METEOR database showing how T2T is implemented by these rheumatologists in daily practice. Since the questionnaire was followed up by an educational program on the EULAR and T2T recommendations, we will be able to give an impression on whether such an educational program is useful in the process of implementing recommendations in clinical practice.

In **chapter 8** we summarized and discussed the results of the studies reported in the thesis. Also we will give a future perspective on recommended research in this field.

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