Worldwide treatment opportunities of rheumatoid arthritis

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CHAPTER 1

General Introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is among the most common rheumatic diseases, with an estimated global prevalence of 0.24%. This prevalence varies worldwide, with a lower prevalence in Asia, North Africa and the Middle East (0.16%) and a higher prevalence in Western Europe and Northern America (0.44%).[1]
RA is a chronic and systemic autoimmune disease, which is characterized by inflammation in joints and potentially in multiple organs. The aetiology of the disease is not completely clear, although genetic as well as environmental risk factors, such as smoking, are thought to play a role.[2, 3] The disease occurs more often in women than in men, with a ratio of approximately 3:1 for women compared to men.[1]
Patients with RA often present with pain, swelling and/or (morning) stiffness in small peripheral joints of the hands, wrists and feet, but other peripheral joints are also commonly affected.[4] If the disease is insufficiently treated severe joint damage can occur, which can lead to pain and joint deformities and consequently limitations in performing daily live activities.[5, 6] Although the disease is characterized by joint inflammations, RA can also have systemic consequences, at least if left untreated, including an increased risk of infections and cardiovascular disease, which can lead to an increased mortality rate in RA patients.[7, 8] Experts think there are at least two RA phenotypes, most obviously based on presence or absence of autoantibodies.[9, 10] The two most important autoantibodies involved in the diagnosis and prognosis of RA are rheumatoid factor and anti-citrullinated protein antibodies (ACPA). Rheumatoid factor is present in 60-80% of RA patients and ACPA is found in 70-90% of RA patients.[11] ACPA has a slightly higher sensitivity, but definitely a better specificity than rheumatoid factor.[12] Both rheumatoid factor and ACPA can be present years before symptom onset and are associated with the development of RA.[13] Patients can test positive for one or both of these antibodies, or negative for both. Although the initial presentation with arthritis may be similar, the presence of autoantibodies is associated with a high risk of developing characteristic rheumatoid joint damage, with destruction of joint cartilage, erosions of bone, and associated insufficiency of ligaments.[14] In recent onset arthritis, the presence of autoantibodies is also predictive of progression to more severe RA.[15] There are conflicting data on whether patients without autoantibodies achieve more drug free remission.[16-18] More recently, anti-CarP antibodies were identified. Often present together with ACPA, they have been identified as independent risk factor for radiologic progression.[19, 20]

In recent years, there have been significant changes in the approach to treatment of RA, at least for those who can afford specialized rheumatologic care. As it appears to be more difficult to effectively suppress inflammatory processes when the disease course is well

underway, efforts have been made to start treatment early, and to allow this, to diagnose patients earlier.[21] This not only helps to alleviate the burden of trying to function with painful and stiff affected joints, it also can prevent permanent damage.[22] There may be even a window of opportunity where chronicity of inflammation can be prevented and permanent remission even after discontinuation of the initial medication can be obtained.[23, 24] In the effort to achieve effective suppression of the disease, rheumatologists have been helped by the development of newer anti-rheumatic drugs, the so-called biologics. These treatment options will be described in detail in this chapter. Although often very effective, they are costly and can have severe infections as side effects.[25, 26] Even in effectively treated patients, due to this expensive medication, often live-long increased healthcare use and potential limitations in physical functioning and the ability to work, rheumatoid arthritis has a high personal and societal burden.[1]
However, access to treatment differs in different countries.[27] Different causes may underlie these differences in access to efficient rheumatologic care. A lack of knowledge among patients and local health care providers about the early manifestations of RA and a lower availability of specialized rheumatology clinics may cause patients to present to a rheumatologist at later disease stages. Furthermore, differences in financial resources of patients and hospitals and lower healthcare budgets at a government level may hamper regular follow-up visits of patients and especially treatment with bDMARDs (see below) may be unaffordable. Therefore the prognosis of RA patients differs worldwide and efforts are needed to enable the most effective treatment of RA in all patients.

OUTCOME MEASURES

Throughout this thesis, treatment response is mainly assessed by measuring disease activity and functional ability.

Disease activity

Initially to monitor outcomes in clinical drug trials, and subsequently to monitor treatment response in daily practice, several composite scores have been developed, to measure disease activity in RA. In this thesis, we will use the Disease Activity Score (DAS) and the DAS28. The DAS is based on the Ritchie Articular Index (RAI) to measure tenderness on joint examination of 53 joints, a Swollen Joint Count of 44 joints, the Erythrocyte Sedimentation Rate (ESR) in blood, and the patient's evaluation of global health, measured on a visual analogue scale (VAS).[29] Different cut-offs have been defined to indicate disease severity: DAS >2.4 indicates high disease activity, DAS between 1.6 and 2.4 indicates low disease activity and DAS <1.6 indicates remission[30]. The DAS28 is a later version of the DAS, including a swollen and tender joint count of only 28 joints, ignoring,

among others, the joints of the ankles and feet .[31] Cut-offs for the DAS28 are DAS28 >3.2 for high disease activity, DAS28 between 3.2 and 1.6 for low disease activity and DAS < 2.6 for remission.[32] The ultimate aim for the treatment of RA would be drug free remission, which, particularly when of considerable duration, is the outcome measure closest approximating cure.[33].

2010 criteria for the classification of RA	
• Joint involvement	
1 large joint	0
2 to 10 large joints	1
1 to 3 small joints	2
4 to 10 small joints	3
>10 joints with at least 1 small joint	5
• Serology	
Negative RF and ACPA	0
Low-positive RF or ACPA	2
High-positive RF or ACPA	3
• Acute-phase reactants	
Normal CRP and ESR	0
Elevated CRP and/or ESR	1
• Duration of symptoms	
<6 weeks	0
≥6 weeks	1
A score of ≥6 of 10 points is needed for classification of RA, in a target population with at least one joint with definite clinical synovitis, not better explained by another disease. RA can also be classified in case of typical erosions or long-standing disease previously satisfying criteria.	

Figure 1. 2010 EULAR/ACR criteria for the classification of RA

Although diagnostic criteria are not available, classification criteria for RA exist, of which the newest version has been published in 2010.[28] Next to joint pain and/or swelling, these include the presence of autoantibodies, elevated plasma levels of acute-phase reactants and chronicity of symptoms.

Joint involvement: any swollen or tender joint on examination. Large joint: shoulders, elbows, hips, knees and ankles. Small joints: joints in the hands, wrists and feet. ACPA = anti-citrullinated protein antibodies; CRP= c-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis, RF = rheumatoid factor.

Functional ability

Since patients with active RA have difficulty in performing daily activities due to joint inflammation and/or destruction, functional ability is an important disease outcome. It can be measured using the Health Assessment Questionnaire (HAQ).[34, 35] This is a self-administered questionnaire, available in more than 60 different languages. The questionnaire includes questions on eight components representing activities of daily living: dressing and grooming, rising, eating, walking, hygiene, reach, grip and activities. The results of the HAQ range from 0 to 3, with a higher score indicating more functional impairement.For individual patients, an improvement in HAQ of at least 0.22 is considered a clinically relevant improvement[36].

TREATMENT

In recent decades, there has been a tremendous improvement in the treatment of RA patients.[37-39] Whereas treatment used to consist of NSAIDs in order to try and reduce joint pain, the introduction of disease modifying anti-rheumatic drugs (DMARDs) enabled rheumatologists to actually treat the underlying joint inflammation.

Current anti-rheumatic drugs can be divided into several categories: conventional synthetic (cs)DMARDs, glucocorticoids, biologic (b)DMARDs and JAK-kinase inhibitors. To date, the csDMARD methotrexate is internationally recommended as initial treatment for all RA patients, due to its reputed efficacy and favorable toxicity profile, easy use and low medication costs.[40, 41] Other commonly prescribed csDMARDs include sulfasalazine, leflunomide and hydroxychloroquine.[42]

The biologic (b)DMARDs limit joint inflammation by various modes of action. Currently the majority of available bDMARDs target TNF-α pathways (Infliximab[43, 44], Adalimumab[45], Certolizumab Pegol[46], Etanercept[47] and Golimumab[48]). Other bDMARDs have different modes of action, such as Abatacept[49] (binds CD80 and CD86 to selectively inhibit T-cell activation), Rituximab[50] (anti CD20, B-cell depleting) and Tocilizumab[51] (interleukin 6-receptor antagonist). Although bDMARDs are highly effective, they are currently not recommended as initial treatment due to their high costs, but only after failure of initial treatment with csDMARDs. In countries with lower wealth, the availability of bDMARDs is often limited and in these countries treatment with bDMARDs is not accessible for most patients.[52]

The most recently developed drugs to treat RA are the JAK-kinase inhibitors. In 2017 tofacitinib and baricitinib were approved by the European Medicine Agency[53] but these drugs are not yet available worldwide. Thus, although clinical trials have been very promising, experience in daily practice is still limited.

Glucocorticoids are recommended as bridging therapy (possibly starting with a high(er)

dose which is then tapered to nil), or for prolonged use at low doses, or as single parenteral depot.[40] This has been very effective in quickly suppressing inflammation and limiting joint damage.[54] Several studies have shown that it is more effective to initiate treatment with a combination of DMARDs and a bDMARD and/or glucocorticosteroid than to start with a single drug.[45, 55, 56] Whether this indicates that drugs in combination therapy may be dosed lower than in monotherapy remains to be investigated.

The currently most important improvements in the treatment of RA are early treatment and a treat-to-target approach. Efforts are being made to establish a diagnosis of the disease and start DMARD treatment as early as possible. It is suggested that a window of opportunity exists, during which the effectiveness of treatment is disproportionally higher and sustained long term benefits can be expected, and chronicity may be prevented.[23] This window of opportunity is often suggested to be 12 weeks, although this is more based on expert opinion than on scientific evidence.[24] To optimally benefit from early treatment initiation, in recent trials patients can start DMARD treatment before the diagnosis of RA is made, for example patients with unclassifiable ('undifferentiated') arthritis (UA) or with clinically suspect arthralgia, with the aim to delay or event prevent the development of RA.[57-59]

The availability of composite scores to measure disease activity as well as more effective treatment options has also given momentum to the application in daily practice of the treat-to-target approach. This requires rheumatologists to start treatment as soon as the diagnosis of RA is made, assess disease activity regularly (every 1-3 months) and change or intensify treatment as soon and as long as a predefined treatment target is not met. This target should be preferably remission, but at least low disease activity.[60]

Composite scores may be influenced by symptoms that are not (only) determined by rheumatic disease activity. Several studies have suggested that patients with a high BMI respond less well to certain DMARD than patients with a lower BMI. It appears that obese patients experience more pain even when other signals indicate that disease activity is sufficiently suppressed.[61, 62] In other studies it has been reported that women respond differently (possibly less well) to DMARD treatment than men.[63-65] These reports might indicate that individualized treatment, possibly gender and/or BMI related, rather than following a uniform order of treatment options should be integrated in treatment to target in daily practice.

Especially in countries with sufficient resources, the combination of earlier diagnosis, treatment-to-target and the availability of a wide array of effective anti-rheumatic drug therapies, has strongly improved the prognosis of patients who did not respond well to initial treatment with csDMARDs. In these countries, it has limited the occurrence of joint damage and joint deformities in RA patients, as well as extra-articular manifestations of rheumatoid inflammation, which used to be very common, and it has improved functional

ability and mortality rates.[4, 66, 67] However, worldwide it can be still challenging to focus on early recognition and treatment to target. In many countries due to restricted financial resources and availability of effective medication, limited access to healthcare systems, and insufficient availability of specialized rheumatology clinics, early recognition and early referral of RA patients is often not feasible. Consequently, consistently using a treat-to-target approach is very challenging.

The chapters in this thesis focus on optimization of treatment of RA patients in daily practice, based on previous studies and databases.

RESEARCH DATABASES

The chapters included in this thesis were based on research in three different databases: the METEOR database, the database of the BeSt study and the database of the IMPROVED study. Below, a brief introduction to each of these databases will be provided.

METEOR

In 2006 a group of rheumatologists developed the Measurement of Efficacy of Treatment in the " Era of Outcome" in Rheumatology (METEOR) tool, with the aims to stimulate treat-to-target, to improve patient care and to create an international RA research database. The METEOR tool is a free, online tool available worldwide in which daily practice data of all RA patients visiting a rheumatologist can be entered. Using this tool, patient and disease characteristics, patient and physician reported outcomes, physical functioning and prescribed treatment can be registered Based on the available information, a range of disease activity measures is automatically calculated (e.g. DAS, SDAI, CDAI). Medication, disease activity and physical functioning are then displayed in graphs, in order to facilitate treatment decisions and the interaction between patient and physician.
Data entered with the METEOR tool, with patient identifying data anonymized, are available in a large research database, which has been used in several chapters of this thesis.
Currently, data from 32 different countries are available in the METEOR database, which offers the opportunity to investigate cross-country differences and to answer research questions regarding real life clinical practice. An extended description of the METEOR database can be found in **Chapter 2**.

BeSt

The BeSt study (Dutch acronym for 'treatment strategies') is a multicentre, randomized, single-blind clinical trial in 508 patients with recent-onset RA.[55] The aim of the BeSt

study was to compare four different treatment strategies: 1) sequential monotherapy starting with MTX, 2) step-up combination therapy, also starting with MTX, 3) initial combination therapy with MTX, sulfasalazine and a tapered high dose of prednisone and 4) initial combination therapy with methotrexate and infliximab. Patients were treated to target aimed at DAS≤2.4, calculated at three-monthly intervals. Thus, treatment was changed, intensified or restarted if the treatment target was not achieved or lost and tapered when the treatment target was achieved and maintained. Total follow up duration was 10 years. **Chapters 9** of this thesis is based on the BeSt study.

IMPROVED

The IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid or Very Early arthritic Disease) study is a multicentre, randomized, two-step, single-blind clinical trial in 610 patients with recent-onset RA or undifferentiated arthritis[68]. The aims of the IMPROVED study were 1) to determine the percentage of patients with recent-onset RA or undifferentiated arthritis who achieve and maintain clinical remission on initial combination therapy with MTX and prednisone and 2) to determine whether combination therapy with MTX, sulfasalazine, hydroxychloroquine and prednisone (arm 1) or with MTX and adalimumab (arm 2) is most efficient if remission is not achieved. **Chapter 7** of this thesis is based on the IMPROVED study.

Patients were followed during 5 years, with evaluations of disease activity every 4 months. All patients started treatment with MTX and a tapered high dose of prednisone and where then treated-to-target aimed at drug-free DAS remission. If patients were in remission at 4 months, treatment was tapered and subsequently discontinued as soon and as long as DAS-remission (DAS<1.6) was achieved and maintained. If patients were not in remission at 4 months, patients were randomized directly into one of the two treatment arms. Likewise, patients in early remission could later become eligible for randomization if remission was lost and not regained on the initial treatment. For all patients, treatment was changed, intensified or restarted if DAS-remission was not achieved or lost, but always again tapered and possibly discontinued if DAS-remission was regained. Figure 3 shows the treatment steps of the IMPROVED study.

AIMS AND OUTLINE OF THIS THESIS

Despite the major advances described above that have been made in the treatment of RA, for individual patients there remain uncertainties. Most notably, it is still unclear which treatment is the best choice for each individual patient. As a consequence, some patients still experience non-response, and have to switch treatment several times before disease activity is sufficiently suppressed. In addition, many of the available drugs may have

potentially serious side effects and treatment costs are often huge. In addition, uncertainty about which is the optimal treatment target for an individual patient may result in both undertreatment, risking damage in the future, and overtreatment, risking side effects without relevant benefits. Therefore in this thesis, we aim to investigate ways to optimize treatment strategies and the choice of treatment for different patients.
In the first part of this thesis, we will aim at optimizing treatment with currently available drugs for the treatment of RA patients. In the second part of this thesis, we will focus on worldwide differences in RA patients and in rheumatologic care.

Part 1: optimizing current RA treatment
In **chapter 2** we first give an extensive description of the development of the METEOR database over 10 years, its research opportunities and future perspectives. In **chapter 3** and **4** we focus on methotrexate, the drug of first choice in the treatment of RA. Current MTX dose recommendations exist for monotherapy, but specific dose recommendations for MTX used in combination therapy are lacking [40, 69] We hypothesized that in the presence of other effective anti-rheumatic mediation, the dose of MTX might be lowered without losing effectiveness. Therefore in **chapter 3** we provide a systematic literature review that investigates whether starting with higher MTX doses in newly diagnosed, early RA patients leads to better short term outcomes, when MTX is used in monotherapy or in combination with glucocorticoids or bDMARDs. In **chapter 4** we have asked a similar type of question, but now addressed it longitudinally in the METEOR database. We compared a high versus a lower MTX dose in newly diagnosed RA patients, with MTX used in monotherapy, or in combination with other csDMARDs and/or glucocorticoids.
It is commonly thought that in general, men with RA have a better prognosis than women. However, conflicting evidence exists regarding the nature of this evidence.[63, 70] In **chapter 5** we investigated in the METEOR database whether men and women are treated differently in clinical practice. Furthermore, we assessed whether they respond differently to treatment by looking at disease activity and HAQ over time and whether there are differences between men and women regarding the time to switch from their initial treatment strategy to a next treatment step.
In about half of the patients initially treated with MTX or with MTX and a glucocorticoid, the desired treatment target of remission or low disease activity is still not met and treatment should be adapted.[71]
In **chapter 6** we analysed data of the BeSt study. Since the follow-up of the BeSt study was 10 years, it provides the opportunity to study long-term outcomes of targeted treatment. In **chapter 10** we selected patients from the BeSt study who responded well to their initial treatment during 10 years. We compared patients initiating monotherapy and patients initiating combination therapy to assess whether patients starting combination therapy had additional benefits regarding disease activity, physical functioning and radiographic

damage progression, compared to patients starting monotherapy.
In **chapter 7** we analysed data from the IMPROVED study. International recommendations advise targeted treatment, preferably aimed at remission but at least low disease activity. [60] In this chapter we assessed whether aiming at remission and thus changing treatment if patients were already in low disease activity, led to an improvement in functional ability, measured as a change in HAQ.

Part 2: Worldwide differences in RA

Differences between countries might exist in the type of patients and treatment choices. A major contributor to these differences might be the access to certain (expensive) medications.[52] In **chapter 7** we compare the access to medication across different countries in the METEOR database and we assess whether a lower access to medication leads to less prescription of bDMARDs and a worse management of disease activity. In **chapter 8** we compare the distribution of painful and swollen joints in early RA patients in different countries, in order to investigate whether the disease phenotype is comparable in both countries at presentation.

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PART 1

Optimizing current treatment of RA