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

CHAPTER 2

10 years of METEOR (an international rheumatoid arthritis registry): development, research opportunities and future perspectives

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ABSTRACT

Objective: Ten years ago, the METEOR tool was developed to simulate treatment-to-target and create an international research database. The development of the METEOR tool and database, research opportunities and future perspectives are described.
Methods: The METEOR tool is a free, online, internationally available tool in which daily practice visits of all rheumatoid arthritis patients visiting a rheumatologist can be registered. In the tool, disease characteristics, patient and physician reported outcomes and prescribed treatment could be entered. These can be subsequently displayed in powerful graphics, facilitating treatment decisions and patient-physician interactions. An upload facility is also available, by which data from local electronic health record systems or registries can be integrated into the METEOR database. This is currently being actively used in, among other countries, the Netherlands, Portugal and India.
Results: Since an increasing number of hospitals use electronic health record systems, the upload facility is being actively used by an increasing number of sites, enabling them to benefit from the benchmark and research opportunities of METEOR. Enabling a connection between local registries and METEOR is a well-established but time-consuming process for which an IT-specialist of METEOR and the local registry are necessary. However, once this process has been finished, data can be uploaded regularly and relatively easily according to a pre-specified format. The METEOR database currently contains data from >39,000 patients and >200,000 visits, from 32 different countries and is ever increasing. Continuous efforts are being undertaken to increase the quality of data in the database.
Conclusion: Since METEOR has been founded 10 years ago, many rheumatologists worldwide have used the METEOR tool to follow-up their patients and improve the quality of care they provide to their patients. Combined with uploaded data, this has led to an extensive growth of the database. It now offers a unique opportunity to study daily practice care and to perform research regarding cross-country differences in a large, worldwide setting, which could provide important knowledge about disease and its treatment in different geographic and clinical settings.

INTRODUCTION

Treat-to-target has been repeatedly shown to be highly effective in rapidly reducing disease activity in rheumatoid arthritis (RA) patients [1]. Such treat-to-target strategy requires a long-term follow-up of patients with regular assessments of treatment effectiveness, using validated disease activity measures such as the Disease Activity Score[2] (DAS), the Simplified Disease Activity Index[3] (SDAI) or the Composite Disease Activity Index[4] (CDAI). Although highly effective, treat-to-target is not always followed in clinical practice[5], possibly because it is not always easy to obtain a fast disease activity measurement. Therefore 10 years ago, in 2006, the Measurement of Efficacy of Treatment in the "Era of Outcome" in Rheumatology (METEOR) tool was developed to stimulate treat-to-target, improve patient care and create an international RA research database[6].

The METEOR tool

The METEOR tool is a free, online tool available worldwide in different languages. The tool is entirely web-based and easy to use and can therefore be used without involvement of the local IT department. Within each centre using METEOR, one coordinator (e.g. a rheumatologist or research nurse) is appointed and receives administrator rights from the METEOR organisation. This administrator can create all user accounts necessary for that centre. All METEOR users within each centre can access the METEOR tool with their own account and can at the same time access all patient data entered by their colleague users in the same centre. This easy implementation strategy has facilitated worldwide spread of the METEOR tool.

In the tool, data of all RA patients visiting a rheumatologist can be entered. This can be new as well as existing RA patients, who are followed according to usual care. Each visit of the patient can be registered in METEOR. In 7 structured screens within the tool, data about patient and disease characteristics, patient and physician reported outcomes and prescribed treatment could be registered (table 1). Based on the available data, the tool automatically calculates a range of disease activity scores: DAS, DAS-3 (DAS calculated with 3 components), DAS28 (DAS based on 28 joint count), DAS28-3 (DAS based on 28 joint count and 3 components), SDAI, CDAI and Routine Assessment of Patient Index Data (RAPID3) [7]. Medications, disease activity and physical functioning are subsequently displayed in illustrative and user-friendly graphics, facilitating treatment decisions and patient-physician interactions. The METEOR tool also offers benchmarking possibilities, to compare patient data, care indicators and treatment at the level of the rheumatologist, site, country or the complete METEOR database. Furthermore, it is possible to provide limited user access to patients, such that patients can complete the HAQ[8] at home prior to the consultation, in order to enhance the quality of the consultation.

Table 1. Variables collected in METEOR (adapted from van den Berg et al.[10], with permission)

Patient characteristics	**Disease characteristics**
Age	Date of symptom onset
Gender	Date of diagnosis
Marital status	Erosions (present/absent/unknown)
Smoking habits	Rheumatoid factor (present/absent/unknown)
Height	ACPA (present/absent/unknown)
Weight	Tender joint count (53 or 28)
	Swollen joint count (44 or 28)
Treatment	Ritchie Articular Index
Drugs (type, dose, start and end date)	Erythrocyte Sedimentation Rate levels
Intra-articular injections	C-Reactive Protein levels
Surgery	Comorbidities
	Physician reported outcomes
	Physician global disease activity
	Patient reported outcomes
	Patient global disease activity
	Visual Analogue Scale for pain
	Health Assessment Questionnaire
	RAPID3

ACPA = anti-citrullinated protein antibodies RAPID3 = Routine Assessment of Patient Index Data

Data protection and safety

All patient data in the METEOR database are anonymized, by storing all patient identifying data in an encrypted manner. Therefore, for none of the included countries – for example the Netherlands, Portugal, South Africa, Mexico and the USA – an informed consent is needed when adding new patients to the database. Identifying data can only be decrypted by the site that has created the data, such that rheumatologists always have access to detailed data regarding their own patients. Since the METEOR database contains medical data, it is impossible to delete data. Instead, data may be invalidated in case of errors, such that new and correct data may be created. A yearly check is performed to ensure that data protection and safety are in accordance with data protection regulations of all included countries.

Upload and download facilities

In recent years, an increasing number of hospitals have implemented Electronic Health Records (EHR) to record daily patient care. This means that using METEOR as a separate

tool necessitates double data entry, thereby costing instead of saving time for the physician. In order to overcome the burden of double data entry, METEOR has developed upload and download facilities. With the download facility, data from the METEOR database can be uploaded in the local EHR system. The upload facility can be used to upload data from the local EHR system into the METEOR database, but it can also be used to link data from local databases to the METEOR database. The upload facility is currently being actively used in, among other countries, the Netherlands, Portugal[9] and India. Using the upload or download facilities enables users to benefit from the benchmark and research facilities, without the problem of double data entry or having to give up the local registries.

The METEOR database contains a total of 200 data elements, grouped in a complex structure of 7 tables. This structure ensures high speed data entry and data extraction for research purposes. It also allows for missing data, since tool users are not obliged to fill out all fields and it ensures internal consistency of the database. However, it also results in a very specific structure that is needed before data can be uploaded into the database. In general, between 150 and 200 data elements must be integrated in the METEOR database via the upload file.
A standardised XML-file, together with a reference guide and additional documentation, have been developed, to convert data from local registries into the correct format for upload into the database. Data from the local registry must be extracted and stored in this XML-file before they can be uploaded. Since this process is rather complicated, a local IT-expert is needed, who can cooperate with a METEOR IT-expert in order to develop a standardised procedure for data extraction, conversion and upload. The completed XML-file may be uploaded in a testing environment for validation. During this validation procedure, the quality and internal consistency of the XML-file is tested, as well as the correct format of each item. Due to the complex database structure, the validation cannot be performed only on a field-by-field level, but the correct relationship between fields also must be tested in order to lead to a consistent database. For example, not only the individual joint scores are stored, but also the complete DAS.
Whereas some items can be transferred directly from a local registry into METEOR, others require conversions. For example, medication data are often stored in different ways, which are not always consistent within one register. During the validation process, all possible errors and differences between the METEOR database and the register are identified, until all data can be uploaded in the correct format. When uncertainty still exists about the correctness of the data, these data are deleted, possibly leading to some missing values. According to experiences with already coupled registries, this is a relatively time-consuming process, requiring up to 5-10 subsequent attempts before all errors are eliminated. However, once this process has been completed, data from the XML-file can be

relatively easily uploaded, according to the specified format. Then not only new data can be added to the database, but replacement of old data is also possible, in order to allow correction of erroneous data.

Research opportunities

All METEOR users who are actively contributing data to the database, including those centres that add data through the upload facility, can perform research in the database. The leading principle is that each participating rheumatologist or centre is the owner of its own data. Therefore, each user can at any time perform research using her/his own data. Researchers also may submit research proposals with a request to perform research on part of or the complete METEOR database. These research proposals are assessed by a scientific committee regarding relevance, quality and ethical aspects. Once approved by the scientific committee, a representative rheumatologist of each site can decide if they allow their data to be used in that particular research project.

Currently, the METEOR database contains data from >39,000 patients and >200,000 visits, added by 78 sites using the METEOR tool and 50 sites using the upload facilities. These data stem from 32 different countries, which are ever increasing. Since rheumatologists are not obliged to complete all fields and sometimes technical issues exist when coupling local registries to the database, not all data are complete. Therefore, continuous efforts are being undertaken to increase the quality of the data in the database.

Nonetheless, the METEOR database offers unique research opportunities. Not only does its large size ensure a large statistical power to investigate an extensive variety of research questions. Furthermore, the strong international character of the database also offers a rare possibility to investigate cross-country differences. Although an increasing number of national databases exist, research questions regarding cross-country comparisons can be answered only by pooling information from these databases, which has already been performed in METEOR. Furthermore, since data are gathered in clinical practice, research questions regarding real life clinical practice can be answered. Some examples of research that has been performed in the METEOR database can be found in table 2.

Table 2. Examples of research projects performed in the METEOR database (adapted from van den Berg et al.[10], with permission).

Topic	Aim	Conclusions
Patient's versus physician's global disease activity[11;12]	To compare the differences between patient and physician global disease activity and identify factors that might influence these differences. In addition, to assess whether these differences vary across 13 countries.	Differences between patients and physician global disease activity vary across countries. In general, agreement between patient and physician was moderate. In most countries patients scored on average higher than physicians. Patients based their judgment primarily on pain, whereas rheumatologists based it on swollen joint count and ESR level.
DAS steered therapy in clinical practice[13]	To evaluate treatment adjustments in response to DAS in RA patients in clinical practice in one centre in the Netherlands.	The majority of patients assessed had already achieved low disease activity, reflecting appropriate treatment intensity. When DAS ≥2.4, treatment was often not intensified due to high tender joint count or specific treatment combinations. This suggests that while aiming for low DAS, physicians have an individual approach, weighting whether all DAS elements are consistent with the total DAS and weather individual variables are likely to respond to DMARD adjustment or not.
Obesity and disease activity[14]	Is BMI associated with RA disease outcomes?	In patients with established RA obesity was associated with higher DAS28 and reduced odds of achieving DAS28 remission. In early RA, obesity was not associated with adverse disease activity outcomes.

Topic	Aim	Conclusions
Is there an effect of treat-to-target training?[15]	To investigate if rheumatologists from several countries that report to agree with existing guidelines indeed follow them up in clinical practice.	Reporting to be compliant with EULAR recommendations and T2T principles, even after dedicated education, does not mean that rheumatologists actually comply with it in clinical practice.
TNF inhibitor use across countries[16]	To investigate whether the relative distribution of TNFi prescriptions for RA varies among countries with different healthcare systems, during two time periods.	The relative prescription of various TNFi differed significantly across several EU countries and the US. Infliximab was prescribed significantly more in EU countries compared to US sites in period 1 (2009-2010). In Italy and Portugal, etanercept was prescribed significantly more than other TNFi in period 2 (2011-2012).
Comparison of RA disease activity indices in two populations[17]	To assess disease activity states using DAS28, CDAI and SDAI and to compare their outcomes in two RA populations.	CDAI and SDAI classified approximately the same number of patients in remission in Portugal and the Netherlands. DAS28 classified a higher percentage of Dutch patients as being in remission, due to a lower ESR.
Quality indicators in RA in clinical practice[18]	To test the feasibility of collecting, storing, retrieving and analyzing necessary information to fulfil a preliminary set of quality indicators that have been proposed by an international task force.	Most of the quality indicators that were proposed by the task force were feasible in clinical practice in most parts of the world.

ESR = erythrocyte sedimentation rate, DAS = disease activity score, DMARD = disease modifying anti-rheumatic drug, EULAR = European League Against Rheumatism, T2T = treat to target, RA = rheumatoid arthritis, TNFi = TNF inhibitors, EU = European, US = United States, CDAI = clinical disease activity index, SDAI = simplified disease activity index

Conclusions and future perspectives

The METEOR database was founded 10 years ago to stimulate treat-to-target, to improve patient care and to create an international RA research database. During these 10 years, many rheumatologists worldwide have started using the METEOR tool to follow-up their patients and to treat their patients more efficiently. Also, an increasing number of sites use the upload facilities to add data to the METEOR database, enabling them to benefit from the benchmark and research opportunities. This has led to the creation of a large international research database that offers a unique opportunity to study daily clinical practice and to perform research regarding cross-country differences. In the future, METEOR will continue to stimulate the worldwide use of the METEOR tool. Furthermore, in sites or countries in which EHRs are used in daily practice, efforts are being made to enable upload facilities; not only to increase the size of the database, but also its quality and the representativeness of the data for the country from which the data were obtained. These efforts will increase the potential value of the database and the number of research questions that METEOR has the capacity to answer, helping us to better understand the disease and its treatment in different geographic and clinical settings, and to improve outcomes for our patients.

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2

CHAPTER 3

Meta-regression of a dose-response relationship of methotrexate in mono- and combination therapy in DMARD naive early rheumatoid arthritis patients

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ABSTRACT

Objective: To investigate a possible short term dose-response relationship of initial treatment with methotrexate in monotherapy and combination therapy in recent onset rheumatoid arthritis (RA) patients.
Methods: A systematic literature search was performed on trials and cohorts including early, Disease Modifying Antirheumatic Drugs (DMARD) naive RA patients, treated with methotrexate, with data on clinical results within 6 months from treatment start. Cohen's effect sizes were calculated for the HAQ, ESR/CRP and/or DAS/DAS28 in 4 treatment groups: methotrexate monotherapy, or methotrexate in combination with synthetic (cs)DMARDs, biologic (b)DMARDs or glucocorticoids. Random-effects meta-regression analyses were performed for each outcome, with treatment group as predictor corrected for baseline HAQ or disease activity and assessment point.
Results: Thirty-one studies including 5589 patients were included. The meta-regression did not support higher effectiveness of increasing methotrexate dose in monotherapy. The number of treatment groups using combination therapy with csDMARDs was too small to perform meta-regression analyses.
In combination therapy with glucocorticoids a higher methotrexate dose was associated with higher (worse) outcome HAQ, but not with DAS/DAS28 or ESR/CRP. In combination therapy with bDMARDs a higher methotrexate dose was associated with higher outcome HAQ and DAS/DAS28, but not with ESR/CRP. All effect sizes were small.
Conclusion: In DMARD naive early RA patients who start methotrexate, either as monotherapy or in combination with bDMARDs or glucocorticoids, a higher initial dose of methotrexate was not associated with better clinical outcomes. This finding suggests that there is little short term gain from starting with high compared to low methotrexate doses.

INTRODUCTION

Methotrexate (MTX) is recommended and widely used as the drug of first choice in the treatment of newly diagnosed rheumatoid arthritis (RA) patients, either as monotherapy or in combination with other drugs, because it is (cost)effective and has an acceptable safety profile[1-3]. Although several mechanisms of action have been proposed, the exact mechanisms of action of MTX in reducing inflammation in RA patients are unknown[4, 5]. In the early trials MTX was used as subcutaneous injection in patients with severe RA refractory to other available medications such as non-steroidal anti-inflammatory drugs[6, 7]. In later years, the importance of initiating early antirheumatic treatment has become apparent [8, 9] and methotrexate was used in earlier disease stages. Initially, MTX was used as monotherapy in low dosages only (7.5-15 mg/week), as a precaution against possible side effects. Current recommendations are to start MTX in a dosage of 15 mg/week orally, escalating with 5 mg/month to 25-30 mg/week or the highest tolerable dosage[1, 3, 4].

Since it was shown that the safety profile of MTX is acceptable in most RA patients[10], higher initial MTX dosages were used in recent trials (20-30 mg/week)[11, 12]. Higher dosages have been reported to be more effective than lower dosages of MTX, although the number of adverse events also slightly increased[4, 12, 13].

Despite the reputation of high effectiveness of MTX, up to 75% of DMARD naive patients (depending on the outcome definition) do not reach a state of low-disease activity within 3 to 6 or even 12 months after starting MTX monotherapy in dosages of 20-25 mg/week[1]. Therefore, the effectiveness of MTX in combination with several other drugs has been investigated, including other conventional synthetic (cs)DMARDs and/or prednisone (or other corticosteroids) or biologic (b)DMARDs. These combination therapies have been shown to be superior to MTX monotherapy in reducing disease symptoms more rapidly and preventing radiographic damage in more patients[9, 14-16]. However, some combination therapies may also lead to more adverse reactions than MTX monotherapy[17, 18]. Specific recommendations regarding the MTX dosage when used in combination with other (types of) medication do not exist. Recently there is a trend in trials investigating combination therapy with bDMARDs – and possibly in daily practice too – to start MTX at the same high dosages as recommended for MTX monotherapy in order to decrease disease activity as quickly as possible[9, 11, 14, 19, 20]. Yet, it might still be that in the first 6 months of treatment, in combination with other drugs there is little additional benefit of higher doses of MTX compared to lower doses[21]. The CONCERTO study[22] recently investigated the effects of starting with various dosages of initial MTX (2.5, 5, 10 or 20 mg/week) in combination with adalimumab 40 mg/2 weeks. A statistically significant positive dose-response between MTX dose and number of patients reaching DAS28 low disease activity or remission was found over 26 weeks. However, among

patients on 10 mg or on 20 mg MTX per week, the proportion who achieved low disease activity or remission was similar. Also radiographic progression and HAQ were similar in all 4 MTX dosage groups.
We have conducted a systematic review of multiple trials and cohorts, in order to investigate the short term dose-response relationship of MTX in monotherapy and in combination therapy in DMARD naive early RA patients.

PATIENTS AND METHODS

Systematic search strategy
A literature search was performed with the help of a trained librarian in the following databases at February 27, 2015: Pubmed, Embase (OVID-version), Web of Science, COCHRANE, CENTRAL, CINAHL, Academic Search Premier and Science Direct. A separate literature search for meeting abstracts was performed in the databases Embase and Web of Science.

The search consisted of the combination of four subjects:

- Methotrexate
- Rheumatoid arthritis
- Drug administration and dosage
- Start of treatment

To optimize resemblance with daily practice, rheumatoid arthritis was defined by a clinical diagnosis of RA, and undifferentiated arthritis with a clinical suspicion of RA. In the majority of studies, the patients also fulfilled the current classification criteria for RA. The same query was applied in all databases, taking into account the terminological and technical differences between these databases. Various synonyms and related terms for all subjects were used. The exact search queries for each database can be found in online supplementary file 1.

Study selection
The following inclusion and exclusion criteria were used for study selection:

- Patients should have a clinical diagnosis of recent onset rheumatoid arthritis or undifferentiated arthritis with a clinical suspicion of RA
- Patients should be DMARD naïve
- MTX should be part of the first treatment strategy, either as monotherapy or in combination with other antirheumatic drugs (“combination therapy”).
- The exact dosage of all study medications should be described.

- Study results within 6 months after treatment start should be described.
- The study results should include measures of treatment effects.

One reviewer (SAB) selected articles for inclusion by title and abstract reading of each article. Abstracts and articles not written in English were translated if possible. A full-text assessment was performed when further information was required to determine whether an article met the inclusion criteria.

Data extraction

Relevant data regarding the outcome measures was extracted from each article. If necessary, authors were contacted to provide additional results. A quality assessment of each study was performed[23] and presented in online supplementary file 2. This quality assessment had no consequences for in- or exclusion of individual study results in the analyses.

Based on the availability of data and the sensitivity of the outcome measures to assess disease activity, the Health Assessment Questionnaire[24] (HAQ), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), disease activity score[25] (DAS) and DAS28[26] (either based on ESR or CRP, both based on 4 components) were chosen as main outcome measures. For each of these outcomes a lower value indicates or is fitting with a lower disease activity or functional ability. Means and standard deviations (SD) were extracted. If these were not available, mean and SD were estimated from median and range.[27] If data were only reported in graphs, data were extracted using Web Plot Digitizer version 3.9.[28] Only if means and SD could not be extracted from the article and authors could not provide the data, the study was excluded.

For each study it was determined at which time point the outcome measures were provided prior to a possible treatment change (this excludes a dose escalation protocol for the same medication). If the MTX dosage was increased within 6 weeks of treatment start, the final dosage was presented.

Data analysis

Cohen's effect size (ratio of mean change in score and baseline SD) and the corresponding standard errors and 95% confidence intervals were calculated for each treatment group. An effect size of 0.2 was considered small, an effect size of 0.5 was considered moderate and an effect size of 0.8 was considered large. In order to analyze the effect of MTX dose on disease activity, multivariate random-effects meta-regression analyses were performed with HAQ, ESR/CRP or DAS/DAS28 as outcomes. Unstructured variance-covariance matrices were used. Models were estimated using restricted maximum likelihood. If models did not converge, the multivariate method of moments procedure was used[29]. The meta-regressions were based on the effect sizes and variances (=squared standard errors) of the included treatment groups. Since effect sizes were calculated and ESR and

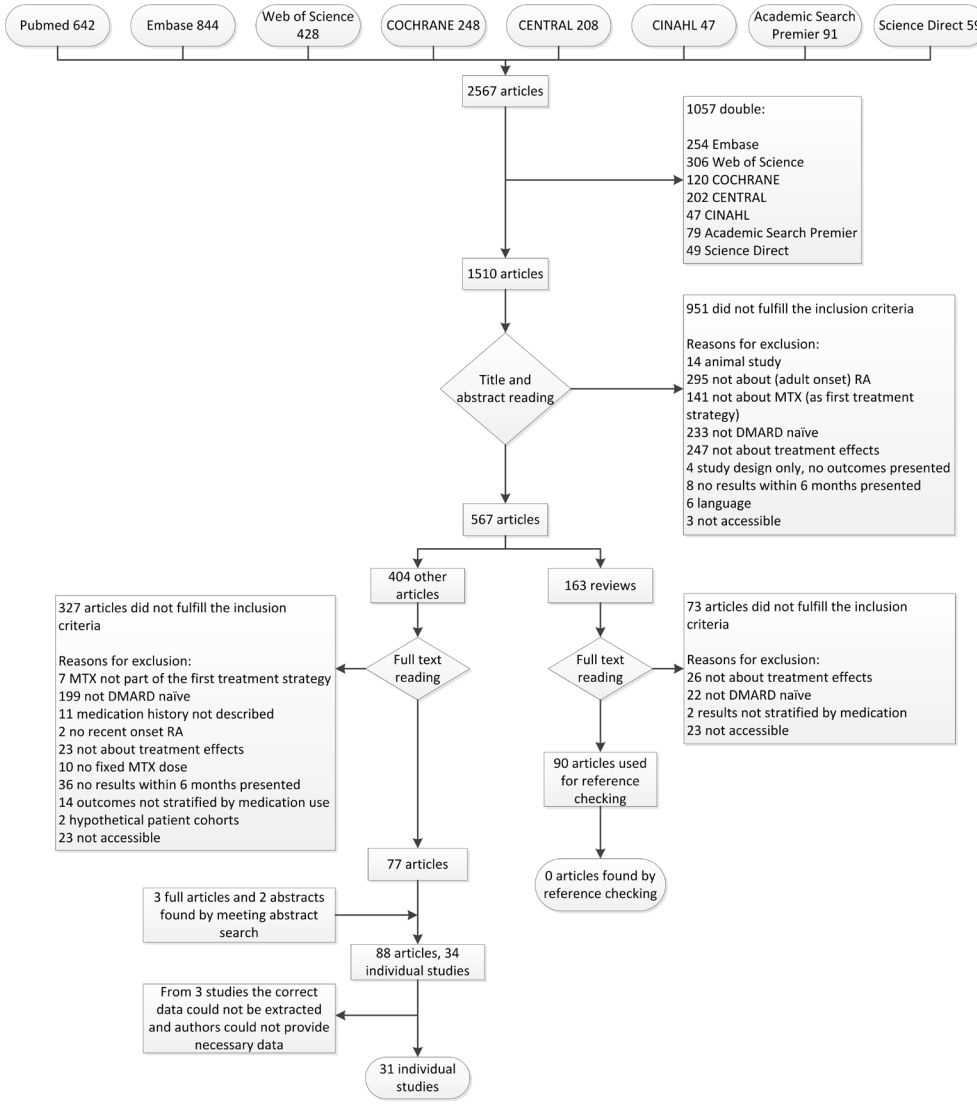

Figure 1: flow diagram of the research article selection procedure

CRP both measure similar constructs, the results for the ESR and CRP were combined in one meta-regression. The same applies to the DAS and DAS28. For the multivariate meta-regression analyses treatment groups were categorized in different medication strategies: 1) MTX monotherapy, 2) MTX in combination with other csDMARDs, 3) MTX in combination with a glucocorticoid (with or without csDMARDs) and 4) MTX in combination with a bDMARD (with or without csDMARDs). If two or more treatment groups fell in the same medication strategy, the results of these treatment groups were combined by taking

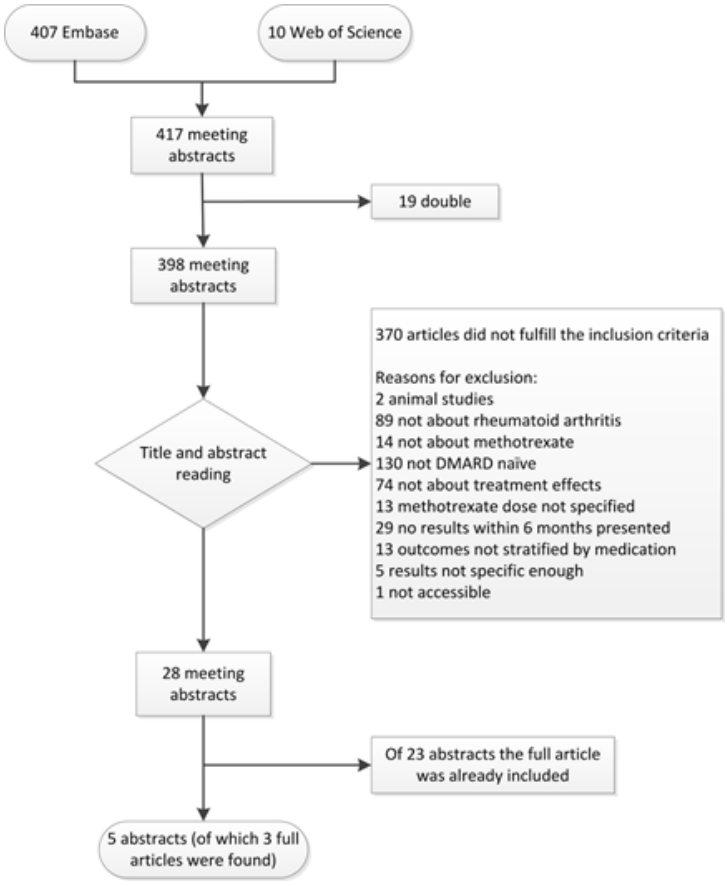

Figure 2: flow-diagram of the meeting abstract selection procedure.

the mean weighted by the sample sizes. Thus, each study could give up to at most 4 effect sizes and corresponding variances, which can be viewed as components of a 4-dimensional multivariate outcome which were analyzed by multivariate meta-regression using the program mvmeta of Stata. MTX dose was added as predictor to the model, together with the time point of assessment in months and the baseline HAQ, ESR/CRP or DAS/DAS28, in order to correct for the different follow up durations of the included studies and the baseline physical functioning or disease activity. Baseline ESR/CRP and DAS/DAS28 values were standardized by calculating [(mean at baseline minus cut-off value) / baseline standard deviation] in order to make values at baseline comparable. Cut-off values for DAS and DAS28 were remission (1.6 and 2.4 respectively) and for ESR and CRP no inflammation (25 and 10 respectively). The coefficient for MTX dose reflects the change in effect size of MTX dose within a medication strategy, independent of time point of assessment and baseline physical functioning or disease activity.

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
MTX monotherapy								
CAMERA[2] *[1, 2]*	7.5	148	3 months	-0.30 (-0.22; -0.38)	-0.37 (-3.32; 2.58)			
CIMESTRA[13] *[2]*[a]	7.5	80	3 months	-0.81 (-0.95; -0.66)	-0.41 (-5.74; 4.93)			-2.20 (-2.44; -1.96)
Quinn et al.[25] *[1]*	7.5[b]	10	3 months	0.058 (-0.54; 0.66)		0.10 (-23.95; 24.15)		-0.75 (-1.56, 0.07)
Haagsma et al.*[1]*	7.5	35	3 months		-0.38 (-9.19; 8.44)		-1.11 (-1.41; -0.81)	
BeSt[1] *[1, 2]*	15	237	3 months	-0.60 (-0.52; -0.68)	-0.45 (-4.00; 3.10)		-1.20 (-1.31; -1.10)	
HIT HARD[9] *[2]*	15	85	6 months	-0.94 (-1.07; -0.80)	-1.09 (-5.25; 3.08)			-3.00 (-3.19; -2.81)
OPERA[14] *[2]*	15[c]	91	3 months	-1.10 (-1.24; -0.96)		-0.38 (-8.69; 7.94)		-2.82 (-3.03; -2.61)
PROMPT[28] *[1]*	15	55	3 months	-0.20 (-0.33; -0.06)	-0.27 (-4.14; 3.60)		-3.54 (-3.74; -3.33)	
CareRA LR[29] *[1]*	15	47	4 months	-0.60 (-0.79; -0.41)				-1.08 (-1.55; -0.61)
Haroon et al.[12] *[1]*	17.5[d]	25	4 months				-3.49 (-4.01; -2.97)	
Chara et al.[31] *[1]*[e]	20[f]	52	6 months	-0.49 (-0.63; -0.36)		-0.93 (-3.03; 1.17)		-1.43 (-1.52; -1.05)

SWEFOT[7] *[1]*	20	405	3 months	-0.73 (-0.79; -0.67)	-0.63 (-3.15; 1.90)		-1.68 (-1.78; -1.58)
Ducreux et al.[10] *[2]*	20[g]	13	6 months				-1.17 (-1.88; -0.46)
TEAR[16] *[3, 4]*	20[h]	379	3 months			-1.17 (-1.28; -1.06)	
Revu et al [19] *[1]*	20[d]	20	2 months			-10.5 (-10.60; -10.40)	
Schipper et al.[20] *[1]*	20[i]	126	3 months				-1.15 (-1.36; -0.94)
Tan et al.[21] *[1]*[f]	20[d]	69	3 months	-0.75 (-0.88; -0.63)	-2.12 (-4.67; 0.44)		-0.71 (-0.93; -0.50)
Lisbona et al.[22] *[1]*	25[j]	33	4 months	-0.45 (-0.63; -0.26)	-0.64 (-6.10; 4.82)		-0.91 (-1.46; -0.37)
CAMERA-II[8] *[2]*	30[d]	119	3 months	-0.93 (-1.04; -0.82)	-0.33 (-4.65; 3.98)		-1.23 (-1.43; -1.03)
MTX + csDMARD							
CIMESTRA[13] *[1]*	7.5	80	3 months	-0.82 (-0.98; -0.67)	-0.63 (-6.15; 4.91)		-2.07 (-2.33; -1.80)
Haagsma et al.[26] *[3]*	7.5	35	3 months		-0.31 (-10.83; 10.21)	-1.38 (-1.64; -1.11)	
MTX + 2 csDMARDs							
Proudman et al.[24] *[1]*	10[k]	139	3 months		-0.57 (-4.82; 3.68)		-1.27 (-1.48; -1.07)
Roivainen et al.[23] *[1]*	15[l]	17	2 months		-0.82 (-17.03; 15.39)		2.83 (-3.40; -2.26)

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
TEAR[16] *[2]*	20[f]	132	3 months					-1.68 (-1.86; -1.49)
MTX + glucocorticoid								
CareRA LR[29] *[2]*	15[m]	43	4 months	-0.91 (-1.10; -0.71)				-1.3 (-1.79; -0.81)
CareRA HR[30] *[2]*	15[m]	290	4 months	-0.87 (-1.01; -0.73)			-2.64 (-2.85; -2.42)	
COBRA light[4] *[1]*	17.5[n]	81	6 months	-1.13 (-1.28; -0.97)	-0.98 (-5.91; 3.95)		-3.08 (-3.26; -2.91)	
Prioreschi et al.[18] *[1]*	20[g]	18	3 months	-1.10 (-1.51; -0.70)				
IDEA[17] *[2]*	20[d]	57	6 months	-1.13 (-1.27; -0.99)				
tREACH[3] *[3]*	25[d]	97	3 months	-0.54 (-0.68; -0.41)	-0.60 (-4.78; 3.59)		-1.21 (-1.40; -1.01)	
IMPROVED[6]	25[d]	610	4 months	-1.08 (-1.13; -1.03)	-0.74 (-2.65; 1.17)		-1.87 (-1.94; -1.78)	
CAMERA-II[8] *[1]*	30[d]	117	3 months	-0.76 (-0.89; -0.64)	-0.81 (-5.34; 3.72)			-2.34 (-2.57; -2.10)
MTX + csDMARD + glucocorticoid								
COBRA light[4] *[2]*	7.5	81	6 months	-1.21 (-1.36; -1.07)	-0.63 (-6.54; 5.28)		-2.45 (-2.64; -2.26)	
COBRA[5] *[1]*	7.5	76	6 months	-1.57 (-1.72; -1.41)	-1.18 (-8.82; 6.47)			

BeSt[1] *[3]*	7.5	97	3 months	-1.16 (-1.28; -1.04)	-0.96 (-5.19; 3.26)		-2.33 (-2.47; -2.18)	
CareRA HR[30] *[1]*	15[n]	290	4 months	-1.14 (-1.28; -1.00)			-2.33 (-2.57; -2.10)	
CareRA HR[30] *[3]*	15[m]	290	4 months	-1.09 (-1.22; -0.96)			-2.00 (-2.24; -1.76)	
Verschueren et al.[11] *[1]*	15	19	4 months	-1.01 (-1.35; -0.68)				-2.10 (-2.68; -1.53)
MTX + 2 csDMARDs + glucocorticoid								
FIN-RACo[27] *[2]*	7.5	97	3 months		-1.05 (-8.82; 6.47)			
NEO-RACo[15] *[2]*	10	49	3 months	-1.03 (-1.22; -0.83)	-0.95 (-7.11; 5.21)			-3.50 (-3.78; -3.22)
tREACH[3] *[1, 2]*	25[d]	184	3 months	-0.48 (-0.61; -0.35)	-0.21 (-3.53; 3.11)		-0.99 (-1.21; -0.77)	
MTX + bDMARD								
Quinn et al.[25] *[2]*	7.5[b]	10	3 months	-1.24 (-1.78; -0.70)		-1.43 (-18.72; 15.86)		-4.21 (-4.71; -3.72)
HIT HARD[9] *[1]*	15	87	6 months	-1.49 (-1.62; -1.36)	-1.62 (-4.16; 0.91)			-4.00 (-4.17; -3.83)
OPERA[14] *[1]*	15[o]	89	3 months	-1.34 (-1.48; -1.19)		-0.67 (-8.08; 6.74)		-2.66 (-2.90; -2.42)
TEAR[16] *[1]*	20[f]	244	3 months	-1.17 (-1.28; -1.06)				-1.79 (-1.93; -1.65)
IDEA[17] *[1]*	20[d]	55	6 months	-1.33 (-1.47; -1.19)				

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
BeSt[1] *[4]*	25[p]	126	3 months	-1.07 (-1.19; -0.95)	-0.63 (-5.45; 4.20)		-1.98 (-2.13; -1.83)	
MTX + 2 csDMARDs + glucocorticoid + bDMARD								
NEO-RACo[15] *[1]*	10	50	3 months	-1.70 (-1.87; -1.53)	-1.23 (-7.33; 4.87)			-2.57 (-2.96; -2.18)

[ ] denotes treatment group in study
Reference numbers refer to Supplementary File 4.
Treatment groups within each study which received equal treatment were combined.

[a] Betamethasone injections were given each visit to each swollen joint. [b] Initial dosage 7.5 mg/week, increased to 15 mg/week at 14 weeks. [c] Initial dosage 7.5 mg/week, increased to 20 mg/week in 2 months [d] If medication increased within 6 weeks, final dosage taken as dosage. [e] Initial dosage 10 mg/week, increased with increments of 5 mg/week to 20 mg/week. [f] Results in study shown for responders [1] and non-responders [2] separately. [g] Initial dosage 15 mg/week, increased to 20 mg/week [h] Escalated to 20 mg/week, initial dosage and time to highest dose unknown.
[i] Initial dosage 15 mg/week, increased with 5 mg per month [j] Initial dosage 2.5 mg/week, increased to 20-25 mg/week, time to highest dose unknown.
[k] Difference is the fish oil dosage. [l] Exact dosage not indicated, between 7.5 and 15 mg/week. [m] If disease activity remains high, MTX increased to 20 mg/week by week 8. [n] Initial dosage10 mg/week, increased to 25 mg/week in 9 weeks [o] Initial dosage 7.5 mg/week increased to 15 mg/week after 1 month and to 20 mg/week after 2 months [p] Initial dosage 25-30 mg/week

Table 2: Meta-regression on the effect of methotrexate-dose on HAQ (n=23), DAS/DAS28 (n=25) and ESR/CRP (n=21).

HAQ		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.008	0.584	-0.035; 0.020
	Month of assessment[a]	-0.0021	0.980	-0.17; 0.16
	Baseline HAQ	-0.11	0.570	-0.49; 0.27
Combination therapy with glucocorticoids	MTX dose (mg)	0.012	0.037	0.00070; 0.023
	Month of assessment[a]	-0.033	0.380	-0.11; 0.041
	Baseline HAQ	-0.42	<0.001	-0.63; -0.21
Combination therapy with bDMARDs	MTX dose (mg)	0.042	0.007	0.012; 0.073
	Month of assessment[a]	0.094	0.430	-0.14; 0.33
	Baseline HAQ	-0.71	0.240	-1.88; 0.47
DAS/DAS28		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.042	0.170	-0.10; 0.018
	Month of assessment[a]	-0.064	0.766	-0.48; 0.35
	Baseline DAS/DAS28	-0.62	<0.001	-0.78; -0.47
Combination therapy with glucocorticoids	MTX dose (mg)	-0.0010	0.954	-0.035; 0.033
	Month of assessment[a]	-0.046	0.672	-0.26; 0.17
	Baseline DAS/DAS28	-0.91	<0.001	-1.23; -0.60
Combination therapy with bDMARDs	MTX dose (mg)	0.033	0.013	0.0070; 0.059
	Month of assessment[a]	0.10	0.503	-0.19; 0.39
	Baseline DAS/DAS28	-1.03	<0.001	-1.38; -0.69
ESR/CRP		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.043	0.372	-0.14; 0.052
	Month of assessment[a]	-0.20	0.593	-0.92; 0.53
	Baseline ESR/CRP	-0.81	0.281	-2.29; 0.66
Combination therapy with glucocorticoids	MTX dose (mg)	0.00074	0.994	-0.18; 0.18
	Month of assessment[a]	-0.061	0.926	-1.34; 1.22
	Baseline ESR/CRP	-0.83	0.848	-9.32; 7.66
Combination therapy with bDMARDs	MTX dose (mg)	0.037	0.880	-0.44; 0.52
	Month of assessment[a]	-0.25	0.841	-2.66; 2.17
	Baseline ESR/CRP	0.21	0.982	-18.15; 18.57

[a]Number of months after treatment start

RESULTS

The literature search resulted in 2,567 articles and 417 meeting abstracts. After removing duplicates, 1,518 articles and 398 meeting abstracts remained. Of these, 77 articles and 5 meeting abstracts (of which 3 full text articles were available) were included, providing information on 34 separate studies. Three of these studies had to be excluded, since means and SD could not be extracted for any of the outcome measures. This resulted in 31 studies (including 1 meeting abstract) with a total of 5,589 patients, of which 2,029 patients had received MTX monotherapy, 403 patients had received combination therapy with csDMARDs, 2,496 patients had received combination therapy with glucocorticoids and 661 patients had received combination therapy with bDMARDs. Several trials in which different medication strategies were investigated in early RA patients could not be included, since not all participants were DMARD naive (e.g. the PREMIER study[30], the COMET study[19] and the OPTIMA study[31]). Figure 1 shows a flow diagram of the selection procedure of the research articles and figure 2 a flow diagram of the meeting abstract selection procedure. In table 1 an overview of the effect sizes of the disease activity outcomes per treatment group is shown. Studies are grouped by medication strategy and ordered by increasing MTX dosage. The number of patients per treatment group ranged from 10 to 610 and the MTX dose ranged from 7.5 to 30 mg/week. Results could be presented at 2, 3, 4 or 6 months. A description of the exact treatment strategies can be found in supplementary file 2. Baseline disease activity for each treatment group varied from 'moderate' to 'high disease activity' according to the DAS (means ranging from 2.7 to 5.8) and DAS28 (means
ranging from 3.4 to 7), with most patients being in high disease activity. The HAQ varied from low to moderate (means ranging from 0.75 to 1.8), with most patients having a moderate HAQ. Baseline ESR ranged from 12 to 70 mm/hour, with most treatment groups having an average ESR close to 50 mm/hour. In table 1 it can be seen that all treatment groups showed an improvement in all outcomes at all assessment points, except for 1 small study, which showed small positive effect sizes for the HAQ and CRP[32]. Across all outcomes most of the effect sizes were large, with the DAS exclusively showing large effect sizes. Combination therapy with bDMARDs most often showed large effect sizes (89% large effect sizes), followed by combination therapy with glucocorticoids (87% large effect sizes), combination therapy with csDMARDs (70% large effect sizes) and MTX monotherapy (63% large effect sizes). In supplementary file 4,'bubble plots' are presented with effect sizes of the main outcome measures HAQ, ESR/CRP and DAS/DAS28 by MTX dosage. The results are grouped by the time point of assessment (in months) and medication strategy. For none of the medication groups there was a clear increase or decrease of effect size by increasing MTX dosages.
In table 2 the results of the meta-regression analyses are described for the HAQ, ESR/

CRP and DAS/DAS28, with the effect of MTX dose corrected for time of assessment (in months) and (standardized) baseline HAQ, ESR/CRP or DAS/DAS28, within the treatment strategies MTX monotherapy, combination therapy with glucocorticoids and combination therapy with bDMARDs. The effects of MTX dose within the combination therapy with csDMARDs could not be analysed because the number of treatment groups with csDMARD combination therapy was too small, and none of the studies compared csDMARD combination therapy to combination therapy with glucocorticoids.
Results for the HAQ showed that increasing MTX doses were not associated with higher efficacy in MTX monotherapy (i.e. no dose-response relationship). For the combination therapy with glucocorticoids (β= 0.012, 95% CI= 0.0007; 0.023) and the combination therapy with bDMARDs (β= 0.042, 95% CI= 0.012; 0.073) a small but statistically significant positive association was found with MTX dose. Results for the DAS/DAS28 also showed a small statistically significant positive association with MTX dose in combination therapy with bDMARDs (β=0.033, 95% CI=0.0070; 0.059), but not with glucocorticoids. Rather than denoting a better HAQ and/or DAS/DAS28 response, these results indicate a small increase in HAQ and DAS/DAS28 by increasing MTX doses for the respective combination therapy groups, although results were not clinically relevant. We did not find an association between ESR/CRP with increasing MTX dose in any of the 3 medication therapy groups.

DISCUSSION

This comprehensive meta-analysis did not provide support for starting MTX in higher dosages for DMARD naive early RA patients, neither as MTX monotherapy nor in combination with glucocorticoids or bDMARDs. In combination with glucocorticoids a higher MTX dose was even associated with a higher (instead of a lower) HAQ outcome and in combination with bDMARDs with a higher HAQ and DAS/DAS28 (but the effect sizes were only trivial).
As far as we know, this review is the first to investigate the dose-response relationship of MTX in combination therapy as initial treatment. There is a general expectation that, as in daily practice many patients require a dose increase to achieve optimal response to MTX, more patients will respond better after 3-6 months when starting on a higher rather than a lower MTX dose. A previous review [4] suggested that for MTX monotherapy a dosage of 15 mg/week escalating with 5 mg/month to 25-30 mg/week was the optimal strategy, which has consequently been implemented in current recommendations [1, 3]. The review included patients with established RA who were previously treated with other DMARDs. The aim of our study was to test the hypothesis that DMARD naive RA patients will have more clinical improvement on a higher dose of MTX than on a lower dose, not only with

MTX as monotherapy, but also with MTX as partner in combination therapy. Based on our results, we could not confirm the previously reported dose-response effect for MTX monotherapy after 3-6 months of initial treatment. It may be possible that DMARD-naive RA patients are more responsive to relatively low doses of MTX when assessed within 6 months than patients with a more advanced disease.

Recent trials have implemented the policy to start MTX in higher dosages in combination with corticosteroids or bDMARD. There is little evidence that in case of an insufficient response on MTX in combination with corticoids or bDMARDs, a dose increase in MTX will provide better outcomes. We hypothesized that the dose of MTX as partner in combination therapy with a corticosteroid or a bDMARD might not have much impact. In the CONCERTO trial[22], in MTX- naive, although potentially DMARD-treated patients, no differences in disease activity, radiographic progression or functional ability response after 6 months were found between MTX dosages of 10 or 20 mg/week in combination with adalimumab. Our results show that there is indeed no additional benefit for early response of starting with a higher rather than a lower dose of MTX in combination therapy. Although we corrected for baseline disease activity, it may be possible that the patients included in the studies with the highest starting doses had more severe disease, resulting in even higher HAQ and DAS28/DAS outcomes compared to the lower dosed studies. Another factor which could possibly influence the effect of MTX dose on disease activity is oral versus subcutaneous administration of MTX[33]. However, since subcutaneous MTX was used in only one study included in this review[34], this factor was not taken into account in the analyses. Considerations on which is the optimal starting dose of methotrexate are important because current recommendations focus on achieving early remission or at least low disease activity in all patients, as soon as possible[1]. For patients who do not achieve this within 3-6 months, tight control and treat to target strategies proclaim the intensification and extension of treatment, as soon as possible[35], since such a strategy may prevent progressive joint damage and irreversible functional disability[36]. Although we did not find evidence that a higher dose of MTX is associated with a better response by 3-6 months, starting with a higher dose may effectively reduce the time to switch to a more effective (combination of) drug(s), while the start of MTX in a lower dose may be associated with a delay in the start of more effective treatments.

In addition, several studies have now shown that a proportion of patients who have achieved rapid suppression of disease activity may taper medication without an ensuing disease flare or damage progression [37-39]. It is possible, though not studied, that the option to taper and stop glucocorticosteroids or bDMARDs is dependent on the dose of MTX co-medication. If true, this would be an argument why the initial MTX dose, either in combination with glucocorticosteroids or with bDMARDs, should be rather high or rapidly escalating.

On the other hand, a higher starting dose may result in more side effects, causing patients

to reduce the dose to ineffective levels or stop MTX. This could not be investigated in the current study since few of the included articles provided information on short-term side effects of the different MTX dosages. Earlier studies have suggested that higher MTX doses are associated with more (subjective) side effects, even though side effects appear to be less common when MTX is combined with glucocorticoids or bDMARDs [40, 41].
Only one study included in this review made a direct comparison between two MTX dosages in combination with a glucocorticoid[42]; therefore indirect comparisons between treatment groups of different studies had to be made, which have a higher risk of bias than direct treatment comparisons[43]. We have tried to reduce possible bias by adjusting for baseline disease activity and time of assessment, but we have insufficient data on -for instance- symptom duration at baseline, and presence or absence of autoantibodies and radiologic damage. We have to make a further reservation to extrapolate results of clinical trials with selected patients to daily practice with unselected patients.
To conclude, the results of this systematic review suggest that for DMARD naive RA patients who start on MTX either as monotherapy or in combination with glucocorticoids or bDMARDs, there is little if any additional benefit to be expected from starting with a high instead of a lower dose of MTX between 3 to 6 months from start of treatment. We therefore suggest that rheumatologists may consider to start MTX at a lower dose, in particular when prescribed in combination with a bDMARD or a glucocorticoid, and increase or change therapy in the setting of a treat-to-target protocol as recommended.

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3

CHAPTER 4

Similar Short Term Clinical Response to High versus Low Dose Methotrexate in Mono- and Combination Therapy in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Aiming at rapid decrease of disease activity, there has been a trend to start with higher doses of methotrexate (MTX) in newly diagnosed rheumatoid arthritis (RA) patients, both as monotherapy and in combination with other antirheumatic drugs. We aimed to study the relationship between clinical response and MTX-dose as mono- or combination therapy in early RA patients.
Methods: DMARD naive early RA-patients from a large international observational database, the METEOR database, were selected if MTX was part of their initial treatment. Patients were divided into 4 groups: MTX monotherapy, MTX + csDMARDs, MTX + glucocorticoids or MTX + bdMARDs. MTX-dose was dichotomized: low dose ≤10 mg/week; high dose ≥15 mg/week. Linear mixed model analyses for DAS, DAS28 and HAQ were performed for each medication group, with MTX-dose and time as covariates. Outcomes were assessed from baseline until 3-6 months follow-up. Associations were adjusted for potential confounding by indication by propensity score (PS) modelling.
Results: For patients starting MTX monotherapy (n=523), MTX + csDMARDs (n=266) or MTX + glucocorticoids (n=615), the PS-adjusted effects of MTX-dose (high versus low) on DAS, DAS28 and HAQ were small and not clinically meaningful. Patients starting MTX + bDMARDs were disregarded due to low numbers (n =11).
Conclusions: In newly diagnosed RA-patients, no clinical benefit of high over low initial MTX-doses was found for MTX monotherapy or for MTX combination therapy with csDMARDs or glucocorticoids.

BACKGROUND

Methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA). Current recommendations for MTX monotherapy suggest to initiate 15 mg/week orally, and escalate with 5 mg/month to 25-30 mg/week or the highest tolerable dose.[1, 2] No specific recommendations exist for MTX used in combination with other antirheumatic drugs (glucocorticoids, csDMARDs and/or biological DMARDs (bDMARDs)). Many studies have shown faster reduction of disease activity, quicker improvement in physical functioning and less radiographic damage progression on MTX combination therapy than on MTX monotherapy.[3-6] It is questionable whether a higher initial MTX-dose in combination with other effective medication is more effective than lower initial MTX-dose regarding short-term results. The CONCERTO study compared four treatment arms with different MTX-doses (2.5, 5, 10 or 20 mg/week) in combination with adalimumab 40 mg/2 weeks in early RA-patients.[7] More patients achieved Disease Activity Score 28 (DAS28) low disease activity or remission with increasing MTX-doses over 26 weeks. However, radiographic progression and Health Assessment Questionnaire (HAQ) scores were similar in the various arms. Proportions of patients achieving low disease activity or remission were similar in the MTX 10 and 20 mg/week arms.
Recently, a meta-regression analysis of trials in recent onset RA-patients showed that higher initial MTX-doses were not associated with better short term clinical outcomes, neither for MTX monotherapy, nor in combination with bDMARDs or glucocorticoids.[8] In the current study we aim to assess the influence of MTX-dose on disease outcomes and physical functioning in an international cohort with real-life data. We hypothesized that in patients with newly diagnosed RA the initial MTX-dose as monotherapy or in combination with other csDMARDs, bDMARDs or glucocorticoids will not determine short-term outcomes.

METHODS

Data selection

Data from the international, observational METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology) database were used, which has been described previously.[9] For the current study, we selected all DMARD-naive early RA-patients with symptom duration <5 years, with ≥1 follow-up visit after 3-6 months. At both baseline and follow-up visits, patients had to have at least one of the following outcome measures: DAS, DAS28, ESR, CRP or HAQ. MTX had to be part of the initial treatment, (as monotherapy or in combination with other csDMARDs/bDMARDs/glucocorticoids). Variation in dose was allowed (e.g. step-up MTX-dose or step-down prednisone dose) but

no change in medication type was allowed between initial treatment and follow-up visit after 3-6 months. Since the METEOR database consists of observational data gathered in clinical practices, irregular time intervals between follow-up visits exist and number of follow-up visits differ per patient. Therefore, the last visit within 3-6 months after treatment initiation meeting all in- and exclusion criteria was defined for each patient, and all follow-up visits between baseline and this last follow-up visit were selected. In order to take into account step-up dosing schedules, the MTX-dose prescribed at the final visit before 3 months follow-up was used.

Statistical analysis

Patients were analysed in four groups, based on initial MTX-strategy: 1) MTX monotherapy, 2) MTX+other csDMARDs, 3) MTX+glucocorticoid (+/- additional csDMARDs) or 4) MTX+bDMARD (+/- additional csDMARDs). Missing data were imputed using multivariate normal multiple imputation (30 cycles). Linear mixed model (LMM) analyses were performed to assess the effectiveness of MTX-dose on the outcome measures DAS, DAS28 and HAQ, within the 4 groups. To account for irregular time intervals, random intercept and slope were added to each model, with 'independence' covariance matrix. MTX-dose was dichotomized ('low dose' ≤10 mg/week; 'high dose' ≥15 mg/week). Time in days between baseline and each follow-up visit was added as continuous variable. Differences in environmental and patient characteristics may affect the initial MTX-dose, and therefore may have caused confounding by indication. To adjust for potential confounding, a propensity score (PS) was calculated in the imputed dataset, using multiple probit regression analysis based on observed baseline patient and environmental characteristics[10]. Several PS models were tested and compared regarding best data fit, in all 30 imputations. Representing the probability of receiving an intervention given observed baseline variables, the PS was then added as covariate adjustment to the LMM analyses. Details regarding the PS are described in online Supplementary file 1. All LMM analyses were performed with and without PS, to see whether confounding by indication was present. All analyses were performed using STATA SE 14 (StataCorp LP).

RESULTS

From the METEOR database, 1438 patients (3193 visits) were selected: 523 patients (1120 visits) started MTX monotherapy, 266 patients (581 visits) started MTX+csDMARDs, 615 patients (1416 visits) started MTX+glucocorticoids and 11 patients (26 visits) started MTX+bDMARD (figure 1). Detailed information regarding concomitant treatment is presented in online supplementary file 2. Patients originated from 20 different countries,

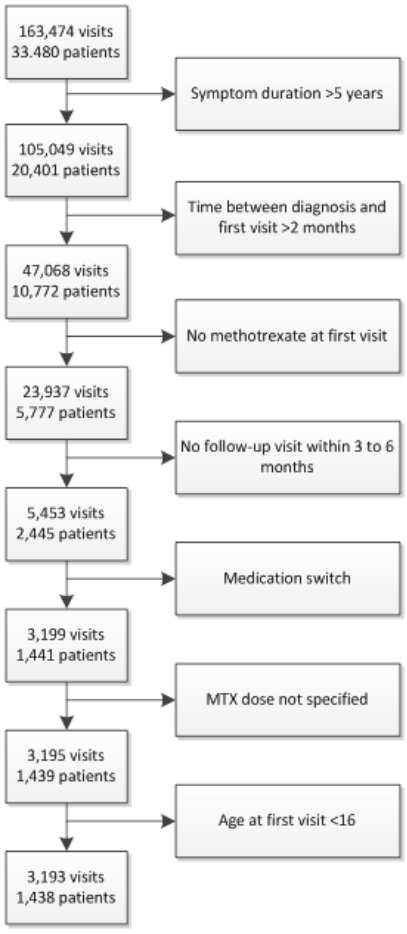

Figure 1. Flow chart of the patient selection.

with 94% of data originating from India, South-Africa, Portugal, the Netherlands, the United States, Ireland and Mexico. Too few patients started MTX+bDMARDs to perform meaningful analyses. In addition, 23 patients (50 visits) who started MTX 12.5 mg/week (the intermediate dose) were disregarded. Baseline characteristics of the other patients are shown in table 1. There was a trend over time to start higher MTX doses (online supplementary file 3).

Since physicians were free to choose their own disease activity measure, DAS and DAS28 based on ESR were missing in 40% and 35% of all visits, respectively. However, in only 4% of all visits no official disease activity measure was available and in only 0.3% of all visits no disease activity measure component was available.

In table 2, the PS-adjusted and unadjusted coefficients for the association between initial MTX-dose and outcomes within 3-6 months follow-up are presented, stratified

per treatment group. For patients starting MTX monotherapy, MTX+csDMARDs or MTX+glucocorticoids, the PS adjusted effects of MTX-dose (high vs low) on DAS, DAS28 and HAQ were small and not clinically meaningful. For example, in the MTX monotherapy group, β (95% CI) for outcome DAS was 0.070 (-0.15;0.29), indicating an increase in DAS of 0.070 for a high versus a low MTX-dose.

The unadjusted main associations between MTX-dose and outcomes were often in opposite direction and/or much larger than the PS adjusted associations, suggesting that confounding by indication indeed plays a role and that it has been (at least partly) corrected for by adjusting for the PS. Two sensitivity analyses were performed: one excluding the country which added most patients to the analyses (India) and one excluding all patients with a symptom duration >2 years, both resulted in similar outcomes (data not shown).

Table 1. Baseline characteristics per treatment group, non-imputed data. Data per number of patients are means (SD), unless indicated otherwise.

	MTX monotherapy (n=523)		**MTX+csDMARDs (n=266)**		**MTX+glucocorticoids (n=615)**	
	n		n		n	
Age at first visit *(years)*	522	47.9 (13.1)	264	44.6 (10.9)	479	48.3 (14.8)
Gender *(% female)*	520	78	266	83	609	81
Body Mass Index	281	26.6 (6.7)	184	27.6 (6.3)	272	27.2 (6.0)
Symptom duration at diagnosis *median (IQR)*	451	365 (169-731)	266	730 (365-1095)	482	458 (181-1095)
Rheumatoid factor *(% positive)*	511	77	263	84	585	81
ACPA *(% positive)*	300	72	98	85	342	76
Erosions present *(% positive)*	305	40	62	55	293	52
ESR	462	56.5 (33.0)	241	69.3 (31.7)	543	59.5 (35.5)
CRP	415	33.1 (33.9)	219	40.3 (35.5)	515	37.7 (37.1)
HAQ	439	1.0 (0.6)	249	1.1 (0.6)	506	1.3 (0.7)
DAS	314	3.7 (1.2)	189	4.0 (0.96)	347	3.9 (1.2)
DAS 28	340	5.7 (1.5)	192	6.2 (1.2)	415	6.0 (1.5)
MTX-dose *(% high dose)*	523	28	266	14	615	46
Follow-up duration *(days)*	523	134 (28)	266	135 (28)	615	139 (31)

Table 2. Unadjusted and propensity score adjusted results of the linear mixed model analyses to investigate the effectiveness of high versus low methotrexate doses on disease activity (DAS and DAS28) and physical functioning (HAQ), stratified per medication group.

Methotrexate monotherapy (n patients=522, n visits=1090)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	0.070 (-0.15; 0.29)	0.12 (-0.19; 0.43)	0.060 (-0.09; 0.21
MTX-dose group unadjusted	-0.63 (-0.79; -0.47)	-0.90 (-0.13; -0.67)	0.16 (0.055; 0.26)
Methotrexate+csDMARDs (n patients=262, n visits=567)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	0.051 (-0.23; 0.33)	0.024 (-0.37; 0.42)	-0.0058 (-0.20; 0.19)
MTX-dose group unadjusted	-0.18 (-0.44; 0.072)	-0.28 (-0.63; 0.072)	0.092 (-0.085; 0.27)
Methotrexate+oral glucocorticoid (+/-csDMARDs) (n patients=615, n visits=1403)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	-0.047 (-0.26; 0.16)	-0.16 (-0.44; 0.12)	-0.028 (-0.16; 0.11)
MTX-dose group unadjusted	-0.42 (-0.56; 0.28)	-0.74 (-0.93; -0.55)	0.13 (0.045; 0.22)

DAS=disease activity score, HAQ=Health Assessment Questionnaire, PS=propensity score, 95% CI=95% confidence interval. MTX-dose group is a binary variable with low dose ≤10 mg/week and high dose ≥15 mg/week. Time is modelled in days between the baseline visit and each follow-up visit. Low dose is the reference category.

DISCUSSION

In this study based on daily practice treatment decisions in newly diagnosed RA-patients, we did not find a clinical benefit of high over low MTX starting doses in monotherapy or in combination with csDMARDs or glucocorticoids: high initial MTX-doses did not result in greater improvement in DAS, DAS28 or HAQ compared to low initial MTX-doses. Co-medication with csDMARDs or glucocorticoids did not influence this effect. In an earlier metaregression analysis we showed that also in clinical trials there was no early clinical benefit of a high over a low MTX starting dose.[8]

We found a trend over time in daily practice to start higher MTX doses. In particular patients receiving co-medication with glucocorticoids as initial treatment were prescribed higher MTX doses, possibly as the rheumatologist estimated their RA to be more severe. Although we used PS to adjust for baseline differences that may have influenced treatment decisions of the rheumatologist as well as outcomes, intangible or unmeasured baseline differences may still affect the results.

We assessed response to treatment within 3-6 months, since current recommendations

advise a treat-to-target strategy, in which medication is intensified or changed as soon as possible if treatment is not effective. The more rapid onset of action of glucocorticoids as co-treatment may mask any effect of the initial dose of slow acting MTX.[3, 11] As demonstrated in clinical trials, this appears also to be true for initial treatment with bDMARDs and MTX, but as this is a rare initial treatment in daily practice, we were unable to investigate this further. However, also for MTX monotherapy a higher dose was not more effective than a low dose. The most likely explanation is in the pharmacokinetics of MTX, where a stable availability of active MTX-polyglutamates seems independent of the weekly MTX dose.[12]

This study has potential limitations. The effect of MTX-dose was assessed within 3 subgroups depending on presence and type of co-medication, but within each group, variations in type, number and dose of additional drugs in individual patients could influence efficacy. However, previous clinical trials have shown comparable disease outcomes of various combination therapies and dosing schedules for many drugs are fixed.[13, 14] We dichotomized MTX-dosages, and defined MTX >15 mg/week as 'high' dose, which is used in current recommendations, but is still an arbitrary cut-off. Results might have been slightly different with other cut-offs. In addition, MTX was mostly administered orally, and uptake can vary between individuals. We have no further data on number and timing of patients who might have switched to subcutaneous treatment. Results might have been different for subcutaneous administration of MTX. Moreover, although we are unware of any evidence that the response to methotrexate could differ between the countries included in the analysis, we took into account a potential influence of country on our outcomes and adjusted for potential country differences by adding country to the propensity score.

Since real-world data were used, no formal procedures were taken to control the quality of clinical assessments, which may have led to more noise compared to clinical trial data. However, our data are in line with previous findings.[8]

CONCLUSION

In conclusion, these real-world data show that in newly diagnosed RA-patients, a higher MTX-dose with or without other csDMARD or glucocorticoids does not result in better clinical efficacy after 3-6 months compared to a low dose. This seems to contradict a general trend over time to start higher MTX-doses. Without apparent early benefit, higher initial MTX-dosages may introduce more side effects which may jeopardise drug retention. However, since side effects were not measured in the METEOR database, we could not assess this. On the other hand, starting a low MTX-dose may induce delays in suppression of disease activity and in the introduction of additional therapies, as previously up to 23%

of patients required higher dosages and up to 56% did not achieve low disease activity on MTX.[15] For the moment, our results suggest that although for MTX monotherapy there may be other considerations, rheumatologists should consider a low instead of a high initial MTX-dose, in particular when prescribed in combination with other csDMARDs or glucocorticoids, and further modify treatment according to a treat-to-target protocol.

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CHAPTER 5

Sex-associated treatment differences and their outcomes in rheumatoid arthritis – results from the METEOR register

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ABSTRACT

Objective: To assess differences in initial treatment and treatment response in male and female rheumatoid arthritis (RA) patients in daily clinical practice.
Methods: The proportion of RA-patients starting different antirheumatic treatments (DMARDs) and the response to treatment were compared in the international, observational METEOR register. All visits from start of the first DMARD until the first DMARD switch or the end of follow-up were selected. The effect of gender on time to switch from first to second treatment was calculated using Cox regression. Linear mixed model analyses were performed to assess whether men and women responded differently to treatments, as measured by DAS or HAQ.
Results: Women (n=4,393) more often started treatment with hydroxychloroquine, as monotherapy, or in combination with methotrexate or a glucocorticoid, and men (n=1,142) more often started treatment with methotrexate and/or sulfasalazine. Time to switch DMARDs was shorter for women than for men. Women had a statistically significantly higher DAS over time than men [DAS improvement per year β (95% CI) -0.69 (-0.75; -0.62) for men and -0.58 (-0.62; -0.55) for women]. Subanalyses per DMARD-group showed for the csDMARD combination therapy a slightly greater decrease in DAS over time in men [-0.89 (-1.07; -0.71)] compared to women [-0.59 (-0.67; -0.51)], but these difference between both genders were clinically negligible.
Conclusion: This worldwide observational study suggests that in daily practice men and women with RA are prescribed different initial treatments, but there were no differences in response to treatment between both genders.

INTRODUCTION

The prevalence of rheumatoid arthritis (RA) is higher in women than in men, with at least a 3:1 ratio for women compared to men.[1] Men may have a different RA phenotype than women, with a later age of onset and a higher percentage of autoantibody positivity. [2] Genetic and hormonal differences and behavioural factors (e.g. smoking) have been suggested to underlie these gender differences.[3-6]
In the past, when treatment possibilities were limited, and higher disease activity was common, RA resulted in unfavourable outcomes in many patients, and potential gender differences were considered irrelevant.[7] New treatment options and strategies have optimized treatment outcomes. While women and men appear to have similar disease activity levels at presentation, the outcomes of RA treatment may still differ: men, for instance, are more likely to reach low disease activity and (drug free) remission and women report more pain and worse functional ability.[5, 7-12] Individually tailored ('personalized') treatment should ensure that the treatment in a patient is chosen in such a manner that the best clinical response will be obtained at the earliest possible time resulting in highest benefit. In such a strategy it may be relevant to consider that male and female patients may have different treatment needs. They may, for instance, respond differently to different treatment strategies, but prescribing physicians may also have different perceptions about the urgency of effective treatment in men versus women, and the likelihood of a favourable response to a particular treatment.
Our research question was to investigate whether rheumatologists make different treatment choices in male and female patients, and whether male and female patients respond differently to the prescribed treatment.

MATERIALS AND METHODS

Data selection
Data were derived from METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology), which is an international, observational register capturing daily clinical practice. METEOR is not an inception cohort, but includes data of all RA patients visiting a rheumatologist. Data are entered through upload from existing electronic health record systems or registers or by using the free, online METEOR tool. Since the register contains data collected in daily clinical practice, the number of visits and the frequency of follow-up visits differed between patients. At the first visit, several patient and disease characteristics are entered (e.g. year of birth, gender, rheumatoid factor and anti-citrullinated protein antibodies (ACPA) status) and during follow-up visits data on disease activity, medication and physical functioning are gathered, all according to regular

care. METEOR has been described extensively before.[13] Data in METEOR were gathered anonymously and captured only daily clinical practice; hence medical ethics committee approval was not required. To investigate the response to the first antirheumatic treatment (conventional synthetic Disease Modifying Antirheumatic Drugs (csDMARDs) and/or oral or parenteral glucocorticosteroids), we selected data of all patients who fulfilled the following criteria: symptom duration <5 years, medication start within 3 months after diagnosis of RA according to the treating rheumatologist, baseline Disease Activity Score (DAS) ≥1.6, available data regarding medication use at baseline and follow-up, and at least 1 visit with available composite disease activity measure (e.g. DAS(28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI)). All available follow-up visits were selected from the start until the first switch in antirheumatic medication, or until the end of follow-up. A medication switch was defined as either a change in type of drug (e.g. from methotrexate to leflunomide) or the addition of a new drug (e.g. from methotrexate to methotrexate + prednisone), but does not include changes in the dose of the current medication, nor tapering of treatment (e.g. from combination therapy with methotrexate + prednisone to methotrexate monotherapy, or tapering to drug free remission).

Outcome measures

Time-to-switch medication, i.e. the time to decide that the first antirheumatic treatment had failed, was used as an efficacy parameter, which was compared between males and females.

Response to the first antirheumatic treatment was measured by the DAS[14] and the Health Assessment Questionnaire (HAQ).[15] Response to treatment was measured over time, taking all available visits into consideration.

Treatment groups

Initiated medications were first divided into 5 treatment groups: 1) csDMARD monotherapy, 2) csDMARD combination therapy, 3) a single csDMARD with a glucocorticoid, 4) combination therapy with more than one csDMARD and a glucocorticoid, 5) glucocorticoid monotherapy. Additional analyses were performed for individual medication combinations.

Statistical analyses

The proportion of patients starting the different medication strategies across genders was compared at baseline. A Cox regression analysis was performed with the time to switch from the first to the second treatment strategy, as proxy for treatment failure, as outcome. Patients were censored when they switched treatment, or at the end of available follow-up. Gender was added as predictor and analyses were adjusted for potential confounders. We considered age, rheumatoid factor, ACPA, country, year of first visit, symptom duration

at diagnosis, BMI, smoking and disease activity as potential confounders and performed linear regression analyses to assess whether these potential confounders were associated with the predictor gender. Each of these variables that was associated with gender ($p<0.20$) was added as confounder. Next, linear mixed model analyses were performed to assess whether men and women respond differently to treatment over time, as measured by DAS and HAQ. First a general effect of gender on treatment response was calculated for all selected patients, by adding gender, follow-up time and the interaction between gender and follow-up time to the model. In the presence of a significant interaction ($p<0.10$), analyses were stratified by gender. Subsequently, subgroup analyses were performed by treatment group and then by individual medication combinations, for medication combinations that were given to at least 100 patients. In these subgroups, the same analyses with the interaction term between follow-up time and gender were conducted. Analyses were adjusted for potential baseline confounders as described above, except for DAS, since this was the outcome of the analysis. To account for irregular time intervals, random intercept and random slope were added to each model, assuming an 'exchangeable' covariance matrix.

Furthermore, effect modification by country was tested by adding an interaction term between gender, time in follow-up and country and effect modification by age was tested by adding an interaction term between gender, time in follow-up and dichotomized age (age <50 and age ≥50). If these interaction terms were non-significant, analyses were performed for all countries and both age categories together and country and age were only added as potential confounders. P-values <0.05 were considered statistically significant.

Missing data regarding disease activity, HAQ, age, body mass index (BMI), smoking, rheumatoid factor and ACPA were imputed using additional information on gender, time in follow-up, country, medication, symptom duration and year of first visit, using multivariable normal imputation (30 imputations).[16] All analyses were performed using Stata SE version 14 (StataCorp LP).

RESULTS

Baseline characteristics and initial treatment

From the 36,576 patients included in the METEOR database, data of 5,820 patients fulfilled the inclusion criteria of the current study (online supplementary figure 1, grey boxes). Of these, 1,142 men and 4,393 women fulfilled the selection criteria for available data and could thus be included in the current analyses. A flowchart of the selection process and a comparison of baseline characteristics of included and non-included patients are presented in online supplementary figure 1 and online supplementary table 1. Non-

included patients had slightly longer symptom duration at diagnosis, but were otherwise mostly similar to included patients. Baseline characteristics of the included patients are shown in table 1. The median (IQR) time in follow-up was 15.3 (8.1; 31.3)months for men and 15.3 (6.7; 35.7) months for women, with a median (IQR) number of 4 (3; 7) visits for both men and women. On average, women were slightly younger and slightly more often rheumatoid factor and/or ACPA positive, had longer symptom duration and higher disease activity compared to men, and there were fewer female smokers compared to male smokers. Initial medication for men and women is presented in table 2.

Table 1. Baseline characteristics of men and women

	Men (n=1142, 21%)		Women (n=4393, 79%)		
		N		N	P
Age at first visit (*years)*	52.0 (14.9)	1139	46.9 (13.9)	4371	<0.001
Body mass index (kg/m^2)	27.1 (4.8)	730	27.0 (6.6)	2500	0.647
Rheumatoid factor *(% positive)*	70.6	1104	75.5	4270	0.001
ACPA *(% positive)*	66.3	656	70.8	2363	<0.001
Smoking *(%)* Never	62.3	900	88.5	3832	<0.001
Previous smoker	14.2		5.2		
Current smoker	23.0		6.3		
Symptom duration at diagnosis *(months) median (IQR)*	10.3 (3.9-23.9)	1142	12.3 (5.9-34.8)	4393	<0.001
Time to treatment initiation from diagnosis *(days)*	4.3 (14.8)	1142	3.8 (14.0)	4393	0.009
HAQ (0-3)	0.96 (0.69)	897	1.1 (0.68)	3668	<0.001
Disease Activity Score	3.5 (1.1)	753	3.7 (1.0)	2689	<0.001
Disease Activity Score 28	5.5 (1.4)	817	5.8 (1.4)	2933	<0.001
Erythrocyte sedimentation rate (mm/h)	46.2 (32.2)	1017	57.4 (33.7)	3809	<0.001
C-reactive protein (mg/L) *median (IQR)*	24 (11-50)	869	21 (9-45)	3391	<0.001
VAS patient global (0-100)	53.5 (23.0)	896	55.0 (22.0)	3295	0.091
Ritchie Articular Index (0-78)	8.6 (6.4)	1061	10.2 (6.6)	4075	<0.001
Swollen Joint Count (0-44)	7.2 (7.4)	1062	6.5 (6.5)	4079	0.027
Tender Joint Count 28 (0-28)	10.9 (8.7)	1129	12.6 (9.3)	4347	<0.001
Swollen Joint Count 28 (0-28)	6.4 (6.2)	1133	5.8 (5.5)	4368	0.021

Mean (SD) reported unless otherwise specified. ACPA = anti-citrullinated protein antibodies, HAQ = health assessment questionnaire, VAS = visual analogue scale, IQR = inter quartile range.

Table 2. Initial treatment of men and women.

	Men (n=1,142)		Women (n=4,393)	
	N (%)	**DAS mean (SD)**	**N (%)**	**DAS mean (SD)**
csDMARD mono	**421 (36.9%)**	**3.4 (1.1)**	**1804 (41.2%)**	**3.6 (1.0)**
MTX	248 (58.9%)	3.6 (1.2)	983 (54.5%)	3.8 (1.0)
SSZ	83 (19.7%)	3.2 (1.1)	181 (10.0%)	3.3 (0.9)
HCQ	80 (19.0%)	2.8 (0.8)	597 (33.1%)	3.4 (0.9)
Other	10 (2.4%)	--	43 (2.4%)	--
GC mono	**103 (9.0%)**	**3.3 (0.9)**	**252 (5.7%)**	**3.3 (0.9)**
csDMARD combi	**233 (20.4%)**	**3.5 (1.1)**	**947 (21.6%)**	**3.9 (1.0)**
MTX + HCQ	95 (40.8%)	3.3 (1.0)	554 (57.9%)	3.9 (1.0)
MTX + SSZ	70 (30.0%)	3.6 (1.0)	192 (20.1%)	3.7 (1.0)
MTX + SSZ + HCQ	40 (17.2%)	3.1 (0.7)	122 (12.8%)	3.5 (0.9)
SSZ + HCQ	19 (8.2%)	3.3 (0.9)	48 (5.0%)	3.5 (0.9)
MTX + LEF	5 (2.2%)	4.8 (0.7)	24 (2.5%)	3.8 (1.2)
Other	4 (1.7%)	--	7 (0.7%)	--
csDMARD + GC	**271 (23.7%)**	**3.7 (1.2)**	**928 (21.2%)**	**3.6 (1.0)**
MTX + GC	226 (83.4%)	3.7 (1.1)	705 (76.0%)	3.6 (1.0)
HCQ + GC	21 (7.8%)	3.8 (1.7)	136 (14.8%)	3.6 (0.9)
SSZ + GC	17 (6.3%)	3.6 (1.3)	53 (5.7%)	3.8 (1.0)
LEF + GC	4 (1.5%)	3.8 (1.2)	26 (2.8%)	3.4 (1.1)
Other	3 (1.1%)	--	8 (0.9%)	--
Combi csDMARD + GC	**114 (10.0%)**	**3.6 (1.1)**	**452 (10.3%)**	**3.9 (1.0)**
MTX + HCQ + GC	48 (42.1%)	3.5 (1.2)	205 (45.4%)	3.8 (1.0)
MTX + SSZ + GC	26 (22.8%)	3.6 (0.9)	111 (24.6%)	3.9 (1.0)
MTX + SSZ + HCQ + GC	20 (17.5%)	3.4 (0.8)	74 (16.4%)	3.6 (1.0)
SSZ + HCQ + GC	13 (11.4%)	3.4 (0.9)	32 (7.1%)	3.6 (1.0)
MTX + LEF + GC	4 (3.5%)	3.1 (1.2)	9 (2.0%)	4.3 (1.1)
Other	3 (2.6%)	--	21 (4.6%)	--

MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, LEF = leflunomide, GC = glucocorticoid. DAS = disease activity score, SD = standard deviation. DAS based on the non-imputed database

Table 3. Evolution of HAQ and DAS over time in men and women[a].

	HAQ **p-value**[b]	**DAS** **p-value**[b]	**DAS** **Men** β (95% CI)	**DAS** **Women** β (95% CI)
All patients			n=1,142	n=4,393
Gender*follow-up time	0.200	0.011	--	--
Follow-up time (years)			-0.69 (-0.75; -0.62)	-0.58 (-0.62; -0.55)
csDMARD combination therapy			n=233	n=947
Gender*follow-up time	0.706	0.014	--	--
Follow-up time (years)			-0.89 (-1.07; -0.71)	-0.59 (-0.67; -0.51)
csdMARD monotherapy			n=421	n=1,804
Gender*follow-up time	0.453	0.178	--	--
GC			n=103	n=252
Gender*follow-up time	0.283	0.462	--	--
csDMARD + GC			n=271	n=928
Gender*follow-up time	0.419	0.263	--	--
csDMARD combination + GC			n=114	n=452
Gender*follow-up time	0.848	0.931	--	--

[a]Results stem from linear multivariable mixed models analyses adjusted for age, rheumatoid factor, ACPA, symptom duration at diagnosis, BMI, smoking and country. Different models were constructed for all patients and then for treatment subgroups. Regression coefficients represent the units of change in the outcome per unit of time, in this case, per year.

[b]p-values are only shown for the interactions between gender and time. In the presence of a statistically significant interaction, results are stratified by gender and the evolution of DAS over time is shown for men and women separately.

In general, men and women were treated with similar strategies according to the 5 treatment groups. But across the treatment groups, women more often than men started a treatment strategy containing hydroxychloroquine (hydroxychloroquine monotherapy, methotrexate + hydroxychloroquine and hydroxychloroquine + glucocorticoid, but not methotrexate + sulfasalazine + hydroxychloroquine). Men more often started a treatment strategy containing sulfasalazine and/or methotrexate (sulfasalazine monotherapy, methotrexate + sulfasalazine and methotrexate + glucocorticoid). Men who started hydroxychloroquine monotherapy had on average a lower baseline DAS than men starting different treatments, and also than women who started hydroxychloroquine. Women who started methotrexate monotherapy on average had a slightly higher baseline DAS

than women starting monotherapy with other csDMARDs. In the group starting with combination therapy of more than one csDMARD and a glucocorticoid, no gender differences were present. In addition, since hydroxychloroquine might be preferentially prescribed to pregnant women or to women with a pregnancy wish, we assessed whether hydroxychloroquine was more often prescribed to women of childbearing age. It was found that women ≥50 years of age were less often prescribed hydroxychloroquine (27.5% compared to 36.8% for women <50 years of age). However, the same was found for men (14.9% for men ≥50 years and 23.8% for men <50 years).
Furthermore, since medication use slightly differed between countries, initial treatment of men and women was shown per country, for countries contributing at least 100 patients (online supplementary file, tables 3 to 10). Specifically, in contrast to the overall findings, women did not receive more often hydroxychloroquine monotherapy in Portugal or in the UK, not more often combination of methotrexate + hydroxychloroquine in the UK and not more often combination of hydroxychloroquine + glucocorticoid in Mexico or in the UK. Lastly, the proportion of patients receiving glucocorticoid monotherapy differed for some countries, with more men in Mexico and Portugal and more women in the Netherlands receiving glucocorticoid monotherapy.

Treatment switch

Time-to-switch medication (i.e. the time to decide that the first treatment step had failed) was shorter in women [median (IQR) 175 (91-384) days (25 (13; 55 weeks), n=2756] than in men [median (IQR) 200 (98; 400) days (29 (14; 57) weeks), n=647]. In total, 2,146 patients (1,637 women, 495 men) did not switch treatment before the end of follow-up and were censored [median (IQR) follow-up time 336 (132; 708) days (48 (19; 101) weeks) for women and 387 (187-733) days (55 (27; 105) weeks) for men]. Cox regression analyses on the effect of gender on time from the initial treatment to a next treatment step confirmed that women were slightly more likely to switch treatment than men [HR (95% CI) 1.22 (1.12; 1.33)]. However, after adjusting for age, rheumatoid factor, ACPA, symptom duration at diagnosis, country, BMI, smoking (all at baseline) and DAS as time-varying co-variate, the effect disappeared [HR (95% CI) 1.02 (0.93; 1.12)].

Treatment response

Analyses on the effects of gender on treatment response revealed that for most treatment groups women had a slightly higher DAS and HAQ already at baseline [β (95% CI) 0.18 (0.13; 0.24) higher for DAS and 0.16 (0.12; 0.19) higher for HAQ for all treatment groups combined, online supplementary table 11]. The interaction term between gender and time was statistically significant for the outcome DAS over time (p=0.011). However, after stratification for gender, differences in improvement in DAS over time proved to be negligible between men [β (95% CI) -0.69 (-0.75; -0.62) per year] and women [β (95% CI)

-0.58 (-0.62; 0.55) per year] and the change in HAQ over time was not different between men and women (p=0.200), table 3.
When analyses were repeated in the subgroups of the different medication strategies, the interaction term between gender and time was statistically significant for the outcome DAS over time only in the csDMARD combination therapy subgroup (p=0.014), but analyses stratified for gender revealed no clinically relevant differences in improvement in DAS over time [β (95% CI) -0.89 (-1.07; -0.71) for men and -0.59 (-0.67; -0.51) for women per year, table 3]. For all other treatment strategies, there were no differences in DAS and HAQ improvement between men and women (table 3). Detailed outcomes for the subgroup analyses on the effect of gender on treatment response are shown in online supplementary file 11. When subanalyses were performed within the strategy subgroups for individual medication combinations, there were no gender differences in treatment response as measured by DAS and HAQ, online supplementary table 13.

DISCUSSION

In this study based on real world clinical data we aimed to assess whether men and women with RA are treated differently and whether the response to various therapies differs between them. Previously, a concern has been raised that women with RA might be treated less aggressively than men. For instance, a study in the NOR-DMARD registry reported lower access to bDMARDs for females in the period 2000 – 2003, but not anymore in more recent time periods (2009 – 2011).[17] Another study in the QUEST-RA database found no significant differences in the proportion of men and women taking prednisone, methotrexate or bDMARDs and showed similar delays of initiation to therapy.[7] In the current study, we found that women had, at the start of treatment, slightly longer symptom duration than men, and more often started treatment with hydroxychloroquine, as monotherapy (33% vs 19% in men) or in combination with methotrexate (41% vs 58% in men) or with a glucocorticoid (15% vs 8% in men), whereas men more often started treatment with methotrexate and/or sulfasalazine. This indeed suggests a slightly less aggressive approach in women compared to men: hydroxychloroquine monotherapy reportedly has only a small effect on reducing the swollen joint count, and its effects on delaying joint damage is smaller compared to sulfasalazine.[18, 19] We found that hydroxychloroquine was prescribed to male patients mostly if they had low disease activity, but women were treated with hydroxychloroquine or other csDMARDs irrespective of disease activity. It has to be said, though, that gender differences in medication use were slightly country-dependent. This could be influenced by political, economic or cultural factors that might differ per country but fall beyond the scope of this article.

We found a slightly worse response to treatment for women than for men, but the difference in this effect was small (decrease in DAS, when extrapolated to a year, differed by 0.1 point), and appeared to be based on a statistically significant difference in DAS improvement only for initial treatment with csDMARD combination therapy. But also this difference between men and women was in clinical terms negligible.

It could be argued that women more often receive hydroxychloroquine since hydroxychloroquine is considered safe during pregnancy, in contrast to for example methotrexate, and might therefore be prescribed to pregnant women or to women with a pregnancy wish.[20] It was indeed observed that women ≤50 years of aged more often received hydroxychloroquine, however, this effect was the same for men and therefore does not seem to be related to (wish for) pregnancy. Moreover, we assessed whether age (<50 years or ≥50 years) was an effect modifier for the association between gender and treatment response, but did not find a different response to treatment for these different age categories.

Previous studies in different registers have reported higher response rates in men as compared to women for several treatment strategies with bDMARDs.[8, 9, 21] However, the selection of patients in these studies differs from the current study, in which initial treatment in newly diagnosed RA patients were compared. An analysis in the BeSt study, a randomized clinical trial, identified male gender as a predictor of methotrexate efficacy, which has not been found in the current study.[22] This might be due to differences in patient selection, such as a 1 point higher DAS at baseline in the BeSt study, or to differences in for example dosing schedules in a trial setting compared to daily clinical practice.

It has been suggested that a higher level of disease activity in women is inherent to the components of disease activity composite scores, rather than to differences in 'specifically rheumatic activity in men and women.[7] For example, usually ESR levels are higher in women than in men, especially in older women,[7, 23] and women often report more symptoms and pain in questionnaires as compared to men.[1, 7] In addition, men may have a tendency to underreport problems, as has been described with regard to the HAQ.[24] This may explain part of the previously found gender differences in response to treatment.

We also found that women had a shorter time to switch medication than men. However, after adjusting for several confounders including disease activity over time, gender did not determine the likelihood to switch medication anymore.

This study has several potential limitations. We compared different treatment combinations, but did not take into account differences in dosing schedules between patients. Although dosing schedules for many drugs are fixed, this may still influence outcomes. Moreover, since this is an observational study, associations between variables should not be interpreted in a causal manner. Furthermore, since the prescription of

medication is not randomized, several known and unknown variables may have influenced the choice of the physician to prescribe certain medication (confounding by indication). Confounding by indication may also have influenced the response to treatment. Since only part of the potential confounders is known and measured, it is always possible that residual (unmeasured) confounding exists.

In conclusion, this study shows that men and women are prescribed different treatments: women more often started hydroxychloroquine, as monotherapy or in combination with methotrexate or a glucocorticoid, whereas men more often started treatment with methotrexate and/or sulfasalazine. Although we found a statistically significantly worse response to treatment (decrease in DAS, but not HAQ) for women compared to men to csDMARD combination therapy, these differences between genders were clinically negligible. In general, although the initial treatments prescribed to men and women may differ, it appears that the clinical response is similar for both genders.

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CHAPTER 6

Rheumatoid Arthritis Patients with Continued Low Disease Activity have Similar Outcomes over 10 Years, Regardless of Initial Therapy

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ABSTRACT

Objective: To compare 10 years disease outcomes of rheumatoid arthritis (RA) patients with continuous low disease activity on methotrexate (MTX) with or without initial combination therapy with infliximab or prednisone and sulfasalazine.
Methods: recent onset RA patients with 10 years follow-up from the BeSt study were analyzed. Treatment was tightly controlled, targeted at DAS≤2.4. Selected patients had low disease activity from 6 months until 10 years and therefore did not intensify treatment. Patients were grouped in MTX monotherapy or initial combination therapy. Between-group differences over time were compared using (generalized) linear mixed model analyses, for the outcomes DAS, HAQ, ESR, VAS patient global health, % patients in (drug free) remission and % patients with Sharp/van der Heijde score progression ≥5.
Results: At 10 years 28/247 (11%) patients on MTX monotherapy (some tapered to drug free) had continued DAS≤2.4 compared to 68/261 (26%) patients on combination therapy (all tapered to monotherapy or drug free). No between-group differences in continuous responders were found over time, except for a higher percentage of patients in drug free remission after MTX monotherapy. Significant group-time interactions were found for DAS, ESR and VAS patient's global health, but results seem clinically negligible.
Conclusion: more patients achieved continuous low disease activity on initial prednisone or infliximab combination therapy than on initial MTX monotherapy, but there appear no additional benefits. Regardless of induction therapy, patients with continuous low disease activity have similar long term outcomes, with only a higher proportion of patients in drug free remission after MTX monotherapy.

INTRODUCTION

Earlier initiation of treatment, targeted treatment and the use of disease modifying anti-rheumatic drugs (DMARDs) have led to great improvements in the treatment of rheumatoid arthritis (RA).[1, 2] Current guidelines recommend the use of methotrexate (MTX) as (part of) the first treatment of RA.[3] Although MTX can be highly effective in reducing disease activity, 50–75% of early RA patients do not achieve low disease activity within 3–6 months after initiation of MTX monotherapy in dosages of 20–25 mg/week.[3-6] Previous studies have shown that combination therapy including corticosteroids or a biologic DMARD is more efficacious than MTX monotherapy,[7-10] with more patients reaching early low disease activity or even remission when starting combination therapy including corticosteroids or a TNF-blocker. However, it remains to be determined whether patients who have an early good response to combination therapy also have better *long term* outcomes than patients who have an early good response to MTX monotherapy. For instance, radiologic damage progression may be better suppressed in patients on combination therapy, since for infliximab and other TNF-inhibitors as well as for prednisone it has been suggested that there may be a 'disconnect' between clinical and radiologic outcomes. Thus, in patients who have insufficient clinical improvement on these medications there may still be prevention of radiologic damage progression.[11-13] According to the 'window of opportunity' theory, earlier suppression of inflammation with initial prednisone or infliximab combination therapy may prevent chronicity of inflammation, resulting in long term remission and drug free remission more readily than MTX monotherapy with slightly delayed clinical response.

Therefore we hypothesized that compared to patients who have a good clinical response on MTX monotherapy, patients who have a good clinical response on initial combination therapy with prednisone or infliximab may have superior disease outcomes during 10 years follow-up.

METHODS

Data from the BeSt (Dutch acronym for Treatment Strategies) study were used. The BeSt study is a multicenter randomized trial (Dutch trial registry, NTR262 and NTR265) with 10 years follow-up, in which 508 recent onset RA patients (1987 American College of Rheumatology criteria[14]) were included. Patients were included between April 2000 and August 2002 and randomized into one of four treatment strategies: sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone or initial combination therapy with infliximab. Patients were treated to target based on three-monthly calculations of the Disease Activity Score in 44/53 joint (DAS).[15].

Treatment was intensified or changed according to treatment protocol if DAS>2.4. Patients in the sequential monotherapy and step-up combination therapy groups initiated 15 mg/week MTX. If DAS≤2.4 for at least 6 consecutive months, MTX was tapered to 10 mg/week. Patients in the initial combination therapy with prednisone group initiated 7.5 mg/week MTX + 2,000 mg/day sulfasalazine + 60 mg/day prednisone (prednisone was tapered to 7.5 mg/day in 7 weeks). In these three groups MTX could be increased to 25-30 mg/week in case DAS≥2.4. If DAS remained ≤2.4 from week 28, prednisone was tapered and stopped and from week 40 the MTX dose was tapered and stopped, until sulfasalazine monotherapy remained. From year 3, if patients who had tapered to MTX 10 mg/week monotherapy or sulfasalazine monotherapy and who were in DAS-remission (DAS<1.6) for at least 6 consecutive months, the last DMARD was tapered to null, but restarted when DAS was >1.6. Patients randomized to initial combination therapy with infliximab started with 25 mg/week MTX + 3 mg/kg infliximab. In this group infliximab could be increased to 6 mg/kg/8 weeks (but not higher in this subgroup, because of the requirement to have DAS≤2.4 from month 6). Tapering to 3 mg/kg/8 weeks occurred if DAS≤2.4 for at least 6 months, and ultimately with persistent DAS≤2.4, infliximab was stopped. Then, if DAS remained ≤2.4, MTX could also be tapered, by the same schedule as described above.
At baseline extensive patient characteristics and disease measures were recorded. Every 3 months clinical outcomes were measured. At baseline and at each following year, radiographs of the hand and feet were made and assessed according to the Sharp/van der Heijde score[16]. The Medical Ethical Committees of all participating centres approved the study protocol and all patients gave written informed consent. A more detailed description of the BeSt study has been previously published.[17]
For the present study, patients ('responders') from all 4 randomization arms were selected with continuous DAS≤2.4 from 6 months until the final visit at 10 years. This includes patients who at three months increased MTX to 25 mg/week because the DAS was still >2.4. Patients were divided into two groups: MTX monotherapy responders (in randomization arms 1 and 2) and combination therapy responders (in randomization arms 3 and 4). Although the medications used in combination with MTX in group 3 and 4 differed, previous results from the BeSt study showed that both groups had equal outcomes over time. Therefore these arms were combined for this analysis.[18]
Between-group differences at baseline were compared using *t*-tests, Mann-Whitney *U* tests or χ^2-tests, as appropriate. Between-group differences over time were compared for the outcomes DAS, ESR, patient global health (visual analogue scale (VAS) 0 – 100, 100 worst score), HAQ, percentage of patients in remission and in drug free remission and the percentage of patients with Sharp / van der Heijde score progression ≥5. For continuous, normally distributed outcomes linear mixed model (LMM) analyses with unstructured covariance matrix were performed, estimated using restricted maximum likelihood, to compare groups over time. For continuous, non-normally distributed outcomes and

for dichotomous outcomes generalized linear mixed model (GLMM) analyses with unstructured covariance matrix using adaptive Gauss-Hermite quadrature were performed to compare groups over time. All analyses were performed using Stata SE version 14 (StataCorp LP). A p-value <0.05 was considered statistically significant.

RESULTS

In figure 1 the flow chart of patients initiating MTX monotherapy or combination therapy and responding to initial treatment over 10 years is displayed. Of the 247 patients who initiated MTX monotherapy, 86 (34.8%) patients had a DAS≤2.4 on MTX monotherapy at 6 months (43 had increased the MTX dose to 25 mg/week at month 3). Of these 86 patients, 36 dropped out, 22 changed therapy because of DAS>2.4 and 28 (11.3% of initial 247, 32.9% of initial responders) kept responding to MTX monotherapy with DAS≤2.4 until year 10. Of the 261 patients who initiated combination therapy, 155 (59.4%) patients had a DAS≤2.4 on initial therapy at 6 months (21/133 in arm 3 had increased the MTX dose to 25 mg/weeks and 22/128 in arm 4 had increased the infliximab dose to 6 mg/kg/8 weeks at month 3). Of these 155 patients, 47 dropped out, 40 changed therapy because of DAS>2.4 and 68 (26.1% of initial 261, 43.9% of initial responders) remained on the initial treatment step until year 10, which means by protocol they had tapered the initial combination therapy to monotherapy.

Baseline characteristics of MTX monotherapy continuous responders and initial combination therapy continuous responders are shown in table 1. Among MTX monotherapy responders there were fewer ACPA positive patients (ACPA positive 46% vs. 54%, p=0.477), with shorter symptom duration at baseline (14.0 vs. 28.3 weeks, p=0.004) and slightly lower SHS score (median 0 vs. 2.5, p=0.014) than combination therapy responders.

In figure 2 the DAS, ESR, VAS patient global health, HAQ, percentage of patients in remission and in drug free remission and the percentage of patients with a Sharp/van der Heijde score progression ≥5 are displayed for MTX monotherapy continuous responders and initial combination therapy continuous responders over 10 years follow-up. Both groups show similar results over time for HAQ, DAS, ESR, VAS patient global health and similar Sharp/van der Heijde score progression (fig 2A, 2B, 2C, 2D, 2G). There seem to be higher remission and drug free remission rates in MTX monotherapy responders than combination therapy responders (fig 2E, 2F). These potential differences were tested with a LMM or a GLMM, as appropriate. In table 2 the results of the LMM and GLMM analyses are shown. For all outcomes an improvement over time was seen, regardless of initial treatment group. For the outcomes DAS, ESR and VAS patient global health (table 2) a small positive interaction between treatment group and time was seen. The results

indicate slightly worse DAS, ESR and VAS patient global health with increasing time for the initial combination therapy responders compared to the MTX monotherapy responders, but the effects seem to be very small. For the outcomes HAQ, percentage Sharp/van der Heijde progression ≥5 and percentage of patients in remission and drug free remission no interaction was observed. The percentage of patients in remission was not statistically significantly different between the two groups, although a trend could be observed for a higher percentage of patients in remission in the MTX monotherapy group. The percentage of patients in drug free remission was higher in the MTX monotherapy group. The same LMM and GLMM analyses were repeated, with an additional adjustment for symptom duration at baseline, since median symptom duration between both groups differed (table 1) and was thought to be a potential confounder. However, this did not lead to a relevant change in results (online supplementary file 1, table 1). Also additional adjustment for baseline Sharp/van der Heijde score did not change the results (online supplementary file 1, table 2).

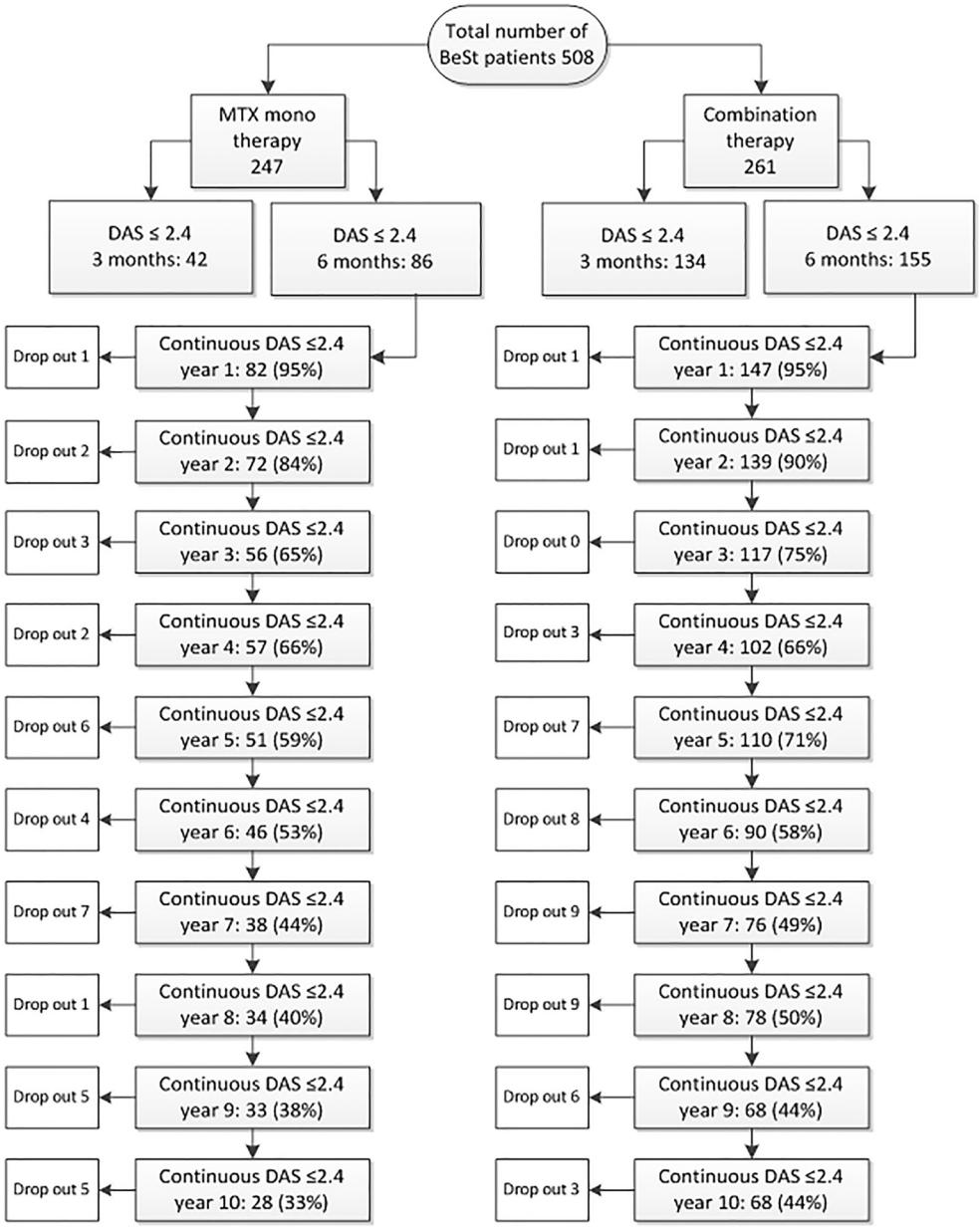

Figure 1: Flowchart of patients with continuous DAS≤2.4 from 6 months until the end of follow-up.

Table 1: baseline characteristics MTX monotherapy continuous responders and combination therapy continuous responders

	MTX monotherapy continuous responders, n=28	Combination therapy continuous responders, n=68	p-value for between-group differences*
Age (years) *mean (SD)*	54.8 (11.7)	54.2 (10.4)	0.797
Gender (% female)	57.1	63.2	0.577
Rheumatoid factor positive (%)	60.7	60.3	0.969
ACPA positive (%)	46.4	54.4	0.477
Body Mass Index *mean (SD)*	25.7 (2.6)	25.1 (3.2)	0.382
Alcohol users (current) (%)	60.7	61.2	0.965
Smoking status (ever) (%)	28.6	22.1	0.497
Symptom duration (weeks) *median (range)*	14.0 (1.14 – 191)	28.3 (3.9 – 263.1)	0.004
Disease Activity Score *mean (SD)*	4.3 (1.0)	4.1 (0.84)	0.300
Erythrocyte Sedimentation Rate (mm/hr) *mean (SD)*	38.8 (31.9)	34.8 (22.2)	0.554
C-reactive protein (mg/l) *median (range)*	38.7 (45.5)	24.5 (29.4)	0.429
Ritchie articular index *median (range)*	9.5 (4-47)	11 (2-29)	0.830
Swollen joint count *median (range)*	13 (6-36)	13.5 (4-31)	0.269
VAS patient global health (mm) *mean (SD)*	47.6 (17.8)	45.2 (20.8)	0.584
VAS physician global health (mm) *mean (SD)*	54.5 (18.6)	50.9 (18.7)	0.391
Health Assessment Questionnaire *mean (SD)*	1.2 (0.7)	1.3 (0.7)	0.452
Sharp / van der Heijde score *median (range)***	0 (0 – 16)	2.5 (0 – 25.5)	0.014

*Tested using *t*-test for continuous, normally distributed variables, tested using Mann-Whitney *U* tests for continuous, non-normally distributed variables, tested using χ^2-tests for categorical/ dichotomous variables.

**n=27 in MTX monotherapy responders, n=66 in combination therapy responders.

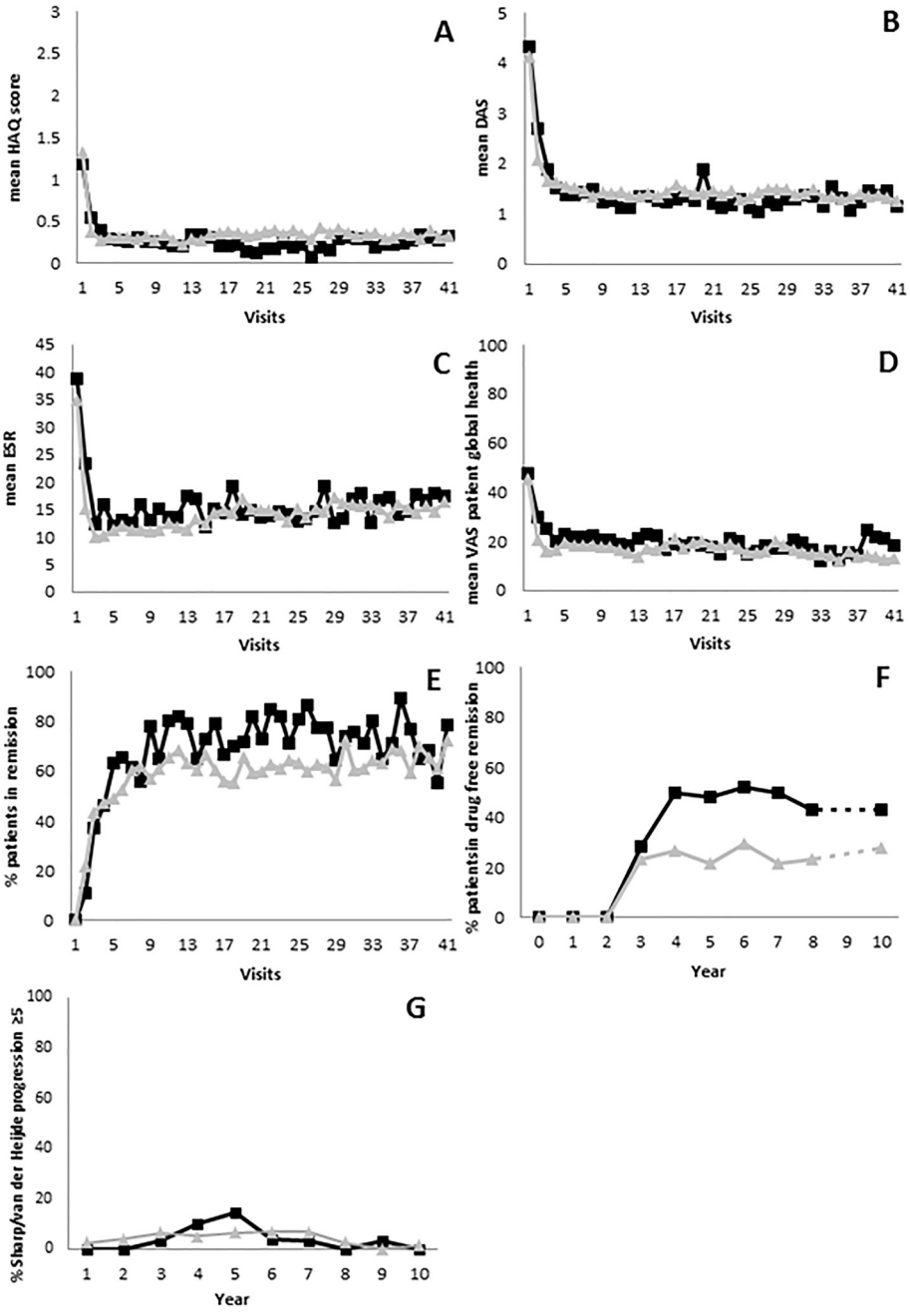

Figure 2: Clinical and radiological outcomes over time in methotrexate monotherapy responders (black lines) and combination therapy responders (grey lines) during 10 years follow-up. Results for drug free remission at year 9 are not shown, due to a high amount of missing data at this time point.

Table 2: Differences over time between MTX monotherapy responders (n=28) and combination therapy responders (n=68).

Linear Mixed Model Analyses		β	**95% CI**
HAQ	Treatment group[a]	0.08	-0.07; 0.22
	Time in years	-0.01	-0.02; -0.01
	Constant	0.27	0.02; 0.53
DAS	Treatment group[a]	-0.03	-0.24; 0.19
	Time in years	-0.12	-0.15; -0.08
	Treatment group*Time	0.01	0.00; 0.04
	Constant	1.91	1.53; 2.28
ESR	Treatment group[a]	-3.20	-7.41; 1.02
	Time in years	-0.76	-1.23; -0.29
	Treatment group*Time	0.43	0.16; 0.70
	Constant	20.23	12.78; 27.68
VAS patient global health	Treatment group[a]	-3.98	-9.39; 1.43
	Time in years	-1.70	-2.30; -1.09
	Treatment group*Time	0.36	0.02; 0.70
	Constant	30.17	20.60; 39.74
Generalized Linear Mixed Model Analyses		**OR**	**95% CI**
SvdH score progression ≥5	Treatment group[a]	0.83	0.17; 4.01
	Time in years	0.94	0.83; 1.07
	Constant	0.00	0.00; 0.16
Remission	Treatment group[a]	0.58	0.32; 1.08
	Time in years	1.18	1.15; 1.21
	Constant	1.68	0.56; 5.04
Drug free remission	Treatment group[a]	0.14	0.03; 0.61
	Time in years	1.06	1.03; 1.08
	Constant	0.38	0.03; 4.77

[a]Difference between treatment groups, MTX monotherapy responders as reference group HAQ = Health Assessment Questionnaire, DAS = disease activity score, ESR = erythrocyte sedimentation rate, VAS = visual analogue scale, SvdH = Sharp/van der Heijde, SE = standard error, OR = odds ratio, 95% CI = 95% confidence interval

DISCUSSION

In this study, we investigated whether for RA patients who achieve continuous low disease activity during 10 years on their first DMARD there are differences in clinical or radiological outcomes that can be attributed to whether that first DMARD was MTX monotherapy or MTX initially combined with sulfasalazine and prednisone or with infliximab. We hypothesized that earlier improvement on initial combination therapy, or a disconnect between disease activity and radiologic damage progression associated with prednisone and infliximab, might result in better outcomes in the initial combination therapy group. In contrast, we found that all long term continuous good responders had similar clinical and radiological outcomes, but that initial MTX monotherapy responders achieved drug free DAS-remission more often.

In recent years it has become clear that early initiation of anti-rheumatoid therapy is important to ensure rapid clinical improvement, restore functional ability, prevent productivity loss and avoid radiologic damage. Many studies showed that more patients have rapid clinical improvement on initial treatment with a combination of MTX and a corticosteroid or a biologic DMARD than on initial MTX monotherapy.[4, 5, 7, 19] This suggests, that perhaps through multi-pathway targeting, more 'types' of rheumatoid arthritis (ACPA positive or negative, with signs of high or low systemic inflammation, erosive or likely to rapidly show damage or not, etcetera) and/or more 'types' of patients (male or female, young or old, high or low body mass index, or other 'hidden' characteristics) respond to combination therapy, while only a certain (as yet undefined, maybe 'milder') subgroup will respond to MTX monotherapy. There is also the perhaps instinctive expectation that early treatment with multi-pathway combination therapy in some way can stop or even reverse disease processes that go unchecked with 'only' MTX monotherapy, resulting in lower disease activity, more remission and better functioning and the possibility to taper and stop medication, resulting in drug free remission without radiologic progression and possibly 'cure' of RA.

If that would be the case, patients who respond well on initial combination therapy would fare better than patients who respond well on initial MTX monotherapy. We did not find this. We *did* see that more patients who started on initial combination therapy achieved continuous good response (DAS≤2.4) compared to patients who started on initial MTX monotherapy. Thirty-five percent of patients who started on initial MTX monotherapy achieved DAS≤2.4 after 6 months, and of those, only 33% maintained DAS≤2.4 on MTX monotherapy for the next 9.5 years. This compared to 59% of patients who achieved DAS≤2.4 at 6 months on initial combination therapy, of whom 44% maintained DAS≤2.4, having tapered to sulfasalazine or MTX monotherapy. But all patients who had continuous DAS≤2.4 had mostly similar disease outcomes over time, regardless of initial treatment. We even observed that more MTX monotherapy responders than combination therapy

responders achieved drug free DAS-remission. It is left to speculation whether the differences in drug-free DAS-remission could be due to discontinuation of prednisone or infliximab or indicate slight differences in efficacy between MTX monotherapy and sulfasalazine monotherapy (after discontinuation of prednisone and MTX in one of the initial combination therapy arms). Functional ability and radiologic damage progression were similar between groups, with a trend for a slight increase in the combination therapy group compared to the MTX monotherapy group over time. An interaction between treatment group and time was found for most outcome measures except for the HAQ and the percentages of patients in remission and drug free remission. However, the interaction effects are small and seem clinically negligible.

If fewer patients respond to MTX monotherapy than to combination therapy, patients who respond well to initial MTX monotherapy might be a tighter defined subgroup based on baseline criteria. We only saw a slightly higher percentage of ACPA negative patients in the MTX monotherapy group. Previously it has been suggested that ACPA negative patients may achieve drug free remission more often than ACPA positive patients, possibly irrespective of effort of treatment.[20] In the PROMPT study ACPA negative patients with undifferentiated arthritis did not benefit from MTX compared to placebo, but ACPA positive patients did.[21] On the other hand, more ACPA negative patients achieved drug free remission. In the current analysis a slightly higher percentage of ACPA negative patients in the MTX monotherapy responders was accompanied by a higher percentage of drug free remission over time. MTX monotherapy responders also had slightly shorter symptom duration and slightly lower Sharp/van der Heijde progression scores at baseline than combination therapy responders. Patient numbers are however too small to go beyond these observations.

The ideal of personalized medicine should avoid delays in response as well as unnecessary costs and potential side effects based on baseline predictors. Previous research has focused on predictors of initial, rather than early continuous good response. Male gender, lower age, lower BMI, low baseline disease activity, absence of IgM rheumatoid factor, not-smoking and several genetic factors were found to be associated with response to MTX monotherapy within 6 to 12 months.[22-24] In our early and continuous MTX responders the baseline characteristics do not suggest that continuous response after initial response is associated with these predictors, although we are not informed about the genetic factors. There may be other, additional factors required for continuous good response during prolonged follow-up, that remain as yet unidentified.

As long as personalized medicine is not yet possible, it appears that although MTX monotherapy may be similarly effective, the main benefit from starting with combination therapy in all patients is that more patients achieve and maintain (after tapering to MTX monotherapy) low disease activity. More recent studies have suggested that the initial prednisone dose can be lower[25-27] and that sulfasalazine may be omitted[27], making a

case for low dose corticosteroid bridging therapy combined with MTX as optimal initial treatment.

A strength of this study is that all patients were treated based on randomization across the treatment arms. Although we analysed a selection of the originally randomized patients, additional adjustment for baseline symptom duration, which differed between the groups at baseline, did not change the results. A limitation of this study was the low number of patients in the MTX monotherapy responders group, which might have reduced the power to detect differences between the groups. However, the lower number of patients in the MTX monotherapy group is in line with previous research showing higher effectiveness of combination therapy.[7-10] A second limitation was the high number of drop-outs among responders. An earlier analysis of the BeSt study has shown that having achieved drug-free remission, independent of initial treatment, and having limited joint damage are risk factors for early termination in the BeSt study.[28] Therefore specifically the patients selected for this study, who respond well to therapy early in the study, had a high risk of dropping out. Indeed, on average, patients in both groups were in low disease activity at the last available visit before they dropped out.

We conclude that regardless of initial induction therapy, those who remain in low disease activity have similar long term outcomes, with only the proportion of patients in drug free remission being higher in the MTX monotherapy group. However, more patients achieve early and continuous low disease activity on prednisone or infliximab combination therapy tapered to sulfasalazine or MTX monotherapy than on MTX monotherapy, although there appear no additional benefits.

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CHAPTER 7

Further Treatment Intensification in Undifferentiated and Rheumatoid Arthritis Patients Already in Low Disease Activity has Limited Benefit towards Physical Functioning

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ABSTRACT

Background: It is recommended to optimize treatment as long as a predefined treatment target is not met. But should we aim at remission if patients are in low disease activity? The aim of this study was to assess if in rheumatoid or undifferentiated arthritis (RA, UA) patients with Disease Activity Score (DAS)≤2.4 (LDA) treatment intensification results in better functional ability.
Methods: In the IMPROVED study 610 patients with early RA or UA were treated with methotrexate + tapered high dose prednisone. After 4 months, patients with DAS≥1.6 were randomized to two treatment strategies. Patients with DAS<1.6 tapered treatment. Over 5 years, patients with DAS≥1.6 required treatment intensification, but protocol violations occurred, which allowed to test the effect of treatment intensification regardless of subsequent DAS. A linear mixed model was performed to test in patients in LDA the relationship between treatment intensification and functional ability (Health Assessment Questionnaire, HAQ) over time.
Results: The number of patients in LDA per visit ranged from 88 to 146. Per visit, 27% to 74% of the patients in LDA had a treatment intensification. We found a statistically significant effect of treatment intensification on ΔHAQ, corrected for baseline HAQ, age, gender and treatment strategy (β=-0.085, 95%CI -0.13;-0.044). When ΔDAS was added, the effect of treatment intensification was partly explained by ΔDAS and the association with HAQ was no longer statistically significant (β=-0.022, 95%CI -0.060;0.016). When the interaction between treatment intensification and time in follow-up was added, a statistically significant interaction was found (β=0.0098, 95%CI 0.0010;0.019), indicating lesser improvement in HAQ after treatment intensification if follow-up time increased.
Conclusions: For early RA and UA patients already in LDA, further treatment intensification aiming at DAS remission does not result in meaningful functional improvement.

BACKGROUND

In the past decades, the treatment of rheumatoid arthritis (RA) has considerably changed. Earlier treatment with disease modifying anti-rheumatic drugs (DMARDs) has resulted in a milder disease course, with better functional ability – as measured for example by the Health Assessment Questionnaire (HAQ)[1]– and less joint damage progression.[2, 3] One of the main aims of RA treatment is to achieve or maintain good physical functioning. In order to achieve this, it is recommended to start treatment early and regularly monitor disease activity and optimize treatment as long as a predefined treatment target has not yet been achieved ('treat-to-target' approach).[4] International recommendations state that at least low disease activity (e.g. DAS ≤ 2.4) (LDA), but preferably remission (e.g. DAS ≤ 1.6, or more stringent definitions), are the best treatment targets when treating RA patients.[5] Previous research has shown that a patient's functional ability is related to the level of DAS and, after prolonged disease activity, also to joint damage.[6-9] Moreover, a stronger decrease in DAS is associated with a stronger decrease in HAQ, even if DAS is already low.[10] However, it may be a patient characteristic rather than a further treatment intensification that determines how low a DAS and HAQ can be achieved. It has never been proved that intensifying drug therapy in patients who are already in LDA will result in further improvement in functional ability that is clinically meaningful. As treatment intensification may not always be effective in further lowering disease activity, and may come with potential side effects and costs, it is worthwhile to test the effect on functional ability of the effort itself, independent of the subsequent observed DAS outcome. Here we have assessed whether aiming for remission – and modifying or intensifying treatment accordingly – in patients who are already in LDA, results in further clinically relevant improvements in functional ability, irrespective of a subsequent change in DAS.

METHODS

Study design

The present study was an observational secondary analysis of data from the IMPROVED study. For this study, visits of patients in LDA (DAS >1.6 but ≤2.4) were selected at each time point of the original study and the effect of treatment intensification versus no treatment intensification on the change in HAQ observed at the next visit was analysed. The IMPROVED study is a multicentre, randomized, single-blind, two-step clinical trial in patients with recent-onset RA and UA. Patients were recruited between March 2007 and September 2010 from 12 hospitals in the western part of The Netherlands. Recent-onset RA was diagnosed according to the 2010 ACR/EULAR classification criteria, with

symptom duration ≤2 years.[11] UA was defined as arthritis in at least one joint and at least one other painful joint, clinically suspected by the rheumatologist to be early RA, but not fulfilling the 2010 criteria. The study protocol was approved by the Medical Ethics Committee of each participating centre and all patients gave written informed consent. A detailed description of the study has been reported previously.[12]
Patients were 'treated-to-target', aimed at DAS-remission (DAS <1.6), with assessment of disease activity every 4 months, during 5 years. Treatment was tapered and discontinued if DAS-remission was achieved and henceforth maintained. Treatment was restarted, changed or intensified (henceforth called 'treatment intensification') if DAS remission was not achieved or lost. The protocol required that all patients started induction therapy with methotrexate 25 mg/week for 4 months and a tapered high dose of prednisone, starting with 60 mg/day and tapered to 7.5 mg/day in 7 weeks. For patients in early DAS-remission (DAS <1.6 after 4 months), prednisone was tapered to 0, and if DAS-remission persisted after 8 months, methotrexate was also tapered to 0. If DAS was ≥1.6 after 8 months prednisone was restarted at 7.5 mg/day. In case of DAS≥1.6 after restarting prednisone, patients were randomized ("delayed randomization") to arm 1 or arm 2. Patients not in early DAS-remission were randomized either to methotrexate 25 mg/week + hydroxychloroquine 400 mg/day + sulfasalazine 2000 mg/day + prednisone 7.5 mg/day (arm 1) or a combination of adalimumab 40 mg/2 weeks + MTX 25 mg/week (arm 2). When patients did not achieve DAS-remission at 8 months, those in arm 1 were switched to adalimumab + methotrexate and for those in arm 2, the dosage of adalimumab was increased to 40 mg/week. For patients in both arms who achieved DAS-remission within 8 months, treatment was tapered to methotrexate monotherapy. If patients in both groups did not achieve DAS-remission with ADA 40 mg/week, further treatment was left to the opinion of the treating rheumatologist.
During the follow-up of the IMPROVED study, several protocol violations occurred and were monitored every four months. If treatment was not intensified in patients who were in LDA, this was registered as a protocol violation. In the current article, subsequent changes in functional ability for patients in LDA (DAS >1.6 but ≤2.4) were compared, who did or did not have a protocol violation (no treatment intensification versus treatment intensification), which allowed us to investigate the effect of treatment intensification on HAQ change.

Statistical analysis

Functional ability was measured every 4 months using the Dutch version of the Health Assessment Questionnaire (HAQ).[13] A change in HAQ score ≥0.22 in a patient is considered clinically relevant.[14] At each time point, all visits where patients were in LDA (DAS ≤2.4 but >1.6) were selected. Thus, the number of included visits could differ per patient. Visits of patients in LDA with treatment intensification (according to protocol)

and without treatment intensification (protocol violation) were compared. Differences in HAQ and DAS at each visit compared to the next visit were calculated (ΔHAQ and ΔDAS, i.e. Y{t+1} – Y{t}), and a negative ΔHAQ or ΔDAS implies improvement. Linear mixed model analyses with random intercept were performed to test the relationship between treatment intensification and ΔHAQ over time, taking into account the correlation of visits within a patient. Models were fitted using restricted maximum likelihood. For each model it was tested whether allowing a random slope improved the fit of the model. If not, it was tested which covariance matrix for within-cluster residuals gave the best fit of the model. Three models were fitted and each model was adjusted for the possible confounders follow-up time, baseline HAQ, age, gender and treatment arm. In the second model, additionally, the effect of ΔDAS on the model was tested. In the third model the interaction effect between change in treatment and follow-up time was added. All analyses were performed using STATA SE version 14 (StataCorp LP).

RESULTS

Over a period of 5 years, both DAS and HAQ showed statistically significant improvement across all patients included in the original study [mean (SD) baseline HAQ 1.2 (0.7), ΔHAQ -0.59, 95% CI -0.61, -0.57; mean (SD) baseline DAS 3.2 (0.9), ΔDAS -1.77, 95% CI -1.79; -1.75]. In 69% of the patients the change in HAQ was clinically meaningful (≥0.22).
The number of patients in low disease activity ranged from 88 to 146 per visit, of which 26% to 73% did not get treatment intensification, with an increase in such protocol violations towards the end of study (online supplementary file 1). In total, 482 patients were in low disease activity at one or more visits where there was information available regarding medication use as well as a follow up visit, resulting in a total number of 1532 visits available for analyses. The average patient and disease characteristics over all included visits where patients were in LDA are provided in table 1. Patients with a treatment intensification more often fulfilled the ACR/EULAR 2010 criteria and were more often male and rheumatoid factor and anti-citrullinated protein antibodies positive, although most differences were small.
For patients in LDA, after treatment intensification the mean (SD) change in DAS at the next visit was -0.48 (0.71), resulting in remission in 59% of the visits. In cases where there was no treatment intensification this was -0.15 (0.67) , resulting in remission in 38% of the visits. The mean (SD) change in HAQ at the next visit for patients in LDA was -0.083 (0.37) after treatment intensification, resulting in a clinically meaningful change in HAQ in 24% of the visits, and -0.0011 (0.35) without treatment intensification, resulting in a clinically meaningful change in HAQ in 25% of the visits.
Results of the linear mixed model analyses to assess the effect of treatment

Table 1. Average patient and disease characteristics over all included visits where DAS ≤2.4 but >1.6.

		No treatment intensification	Treatment intensification
Age, *mean (SD)*		52.6 (12.6)	51.0 (12.4)
Gender, n (*% female)*		46 (78.9)	39 (68.4)
Treatment arm	early remission	46.2	57.2
	MTX + SSZ + HCQ + prednisone	20.9	19.9
	MTX + adalimumab	19.1	16.0
	Out of protocol	13.8	6.7
Symptom duration in weeks, *median (IQR*)		20 (9; 35)	19 (9; 32)
Diagnosis RA, *% meeting 2010 criteria*		46 (79.2)	47 (84.5)
Anti-citrullinated protein antibodies, *% positive*		34 (57.6)	35 (61.9)
Rheumatoid factor, *% positive*		33 (58.9)	34 (63.0)
Health Assessment Questionnaire (0-3)[a], *mean (SD)*		0.78 (0.56)	0.63 (0.48)
Disease Activity Score, *mean (SD)*		1.95 (0.23)	1.99 (0.23)
Tender joint count, *median (IQR)*		2 (2; 4)	3 (2; 4)
Swollen joint count, *median (IQR)*		0 (0; 1)	1 (0; 2)
VAS general health (0-100)[b], *mean (SD)*		31.0 (19.6)	31.7 (20.3)
Erythrocyte Sedimentation Rate, *median (IQR)*		15.7 (13.0)	13.9 (11.2)

The average number of patients per visit with low disease activity without a treatment intensification was 56 (range 24-103) and the average number of patients per visit with low disease activity with treatment intensification was 61 (range 30-77). RA: rheumatoid arthritis, VAS: visual analogue scale, SD: standard deviation, IQR: interquartile range. MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine. [a]0 no functional limitations, [b]100 best score, [c]0 no radiographic damage.

intensifications on ΔHAQ are shown in table 2. All models had a random intercept and an independent covariance matrix. We found a small but statistically significant effect of treatment intensification on ΔHAQ, corrected for baseline HAQ, time in follow-up, age, gender and treatment arm [model 1, β (95% CI) -0.085 (-0.13; -0.044)]. The unadjusted model showed a larger effect [β (95% CI) -0.12 (-0.15; -0.08)]. This points to a weak association between treatment intensification and an improvement in HAQ: patients with a treatment intensification had a 0.085 additional improvement in ΔHAQ over time compared to patients without treatment intensification. When ΔDAS was added (model 2), the association between treatment intensification and delta HAQ became weaker and was no longer statistically significant [β (95% CI) -0.022 (-0.060; 0.016)]. Patients with treatment intensification now only had a 0.022 additional improvement in ΔHAQ over time compared to patients without treatment intensification. When the interaction between treatment intensification and time in follow-up was subsequently added (model 3),

Table 2. Linear Mixed Model analysis to assess the effect of treatment intensification on change in HAQ.

	β	95% CI	P
Model 1 (n patients = 479, n visits = 1528)			
Treatment intensification	-0.085	-0.13; -0.044	<0.001
Follow-up time[a]	0.0057	0.00094; 0.010	0.019
Model 2 (n patients = 476, n visits = 1509)			
Treatment intensification	-0.022	-0.060; 0.016	0.246
Follow-up time[a]	0.0022	-0.0021; 0.0066	0.313
DAS change	0.23	0.21; 0.26	<0.001
Model 3 (n patients = 476, n visits = 1509)			
Treatment intensification	-0.10	-0.18; -0.021	0.013
Follow-up time[a]	-0.0034	-0.010; 0.0033	0.323
Treatment intensification * follow-up time	0.0098	0.0010; 0.019	0.029
DAS change	0.23	0.21; 0.26	<0.001

HAQ = health assessment questionnaire, SE = standard error, CI = confidence interval.

[a]Follow-up time is added to the model as visit number, with time between visits being 4 months. All models were adjusted for baseline HAQ, gender, age and treatment arm.

a statistically significant interaction was found [β (95% CI) 0.0098 (0.0010; 0.019)], suggesting that the association between treatment intensification and HAQ-improvement, already weak in the early phases, only becomes weaker over time. Again, the unadjusted model showed a larger effect [β (95% CI) treatment intensification -0.24 (-0.32; -0.15); time -0.005 (-0.012; 0.0027); treatment intensification*time 0.017 (0.0075; 0.027)].

DISCUSSION

In this observational secondary analysis of data from a randomized clinical trial it was assessed whether intensifying drug therapy in patients who are in low disease activity, but not in remission, results in a clinically meaningful improvement in physical functioning, as measured by the HAQ. It was found that intensifying treatment in RA or UA patients in low disease activity resulted in a statistically significant improvement in ΔHAQ over time. However, the effect was rather small and appears clinically irrelevant. The improvement in ΔHAQ was partly explained by ΔDAS, and the effect of treatment intensification or change on ΔHAQ decreased by increasing follow-up time.

It is currently recommended that treatment efforts in patients with rheumatoid arthritis should be aimed at remission or low disease activity.[15] It remains the question if patients

would further benefit from aiming at remission if they are already in low disease activity. Several studies already confirmed the relationship between ΔDAS and ΔHAQ, also with longer follow-up time,[6-8, 10] however, those studies aimed for low disease activity and/or assessed the relationship between ΔDAS and ΔHAQ in a cross-sectional manner. Previous research also showed that patients with sustained clinical remission (≥24 weeks) had a continuous improvement in HAQ values and that remission implies better physical functioning than low disease activity.[16-18] However, finding that some patients achieved remission and had lower HAQ than the patients who did not achieve remission may have been coincidental and not the result of a therapeutic intervention, as none of these studies assessed prospectively whether further aiming for remission by intensifying treatment in patients who had already achieved low disease activity, results in further clinically relevant improvement in HAQ. The IMPROVED study provided the opportunity to test this, since the study protocol formally required treatment intensification as long as DAS was not <1.6. But rheumatologists did not always comply with this formal requirement, thus allowing us to compare outcomes after treatment intensification vs. lack thereof in patients with DAS<2.4 but still >1.6. In addition, we could investigate if such an association was dependent of the time of follow up.

Our results suggest that the minimally positive effect of a treatment intensification on ΔHAQ is mainly present at the start of treatment and that it decreases by increasing treatment duration. This observation is in line with earlier findings and current guidelines that RA patients should be treated early in the disease process.[19-21] It also suggests that in early RA and UA patients, initial treatment should consist of (a combination of) highly effective drugs, in order to decrease disease activity rapidly and thus maximally improve physical functioning. Persistently aiming for remission in patients already in low disease activity may lead to inappropriate treatment intensifications and increased use of antirheumatic drugs (overtreatment), without additional benefits. This was recently found in studies were clinical remission and imaging remission were compared as treatment target.[22, 23]

A limitation of this study was that we only looked at treatment intensifications in general, and did not specify the type of treatment changes. Different treatments may have different effects on physical functioning. A second limitation of our analysis is that patients with low disease activity in whom treatment was intensified may differ from those in whom treatment was not intensified with respect to characteristics that are relevant to the outcome of interest, but that we have not measured (intangible confounders). Previous studies also showed that ΔHAQ is not only associated with ΔDAS, but also that an increase in joint damage may lead to worse physical functioning, especially with longer follow-up time.[6-9] Since in the remission steered IMPROVED study the majority of the patients hardly had any radiographic damage, joint damage was not further considered in this analysis.[24]

CONCLUSIONS

In conclusion, treatment intensification in early RA or UA patients who have already achieved LDA is associated with a statistically significant decrease in HAQ, but not with a clinically meaningful improvement in functional ability during 5 years of DAS remission steered treatment. Therefore not remission or LDA, but good functional ability may be the optimal treatment target at which to steer treatment adjustments. Thus, it might be sufficient to accept achieved LDA rather than continue treatment intensifications aiming at remission. Further treatment intensifications may not lead to a clinically relevant improvement in HAQ, but it may have downsides such as side effects and costs.

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PART 2

Worldwide differences in RA

CHAPTER 8

Inequity in access to bDMARD care and how it influences disease outcomes across countries worldwide: results from the METEOR-registry.

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ABSTRACT

Objective: To establish in a global setting the relationships between countries' socioeconomic status (SES), measured biologic (b)DMARD-usage and disease outcomes. To assess if prescription- and reimbursement rules and generic access to medication relates to a countries' bDMARD-usage.
Methods: Data on disease activity and drug use from countries that had contributed at least 100 patients were extracted from the METEOR database. Mean disease outcomes of all available patients at the final visit were calculated on a per-country basis. A questionnaire was sent to at least two rheumatologists per country inquiring about DMARD-prices, access to treatment and valid regulations for prescription and reimbursement.
Results: Data from 20.379 patients living in 12 different countries showed that countries' SES was positively associated with measured disease activity (meanDAS28), but not always with physical functioning (HAQ-score). A lower country's SES, stricter rules for prescription and reimbursement of bDMARDs, as well as worse affordability of bDMARDs were associated with lower bDMARD-usage. bDMARD-usage was negatively associated with disease activity (albeit not with physical functioning), but the association was moderate at best.
Conclusions: Disease activity in RA-patients as well as bDMARD-usage varies across countries worldwide. The (negative) relationship between countries' bDMARD-usage and level of disease activity is complex and under the influence of many factors, including – but not limited to- countries' SES, affordability of bDMARDs and valid prescription- and reimbursement rules for bDMARDs.

INTRODUCTION

Earlier diagnosis and treatment, the implementation of treat-to-target and new treatment options, including biologic disease modifying anti-rheumatic drugs (bDMARDs), have improved treatment and prognosis of rheumatoid arthritis (RA) patients tremendously.[1-3] Since many of these treatments are costly, patients across the world may not benefit similarly. Indeed, a lower level of welfare has been associated with higher disease activity in RA-patients in the past.[4]

One of the potentially critical factors is poorer access to bDMARDs.[2, 5] Current recommendations advise starting bDMARDs after a first csDMARD strategy has failed.[5] But such a strategy may not be feasible in greater parts of the world. In many countries there are various restrictions in the prescription and reimbursement of bDMARD.[6-9] Within Europe, differences in socioeconomic welfare are associated with differences in prescription and reimbursement of bDMARDs.[6, 10] Stricter prescription rules and reimbursement criteria of bDMARDs may result in more infrequent use of bDMARDs and in worse health outcomes.[6, 9] To date, only one study, limited to European countries, has been performed that has taken into account all currently available bDMARDs.[6]

We have investigated here daily-practice data regarding bDMARD-use in different countries worldwide and have assessed if a lower country's socioeconomic status (SES) is associated with worse clinical outcomes and lower bDMARD-usage. We have also assessed if countries' bDMARD-usage was associated with stricter prescription- and reimbursement rules and worse access to medication.

METHODS

Data selection

Disease activity and medication use in RA-patients in various countries on various treatments were extracted from the METEOR registry, an international database capturing data of daily clinical practice of patients with a clinical diagnosis of RA.[11] Data were gathered retrospectively and anonymously; hence no informed consent was needed. We selected visits after 1-1-2000, from countries that had included at least 100 patients with follow-up data available.

Missing data on disease activity and function (HAQ-score) were imputed using multivariate normal imputation (30 imputations).[12] For each country average DAS28 and HAQ and the proportion of patients in DAS28-remission (DAS28<2.6) were calculated by taking the average of all patients at the last available visit. Furthermore, the proportion of patients that ever used a biological was calculated per country.

Questionnaire

Per participating country, preferably in the region of data collection, at least 2 rheumatologists answered a questionnaire, based on questionnaires used by Putrik et al.[13] In case of disagreement between rheumatologists they were contacted by email, and if necessary additional rheumatologists were contacted to also complete the questionnaire. The questionnaire included questions about availability and affordability of DMARDs, acceptability, reimbursement and prescription rules (supplementary file 1). Drug prices provided in local currency were converted into euros or international dollars at the rate of 10-1-2017. When all questions were processed, a preliminary report was sent to all collaborators, to check correctness of the data.

Outcome measures

Based on the questionnaire results 2 composite scores were calculated: a composite score for clinical eligibility criteria for the start of bDMARDs, based on 3 questions from the questionnaire and with an optimum score of 5 indicating 'least requirements', and a composite score for access to mediation, based on questions on availability, affordability and acceptability, with an optimum score of 9 indicating 'highest level of access' (table 1).[6, 13]

In addition, we calculated the average annual national price of the most frequently used csDMARDs and bDMARDs. These included the csDMARDs methotrexate, sulfasalazine, hydroxychloroquine and leflunomide and prednisone and the bDMARDs etanercept, adalimumab, infliximab, rituximab, certolizumab, tocilizumab, abatacept and golimumab. For each DMARD a most common treatment scheme was used to calculate the costs for one year usage (the annual national price, averaged over the first 2 treatment years).[13] Furthermore, an affordability index for bDMARDs was constructed by dividing the average annual national price for all bDMARDs by the gross domestic product. All medication prices reflect official manufacturer's prices per country, not taking into account local or temporary discounts.

The gross domestic product (GDP) per capita in international dollars and the minimum wage per year, the household-net-adjusted-disposable-income and the health-expenditure-per-capita in US dollars were derived from web-based sources.[14-16] Data regarding the minimum wage and the average price for csDMARDs and bDMARDs were used to calculate the days to work at the minimum wage to cover 30 days of treatment with a csDMARD or bDMARD.[13]

Statistical analyses

At a country level, associations between several indicators of SES, clinical outcomes, medication use, access to medication and prescription and reimbursement rules were assessed using univariable linear regression analyses.

Since analyses were performed at a country level and the number of included countries was limited, multivariable regression analyses were not performed. Regression results for the GDP per capita, the household-net-adjusted-disposable-income and the health-expenditure-per-capita were assessed per 10.000 Intl$ or US$. All analyses were performed using Stata SE 14 (StataCorp LP).

Table 1. Composite scores for the clinical eligibility criteria for the start of bDMARDs and for the access to medication.

Composite score clinical criteria start of bDMARDs				
	0	**1**	**2**	
Is there any requirement for disease duration?	Any requirement	No requirement	*NA*	
Number of DMARDs to be failed	>2	2	<2	
Level of DAS28	>3.2	≤3.2	No requirement	
Composite score access to medication				
	0	**1**	**2**	**3**
Number of reimbursed bDMARDs	0	1-5	6-7	8
Average annual price of all reimbursed bDMARDs	Highest quartile	Second quartile	Third quartile	Lowest quartile
Average score on the 6 acceptability questions	Highest quartile	Second quartile	Third quartile	Lowest quartile

NA = not applicable

RESULTS

Country and database characteristics

Twelve countries with 20.379 patients were analysed: United States (state of Massachusetts), Mexico, South-Africa, Japan, Brazil, United Kingdom, Spain, Ireland, Portugal, France, India (state of Maharashtra) and the Netherlands. Data from Qatar and Italy were ultimately excluded from the analyses, since only one rheumatologist in Qatar was available to complete the questionnaire and data from Italy were mainly derived from a biologics register. The number of questionnaire responders per country is listed in supplementary file 2.

Table 2 presents average country and database characteristics. The number of patients

per country ranged from 123 (Spain) to 7.749 (India) and the number of patients ever using a bDMARD ranged from 0.9% (South-Africa) to 75% (Ireland). There were important differences in DAS28- and HAQ-scores across countries. Overall, and expectedly, DAS28 was positively associated with HAQ-score, except in India, where the average DAS28 was highest but the average HAQ-score was among the lowest of all countries. As expected, there were important differences in SES between countries, reflected – for example – by differences in GDP per capita (ranging from Intl$ 5,733 in India to Intl$ 61,378 in Ireland) and by large differences in the country's number of days required to work at the minimum wage to cover 30 days of treatment with a bDMARD (ranging from 562 days in India to only 19 days in France).

Average annual medication prices also substantially differed between countries (figure 1). For bDMARDs, drug prices (Intl$) in the US (highest) were 5.9 times higher than in France (lowest) and for csDMARDs, drug prices in the US (highest) were 14.7 times higher than in the Netherlands (lowest).

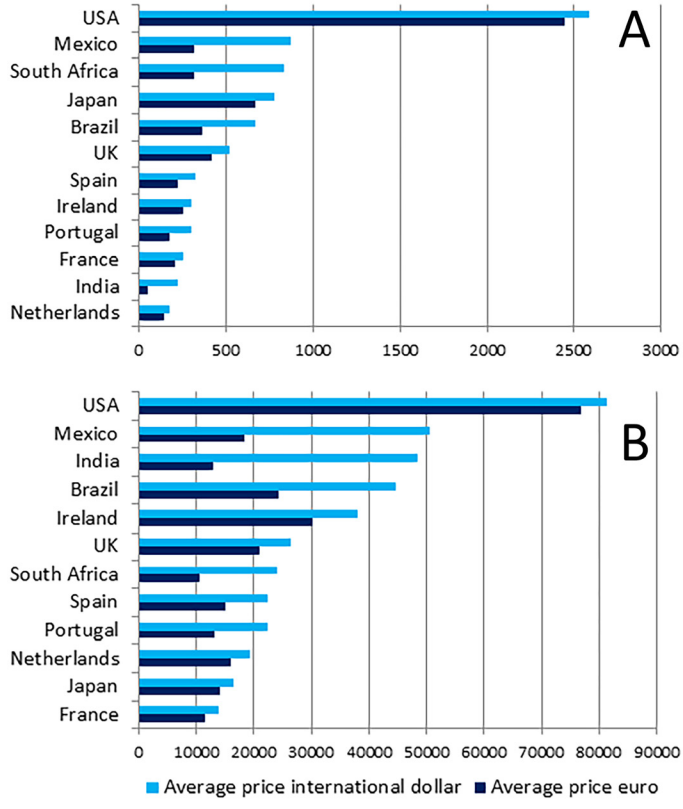

Figure 1. Average annual price for csDMARDs (fig 1-A) and bDMARDs (fig 1-B) per country in international dollars (light blue) and in euros (dark blue), prices first quarter 2017.

Countries' SES and clinical outcomes

We first assessed if a lower SES was associated with worse clinical outcomes, by testing associations between GDP per capita and DAS28. Indeed, patients in countries with a higher GDP per capita had a lower average DAS28 and a higher proportion of them were in DAS28-remission [DAS28 lower by β (95% CI) -0.32 (-0.41; -0.021) and an additional 4.2 (0.14; 8.26) percent of patients in DAS28-remission for every 10.000 Intl$ additional GDP]. The effect was less prominent in the US and Ireland, both countries with the highest GDP per capita (figure 2A, 2C).

Then, we factored drug-prices into the 'model' by testing the association between the number of days needed to work at the minimum wage in order to afford 30 days of treatment with a bDMARD. Now the association was largely driven by two low-GDP countries (Mexico and India) (figure 2B, 2D) that yet have among the highest drug prices relative to the income. In most other countries, DAS28 and remission percentages were only slightly higher with each extra working day needed to afford bDMARDs: DAS28 higher by β (95% CI) 0.026 (0.012; 0.041) and -0.052 (-0.084; -0.020) less patients in DAS28-remission per additional minimal wage day required to afford 30 days bDMARDs.

Finally, we tested health-expenditures-per-capita as well as household's-net-adjusted-disposable income as proxies for SES and assessed the associations with DAS28. In general, the effects were similar: mean DAS28 was -1.3 (-2.6; -0.015) points lower for every additional $10.000 health-expenditure-per-capita, which culminated into 25 (-2.3; 52.0) percent more patients in DAS28-remission. Such effects were not found for household's net-adjusted disposable income (data not shown).

Overall, RA-patients from low-GDP-countries –on a per-capita basis- appear to have a higher DAS28 than patients from high-GDP-countries, regardless of countries' drug prices. It may be that in some countries drug-prices may mitigate the effects of SES on RA outcomes, (drug prices were for instance importantly lower in Brazil and South-Africa). For HAQ-score, however, the associations with all indicators of SES were less clear: e.g. -0.031 (-0.13; 0.064) lower HAQ per 10.000 Intl$ increase in GDP per capita and 0.000034 (-0.00091; 0.00098) higher HAQ per additional minimal wage day required to afford 30 days bDMARDs.

SES and bDMARD-usage

It is attractive to assume that the inverse association between SES and DAS28 is mediated by the countries' bDMARD use (or: RA care in high-income countries is better since these can afford bDMARDs). We have sought evidence to underscore this assumption. First, we assessed whether SES was associated with bDMARD-usage per country. Indeed, a statistically significant association was found between GDP per capita and the proportion bDMARD-usage [11.2 (4.82; 17.5), fig3-A], indicating that per additional 10.000 Intl$ GDP per capita an additional 11% of patients used a bDMARD.

Table 2. Baseline characteristics per country.

	India	South-Africa	Brazil	Mexico	Portugal	Spain
Country characteristics						
Population (x1.000.000)	1311.1	10.4	207.8	127.0	10.4	46.4
GDP per capita (Intl$)	5733	12393	14533	16490	26549	32219
Minimum wage per year (US$)	778	2197	3660	1438	8384	10365
Household net adjusted disposable income (US$)	NA	8712	11487	12806	19882	22007
Health expenditure per capita (US$)	75	570	947	677	2097	2658
Days work at minimum wage to cover 30 days treatment bDMARD	562	160	223	431	53	49
Days work at minimum wage to cover 30 days treatment csDMARD	2.2	4.9	3.3	7.4	0.7	0.7
Mean price bDMARDs year / GDP per capita	8.45	1.93	3.07	3.07	0.84	0.70
Composite score access to medication	3	3	5	1	6	5
Composite score clinical criteria	4	1	1	4	5	4
Database characteristics						
Number of patients	7749	670	189	1191	3874	123
Mean time since diagnosis at last recorded visit (days)	1304	577	4900	2898	5599	1327
% patients bDMARD use	0.95	0.90	19.6	9.0	44.5	16.3
Mean last DAS28	5.1	4.2	4.2	4.0	3.5	3.3
% patients in DAS28-remission	2.3	19.9	17.0	20.9	32.4	42.7
Mean last HAQ	0.67	1.27	1.26	0.71	1.05	0.55

	France	Japan	UK	Netherlands	USA	Ireland
Country characteristics						
Population (x1.000.000)	66.5	127.0	65.1	16.9	321.4	4.64
GDP per capita (Intl$)	37775	37872	38509	46354	52704	61378
Minimum wage per year (US$)	19886	12269	21793	20673	15080	20967
Household net adjusted disposable income (US$)	29759	27323	26687	27759	41071	22969
Health expenditure per capita (US$)	4959	3703	3935	5694	9403	4239
Days work at minimum wage to cover 30 days treatment bDMARD	19	39	32	26	171	48
Days work at minimum wage to cover 30 days treatment csDMARD	0.3	1.8	0.6	0.2	5.4	0.4
Mean price bDMARDs year / GDP per capita	0.37	0.44	0.69	0.42	1.55	0.62
Composite score access to medication	9	4	5	6	4	4
Composite score clinical criteria	4	5	2	4	5	4
Database characteristics						
Number of patients	161	309	1291	3330	803	689
Mean time between diagnosis and last visit (days)	5375	2503	3256	3181	3513	3921
% patients bDMARD use	60.2	50.5	14.7	28.2	48.6	75.0
Mean last DAS28	2.5	3.2	3.9	3.2	3.6	3.8
% patients in DAS28-remission	61.5	38.2	26.0	39.1	30.5	28.8
Mean last HAQ	0.61	0.59	1.29	0.85	0.67	0.85

GDP = Gross Domestic Product, Intl$ = international dollar, US$ = United States dollar, bDMARD = biologic disease modifying anti-rheumatic drug, csDMARD = conventional synthetic disease modifying anti-rheumatic drug, NA = not available. 'Number of patients' indicates the number of patients with >1 available visit. '% patients bDMARD use' indicates the number of patients using a biological DMARD during at least 1 visit. 'Mean last DAS28' and 'mean last HAQ' are the DAS28 and HAQ at the last available visit in the database.

When taking drug-prices into account, the picture is more obscure. Although in Mexico and India bDMARD-usage was lowest, in the countries with highest GDP per capita bDMARD-usage was highly variable (ranging from close to 10% in the UK to 75% in Ireland), [fig3-B, β (95% CI) -0.080 (-0.16; 0.0021)]. This suggests that not only GDP and drug-prices but also other mechanisms (such as limitative regulations for reimbursement) determine bDMARD-usage.

bDMARD-usage and clinical outcomes

It is questionable, however, if a higher percentage of bDMARD-usage translates automatically into better disease outcomes. We assessed whether bDMARD-usage across

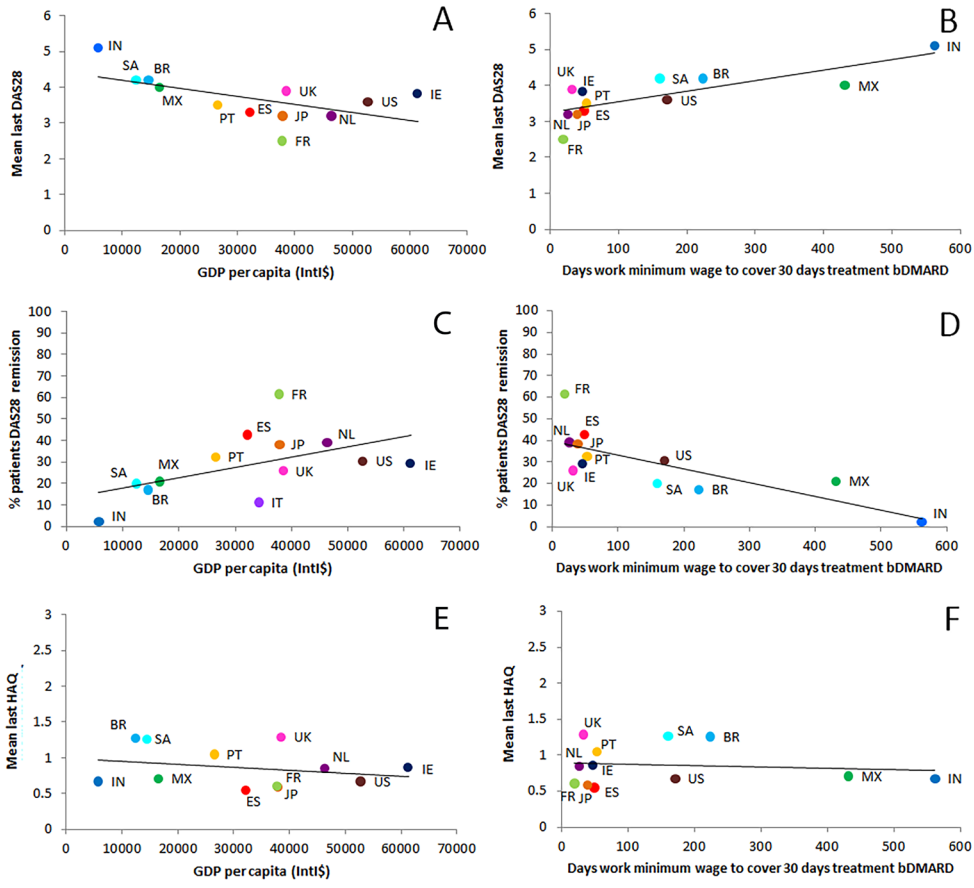

Figure 2. Associations between 'GDP per capita (IntI$)' and 'days to work at the minimum wage to cover 30 days of treatment with a bDMARD' with clinical outcomes per country.

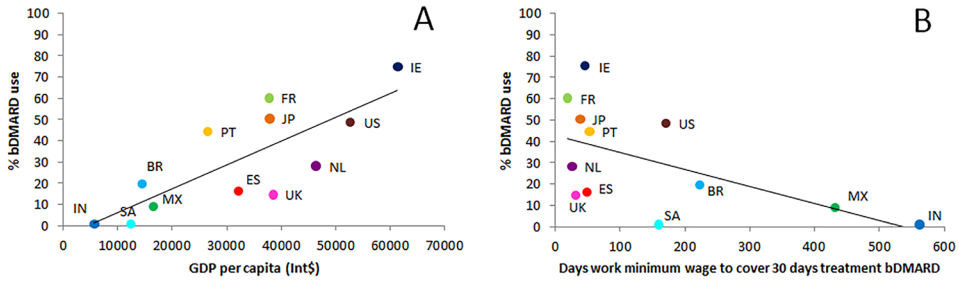

Figure 3. Associations between 'GDP per capita' and 'days to work at the minimum wage to cover 30 days of treatment with a bDMARD' with '% bDMARD use'.

countries are associated with clinical outcomes. Indeed we found a statistically significant relationship between a country's proportion of bDMARD-usage and DAS28 or proportion of patients in DAS28-remission (Fig 4A, 4B). DAS28 was -0.14 (-0.28; -0.0054) point lower, and 2.8% (-0.13; 5.8) more patients achieved DAS28-remission, for every 10% increase in proportion of patients using a bDMARD. However, bDMARD-usage was not associated with better functional ability [-0.024 (-0.091; 0.042) lower HAQ-score for

Prescription and reimbursement rules, access to medication and bDMARD-usage

Since bDMARD-usage is not only influenced by a country's SES, it was subsequently assessed whether the stringency of prescription- and reimbursement-rules and 'access to medication' were associated with proportion of bDMARD-usage.

We found that bDMARD-usage is less if limitative regulations are stricter: 8.5 (-2.7; 19.8) percent more bDMARD use per point increase (i.e. fewer limitations) in clinical criteria score and a trend [5.9 (-2.0; 13.8)] that better access to bDMARD-care led to more bDMARD-usage (figure 4D and 4E).

This shows that the previous relationship found between a country's SES and quality of RA care measured as a country's mean DAS28, is (among others) confounded by regulations. Relatively strict prescription- and reimbursement rules in the UK, a high SES country, result in a proportion of bDMARD-usage as low as in India and Mexico, which both have a low GDP per capita.

Finally, we calculated the quotient of a country's mean drug-price and the GDP per capita (as proxy for affordability, the lower the quotient, the less affordable the drug) and found 1) that even in countries with a same level of affordability (e.g. EU countries) significant differences in bDMARD-usage exist, apparently due to other mechanisms than drug-prices alone; and 2) that affordability of bDMARDs in some countries is so low that bDMARD-usage is virtually zero.

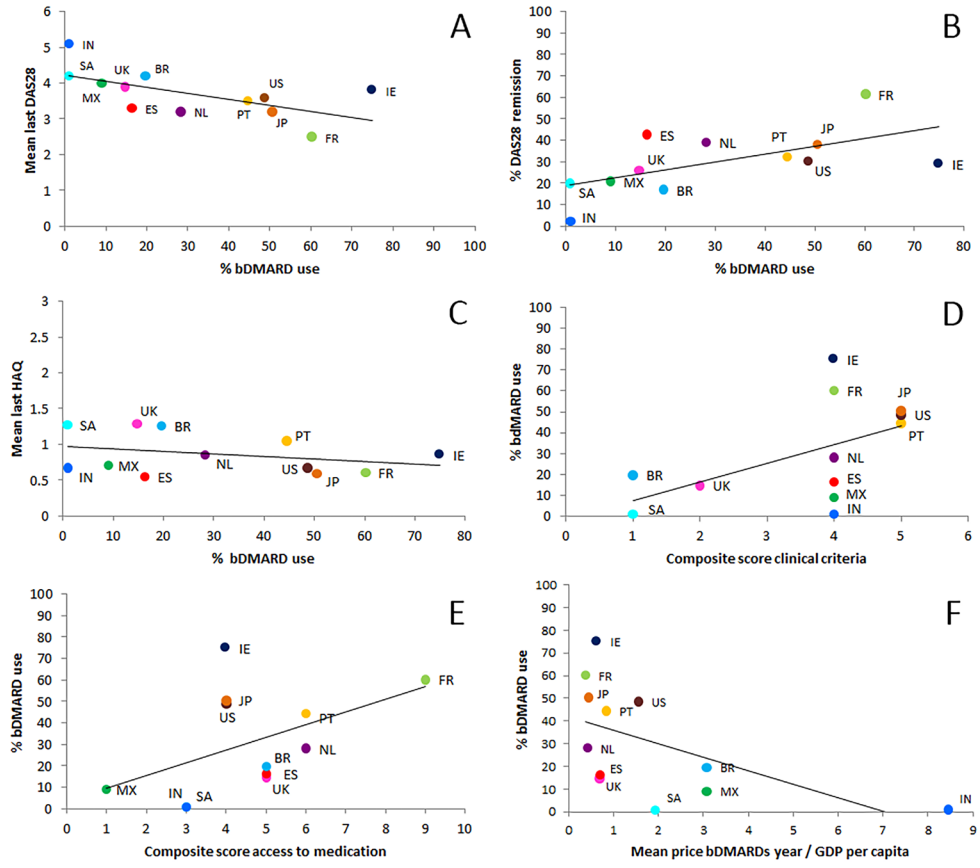

Figure 4. Associations between the '% of patients that ever used a bDMARD' and the 'composite score clinical criteria', 'composite score access to medication' and clinical outcomes.

DISCUSSION

Worldwide, treatment options and clinical outcomes of RA-patients have greatly improved, but not all RA-patients have benefitted similarly. We hypothesized that differences in SES have an impact on bDMARD-usage and on clinical outcomes across countries. Indeed, in this study including a large number of patients from 12 countries, among which several countries that have never been investigated before in this context, we have found substantial differences in DMARD-prices, affordability of these medications and bDMARD-usage across countries. We found that in countries with a lower SES disease activity was generally higher and bDMARD-usage was lower. But a country's proportion of bDMARD-

usage was also associated with restrictions through prescription and reimbursement rules, and with affordability of bDMARDs, as defined by us.

It is attractive to assume that higher country's bDMARD-usage will result in a lower country's mean DAS28, and that a lower country's GDP will hinder a sufficiently high proportion of RA-patients getting proper access to care with bDMARDs. But reality is more complicated. The effectiveness of bDMARD-usage in countries' all-day clinical practice may be overstated: previous research estimated that 'only' 7% of the effect of GDP per capita on DAS28 was mediated by the uptake of bDMARDs.[4] We found 'only' 2.8% more patients in DAS28-remission for every additional 10% patients using a bDMARD. A positive effect of bDMARDs on RA treatment effectiveness thus appears to be quite small. Vice versa, this suggests that in low-income countries other factors than 'only' access to bDMARDs determine the success of RA treatment. Nevertheless, a general trend between countries' proportions of bDMARD-usage and countries' mean-DAS28 remains obvious. Remarkably, we did not find an association between countries' SES and countries' mean HAQ-score. Here, the effect of outliers is relatively important. In particular India, the country with lowest GDP, reported a low HAQ-score compared to a high DAS28. Moreover, there may be socio-demographic and cultural differences in the way patients experience or report limitations in function.[17, 18] We could not assess the potential contribution of factors such as general access to health care and other drug and non-drug therapies, co-morbidities and health barriers and support systems.[19]

Previous studies have mentioned associations between access to medication, SES and disease activity.[6, 13, 20] Such findings point to the negative effects of inequity: budget restrictions, strict regulations as well as limited access to drugs may be a hurdle for starting optimal treatment as recommended in clinical guidelines.[13, 21]

But this study also shows that several other factors play a role in determining the success of RA-treatment (here approximated by the countries' mean DAS28). We know several of these factors: countries' SES in general, the presence of a proper functioning health-care system that may assure access to care to those who are in need, DMARD prices and valid national regulations that are in place to constrain the expenses for bDMARD-usage.[4, 6-9, 13, 21] It appears obvious that the country's mean level of DAS28 is the resultant of a complicated interplay of a country's SES, drug prices and regulations. In addition, it is difficult to argue that unlimited access to expensive effective treatments makes the difference between 'good and bad care' for RA-patients, nor can we claim that countries with similar GDP per capita or similar levels of access to care have similar proportions op patients on expensive bDMARDs; there is huge variation. Nevertheless, penetration of bDMARDs in low GDP-countries stays behind and it is to be expected that this –among others- may go at the cost of effectiveness of RA-care. It is impossible to conclude from this study whether this is due to drug-prices, failing health care systems or simply worse access to optimal care. We can only conclude that there are substantial differences in

mean DAS28 (as a proxy for quality of RA-care) across countries.
This study has some strengths and many limitations. A strength of this study is that it captures real life clinical data from 12 countries world-wide with large differences in wealth, totally different (if any) health-care and health-insurance systems and many RA-patients. As such, this study can be considered a 'big-data study' allowing subtle differences across countries to be elucidated.
But the strengths of our study (real life observational, size and international diversity) also carry limitations: case-ascertainment (cases cannot be verified), completeness of data (we had to statistically impute missing data) and reliability of data-points (we had to rely on the report of the participating physicians) are among them. Other epidemiological limitations are that only few centres per country participated and we had to assume that these centres were to some extent representative of the country. In addition, we had to make certain assumptions to facilitate computations, such as declaring bDMARD-reimbursement as 'absent', if according to the rheumatologist's questionnaires less than 20% of patients in a country had health insurance coverage. Such assumptions –if flawed- may influence the reported associations. In a few cases, we relied on regional health-economical information rather than on country-specific data, in the appreciation that within a big country access to health care and regulations can be very different.
A final limitation of this database is that it will only include RA-patients that have come to the attention of the rheumatologist. If countries differ with regard to access to a rheumatologist, patients per country cannot be assumed to be comparable. Consequently, associations may be spurious. With regard to this latter argument, it can be postulated that the associations in this study are conservative and will likely be more exaggerated in real life.
Epidemiological limitations of 'big-data studies' restrict their interpretability. As such, causal interpretations will never be possible and should always be mistrusted. We have taken care to not exaggerate our conclusions that all remain at the level of associations and allow the possibility of bias and confounding as explanatory factors. Still, 'big data studies' make sense in that they can point to relevant differences between countries, that may help policymakers to guide necessary change, pharmaceutical industry to direct market access and drug-prices, and rheumatologists and health-care workers to help improving access to rheumatology care.
In conclusion, we have documented using a registry of patients with RA spanning 12 countries world-wide that mean DAS28 as well as bDMARD-usage varies across countries. While we suggest an inverse relationship between the countries' bDMARD-usage and mean DAS28, this relationship is influenced by many other factors, including countries' GDP per capita, strictness of prescription and reimbursement rules and affordability of bDMARDs. All together these findings point to the existence of worldwide inequity with regard to optimal (access to) RA health care.

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CHAPTER 9

An evaluation of the joint distribution at disease presentation of rheumatoid arthritis – a large study across continents

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ABSTRACT

Background: Genetic and environmental risk factors for RA are population dependent and may affect disease expression. Therefore we studied tender and swollen joint involvement in newly diagnosed RA-patients in 4 countries and performed a sub analysis within countries to assess whether the influence of autoantibody positivity affected disease expression.
Methods: Patients with symptom duration <2 years fulfilling the ACR/EULAR 2010 RA-classification criteria were selected from METEOR, an international observational database, and the Dutch Leiden Early Arthritis Clinic. Indian (n=947), Mexican (n=141), South-African (n=164) and Dutch (n=947) autoantibody positive and negative RA-patients, matched by symptom duration, were studied for swollen and tender joint distribution.
Results: Between countries, the reported distribution of swollen joint distribution differed, with more knee synovitis in Mexico, South-Africa and India compared to the Netherlands (37%, 36%, 30% and 13%) and more elbow (29%, 23%, 7%, 7%) and shoulder synovitis (21%, 11%, 0%, 1%) in Mexico and South-Africa compared to India and the Netherlands. Since the number of autoantibody negative patients in Mexico and South-Africa was limited, Indian and Dutch autoantibody positive and negative RA-patients were compared. The number of swollen and tender joints was higher in autoantibody negative patients, but the overall distribution of involved joints was similar.
Conclusion: Joint involvement at diagnosis does not differ between autoantibody positive and negative RA-patients in India and the Netherlands. However, joint involvement is reported differently across countries. More research is needed whether these differences are cultural and/or pathogenetic.

INTRODUCTION

The disease phenotype of rheumatoid arthritis (RA) may be influenced by different factors, including the presence of autoantibodies. Many RA-patients are positive to one or more autoantibodies, which can precede symptom onset by years.[1, 2] Currently, the two most important autoantibodies involved in the diagnosis and prognosis of RA are rheumatoid factor and anti-citrullinated protein antibodies (ACPA).[3] Although these autoantibodies are thought to be involved in the disease pathogenesis, a proportion of RA patients test negative for both, indicating that the presence of rheumatoid factor and/or ACPA is not a prerequisite for the development of RA.[4] It is even suggested that ACPA positive and negative RA might not be the same disease, supported by differences in genetic backgrounds.[5, 6]

A previous study investigated differences in phenotype of ACPA positive and negative RA in Dutch patients and found similar phenotypes at the time of diagnosis.[7] However, the pathogenesis of RA is complex; genetic and environmental risk factors are involved and both are population dependent. In addition, local cells, systemic factors as well as local mechanical factors are suggested to influence site-specific inflammation.[8-11] Environmental factors are inherently different in different parts of the world. The genetic make-up differs across the world and, consequently, different genetic risk factors for RA are identified in different populations.[12]

Nevertheless, most scientific research on RA is done in Western countries and in line with this, studies describing the phenotype of RA in non-Western populations are rare. Although patients were generally not evaluated at the time of diagnosis, the scarcity of available evidence suggests differences in RA phenotype in various populations.[13, 14] Therefore we studied the distribution of joint inflammation at the time of diagnosis in different RA populations (Mexican, Dutch, Indian and South-African). In addition, within the Indian and Dutch populations, the joint distribution was subsequently compared between autoantibody positive and negative RA-patients.

METHODS

Populations

Patients fulfilling the ACR/EULAR 2010 RA-classification criteria[15] with available joint counts and symptom duration <2 years at the time of diagnosis were selected from two observational databases. Dutch patients were selected from the Leiden Early Arthritis Clinic (EAC) cohort. This is an inception cohort including patients presenting with symptoms <2 years and clinically confirmed arthritis at the Leiden University Medical Center (LUMC), which is the only center for rheumatic diseases in a semi-rural area

with >400.000 inhabitants. Indian, Mexican and South-African patients diagnosed with RA were selected from METEOR. This is a large international, observational database including patients with a diagnosis of RA according to the rheumatologist, capturing daily clinical practice. Indian patients were included in a private rheumatology facility in a community setting (Pune). South-African patients were included in a large provincial hospital (Johannesburg). Mexican patients were selected from two university hospitals and one regional hospital (Monterrey and Mexico City). In all patients included in this study, the 2010 classification criteria were only applied to patients with a clinical suspicion or diagnosis of RA according to the rheumatologist and patients that fulfilled these criteria were studied. All antibody measurements were performed locally. Both the EAC and METEOR databases have been described extensively before.[16, 17] The EAC was approved by the medical ethics committee of the LUMC and all participants gave written informed consent. Data in the METEOR database were gathered anonymously and captured only daily clinical practice; here informed consent was not required.

Joint counts

The main outcome was the swollen joint distribution at time of diagnosis. Tender joint distribution was also studied. Forty-four swollen and 53 tender joint counts were collected in Dutch and Indian patients; 28 swollen and tender joint counts in Mexican and South-African patients. Small joints included MCP, PIP, MTP2-5, thumb, interphalangeal and wrist joints. Large joints included shoulders, elbows, hips, knees and ankles, similar to the definitions used in the 2010 criteria.[15]

Sensitivity analyses

Because joint distribution is part of the 2010-classification criteria, hence generating circularity between this inclusion criterion and the outcome of interest, joint distributions were also studied for patients diagnosed as RA by the treating rheumatologists (hence ignoring classification criteria).

Statistics

First all patients fulfilling the inclusion criteria were selected from the EAC. Then a symptom duration matched cohort with Indian patients was selected from METEOR. Patients were matched 1:1 on symptom duration, to prevent that differences in symptom duration influenced the number of involved joints. Since fewer patients were available from Mexico and South-Africa and average symptom duration was longer, these patients could not be matched 1:1. For these two countries patients with the longest symptom duration were excluded, to achieve sets of patients with similar symptom duration at baseline.

Frequencies were compared for autoantibody positive (rheumatoid factor and/or ACPA

positive) and negative (both rheumatoid factor and ACPA negative) patients and for patients from different countries. Comparisons between two groups were done with the Mann-Whitney U test, comparisons between several groups with the Kruskal-Wallis equality-of populations rank test. P-values <0.05 were considered statistically significant. All analyses were performed using Stata SE version 14 (StataCorp LP)..

RESULTS

Baseline characteristics

Table 1 presents baseline characteristics. Patients in the Netherlands were more often auto-antibody negative. Patients in Mexico and South-Africa had a higher BMI than Dutch and Indian patients. Since the number of autoantibody negative patients in Mexico and South-Africa was too low (n=22 and n=1, respectively), analyses were only stratified for autoantibody status for the Netherlands and India. Baseline characteristics for autoantibody positive and negative patients were similar, but autoantibody positive patients had slightly longer symptom duration at diagnosis and autoantibody negative patients in the Netherlands had higher disease activity (online supplementary file 1).

Distribution of swollen and tender joints across countries

The swollen joint distribution differed between countries (figure 1). In Dutch RA-patients hand and foot joints were more often swollen than in India, especially MCP1-3, PIP2,3 and MTP2,3. In Mexico and South-Africa the distribution of swollen hand joints was similar to that in the Netherlands. In contrast to the Netherlands, knees were more often swollen in India, Mexico and South-Africa (13% versus 30%, 37%, 36% respectively). RA-patients in Mexico and South-Africa also had more often swelling of other large joints than patients in India and the Netherlands. The shoulder was swollen in Mexico and South-Africa in 21% and 11%, compared to 0% and 1% in India and the Netherlands. Similarly for elbow joints these percentages were 29%, 23% 7% and 7%, respectively. In all countries the number of tender joints was higher than the number of swollen joints, but patterns were similar. When comparing the 28SJC between the four countries, the highest numbers of swollen joints were seen in Mexico and South-Africa (median 7 and 8 versus 3 (India) and 5 (Netherlands)). Overall, tender joint count was highest in India (online supplementary file 2).

Comparing autoantibody positive and negative patients

In general, the number of swollen and tender joints was higher in autoantibody negative than in autoantibody positive patients, especially in the Netherlands (supplementary file 3). Despite higher joint counts, the swollen joint was very similar for autoantibody positive

Table 1. Comparison of baseline characteristics of RA-patients diagnosed in the Netherlands, India, Mexico and South Africa

	Netherlands		India		Mexico[a]		South Africa[a]	
	N	Mean (SD) / %	N	Mean (SD) / %	N	Mean (SD) / %	N	Mean (SD) / %
Gender (% female)	947	65.6	947	81.2	140	86.4	162	81.5
Age (years)	947	56.8 (15.3)	942	42.9 (12.6)	131	47.7 (12.5)	163	47.7 (12.5)
RF (% positive)	942	61.4	944	87.3	137	80.3	164	99.4
ACPA (% positive)	886	51.5	442	72.4	99	60.6	91	96.7
Body mass index	779	26.1 (4.2)	503	26.6 (6.4)	115	33.8 (41.4)	61	28.1 (7.2)
Cigarette smoking	879		908		104		151	
Current		24.0		2.2		24.0		18.6
Past		36.6		0.0		3.9		8.6
Never		39.4		97.8		72.1		72.8
Symptom duration at diagnosis (months)	947	5.3 (4.7)	947	5.8 (4.5)	141	5.3 (2.5)	154	5.4 (2.4)
DAS	865	3.1 (1.0)	549	3.9 (0.9)	--	--	--	--
DAS28	867	5.0 (1.4)	517	6.1 (1.3)	124	5.6 (1.3)	137	5.9 (1.3)
ESR	939	33.6 (27.1)	779	68.9 (31.2)	128	32.5 (19.3)	141	39.6 (28.7)
CRP	935	24.3 (33.9)	779	37.4 (38.3)	99	16.6 (26.4)	143	31.5 (44.7)
VAS patient global (mm)	875	42.0 (25.7)	656	52.3 (18.4)	136	55.6 (26.0)	156	65.6 (22.4)

DAS = disease activity score, ESR = erythrocyte sedimentation rate, CRP = C - reactive protein, VAS = visual analogue scale [a]In order to achieve sets of patients with similar symptom duration at baseline, 86 patients from Mexico and 139 patients from South-Africa with longest symptom duration were excluded.

and negative patients within both countries (figure 2).

Sensitivity analyses

Because of circularity between the number and distribution of swollen joints and fulfillment of the 2010-criteria, swollen joint distribution was also assessed in patients diagnosed with RA according to the rheumatologist. This showed similar distributions of swollen joints compared to patients fulfilling the 2010-criteria (online supplementary file 4: figure 1).

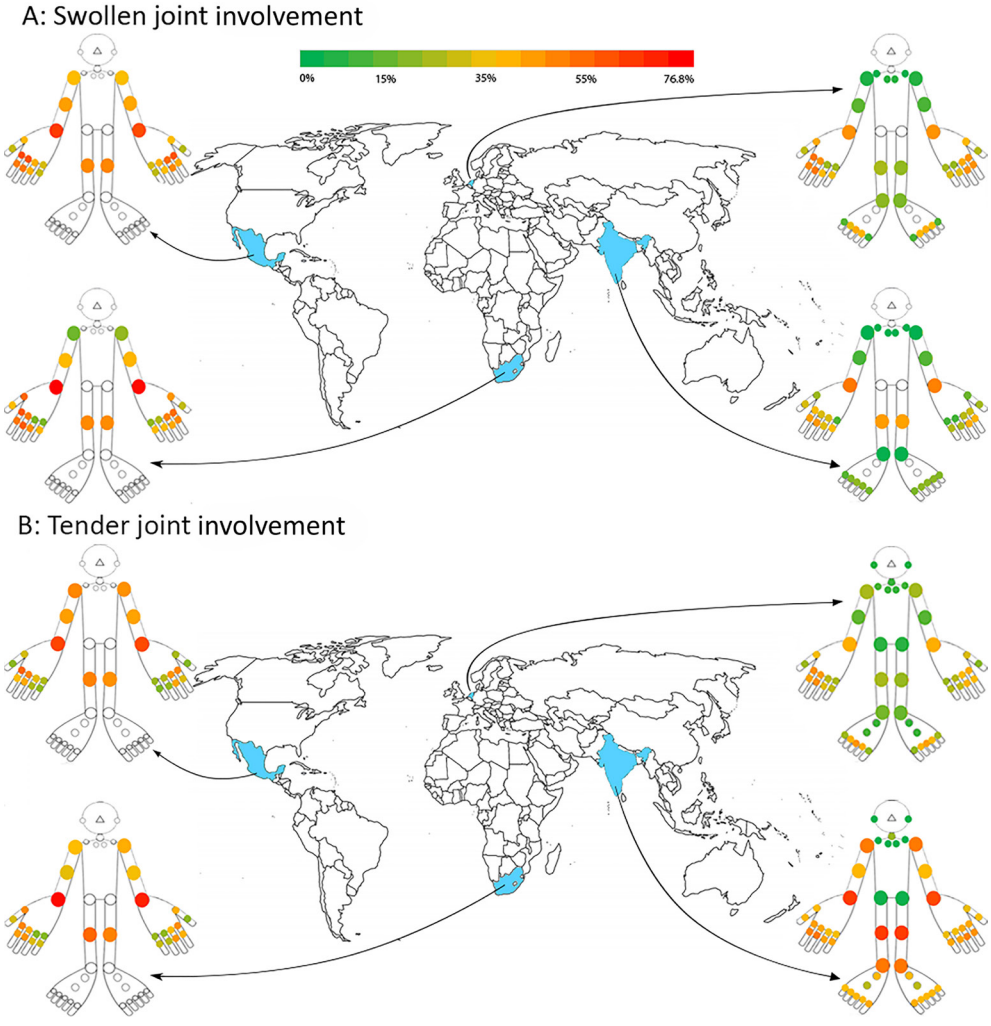

Figure 1. Distribution of swollen (fig. 1-A) and tender (fig. 1-B) joint involvement in Mexico, the Netherlands, India and South-Africa. Coloured circles indicate the percentage of patients with swelling or tenderness in the specific joint per country. White circles indicate that the joint is not included in the joint count.

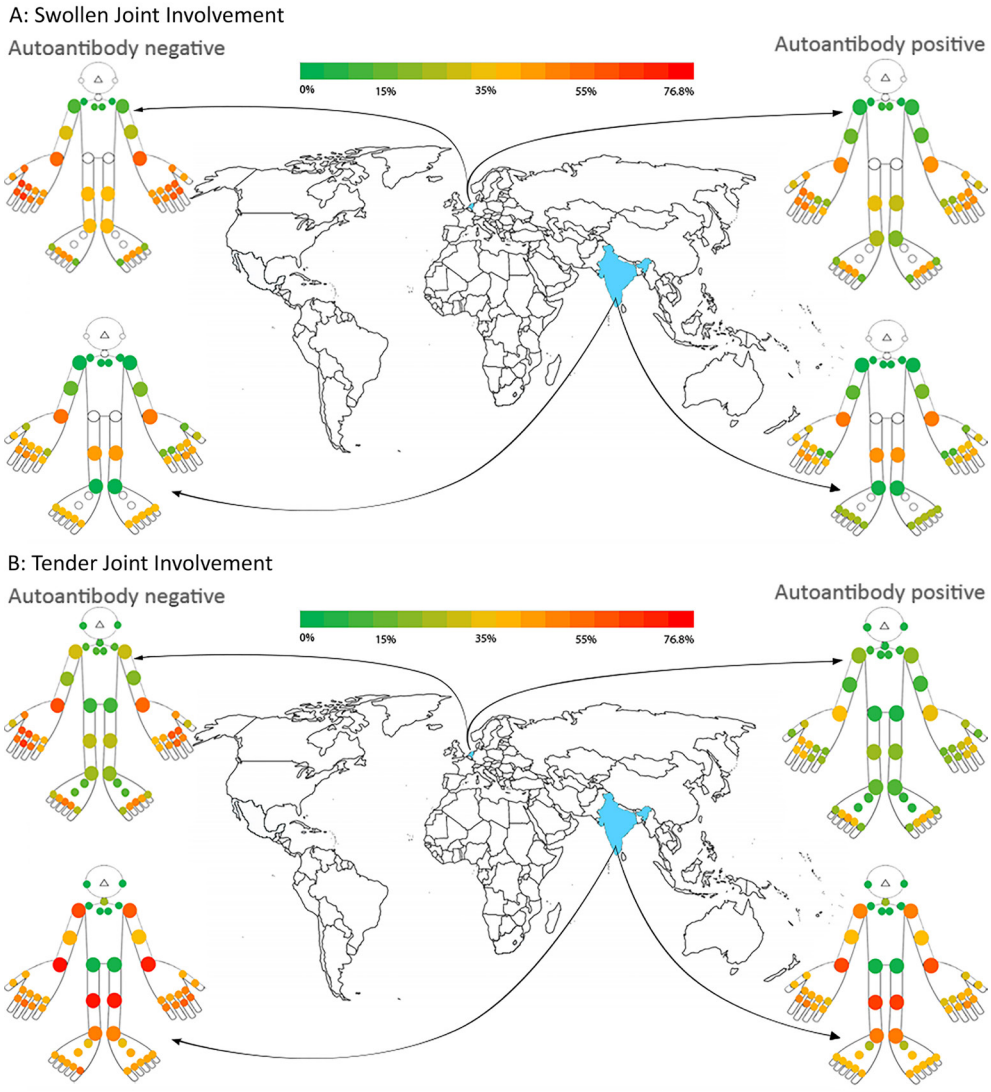

Figure 2. Distribution of swollen joint involvement in India and the Netherlands, for autoantibody negative (left) and autoantibody positive (right) patients. Coloured circles indicate the percentage of patients with swelling in the specific joint per country. White circles indicate that the joint is not included in the joint count.

DISCUSSION

This is the first large study comparing joint involvement in recent-onset RA-patients from different populations. In both the Netherlands and India, the distribution of involved joints

did not differ for autoantibody positive and negative patients within these countries, but joint involvement was reported differently in different countries. Synovitis in large joints was more frequent in India (knees), South-Africa (knees, elbows) and Mexico (knees, elbows, shoulders) than in the Netherlands. Feet involvement was studied in two countries only and was considerably less frequently reported in India than in the Netherlands. Differences observed between the different countries can be caused by differences in reporting by doctors or in referral of patients to rheumatologists in the different countries. Then selection bias may have influenced the results. Alternatively, the observed differences can be 'true'. Then further studies on the underlying pathogenetic mechanisms that drive the difference in distribution of joint involvement are required and can increase our understanding on the mechanisms leading to RA and to inflammation of the predilection places. To evaluate which of these two possibilities is true, validation studies are required. This can either consist of validation studies in other observational cohorts, or based on analyses on RCTs. However the inclusion criteria that are used in most intervention studies can also induce selection bias, as the patients studied here are often a severe subset of RA.

The consequences of different selection methods of patients between centers or countries, if present, do not affect the results of the analyses done within countries. Joint distribution of ACPA-positive and ACPA-negative RA have been studied previously and no differences were observed, which was now replicated in a larger Dutch dataset as well as in an Indian RA population.[7] This finding suggests that some common triggers lead to synovitis in similar joints in autoantibody positive and negative patients, although these may differ between countries. Unfortunately, since the number of autoantibody negative patients included in the database by a rheumatologists from Mexico and South-Africa was limited, stratification on autoantibody positivity could not be performed for these datasets.

The number of autoantibody positive patients was higher in India than in the Netherlands. This is intriguing as smoking is an important risk factor for ACPA-positive RA and the number of patients smoking in India was low.[18] Different explanations are possible. It is known that the number of females smoking in India is low (approximately 3%).[19] Another issue is that the smoking data captured contained information on cigarettes but not information on smokeless tobacco products, while these products are much more prevalent than cigarettes in India.[20] The absence of gathering information on smokeless tobacco products in METEOR illustrates the complexity of investigating potential environmental factors with an international scope and the Western perspective with which we design questionnaires. To what extent these and other environmental factors such as diet, oral hygiene or other factors could potentially influence joint distributions remains a subject for further study.[21, 22]

As noted this study has several limitations. Because of the observed differences in

symptom duration of RA patients in the different countries , that may indicate that patients were in an earlier or later phase of the disease at first presentation to rheumatologists in different countries, patients were matched on symptom-duration (period between symptom onset and diagnosis). The date of start of symptoms as indicated by patients may be subject to recall bias. In addition, it is unknown if this is also subject to cultural differences .

Another limitation is that the data included in this study were captured during daily clinical practice and there has been no standardization of joint counts between all contributing centers. Previous research showed that especially the inter-observer reliability of swollen joint assessments is variable and studies on the effect of standardization and training on swollen joint assessments show conflicting results.[23] This could be a source of bias when comparing the distribution of involved joints between countries. However, in each center multiple and different rheumatologists were involved as well, hence differences in joint examination between persons within and between centers may exist. The influence of such differences on the results are unknown. Another issue is that swelling of shoulder joints was prevalent in Mexico and South-Africa. It is known that swelling is difficult to feel by palpation of this joint. To what extent the experienced rheumatologists also incorporated information on a reduced range of motion when filling information of joint counts is also unknown.

Patients were included when they were newly diagnosed and assessed the baseline visit. Therefore rheumatologists prescribed mediation was not yet started and it is highly likely that patients were DMARD naive, but we have no data on possible prescription of NSAIDs or glucocorticoids by primary care physicians before the first visit to a rheumatologist. A final limitation is that all patients per country originated from a limited number of centers. Hence we are unsure whether the patients included in different centers are reflective for the patient population of the entire country, especially for South-Africa and Mexico for which included patient numbers were smaller.

In our view and despite all limitations, the present findings may be of interest for etiopathological studies. The vast majority of studies on genetic or environmental risk factors that are published now were done in Western countries. However it is know that genetic risk factors differ around the world, e.g. *HLA-DRB1*09:01* is mainly associated with RA in Asian populations and African Americans but is not prevalent in Western populations, whereas *PTPN22* is a risk factor specific to Caucasian populations.[12, 24] To what extent different risk factors account for subtle differences in phenotypic presentation remains to be explored. However such further studies may shed light on pathophysiological processes underlying the predilection locations of synovitis in early RA.

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CHAPTER 10

SUMMARY AND FUTURE PERSPECTIVES

SUMMARY

In this thesis we aimed to investigate ways to optimize treatment strategies and the choice of treatment for individual patients, to be implemented in a worldwide context. Although major advances have been made in the treatment of RA, it is still uncertain which treatment is the best choice for each individual patient. This may result in both undertreatment, risking unnecessary symptom prolongation and irreversible joint damage, but also overtreatment, risking (severe) side effects. Both situations can increase the burden of RA for patients as well as for society. In clinical trials and daily practice there appears to be a development towards earlier treatment with higher dosages of medication and ever more stringent definitions of remission as treatment goal. In the first part of this thesis some of these developments were investigated and challenged. In addition, it was explored whether there are gender differences in use of antirheumatic drugs and response to treatment.

In countries around the world, access to trained physicians and adequate treatment for patients with RA, early recognition and consistently pursuing a treat-to-target approach can be very challenging. Identifying contributing factors to inequalities in access to treatment and care and clinical outcomes across countries may be the first step towards improvement. This was addressed in part two of the thesis.

Part 1: optimizing current treatment of RA

Many of the chapters in this thesis are based on the METEOR database. This is an international, observational database which captures real world clinical data on patient characteristics, disease activity, physical functioning and medication of RA patients.

Chapter 2 gives an extensive introduction to the METEOR database, including its development, research possibilities and future perspectives. Data are entered in the database through a free online tool or through a direct upload from existing patient registers from different centres worldwide. Since the start of METEOR in 2006 the database has grown extensively, including information on >37.000 patients and >190.000 visits. It therefore offers the unique opportunity to study daily practice care and to perform research regarding cross-country differences in a large, worldwide setting, which could provide important knowledge about the disease and its treatment in different geographic and clinical settings.

Methotrexate is widely recommended as the drug of first choice in the treatment of newly diagnosed RA patients, either as monotherapy or in combination with other antirheumatic drugs. Current recommendations are to start methotrexate at 15 mg/week orally and to escalate to 25-30 mg per week or the highest tolerable dose. However, no specific recommendations exist regarding methotrexate dose when used in combination with other antirheumatic drugs. We hypothesized that in combination with other highly

effective medication such as other csDMARDs, glucocorticoids or bDMARDs, there might be little additional benefit of high compared to lower methotrexate doses within the first 6 months of treatment. In **chapter 3** we performed a systematic literature review searching for all studies which evaluated the short term effect of methotrexate, either in monotherapy or in combination therapy, in DMARD naive RA patients. We found 31 studies and evaluated results per treatment group. Effect sizes were calculated in order to be able to compare different outcomes. Main outcomes were the DAS or DAS28, ESR or CRP and HAQ. A meta-regression was performed to test our hypothesis. No evidence was found for a better short term response to methotrexate in higher dosages, neither in monotherapy, nor in combination with glucocorticoids or bDMARDs. Next, in **chapter 4** we investigated the same question in the METEOR database, using daily practice clinical data. Data from newly diagnosed RA patients with a symptom duration <5 year, starting methotrexate treatment, with a follow-up visit within 3 to 6 months and without a change in medication were selected. In contrast to the clinical trial data of **chapter 3**, hardly any patients in daily practice initiated treatment with a bDMARD On the other hand, a substantial proportion of patients initiated treatment with a combination of csDMARDs. Since data were observational, it is possible that confounding by indication exists; meaning that for example baseline patient or disease characteristics could have influenced the choice for a high or low methotrexate dose of the rheumatologist. Therefore a propensity score was calculated, which was used to adjust the performed analyses for this confounding by indication. **Chapter 4** showed very similar results to **chapter 3**, with no short term clinical benefit of high over low methotrexate doses in methotrexate monotherapy or for methotrexate in combination with other csDMARDs or glucocorticoids.
Men are suggested to have a different RA phenotype than women, with a later age of onset and a higher percentage of autoantibody positive patients. Also, several studies showed that men are more likely to reach a state of low disease activity or remission and better functional ability. This suggests that male and female RA patients should possibly be treated differently and/or have different responses to treatment. It may even be that rheumatologists and male and female patients, through shared decision making, already make different treatment choices. Therefore in **chapter 5** we investigated in the METEOR database whether male and female patients are treated differently in daily practice and whether they respond differently to various treatments. We selected all follow-up visits until the first switch in medication, of newly diagnosed RA patients with a symptom duration <5 years from the METEOR database.
We found that men and women are indeed prescribed different treatments: women more often started hydroxychloroquine, as monotherapy or in combination with methotrexate or a glucocorticoid, whereas men more often started treatment with methotrexate and/or sulfasalazine. Women switched treatment earlier than men (i.e. failure of the first treatment step), but the hazard to switch was not higher for women compared to men

after adjusting for several potential confounders.
In general women had only a slightly worse response to treatment than men, with a 0.0065 worse DAS per month for women compared to men [β (95% CI) female gender * follow-up time in months 0.0065 (0.0020; 0.011)]. This effect was mainly caused by a slightly worse response to glucocorticoid monotherapy [0.015 (0.0018; 0.028)] and to csDMARD combination therapy [0.020 (0.0031; 0.036)].
Although methotrexate can be highly effective in reducing disease activity, 50-75% of early RA patients do not achieve low disease activity within 3-6 months after initiation of MTX monotherapy in dosages of 20-25 mg/week. Previous studies have shown that combination therapy including corticosteroids or a biologic DMARD is more efficacious than MTX monotherapy, with more patients reaching early low disease activity or even remission. However, it was unknown whether patients who have an early good response to combination therapy also have better *long term* outcomes than patients who have an early good response to MTX monotherapy. Therefore in **chapter 6** we used data from the BeSt study to investigate whether there are differences in clinical or radiological outcomes for RA patients who achieved continuous low disease activity during 10 years on initial methotrexate monotherapy or on initial combination therapy with methotrexate, sulfasalazine and prednisone or with methotrexate and infliximab. Patients with continuous low disease activity from 6 months until 10 years follow-up were selected. This means that by protocol patients were allowed one increase in the dose of otherwise unchanged medication at 3 months, and from 6 months onwards medication was tapered. Patients starting combination therapy tapered treatment to monotherapy and patients starting methotrexate monotherapy tapered their methotrexate dose. From 2 years onwards, it was possible to taper treatment to ultimately drug free remission.
We compared between-group differences over time and found that regardless of initial induction therapy, those who remain in low disease activity have similar long term outcomes, with only the proportion of patients in drug free remission being higher in the methotrexate monotherapy group. However, more patients achieve early and continuous low disease activity on prednisone or infliximab combination therapy tapered to sulfasalazine or methotrexate monotherapy than on methotrexate monotherapy. Thus, as long as we cannot adequately predict which patients will have a continuous good response to methotrexate monotherapy, combination therapy seems to be a better choice.

One of the main aims in the treatment of RA is to achieve or maintain good physical functioning. In order to achieve this, it is internationally recommended to use a treat-to-target approach, preferably aimed at remission, but at least at low disease activity. Previous research has shown that a decrease in DAS is associated with an improvement in physical functioning, even after prolonged disease activity and even if DAS is already low. Nevertheless, treatment intensification may not always be effective in improving physical

functioning, for example in patients who already reached low disease activity, and may come with potential side effects and costs.
Therefore in **chapter 7** we assessed whether aiming for remission – and modifying or intensifying treatment accordingly – in patients who are already in low disease activity, results in further clinical relevant improvements in functional ability. We selected all visits from the IMPROVED study where patients were in low disease activity. Since these patients were treated-to-target aimed at remission, by protocol all patients should have had a treatment intensification. However, protocol violations occurred during the study in which treatment was not intensified in patients in low disease activity. This allowed us to investigate the effect of treatment intensification on the change in HAQ, independent of a change in DAS.
We found that intensifying treatment in RA or UA patients in low disease activity resulted in a statistically significant improvement in the change in HAQ over time, but the effect was too small to be clinically relevant and even decreased by increasing follow-up time. This suggests that it might be sufficient to accept achieved low disease activity, rather than continue treatment intensifications aiming at remission, especially if patients are in longer follow-up.

Part 2: worldwide differences in RA
Biologic DMARDs are an important treatment option to reduce disease activity successfully, especially for patients with poor prognosis. However, costs of treatment strategies including bDMARDs are high and can limit the use of these drugs. Differences in socioeconomic welfare may influence prescription and reimbursement rules and access to treatment of bDMARDs and may thus directly or indirectly influence health outcomes. Therefore in **chapter 8** we assessed associations between differences in socioeconomic welfare, prescription and reimbursement rules, access to medication, bDMARD use and disease activity and physical functioning in RA in different countries in the METEOR database.
Data regarding disease activity and medication use of countries with >100 patients with available follow-up visits were extracted from the METEOR database. A questionnaire was sent to at least 2 rheumatologists from each included country regarding data on DMARD prices, access to treatment and prescription and reimbursement rules. Data on SES were retrieved from web-based sources and univariable linear regression analyses were used to assess associations between variables.
In total 21.377 patients were included from 13 countries. We found large differences in affordability of anti-rheumatic medication across countries, with prices for bDMARDs in the most expensive country (USA) being 5.9 times higher than in France (lowest prices for bDMARDs). bDMARD use was associated with indicators for socioeconomic status, restrictiveness of prescription and reimbursement rules and with affordability and

reimbursement of bDMARDs. Although bDMARD use was not statistically significantly associated with disease outcomes, disease activity was associated with access to medication and economic indicators, indicating inequity in access to RA care between countries.

The disease phenotype of rheumatoid arthritis (RA) may be influenced by different factors, including the presence of autoantibodies. Furthermore, genetic and environmental risk factors are involved in the pathogenesis of RA and these are both population dependent. Although the available evidence is scarce and patients were generally not evaluated at the time of diagnosis, previous studies suggest differences in RA phenotype in various populations. Therefore in **chapter 9** we studied the distribution of joint inflammation in autoantibody positive and negative RA-patients at the time of diagnosis in different populations (Mexican, Dutch, Indian and South-African) using daily practice clinical data. Data were selected from METEOR and from the Leiden Early Arthritis Clinic cohort. Patients fulfilled the ACR/EULAR 2010 classification criteria and were matched on symptom duration, in order to prevent a longer disease duration to influence joint counts. We found differences in the distribution of swollen joints, with more knee synovitis in Mexico, South-Africa and India compared to the Netherlands (37%, 36%, 30% and 13%) and more elbow (29%, 23%, 7%, 7%) and shoulder synovitis (21%, 11%, 0%, 1%) in Mexico and South-Africa compared to India and the Netherlands. Since the number of autoantibody negative patients in Mexico and South-Africa was limited, Indian and Dutch autoantibody positive and negative RA-patients were compared.

We found differences in joint involvement in in these four countries, with a higher percentage of large joint involvement in India (knees), South-Africa (knees and elbows) and Mexico (knees, elbows and shoulders) than in the Netherlands and less involvement of small joints of the hands and feet in India than in the other countries. The number of swollen and tender joints was higher in autoantibody negative patients, but the overall distribution of involved joints was similar. Since the joint distribution is part of the 2010 classification criteria, there is a circularity between this inclusion criterion and joint counts. Therefore a sensitivity analysis was performed including patients with a diagnosis of RA according to the rheumatologist (hence ignoring classification criteria). This analysis showed similar joint distributions as the main analysis, with only slightly higher joint counts. More research is needed to investigate whether the observed differences are cultural and/or pathogenetic.

FUTURE PERSPECTIVES

In recent decades, major advances in the early identification and treatment of patients have improved the prospect for RA patients dramatically, especially in countries with

higher socioeconomic welfare. Nevertheless, most patients have to use lifelong medications, which are often (very) expensive and have a considerable risk of side effects. Furthermore, we cannot yet adequately predict which patient will respond to which drug and have to go by trial and error, resulting in delays in symptom relief and potentially development of irreversible damage. More patients nowadays are able to taper medication once remission is achieved, but some will experience a disease flare and will need to restart treatment, and some patients can even lose response to previously effective medication after prolonged use. In both cases, we are unable to predict which patients are most at risk for these mishaps. There is a general hope that if adequate treatment is started before the disease becomes chronic and less responsive to medication ('window of opportunity theory') outcomes for patients will further improve. However, this includes a possible downside of starting treatment in patients with types of early arthritis that will not become chronic, or may even spontaneously go into remission. Therefore further optimization of treatment is necessary.

This starts with optimizing treatment with the currently available anti-rheumatic medication. In **chapters 3 and 4** it was shown that in newly diagnosed RA patients, a higher initial dose of methotrexate does not result in better short term outcomes than a lower dose, especially when used in combination with a corticosteroid or biologic DMARD. I**n chapter 6** we showed that although more people respond well to combination therapy, there is a small group of patients that respond well to methotrexate monotherapy during prolonged follow-up. However, in up to 75% of patients methotrexate is insufficiently effective, regardless of dose. We cannot rule out that in the longer term patients who started on the higher dose will have the benefit of not first having to increase the lower dose before switching to more effective drugs. Future studies should include this aspect of potential benefits of the initial dose. In addition, randomized clinical trials could determine the best methotrexate dose in combination with various other anti-rheumatic drugs, and whether, in whom and in what tempo dose reductions can lead to fewer side effects without losing efficacy.

Currently we are unable to adequately predict which patients will sufficiently respond to methotrexate monotherapy and can thus prevent the use of expensive drugs with a potentially higher risk of side effects. At the start of treatment, current prediction models using mainly clinical variables can only discriminate methotrexate responders from non-responders in approximately 60% of patients, of which approximately 80% can be correctly classified. Therefore future prediction models for the efficacy of different anti-rheumatic drugs should be developed. Since only clinical variables do not seem to be able to adequately predict effectiveness, other variables such as biomarkers, imaging and genetics could be investigated to improve current prediction models. This would be an important step towards individualized treatment. With the availability of many different drugs for the treatment of RA and the continuing development of new drugs, prediction

models to choose the most effective medication for individualized patients could result in fast improvements in disease activity for more patients, a reduction in the use of unnecessary medication and reductions in healthcare costs.

It is generally found that women have a worse treatment response than men. In **chapter 5** we found that women seemed to have a slightly worse response to treatment, especially to glucocorticoid monotherapy and to csDMARD combination therapy. It is yet unclear what is the underlying mechanism for this small difference in response to treatment and if and to what extent this can help us to individualize treatment. In addition, **chapter 9** suggests differences in RA phenotype in different countries around the world. This is interesting, since most research is currently performed in so-called Western countries. It remains to be explored to what extent regional differences in risk factors account for differences in RA phenotype across countries. This may shed light on pathogenetic differences underlying these different phenotypes. A subsequent step may be to adapt the choice of treatment per population, as long as this is in the interest of the patient. Data in chapter 8 suggests that current differences in treatment per population may rather be a reflection of differences in socioeconomics. To improve those lies beyond the potential of local rheumatologists but possibly not of the rheumatologic and pharmaceutic community.

In particular for patients who do not respond to the first treatment choice, a vital step in improving treatment of RA patients has been the introduction of treat-to-target. With earlier diagnosis and highly effective antirheumatic medication, treatment targets have become stricter over time. However, we may wonder whether ever stricter treatment targets indeed lead to better functional outcomes for most patients and whether they do not cause unnecessary treatment adjustments. For example in **chapter7** we observed that in patients in low disease activity, further treatment intensifications aimed at remission did not result in clinically relevant improvements in HAQ, especially if patients are in longer follow-up. Future studies could investigate the optimal treatment target, which may also differ for individual patients.

In the future, the ultimate aim would not only be to reduce disease activity, but to cure or even prevent RA. With current treatment, 10% to 26% of patients are able to reach sustained drug free remission of over a year. This is currently the outcome best approximating cure. In order to reach this, efforts are being made to identify patients earlier, even before clinical symptoms of RA develop, for example during the phase of clinically suspect arthralgia. By intervening in such an early disease stage, it can be attempted to postpone the development of RA, or even prevent RA by treating the disease before chronicity develops.

However, in many countries this goal is far from feasible and it is already difficult to offer an effective, clinically recommended treatment to RA patients, due to amongst others differences in healthcare systems, a lower availability of specialized rheumatology clinics and limited financial resources. In **chapter 8** we have shown that there are large

differences in affordability of anti-rheumatic medication across countries and that socioeconomic status of a country is associated with restrictiveness of prescription and reimbursement rules and affordability and reimbursement of bDMARDs. Furthermore, disease activity was associated with access to medication and economic indicators, indicating inequity in access to RA across countries.

Therefore one of our most important aims might not only be to improve treatment of RA, but also to improve the worldwide accessibility of our most effective treatment options. Further research is needed to help understand more pathways by which a lower socioeconomic welfare could influence disease outcomes, and identify factors that could help reduce inequities between countries. Such, that clinical evidence and experience, rather than financial considerations dominate the choice of treatment.

Many chapters in this thesis are based on international, observational data from daily clinical practice. Due to a lack of randomization of patients to intervention groups, there is always a risk of bias involved in these data and advanced statistical techniques are needed to adjust for this bias. However, there is a strong need for real world data. In clinical trials, often very selected patient groups are included. Real world data, as gathered in the METEOR database, can be used to test the generalizability of findings from these trials. Furthermore, not all questions can be answered using clinical trials due to ethical concerns and patient numbers are limited in clinical trials due to the high costs involved. In the future, the availability of real world data will increase, since much data regarding patient care is stored digitally and possibilities to link and use these data for research keep improving. Therefore physicians and others entering patient data should be aware that the data they enter is not only used for patient care, but also, anonymously, for research purposes. In the future, we should keep looking for ways to link these data and make them available for research, for example by establishing recommendations for a more uniform set-up of databases and by stimulating collaborations between different databases. This could help us to provide answers to research questions that remain currently unanswered using data from clinical trials. Furthermore, we should keep improving our ways to handle the bias inherently involved with these types of data. This could help us to use the full potential of these types of data, thereby further improving our knowledge about the optimal treatment of RA patients in a worldwide context.

CHAPTER 11

Nederlandse Samenvatting

SAMENVATTING

Het doel van dit proefschrift was het onderzoeken van manieren om de behandelstrategieën en de keuze van behandelingen voor individuele patiënten met reumatoïde artritis (RA) te optimaliseren, en dit te implementeren in een wereldwijde context. Hoewel er grote vooruitgang is geboekt bij de behandeling van RA, is het nog steeds onduidelijk welke behandeling de beste keuze is voor iedere individuele patiënt. Dit kan zowel leiden tot onderbehandeling, met als mogelijk gevolg het onnodig voortduren van symptomen en het optreden van onherstelbare gewrichtsschade, als tot overbehandeling, wat kan leiden tot (ernstige) bijwerkingen. Zowel over- als onderbehandeling kunnen de ziektelast van RA vergroten, zowel voor patiënten als voor de maatschappij.
In klinische trials en in de dagelijkse praktijk lijkt er een ontwikkeling gaande te zijn richting vroegere behandeling met hogere medicatiedoseringen en steeds strengere behandeldoelen, waaronder steeds strengere definities van remissie. In het eerste deel van dit proefschrift is onderzoek gedaan naar enkele van deze ontwikkelingen en hun effect op de ziekte RA. Bovendien is onderzocht of er verschillen zijn in medicatiegebruik en de reactie op die medicatie bij mannen en vrouwen.

In verschillende landen wereldwijd kan de toegang tot getrainde artsen, adequate behandeling, het vroeg stellen van de diagnose en het behandelen volgens het treat-to-target principe van RA patiënten zeer lastig zijn. Het identificeren van factoren die bijdragen aan verschillen tussen landen in toegang tot behandeling en zorg en aan verschillen in klinische uitkomsten kan een eerste stap zijn tot verbetering. Dit wordt behandeld in deel 2 van dit proefschrift.

Deel 1: het optimaliseren van de huidige behandeling van RA
Veel van de hoofdstukken in dit proefschrift zijn gebaseerd op de METEOR database. Dit is een internationale, observationele database waarin data uit de dagelijkse klinische praktijk wordt opgeslagen over patiëntkenmerken, ziekteactiviteit, fysiek functioneren en medicatie van RA patiënten. **Hoofdstuk 2** geeft een uitgebreide introductie over de METEOR database en beschrijft de ontwikkeling, onderzoeksmogelijkheden en toekomstperspectieven van de database. Data worden aan METEOR toegevoegd door middel van een gratis online tool, of door middel van een directe upload vanuit bestaande patiëntregistratiesystemen in verschillende ziekenhuizen wereldwijd. Sinds de start van METEOR in 2006 is de database sterk gegroeid. Het bevat nu informatie over meer dan 37.000 patiënten en meer dan 190.000 visites. De database biedt daardoor de unieke mogelijkheid om onderzoek te doen naar de dagelijkse klinische praktijk en om onderzoek te doen naar verschillen tussen landen in een wereldwijde setting. Dit kan belangrijke

informatie opleveren over de ziekte en zijn behandeling in verschillende landen en in verschillende klinische omgevingen.

Methotrexaat wordt algemeen aanbevolen als het eerste medicijn in de behandeling van nieuw gediagnosticeerde RA patiënten, zowel als monotherapie als in combinatie met andere reumamedicatie. De huidige aanbevelingen zijn om methotrexaat te starten met 15 mg per week oraal en dit op te bouwen naar 25-30 mg per week of de hoogste getolereerde dosering. Er bestaan echter geen aanbevelingen betreffende de dosering van methotrexaat in combinatie met andere reumamedicatie. Wij veronderstelden dat er weinig extra voordeel zou zijn van een hoge versus een lage methotrexaat dosering binnen de eerste 6 maanden na start van de behandeling, als methotrexaat in combinatie zou worden gegeven met andere zeer effectieve medicatie, zoals csDMARDs, glucocorticoïden of bDMARDs.
In **hoofdstuk 3** hebben we een systematisch literatuuronderzoek uitgevoerd, waarbij we hebben gezocht naar alle studies waarin de korte termijneffecten van methotrexaat, in monotherapie of in combinatie therapie, zijn onderzocht in DMARD naïeve patiënten. We vonden 31 studies en bekeken de resultaten per behandelgroep: methotrexaat monotherapie, combinatie therapie met glucocorticoïden en combinatietherapie met een bDMARD. Om verschillende uitkomstmaten met elkaar te kunnen vergelijken werden effect sizes berekend. De hoofduitkomsten van de studie waren de DAS of DAS28, BSE of CRP en de HAQ. We hebben een meta-regressie uitgevoerd om onze hypothese te testen en vonden geen bewijs voor een beter behandeleffect van een hogere dosering methotrexaat op de korte termijn, zowel in monotherapie als in combinatie met glucocorticoïden of bDMARDs.
Vervolgens hebben we in **hoofdstuk 4** dezelfde vraagstelling onderzocht in de METEOR database, gebruikmakend van data uit de dagelijkse klinische praktijk. We selecteerden data van nieuw gediagnosticeerde patiënten met een symptoomduur korter dan 5 jaar, die startten met methotrexaat en een follow-up visite hadden binnen 3 tot 6 maanden, zonder dat het type medicatie veranderde.
In tegenstelling tot in **hoofdstuk 3**, waarin we uitkomsten van klinische trials bekeken, waren er amper patiënten die in de dagelijkse praktijk startten met een bDMARD. Er was echter wel een groep patiënten die een behandeling startte met een combinatie van csDMARDs. Omdat we te maken hadden met observationele data, is het mogelijk dat 'confounding by indication' een rol speelde. Dit betekent dat baseline patiënt- of ziektekenmerken van invloed kunnen zijn op de keuze van de reumatoloog voor een hoge of een lage methotrexaat dosering. Daarom hebben we een propensity score berekend en die gebruikt om de analyses te corrigeren voor confounding by indication. **Hoofdstuk 4** laat vergelijkbare resultaten zien als **hoofdstuk 3**. We vonden op de korte termijn geen klinisch voordeel van een hoge versus een lage methotrexaatdosering, zowel bij methotrexaat

monotherapie als bij combinatietherapie met andere csDMARDs of glucocorticoïden.

Er wordt gedacht dat mannen met RA een ander fenotype hebben dan vrouwen met RA, gekenmerkt door een latere leeftijd van optreden van symptomen en een hoger percentage autoantistof positieve patiënten. Bovendien hebben verschillende studies laten zien dat mannen vaker lage ziekteactiviteit of remissie behalen en ook een beter fysiek functioneren hebben. Deze verschillen suggereren dat mannen en vrouwen met RA wellicht ook anders behandeld zouden moeten worden. Daarom hebben we in **hoofdstuk 5** in de METEOR database onderzocht of mannen en vrouwen in de dagelijkse praktijk anders behandeld worden en of ze verschillend reageren op verschillende behandelingen. We hebben van nieuw gediagnosticeerde RA patiënten met een symptoomduur korter dan 5 jaar uit de METEOR database alle follow-up visites geselecteerd totdat patiënten voor het eerst van medicatie veranderden. We vonden dat mannen en vrouwen inderdaad een andere behandeling kregen: vrouwen startten hun behandeling vaker met hydroxychloroquine, als monotherapie of in combinatie met methotrexaat of een glucocorticoïd, terwijl mannen hun behandeling vaker met methotrexaat en/of sulfasalazine startten. Vrouwen veranderden eerder van medicatie dan mannen, maar na het corrigeren voor verschillende mogelijke confounders was de kans om van medicatie te veranderen voor vrouwen niet hoger dan voor mannen. Over het algemeen waren er geen klinisch relevante verschillen in respons op behandeling tussen mannen en vrouwen. Een subanalyse per DMARD-groep liet zien dat mannen alleen een iets betere respons hadden op csDMARD monotherapie, maar dat verschil was klinisch verwaarloosbaar.

Hoewel methotrexaat zeer effectief kan zijn in het verlagen van de ziekteactiviteit, bereikt 50 tot 70% van de vroege RA patiënten geen lage ziekteactiviteit na 3 tot 6 maanden behandeling met methotrexaat monotherapie, in doseringen van 20 tot 25 mg per week. Eerdere studies hebben laten zien dat combinatie therapie met glucocorticoïden of bDMARDs effectiever is dan methotrexaat monotherapie: meer patiënten bereikten lage ziekteactiviteit of zelfs remissie door middel van combinatietherapie. Het is echter onbekend of patiënten met een vroege goede respons op combinatietherapie ook betere langetermijnuitkomsten hebben dan patiënten met een vroege goede respons op methotrexaat monotherapie. Daarom hebben we in **hoofdstuk 6** data uit de BeSt studie gebruikt om te onderzoeken of er verschillen zijn in klinische of radiologische uitkomsten voor RA patiënten die gedurende 10 jaar continue in lage ziekteactiviteit bleven, na initiële behandeling met 1) methotrexaat monotherapie of initiële combinatie therapie met 2) methotrexaat, sulfasalazine en prednison of met 3) methotrexaat en infliximab. We selecteerden patiënten die vanaf 6 maanden tot 10 jaar follow-up continue in lage ziekteactiviteit waren. Volgens het protocol van de studie mochten patiënten dan één keer hun medicatiedosering ophogen op 3 maanden. Vanaf 6 maanden werd de medicatie

afgebouwd. Patiënten die gestart waren met combinatietherapie bouwden af naar monotherapie en patiënten die gestart waren met methotrexaat monotherapie bouwden de dosering af. Vanaf 2 jaar was het mogelijk om af te bouwen naar medicatievrije remissie.
We vergeleken verschillen tussen groepen over tijd en vonden dat patiënten die in lage ziekteactiviteit bleven vergelijkbare lange termijn uitkomsten hadden, onafhankelijk van welke initiële therapie zij kregen. Alleen het percentage patiënten in medicatievrije remissie was hoger in de methotrexaat monotherapie groep. Patiënten die hun behandeling startten met combinatie therapie inclusief prednison of infliximab, en vervolgens afbouwden naar sulfasalazine of methotrexaat monotherapie, bereikten echter wel vaker vroege en langdurige lage ziekteactiviteit dan patiënten die hun behandeling startten met methotrexaat monotherapie. Dus zolang we nog niet kunnen voorspellen welke patiënten een langdurig goede respons zullen bereiken na behandeling met methotrexaat monotherapie, lijkt combinatietherapie een betere keuze.

Eén van de belangrijkste doelen van de behandeling van RA is het bereiken of het behouden van een goed fysiek functioneren. Om dit te bereiken is het internationaal aanbevolen om een treat-to-target benadering te gebruiken. Hierbij moet op zijn minst gestreefd worden naar lage ziekteactiviteit, maar bij voorkeur naar remissie. Voorgaand onderzoek heeft laten zien dat een daling in DAS geassocieerd is met een verbetering in fysiek functioneren; zelfs na een lange ziekteduur en zelfs als de DAS al laag is. Desalniettemin hoeft het intensiveren van behandeling niet altijd te resulteren in en verbeterd fysiek functioneren. Dit kan bijvoorbeeld het geval zijn bij patiënten die al in lage ziekteactiviteit zijn. Bovendien kan het intensiveren van een behandeling mogelijk gepaard gaan met het optreden van bijwerkingen en een toename van kosten.
Daarom hebben we in **hoofdstuk 7** onderzocht of het streven naar remissie – en het daarbij aanpassen of intensiveren van de behandeling – zorgt voor een klinisch relevante verbetering in het fysiek functioneren van patiënten die al in lage ziekteactiviteit zijn.
We hebben alle visites van de IMPROVED studie geselecteerd waarin patiënten in lage ziekteactiviteit waren. Omdat deze patiënten behandeld waren volgens een treat-to-target strategie met als doel remissie, zouden volgens het protocol al deze patiënten een intensivering van de behandeling moeten hebben gehad. Tijdens de studie hebben artsen zich echter niet altijd aan het protocol gehouden, waardoor de behandeling niet altijd werd aangepast als patiënten in lage ziekteactiviteit waren. Hierdoor konden wij het effect van het intensiveren van de behandeling op de verandering in HAQ onderzoeken, onafhankelijk van de verandering in DAS.
We vonden dat het intensiveren van de behandeling in RA of UA patiënten in lage ziekteactiviteit resulteerde in een statistisch significante verbetering in de verandering van HAQ over tijd, maar het effect was te klein om klinisch relevant te zijn en nam zelfs verder

af naarmate de tijd in follow-up toenam. Dit suggereert dat het voldoende kan zijn om te accepteren dat een patiënt lage ziekteactiviteit heeft behaald en dat het niet altijd nodig is om de behandeling te blijven intensiveren om remissie te bereiken, vooral als patiënten al langer gevolgd worden.

Deel 2: wereldwijde verschillen in RA

Voorgaande studies hebben laten zien dat binnen Europa een lager welzijnsniveau is geassocieerd met een hogere ziekteactiviteit. Eén van de factoren die daarin een belangrijke rol zou kunnen spelen is de toegang tot bDMARDs, die beperkt kan worden door hoge kosten en/of strikte voorschrijfregels. Daarom hebben we in **hoofdstuk 8** het gebruik van bDMARDs in de dagelijkse klinische praktijk onderzocht in verschillende landen wereldwijd en we hebben bekeken of de sociaaleconomische status van een land is geassocieerd met klinische uitkomsten en het gebruik van bDMARDs. Verder hebben we bekeken of het gebruik van bDMARDs in een land is geassocieerd met voorschrijf en vergoedingsregels en de toegang tot medicatie.

Uit de METEOR database werden data over ziekteactiviteit en medicatiegebruik van landen met minimaal 100 patiënten en beschikbare follow-up visites geselecteerd. Een vragenlijst werd gestuurd naar minimaal 2 reumatologen van de geselecteerde landen over medicatieprijzen, toegang tot behandeling en vergoedings- en voorschrijfregels en data over de sociaaleconomische status van de verschillende landen werd verzameld via websites. Om de associaties op landsniveau tussen de verschillende variabelen te beoordelen werden univariabele lineaire regressie analyses uitgevoerd.

In totaal werden er 20.379 patiënten geïncludeerd uit 12 verschillende landen. We vonden verschillen in de betaalbaarheid van reumamedicatie in de verschillende landen, waarbij prijzen voor bDMARDs in het duurste land (USA) 5.9 keer zo hoog waren als in Frankrijk (met de laagste prijs voor bDMARDs). Bovendien vonden we dat een lagere sociaaleconomische status was geassocieerd met een lagere ziekteactiviteit en minder gebruik van bDMARDs. Verder was het gebruik van bDMARDs geassocieerd met de striktheid van vergoedings- en voorschrijfregels en de betaalbaarheid van bDMARDs, zoals gedefinieerd in deze studie.

Het is aantrekkelijk om er vanuit te gaan dat meer gebruik van bDMARDs zal leiden tot een lagere gemiddelde DAS28 in een land en dat een laag BBP kan voorkomen dat voldoende patiënten toegang hebben tot een bDMARD. De realiteit is echter complexer. Wij vonden ‘slechts’ 2.8% meer patiënten in DAS28-remissie voor iedere 10% toename in patiënten die een bDMARD gebruikte. Als we er vanuit gaan dat bDMARDs een positief effect hebben op de effectiviteit van de behandeling van RA, lijkt dit effect redelijk beperkt. In tegenstelling tot onze verwachting vonden we geen associatie tussen de verschillende indicatoren van sociaaleconomische status en de HAQ. Dit zou veroorzaakt kunnen zijn door outliers, of door culturele verschillen in de manier waarop patiënten hun fysiek functioneren

rapporteren. Samenvattend wijzen deze bevindingen op ongelijkheid in optimale (toegang tot) zorg voor RA tussen de verschillende landen wereldwijd.

De pathogenese van RA is complex en zowel genetische als externe risicofactoren zijn betrokken. Niet alleen hebben externe risicofactoren een verschillende prevalentie in verschillende regio's, ook genetische risicofactoren verschillen in verschillende delen van de wereld. Het is echter onbekend of het fenotype van RA ook wereldwijd verschilt. Daarom hebben we in **hoofdstuk 9** de verdeling van gewrichtsontstekingen in patiënten met recent gediagnosticeerde RA vergeleken in vier populaties (Mexicaans, Nederlands, Indiaas en Zuid-Afrikaans) met data uit de dagelijkse klinische praktijk. Daarnaast hebben we de verdeling van betrokken gewrichten in autoantistof positieve en negatieve RA patiënten uit Nederland en India vergeleken. Data werden geselecteerd uit METEOR en uit het Leiden Early Arthritis Clinic cohort. Patiënten voldeden aan de ACR/EULAR 2010 classificatie criteria en werden gematcht op symptoomduur. Op die manier wilden we voorkomen dat een langere ziekteduur invloed zou hebben op het aantal betrokken gewrichten.
Zowel in Nederland als in India was de verdeling van betrokken gewrichten gelijk voor autoantistof positieve en negatieve patiënten. Tussen de verschillende landen was er echter wel een verschil in de verdeling van gezwollen gewrichten. Er was meer synovitis van de knieën in Mexico, Zuid-Afrika en India vergeleken met Nederland (37%, 36%, 30% en 13%) en meer synovitis van de ellebogen (29%, 23%, 7% en 7%) en schouders (21%, 11%, 0% en 1%) in Mexico en Zuid-Afrika vergeleken met India en Nederland. De betrokkenheid van de gewrichten in de voeten kon alleen worden vergeleken in India en Nederland en was minder vaak gerapporteerd in India dan in Nederland.
Omdat de betrokkenheid van gewrichten onderdeel is van de 2010 classificatie criteria is er een bepaalde mate van cirkelredenering tussen dit inclusie criterium en het aantal betrokken gewrichten. Daarom is er een sensitiviteitsanalyse uitgevoerd waarbij we de analyses hebben herhaald bij patiënten met een diagnose van RA volgens de reumatoloog, waarbij de patiënten dus niet aan de classificatie criteria hoeven te voldoen. Deze analyse liet een gelijke verdeling van de gewrichten zijn als de hoofdanalyse, met alleen een iets hoger aantal betrokken gewrichten.
Deze resultaten suggereren dat de verdeling van betrokken gewrichten ten tijde van de diagnose van RA verschilt tussen landen, maar niet tussen autoantistof positieve en negatieve RA patiënten. Verder onderzoek is nodig om te onderzoeken of deze verschillen cultureel en/of pathogeen zijn.

APPENDIX

CURRICULUM VITAE

Sytske Anne is geboren op 17 augustus 1991 in Heerenveen. In 2009 behaalde zij cum laude haar gymnasium diploma aan het RSG Magister Alvinus in Sneek. In datzelfde jaar begon zij met de bachelor Bewegingswetenschappen. In 2012 startte zij met de tweejarige onderzoeksmaster Human Movement Sciences, met als specialisatie 'Motor function and cognition in healthy ageing'. Tijdens haar master publiceerde ze haar eerste twee wetenschappelijke artikelen, waarna ze in september 2014 cum laude afstudeerde.
In oktober 2015 ging ze aan de slag als onderzoeker in opleiding op de afdeling reumatologie van het Leids Universitair Medisch Centrum, onder begeleiding van prof. Landewé, prof. Huizinga en dr. Allaart.

PUBLICATION LIST

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