Worldwide treatment opportunities of rheumatoid arthritis

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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.