Monitoring rheumatoid arthritis

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Chapter 8

Summary and general discussion

In this thesis we focussed on so-called 'treat to target' therapy in rheumatoid arthritis (RA). Treat to target relies on repetitive measurements of disease activity using a composite score that incorporates signs of disease activity such as laboratory results, findings of physical joint assessments, and the opinion of the patient. It is recommended that rheumatologists intensify treatment when a predefined level of disease activity, the target, has not yet been achieved. The implementation of treatment to target in daily practice depends on the faith of the rheumatologist and the patient to rely on a disease activity composite index (for instance the DAS) rather than on some judgemental estimate of disease activity ('the patient is doing well'). It also relies on a consensual opinion that a pre-set treatment target (for instance a DAS=<2.4, meaning low disease activity, or a DAS<1.6, meaning clinical remission) is a desirable as well as an achievable target, and especially on the willingness to intensify medication every time the treatment target has not been achieved. Several aspects of treat to target, in particular a plea for the improvement of the rheumatologists' awareness about and the implementation of treat to target recommendations in daily clinical practice, are discussed in the thesis. In this chapter the content of this thesis will be summarized and the main findings will be discussed.

Chapter 1 is a general introduction, which describes the characteristics of RA and the importance of treat to target therapy with the use of synthetic (s) DMARDs, biologic (b) DMARDs and corticosteroids.

Chapter 2 offers a systematic review of national and international databases in the field of rheumatoid arthritis. We have found four international databases, which have started between 2004 and 2008. They are quite similar, collecting data on patients with various degrees of disease severity and treated with a wide range of sDMARDs and bDMARDs.[1-3] It remains unclear to what extent these databases are a representation of normal daily practice. The owners of the databases do not collaborate in the EULAR repository of databases. The national databases (n=32) are more heterogeneous in size, year of inception (between 1986 and 2010), inclusion criteria, aims and frequency of data collection. Many databases share similarities in collecting patient-reported outcomes, physician's clinical evaluation and medication use. Only half of these databases, the older and larger ones with most publications, are included in the EULAR repository of databases. We conclude that this review provides a useful overview of RA databases, which can be consulted by researchers to find out which databases are available for collaboration and comparisons between cohorts.

For the future it would be valuable to be connected to the EULAR repository of databases to increase collaboration between researchers. Moreover, to decrease differences in set up, collection of data and other technical details to improve the quality of the databases.

Chapter 3 investigates the efficacy of intra-articular injections in a treat to target strategy study. Patients, in whom the treatment target of low disease activity or remission has not been reached because of residual inflammation in one or two single joints, may sometimes be treated with local intra-articular (IA) glucocorticoid injections. In particular, inflamed large joints may have a significant effect on physical function and general wellbeing, and can often easily be injected with glucocorticoids. This approach has reported to be as effective as adding oral glucocorticoids.[4] In the BeSt study, a 4-arm treat to target strategy trial in recent onset RA patients, intra-articular injections were optional additions to otherwise strictly protocolized treatment adjustments aiming at low disease activity (DAS<2.4). We found that intra-articular glucocorticoid injections most often resulted in short-term satisfactory symptom reduction but had only little impact on long-term clinical outcomes. Although not fully conclusive, IA injections appeared to be safe and not associated with an increase of local joint damage. Some previous studies have suggested that long term glucocorticoid treatment may prevent local radiologic joint damage.[5,6] We do not know if this pertains to intra articular injections with glucocorticoids. Therefore, future studies are needed to confirm our results and to evaluate the long-term benefits and harms of IA glucocorticoid injections.

In **chapter 4 and 5** we have compared patients'- and physicians'-reported outcomes as well as factors that were of influence in scoring differences between patients and physicians in this regard. For these studies we used the METEOR database. METEOR is an online tool, which serves as a software program for daily practice use and can be used by rheumatologists worldwide to register and monitor patients in the METEOR database. The tool has been developed for research and practical purposes, such as to implement guidelines for RA in clinical practice.

Based on data collected in the rheumatology outpatient clinic of the Leiden University Medical Center we have found that patients systematically rate their global disease activity score (GDA) higher (mean difference 11 mm on a 100 mm visual analogue scale (VAS)) than their physicians do; the agreement was only moderate. We found that patients base their decision more on subjective measures (VAS pain) while physicians value objective measures (SJC and ESR) as more important. We compared our results with other studies, in which we

found similar factors explaining PtGDA and PhGDA differences. Other studies performed in the United States and in Europe also described discrepancies in the agreement between physicians and global health assessments.[7,8] These discrepancies may reflect cultural differences between countries with respect to disease activity assessment rated by patient and physician. Therefore, we have investigated the differences in rating between patient and physician in 13 countries (Brazil, Czech, France, Ireland, Italy, Latvia, Mexico, the Netherlands, Pakistan, Portugal, Spain, United Kingdom and the United States), based on the availability of data using the METEOR database. We found differences between PtGDA and PhGDA score related to country of residence of patient and physician, ranging from +13 in Brazil to -2 in Mexico. In some countries, these differences were related to gender (Netherlands and United Kingdom) and disease duration (United Kingdom and United States); while in other countries such a relationship was not evident. These findings raise the question of how important it is that patients and physicians rate disease activity similarly. Pain is a dominant factor in the evaluation of disease activity by the patient, but does not necessarily overlap with 'objective' signs of disease activity that dominate the physician's decision. While the patient may falsely attribute the level of pain to RA-activity, the physician may underestimate the patient's suffering by qualifying the RA as not very active. Shared decision making between patient and physician aims to fill in this gap between patient and physician by increasing mutual understanding. Education is pivotal in this regard. The main question is: should we educate physicians how to understand the patients 'perception', or should we spend more time on teaching patients how physicians interpret their objective assessments? [9-11]And maybe more importantly: Do these discrepancies between patients' and physicians' GDA-ratings truly affect RA care? Future research may focus on a better understanding of the influence of education on the behaviour of physicians and their patients and also on whether education improves the care for RA.

In **chapter 6** we have used the METEOR database to investigate how well DAS-steered therapy is applied in clinical practice**,** based again on data of the Leiden rheumatology outpatient clinic. In 69% of all visits patients were in low disease activity or remission, which suggests that the treat to target approach is properly followed in clinical practice. However, in patients with a DAS>2.4, intensification of treatment (by protocol) was applied in only 35%. We found that medication was less likely to be increased in patients with DAS>2.4 when they were treated with MTX plus a biologic DMARD, or with conventional synthetic DMARD monotherapy. We hypothesized that rheumatologists would not intensify treatment

despite a DAS>2.4 when there had been a substantial improvement since the previous DAS measurement. But this scenario was only found in 9% of the available visits. From this study we conclude that, although in most of the registered visits the patients are in a state of remission or low disease activity, still the detection of moderate and high disease activity does not always lead to treatment intensification. This finding is remarkable since it is in violation with treat-to-target ACR/EULAR recommendations for the management of patients with rheumatoid arthritis, which the rheumatologists claimed to follow meticulously. It seems that individual patients' circumstances rather than protocols determine if treatment guidelines are followed properly. In future research patients' outcomes could be further improved, for instance by implementing treatment protocols with detailed instructions about how to act in case of a high-, a moderate- or a low DAS. Another approach to implement recommendations would be to increase awareness amongst rheumatologists on treat to target by means of educational programs, which will be discussed in the following chapter.

In **chapter 7** we described an international implementation study (IRIS), also conducted within METEOR, which aimed at investigating the awareness of -and improving the implementation of- the European League Against Rheumatism (EULAR) and treat to target recommendations in clinical practice. Participating rheumatologists were asked to complete a questionnaire on their awareness of the recommendations and they were invited to take part in an educational program, which included the reading of two articles and watching an educational video. The participants were asked to include 5-10 newly diagnosed RA patients in METEOR during a follow-up period of 1-2 years. During this period the participants received one recommendation, sent monthly by email, which intended to remind them about treating the patients according to the recommendations. We used the IRIS study to test whether the level of agreement with the recommendations is associated with their true application in clinical practice. For the purpose of this study we have investigated four recommendations and we have found that rheumatologists often report to agree with- and to follow these recommendations. The number of rheumatologists in the study that reported to comply with these recommendations varied from 82 up to 98%. On the other hand we found that only a moderate proportion of their patients were treated according to those same four recommendations: The recommendations were followed in 26-67% of the patients in the METEOR database.

From this study we can conclude that agreement with a recommendation will not necessarily be followed by the actual application of the recommendation. The question is whether the

duration of our 'intervention' was long and profound enough to change the behaviour of the rheumatologists from 'only' agreeing with its content to actually performing it in clinical practice. Future research may focus on the change of behaviour of the rheumatologist over a longer period of time after an educational program. Also, it should be explored which other factors may determine the reluctance to follow recommendations.

In addition, while setting up and conducting the study followed by collecting the data, it has become clear to us (Chapter 2) that there is increasing enthusiasm among rheumatologists to initiate databases and invest time and effort to promote therapies and/or treatment recommendations that may improve patient's lives as well as advance clinical science. However as also suggested by the data in chapter 2, extraction of relevant data from databases in a format that allows analysis often is far more difficult than envisioned at the phase of data collection. Despite best intentions, agreements and recommendable attempts, technical challenges often endanger the scientific success of these initiatives. Future initiatives should look at advanced professional support to ensure that databases are developed in such a manner that they are able to provide the appropriate answers to the relevant questions.

Conclusion and future perspectives

We will now discuss the main goals at the beginning of this thesis and to which outcomes they have led, but more importantly we will discuss what we can learn from this thesis.

The main focus was to improve care in patients with rheumatoid arthritis by investigating the awareness and the implementation of existing treatment-recommendations in clinical practice. Here we aimed at comparing rheumatologists' agreement with - and their actual performance of - treat-to-target recommendations in daily clinical practice and on investigating (cultural) differences in perceptions of both the RA-patient and the treating physician in rating the global disease activity of the patient. How well are these recommendations implemented in daily practice and how can we further improve implementation of recommendations?

Based on **chapter 7**, our main conclusion is that there is a discrepancy between the rheumatologists' agreement and will to follow recommendations and the actual application of recommendations in clinical practice. It seems that rheumatologists are willing to apply guidelines, but that there are still certain factors that inhibit them to follow recommendations

in individual patients. What can we do to reduce the gap between agreement with recommendations and behaviour in clinical practice?

We may want to investigate the effects of implementation initiatives, such as educational programs, meetings or reminders by email and/or telephone. In follow up studies of IRIS we will evaluate the benefits of stimulated training by an educational program on the application of guidelines in RA. However, to actually change the rheumatologist's behaviour we may also want to focus on reasons that hinder rheumatologists to follow recommendations in clinical practice. This may well be related to differences between patients' and rheumatologists' perspectives on the disease as we have observed in **chapter 4**. Here we have found that patients and physicians think about different determinants when assessing global disease activity. Patients put more weight on pain and physicians more on ESR and swollen joint count, which may easily jeopardise so called 'shared decision making' between patients and rheumatologists. In order to promote better agreement between patients and rheumatologists we should focus future research on investigating to what extent treatment goals for rheumatologists and patients differ and why. Interestingly, agreement between rheumatologist and patient about the severity of RA may be dependent on the country in which patient and physician both reside as has been suggested in **chapter 5.** Here we have found that the agreement between the patient and the physician regarding the assessment of global disease activity differs per country; Shared decision making, a common term, may have different cultural implications!

We hypothesize that improving the agreement between patient and physician on the activity of the disease will lead to better performance in clinical practice. Shared decision making may be enhanced if the rheumatologist communicates well with the patient on desirable and realistic target achievements. For instance, the rheumatologist and the patient can agree on a treatment target of DAS low disease activity when remission is not realistic.

In **chapter 6** we have observed that patients with high levels of disease activity are not always receiving the recommended treatment in daily practice. Reasons for this can be related to the physician: For instance, the rheumatologist may value the patient's will not to change treatment, as suggested in **chapter 6**. But also the complexity of RA and the increasing number of treatment options may make it difficult to decide for a rheumatologist which approach is the best to choose. Furthermore, the rheumatologist may believe that a slightly elevated level of disease activity does not justify rigorous treatment change.

On the other hand, the patient may be reluctant to intensify the medication thus following recommendations that she is not familiar with. Patients may, for instance, better accept

additional treatments with local corticosteroids in inflamed joints (**chapter 3**) that may provide short-term relief, and as such in agreement with principles of treat-to-target, but still with uncertain long term consequences.

Implementation research, studies on how recommendations will be adopted and applied in clinical practice, is of pivotal importance to further improve clinical practice. Consulting platforms such as the EULAR repository of databases discussed in **chapter 2**, containing a lot of information about various databases in Europe, with its aim to improve collaboration between researchers, but also initiatives such as METEOR (described in Chapter 4 - 7), with aggregated information available about thousands of patients from all over the world, could be of help with this.

Since only half of the identified European databases are connected to EULAR repository awareness among researchers should be promoted and a worldwide initiative for a repository of databases would be worthwhile to stimulate in the future.

In conclusion, to improve care in patients with rheumatoid arthritis we should seek for effective strategies to better implement recommendations in clinical practice. In addition, we should try to optimize shared decision making between rheumatologists and physicians by improving communication between them with regard to achievable treatment targets. Future studies, such as IRIS, will be carried out to prove whether implementation strategies, such as educational programs, will help to implement recommendations and improve RA care in clinical practice.

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