Strategies for optimal suppression of rheumatoid arthritis

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General discussion and conclusion

This chapter presents the main findings and conclusions of the studies in this thesis.

Chapter 1 gives a general introduction on rheumatoid arthritis (RA) and its treatment. During the last decade, the future perspectives of patients with newly diagnosed RA have improved dramatically. The development of validated monitoring tools and new drugs specifically targeting proinflammatory cytokines in RA were largely responsible for this revolution. In addition, new insights in the utilization of already available therapeutics in RA, such as methotrexate, have been of critical importance. Early institution of DMARDs quickly after the diagnosis reduces the progression of structural joint damage more effectively than delayed institution [1]. Secondly, dynamic treatment strategies that adjust treatment at regular intervals using predefined response criteria have resulted in better disease outcomes than routine care [2,3]. **Chapter 2** provides an overview of recently published studies on treatment strategies striving for remission.

The studies described in **Chapters 3-8** have been conducted as part of the BeSt (Behandel Strategieën) study [4,5]. The BeSt study introduced a novel study design by comparing four different treatment strategies in patients with recent onset RA (symptom duration ≤2 years). Treatment adjustments within these strategies were determined by regular assessments of the disease activity score (DAS) at 3-month intervals. In case of an insufficient response (DAS >2.4) patients proceeded to the next step (increasing dose, switching to or adding of another drug); in case of a continued good response (DAS ≤2.4 for at least 6 months) medication was tapered until one drug remained in a maintenance dose. Treatment strategies were: 1. sequential monotherapy, starting with methotrexate, thereafter switching to other single drugs; 2. step-up combination therapy, starting with methotrexate, thereafter adding other drugs; 3. initial combination therapy with methotrexate, sulfasalazine and a tapered high dose prednisone; 4. initial combination therapy with

methotrexate and infliximab. After 2 years, initial combination therapy (groups 3 and 4) resulted in earlier clinical improvement, less progression of joint damage and fewer therapy adjustments than initial monotherapy (groups 1 and 2). Clinical remission (DAS <1.6) was achieved by 38-46% of the patients in all groups [5].

The aim of this thesis was to evaluate the long term effectiveness of DAS-driven treatment strategies for patients with recent onset RA. Practical suggestions on the frequency of monitoring are discussed. Furthermore, within these treatment strategies we discuss the choices and timing of individual therapies in subsets of patients. We studied clinical and genetic variables to predict the efficacy of methotrexate monotherapy. The effects of DAS-driven treatment strategies on patient's self-assessed functioning and quality of life were also studied.

Frequency of monitoring

Based on the studies favoring tight monitoring of disease activity, current guidelines for the management of early arthritis recommend evaluating disease activity every 1-3 months as long as remission is not achieved [6]. It is unclear, however, how intensive monitoring should be once the treatment target is reached. Too frequent monitoring can be needlessly time consuming and costly. In **Chapter 3** we demonstrated that once low disease activity (DAS of 2.4 or less) is achieved, the median duration of continued low disease activity, without therapy interventions, is 12 months. The probability to maintain low disease activity, once this target has been achieved, was high (74-85% after 3-6 months of low disease activity and 88-97% after 3-6 months of remission, defined as a DAS <1.6). These results suggest that the frequency of scheduled monitoring could be reduced once low disease activity or remission has been achieved. Simple patient-based measures of disease activity could assist patients in determining an increase of RA disease activity and urge them to contact their rheumatologist.

Efficacy of initial methotrexate and subsequent traditional DMARDs

In current daily practice, methotrexate (MTX) is used as anchor drug in 80-90% of RA patients, because of the favorable safety profile, the superior efficacy compared with other DMARDs, and more than 20 years of prescribing experience [7,8]. In observational studies, 5-year MTX retention rates of around 40% have been reported [9,10]. When used in response-driven treatment strategies, the expected efficacy of MTX is lower due to the application of strict response criteria. In **Chapter 4** we discuss the efficacy of initial MTX monotherapy and subsequent traditional DMARDs in patients randomized to groups 1 and 2 of the BeSt study. After 2 years, only one-third of patients were still treated with MTX monotherapy with a sustained DAS ≤2.4. Low disease activity at baseline and male gender were independently associated with a good response to MTX. Strikingly, in patients who failed on MTX, subsequent treatment with other traditional DMARDs was frequently ineffective (most patients did not reach a DAS ≤2.4), indicating the need for more effective therapy in these patients. The inefficacy of traditional DMARDs was also reflected in more radiographic progression after 2 years in MTX failures compared with the patients with an early response to MTX. Previously published studies suggest that TNF antagonists such as infliximab are highly effective in patients with residual disease

activity despite MTX therapy [11-13]. Therefore, in patients who do not respond to MTX with a DAS ≤2.4, prompt institution of TNF antagonists would be a more effective strategy than first trying other traditional DMARDs in a step-up or switch strategy.

Prediction of response to methotrexate

Studies identifying determinants for early differentiation between treatment responders and nonresponders are clearly needed, but still scarce. As a consequence, drug choices in RA are still being made empirically. Recent developments in pharmacogenetic research identified single nucleotide polymorphisms (SNPs) that are associated with variability in the response to MTX in individual patients. In **Chapter 5**, we introduced a predictive model, using clinical and genetic variables, to predict the response to MTX in individual patients. Eight factors were identified that were independently associated with the response to MTX: gender, rheumatoid factor, smoking status, DAS at baseline, and 4 polymorphisms in the AMPD1, ATIC, ITPA and MTHFD1 genes. Sixty percent of patients were categorized into MTX responders and nonresponders, and the true positive and negative response rates were 95% and 86%, respectively. The model indicates that the response to MTX can be predicted, and serves as a first step towards tailor made treatment in RA patients. We validated the model in a small independent cohort of RA patients, but further refinement and validation in large cohorts is essential to facilitate its clinical application.

Patient-reported outcome measures

Many studies in RA report on clinical and radiographic outcome measures such as the DAS and the Sharp-van der Heijde Score. The interest in patient-reported outcome measures has grown, however, since they have proven to be objective, reflect changes in disease severity over time and predict long-term morbidity and mortality [14-17]. Limited data are currently available on the efficacy of DAS driven treatment strategies on patient-reported outcomes for function and quality of life. In **Chapter 6** we show that the DAS driven treatment strategies of the BeSt study all improved function and quality of life to the same extent after 2 years, with the most rapid improvements in the groups treated with initial combination therapy including prednisone or infliximab. Improvements in functioning were reflected by improvements in activities reported by the patients themselves to be most important to them, such as doing housework, paid work and sleeping. RA placed a substantial burden on patient's quality of life compared with an age- and sex-matched normative Dutch population. After treatment, quality of life measures for physical health approached population norms. Measures for mental health achieved population norms in all four groups after 2 years, and improved more rapidly in patients treated with MTX and infliximab. The more rapid improvement with initial combination therapies leads to a quick positive effect, which may positively influence patient compliance. Therefore, these results should be considered when choosing the initial treatment of recent onset RA patients.

Long term follow-up of DAS driven treatment

The results after 2 years follow-up of the BeSt study showed that initial combination strategies are more beneficial than initial monotherapy strategies with regard to achievement

of an early response and less radiographic joint damage progression. Irrespective of this initial effect, different DAS driven treatment strategies all led to similarly high remission percentages and similar functional ability in all 4 groups.
The last decade, strategy studies demonstrating the benefits of tight monitoring have emerged. Loss of tight control during the long term follow-up resulted in increased disease activity [18]. In the BeSt study, however, DAS driven treatment adjustments were continued during the 4-year follow-up extension phase. **Chapter 7** describes the long term benefits of DAS driven treatment in the BeSt study. The results indicate that the achieved clinical and radiographic benefits after 2 years were maintained across the 4 treatment strategies during 4 years.
Remarkably, given the treatment dynamics in all groups, joint damage progression remained significantly lower with initial combination therapies than with sequential monotherapy and step up combination therapy. The clinical relevance of the sustained, but small differences in joint damage progression (5.0, 5.5, 3.0 and 2.5 Sharp units across groups 1-4, respectively) has to be assessed in the next years of follow-up, since it has been reported that joint damage starts to have a significant impact on functioning only after a disease duration of approximately 8 years [19].
The high percentage of patients in clinical remission after 2 years encouraged us to aim for drug-free remission (the discontinuation of all antirheumatic drugs while maintaining a DAS <1.6) in the extension study. Drug-free remission after 4 years was observed in 8-18% of RA patients across the four groups, a remarkable high percentage in a population selected at baseline on criteria associated with progressive disease. Achieving drug-free remission was independently associated with the absence of anti-CCP antibodies, male gender, and short symptom duration, but not with treatment strategy. These findings underline the importance of continued tight disease control regardless of the treatment strategy, and indicate that drug-free remission is a realistic treatment goal in recent onset RA patients. Longer follow-up is necessary to determine the sustainability of drug-free remission, and the development of structural damage in these patients.
We observed no significant differences in safety events after 4 years, except for more serious infections in group 1 versus group 2 (12 versus 2 events). Due to the treatment dynamics in all groups, the percentages of patients treated with infliximab or prednisone continue to change over time, indicating that monitoring of the safety data should remain a major focus in the coming years. Future cost-utility analyses must help to determine the long-term cost-effectiveness of the initial combination therapies including either prednisone or infliximab, taking early infliximab discontinuation into account.

The positioning of TNF antagonists in recent onset RA

The introduction of the highly effective TNF antagonists heralded a new era in the treatment of RA. Unfortunately, these new therapeutics are expensive, and long term safety data are still limited, and difficult to interpret. Until now, in most countries TNF antagonists are reimbursed only for patients who failed on at least 2 different traditional DMARDs. It is now widely accepted that early treatment during the 'therapeutic window of opportunity' is critical to provide the best outcomes [20,21]. This raises the question if even better outcomes can be achieved, when the most effective agents are prescribed

as initial therapy. It has indeed been reported that initial treatment with MTX and infliximab in early RA patients results in sustained improvement of clinical outcomes, even after completely stopping treatment with infliximab [22]. In **Chapter 8**, we aimed to compare patients who started MTX and infliximab as initial treatment versus those patients who started MTX and infliximab after failing on several traditional drugs (as is currently the case in daily clinical practice). Since it is likely that patients who started MTX and infliximab later in the disease process represent a selection of patients with a more severe disease course, we aimed to correct for this bias by using propensity score adjustments.
The corrected results suggest that initial infliximab results in more improvement in functioning and less progression of joint damage during 3 years. Moreover, 56% of patients treated with initial infliximab can discontinue infliximab while maintaining a good response, compared to only 29% of patients treated with delayed infliximab. At the present time, given the severe nature of RA, temporary overtreatment with MTX and infliximab could be a better option than initial undertreatment with traditional DMARDs [23]. The benefits of initial combination therapy on joint damage progression appear to be independent of the clinical response, an elevated acute-phase response and joint damage at baseline [24], and also independent of traditional predictors of joint damage progression such as HLA-genotype and the presence of auto-antibodies [25].

Future perspectives

The current challenge for the rheumatology community is the integration of the routine use of measures of disease activity such as the DAS in daily practice [26]. Different composite indices have been proposed; all these indices are valuable tools for usage in response driven treatment strategies [27]. In the Netherlands, DAS driven treatment was recommended for use in daily practice in January, 2008. The implementation in clinical practice will be facilitated by online databases, providing easy DAS calculations and insight in the patient's disease activity over time. In the coming years, strategies employing regular treatment adjustments striving for a state of remission will be required to achieve permanent suppression of the disease process in as many patients as possible.
We demonstrated that drug-free remission in recent onset RA patients is possible in 8-18% of patients. Patients who achieved drug-free remission had significantly shorter symptom duration than those who did not achieve drug-free remission (18 weeks versus 24 weeks, P=0.007). Probably, the therapeutic window to achieve drug-free remission is smaller than we currently believe. In that case it might be necessary and useful to start treating patients with undifferentiated arthritis (RA), who do not fulfill the criteria for RA yet, but are likely to develop rheumatoid arthritis.
Recent data pointed out that for individual patients with UA, the probability of developing RA is predictable [28]. Treatment of anti-CCP positive UA patients with MTX can only postpone, but not prevent the progression to RA, and in anti-CCP negative UA patients MTX is not beneficial at all [29]. The identification of changing patterns of anti-CCP isotype usage over time in RA patients [30] demonstrates that in anti-CCP positive arthritis, there is an ongoing immune response that needs constant suppression. Early effective therapy may prevent this response from developing, but evidently MTX is not sufficiently effective. These observations suggest that, in order to exploit the 'window of

opportunity', more powerful therapies are needed to aim at remission and prevent progression to chronic destructive RA.

Except for frequent monitoring and adjusting treatments striving for remission, the choice of the initial treatment may also influence long term outcomes. Given the fact that after 4 years of targeted therapy there is still additional radiographic benefit from early disease suppression with initial combination therapy, this approach offers the best chance of sustained functional ability in the long term. From the patient's perspective, initial combination therapies rapidly improve quality of life measures and lead to a quick positive perception of treatment, with the added advantage that medication can be tapered and sometimes stopped. These effects lead to increased treatment compliance and provide additional evidence for the implementation of initial combination therapies in recent onset RA patients in daily practice.

Newly developed therapeutics, specifically targeting inflammatory cytokines, can easily be incorporated into dynamic treatment strategies striving for remission, and will contribute to more patients achieving remission in the future. New treatments that have proven their efficacy in improving the signs and symptoms of RA include rituximab, a B-cell depleter, abatacept, an inhibitor of T-cell costimulatory pathways, and tocilizumab, an anti IL-6 receptor. The positioning of these drugs within current treatment strategies requires the conducting of novel strategy studies in RA patients.

In spite of recent progress in the field of identifying variables that predict the response to available therapies, in clinical practice the accurate prediction of response is not yet possible, making the treatment of patients with RA still a case of 'trial and error'. This carries the risk of missing the window of opportunity, as well as the burden of unnecessary costs. Therefore, there is a continuous need for tools that will allow early and accurate differentiation between treatment responders and nonresponders, to assist clinicians in making treatment choices. Pharmacogenetic research holds the promise to contribute to these treatment decisions, by the identification of genes, polymorphisms and other biological markers that are relevant to the clinical response to DMARDs. Novel biomarkers, that reflect the turnover and activity of the synovium, cartilage and bone tissues, may assist in the prediction of response to therapy and rapidly progressive disease, and could be incorporated in predictive models.

Conclusion

Patients with recent onset RA benefit from dynamic treatment strategies in which treatments are continuously being adjusted on the basis of regular assessments of disease activity, according to a predefined treatment protocol. Remission, with and even without maintenance therapy, is a realistic goal. Pharmacogenetics may provide useful information on initial treatment decisions, but as long as accurate prediction of response to treatment and disease severity is not possible, all patients with RA should be treated with initial combination therapy shortly after symptom onset. Which is the best combination to start with is not crystallized, and depends on the long term outcomes of drug-free remission, safety and cost-utility analyses. By incorporating the newest treatment options into these strategies, hopefully in the future rheumatoid arthritis will no longer be a chronic disease.

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