Benefits and risks of targeted treatment in rheumatoid arthritis

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2012

CHAPTER 11.

Summary and conclusion

In this chapter, the main findings and conclusions of the studies in this thesis will be summarized and discussed.

In **chapter 1** a general introduction is given on the prevalence of rheumatoid arthritis (RA), its clinical manifestations and the role of persisting inflammation on bone, functional ability and quality of life. The treatment of patients with RA has changed dramatically the last decades, with the introduction of more early treatment[1-3], initial combination therapy[4-6] and more frequent monitoring[7,8]. The aim is to achieve remission as quickly as possible, or at least low disease activity. Effectively suppressing the disease process in the early stages of the disease refers to the therapeutic window of opportunity, when symptoms and damage of the joints are not yet irreversible. With the 'treat-to-target' principle, the course of the disease is better controlled and quick treatment adjustments and suppression of disease activity can be achieved. These new strategies have changed the face of rheumatoid arthritis. In the BeSt study, these new strategies are incorporated in one design for the first time and so far applied for 8 years.

The studies described in **chapter 3-9** were conducted as part of the BeSt study, a partnership between 20 hospitals in the Netherlands, including the Leiden University Medical Center and the VU Medical Center. The study described in **Chapter 10** was performed in the Leiden University Medical Center. All patients with the diagnosis rheumatoid arthritis who visited the rheumatology outpatient clinic were included in this study.

The BeSt study incorporated all these new insights into a single study design. This unique study is the first in the world where four treatment strategies were compared and where therapy adjustments were based on intensive monitoring of the disease activity. It is not only about changing medication with active disease, but also tapering and discontinuation of the medication is part of the treatment protocol. The term 'drug-free' remission in rheumatoid arthritis was introduced first with this study.

In more detail, the BeSt study is a randomized clinical trial comparing four different treatment strategies in patients with early active RA; (1) sequential monotherapy, (2) step-up therapy, (3) initial combination therapy with prednisone and (4) initial combination therapy with

infliximab. Treatment adjustments were steered by three-monthly calculations of the Disease Activity Score (DAS) and aimed at low disease activity (DAS ≤2.4). In case of an insufficient response, patients were allocated to the next treatment step. On the other hand, when the DAS was ≤2.4 for at least six months, medication was tapered until monotherapy maintenance dose. From year three onwards, patients on monotherapy maintenance dose who were in remission (DAS <1.6) for at least six months, must stop their medication. The last effective dose was restarted in case of a flare (DAS ≥1.6).

After five years of treatment, 48% of all patients were in clinical remission and 14% were in drug-free remission. Patients treated with initial combination therapy had an earlier clinical response compared to patients initially treated with monotherapy, but at year one there were no statistically significant differences anymore between the treatment groups. In contrast to previous studies where functional ability worsened after several years of treatment, functional ability remained stable over time in the BeSt cohort due to DAS-steered therapy adjustments. Patients treated with initial combination therapy with methotrexate and infliximab did have less radiological damage progression after five years of treatment.[9-11]

This thesis focuses on different aspects of the treatment of patients with rheumatoid arthritis. First, optimal personalized treatment strategies are discussed. Then, the long-term effectiveness of initial treatment strategies and continued DAS-steered treatment are investigated and lastly we discuss the risk of more intensive and aggressive use of disease-modifying antirheumatic drugs (DMARDs) and biologicals in the framework of adverse events.

OPTIMAL TREATMENT STRATEGIES

Personalized treatment goals

At a group level, research revealed that initial combination therapy is more effective in reducing radiological damage progression and functional impairment than initial DMARD monotherapy.[4,5,9-15] However, not all patients will be at high risk of radiological progression or functional impairment and therefore rheumatologists need to estimate which patients need a more progressive approach with initial combination therapy and which patients would sufficiently benefit from initial DMARD monotherapy. This personalized medicine implies risk estimation of patients in a way that the risks of over- and undertreatment are minimized.

To this end there is large consensus that measurement of disease activity is important and that treatment should have predefined goals.[16] However, there is no consensus what the most relevant treatment goal for an individual patient is. In the long term, prevention of radiological damage progression may be most important, whereas functional improvement is important for both the long and short term. Previous risk models have focused on prediction of radiological damage progression and long-term functional ability[17-21], which are inter-related. These are relevant outcomes in particular in patients with expected longevity. Rapid improvement of functional ability and a return to normal daily functioning seem to be important for all patients. Therefore, in **chapter 2** we investigated if known predictors for radiological damage and long-term functional disability are also predictive of short-term functional disability, defined as a Health Assessment Questionnaire (HAQ) score ≥1. We demonstrated that baseline HAQ score, pain, Ritchie Articular Index (RAI) and treatment group were independent predictors of poor functional ability after three months of treatment. The presence of rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), high levels of c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) and baseline radiological damage were not predictive of short-term functional disability, while these are known predictors of radiological damage progression and long-term functional disability. Initial treatment with combination therapy reduced the risk of both radiological damage progression[21] and short-term poor functional ability. Thus, for an individual patient the optimal treatment strategy is dependent on the treatment goal, but in most cases initial combination therapy results in earlier functional improvement and prevention of radiological damage progression. The risk of overtreatment when initiating combination therapy can be reduced if the prediction model is used, and overtreatment should be temporary as in most patients medication can be tapered with good clinical response.

Association between bone mineral density and disease activity

While in the BeSt study the treatment aims to induce low disease activity (defined as a DAS ≤2.4), almost half of the patients achieve clinical remission[11], defined as a DAS <1.6. We investigated whether a DAS <1.6 represents a standstill in the disease process and whether there are measurable benefits if such is achieved. In **chapter 3** we looked at bone mineral density in the metacarpals of the hands (mBMD) and joint erosions in hands and feet as manifestations of bone involvement in the inflammatory processes of RA.[22,23] We hypothesized that, since high disease activity in patients with RA results in an increased BMD loss[24], low disease activity or remission may be associated with BMD gain, given that bone is

a dynamic tissue. We compared the changes in metacarpal BMD (mBMD) in patients with high (DAS >2.4) and low disease activity (DAS ≤2.4 but ≥1.6) and patients in clinical remission (DAS <1.6) during a one year period. We have shown that mBMD gain can occur, but predominantly in patients in continuous clinical remission and rarely in patients with continuous low and high disease activity. No significant difference was found between patients with high or low disease activity. In addition, patients in continuous clinical remission hardly showed radiological damage progression. However, not all patients in continuous clinical remission showed a gain in mBMD, suggesting that there might be some residual inflammation undetected by clinical evaluation.[25] These findings thus suggest that there is a link between inflammation and changes in metacarpal BMD that works two ways. Also, treatment aiming at low disease activity might not be strict enough to prevent BMD loss and therefore remission seems to be the optimal treatment goal.

Measurement of disease activity

Outcomes in patients with RA are improved if treatment is steered by frequent assessments of disease activity ('treat-to-target').[7,8] The gold standard to assess disease activity is the disease activity score (DAS).[26] Other indices are the Clinical Disease Activity Index (CDAI)[27], the Simplified Disease Activity Index (SDAI)[28] and the Disease Activity Score in 28 joints (DAS-28)[29]. All are composite scores incorporating objective and subjective measurements of RA activity. However, such measurement of the disease activity may sometimes be difficult, due to lack of time or limited resources. Thus, alternative procedures for regular assessment of disease activity could aid in optimal management. Biomarkers are interesting as representatives of disease activity as well as the underlying disease processes.

A new multi biomarker-based disease activity (MBDA) score was developed, based on 12 serum proteins with the results entered into an algorithm leading to an objective disease activity score in a patient. In **chapter 4** we investigated the relationship between MBDA scores and the conventional DAS-28. The relationship between the absolute MBDA score and the DAS-28 as well as the relationship between change in MBDA score and change in DAS-28 score was found to be highly significant. This indicates that MBDA is not only useful as a measure of current disease activity but also for evaluating changes in disease activity over time. In addition, MBDA is able to discriminate patients in low (DAS28 ≤3.2), moderate (>3.2 DAS-28 ≤5.1) and high disease activity (DAS-28 >5.1) according to the EULAR criteria.[30] There are a few cases where there was a discrepancy between the classification of patients measured by the MBDA and DAS-28 though. Explanations for this discordance could

be an underlying infection affecting components of the MBDA or an overestimation of the subjective components of the DAS-28 due by for instance fibromyalgia[31,32] or other diseases than RA[33].

Overall, the results demonstrate that the MBDA score reflects RA disease activity, and in the majority of patients it gives a similar result to the DAS28, suggesting that the MBDA score seems to be a good proxy for the conventional disease activity indices.

LONG-TERM CLINICAL OUTCOMES

Clinical and radiological response in ACPA positive and negative patients

Anti-citrullinated protein antibodies (ACPA) are highly specific for rheumatoid arthritis.[34] Although patients positive or negative for ACPA may present with similar clinical characteristics in the early phase of disease, they differ with respect to the disease course.[35] In previous non-DAS steered studies, ACPA positive patients did have higher disease activity [36,37] and worse functional ability[37,38] compared to ACPA negative patients. Presence of ACPA has also been shown to be a risk factor for rapid radiological progression and future damage progression.[17,21] We asked whether the radiological deterioration occurs due to insufficient response to treatment or despite a good clinical response. In **chapter 5** we investigated whether there is a difference between patients positive or negative for ACPA in clinical and radiological response in a setting where treatment is DAS-steered aiming at low disease activity. We found that, over eight years time, the clinical response to DAS-steered treatment was similar for ACPA positive and ACPA negative patients. Disease activity over time was similar in both ACPA groups, although ACPA positive patients had a higher ESR over time. Functional ability over time was also similar for the two ACPA groups as well as the rates of achieving remission. No differences were found in treatment response, for both ACPA groups, between patients treated with initial monotherapy or initial combination therapy. However, ACPA positive patients were less likely to achieve drug-free remission and more likely to loose remission. In addition, ACPA positive patients did show more radiological joint damage than ACPA negative patients, despite a similar clinical response. This was particularly true for ACPA positive patients initially treated with methotrexate monotherapy. These observations suggest that worse radiological outcomes in ACPA positive patients despite a good clinical response may be due to disease specific mechanisms that differ from

those in ACPA negative patients. DAS-steered treatment together with combination therapy can prevent radiological damage progression, even in patients with ACPA-positivity.

Large joint damage

Whereas radiological joint damage in the small joints often occurs in the early years of disease[39], damage of the large joints usually becomes manifest later in the disease course[40,41]. In previous non-DAS steered cohorts an association was found between damage of the small joints and damage of the large joints.[42,43] In **chapter 6** we investigated whether such an association can also be found after eight years of DAS-steered treatment. We compared damage of the large joints in our DAS-steered cohort with that in a historical non-DAS steered cohort of patients with similar disease duration. After eight years of DAS-steered treatment we found that the prevalence of damage of at least one large joint was 64%, compared to 79% in our historical cohort[44]. Although these percentages were similar, large joint damage was significantly less severe compared to the historical cohort. As in previous studies, we found a significant association between damage of the small and large joints. Neither joint space narrowing nor erosions were independently associated with large joint damage.

Our finding that large joint damage was less severe than previously reported could be due to continued DAS-steered treatment in our cohort, but also due to earlier initiation of antirheumatic treatment. Initial combination therapy did not appear to be predictive of large joint damage, in contrast to a previous study.[45] Since we had no baseline or yearly radiographs of large joints, we could not determine if initial combination therapy might have had a temporary effect on suppression of large joint damage progression similar to what was found for small joint damage progression.

Since the disease activity was highest in the first years of treatment[9,10], early local synovitis could result in later joint damage of that specific large joint[46]. Previously, early synovitis was found to be associated with later joint damage of the small joints.[46-48] In **chapter 7** we investigated whether early local swelling and/or tenderness of the large joints is associated with large joint damage in the same joints after eight years of treatment. This indeed appeared to be the case. Sixty-four percent of all patients had large joint damage of at least one large joint. Swelling and tenderness were observed at least once in 46% and 60% and at least twice consecutively in 15% and 27% of the joints, respectively. Adjusted for possible confounders, joints that were swollen at least once in the first two years of treatment more often had joint

damage than joints that were never swollen. Tenderness at least once was not independently associated with large joint damage, but tenderness on two or more consecutive occasions was, as was persistent swelling. These results suggest that local suppression of inflammation may also result in prevention of local damage.

In addition, large joint damage was significantly associated with functional ability after 8 years of treatment, whereas damage of the small joints was not. Although the difference was statistically significant, HAQ scores between patients with and without large joint damage were not above the clinically significant level of 0.19-0.24.[49] The association between large joint damage and functional disability was weaker than in older cohorts[42,43], but this is probably due to the fact that large joint damage is less severe in our DAS-steered cohort. Again, since we have no baseline radiographs, we cannot rule out that early swelling and tenderness were due to early damage.

Vertebral fractures

Vertebral fractures are more common in patients with RA compared to the general population[50] and are found to be associated with lower body mass index, increased age, lower bone mineral density (BMD), the use of corticosteroids and more severe disease.[51-54] In **chapter 8** we investigated if a DAS-steered treatment strategy resulted in less vertebral fractures in patients with RA compared to historical data. Further, we looked at the association of vertebral fractures with disease activity, functional ability and mean bone mineral density over time in our continued DAS-steered cohort.

After 5 years of follow-up, we found a prevalence of vertebral fractures of 15%, which is lower than reported in non-DAS steered cohorts.[50-53,55] Most patients (73%) had only one vertebral fracture and most (69%) deformities were mild. Further, no difference in prevalence was found when stratified for gender, prednisone use and menopausal status. Patients with vertebral fractures did have a significantly higher mean disease activity over time. This supports the hypothesis that there is a relation between disease activity and poor vertebral bone quality. Mean BMD over time in the spine and hips was not significantly associated with the presence of vertebral fractures, although mean BMD appeared to be slightly lower in patients with vertebral fractures. Higher age was independently associated with the presence of vertebral fractures, suggesting that there may be age related factors other than BMD loss that play a role in the development of these vertebral fractures. Use of prednisone was not associated with prevalence of vertebral fractures, nor was the use of bisphosphonates. Possibly, the beneficial effects of prednisone on suppression of disease activity outweigh the

potentially deleterious effects on bone quality. Bisphophonates have a protective effect on bone[56-58], but perhaps due to confounding by indication we did not find this protective effect. Patients with vertebral fractures had greater functional disability over time than patients without, independent of a slightly higher rheumatic disease activity. Our results suggest that vertebral fractures might be caused by rheumatoid inflammation and may be prevented by optimal disease activity suppression.

RISKS OF MORE INTENSIVE TREATMENT

With the introduction of early, DAS-steered treatment including combination therapy, significantly better clinical improvement and better suppression of joint damage progression can now be achieved in RA patients. However, there may also be disadvantages in terms of a higher risk of adverse events.

Alanine transferase (ALT) increases during methotrexate treatment

Methotrexate (MTX) is called the anchor drug in the treatment of rheumatoid arthritis[59] and is used as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs) and biologicals. The dosage and duration of MTX treatment depends on both disease activity and potential adverse events, of which increased serum levels of liver enzymes is thought to occur most frequently.[60] Since in recent years MTX dosages are more rapidly increased and used in combination with other DMARDs and biologicals, the frequency of liver enzyme increases might have changed since previous reports. Therefore, in **chapter 9** we investigated the incidence of increased levels of ALT >2x upper limit of normal (ULN) in RA patients treated with MTX mono- or combination therapy in a DAS-steered strategy.

The incidence of increased levels of ALT >2x ULN was 6.3/100 patients years, which is lower than previously reported.[60] The cumulative incidence of increased levels of ALT >2x ULN was 18%. Of all increases, 50% occurred in the first year of treatment and an additional 25% in the second year. This suggests that monitoring of ALT levels could be less intensive after 2 years of MTX treatment. Moreover, persistence of increased liver enzymes was rare, even when the MTX dose remained unchanged. An increased level of ALT (>1x ULN) at baseline and ACPA positivity were risk factors of having a first ALT >2x ULN, whereas smoking showed a trend. Patients without an increased level >2x ULN did use more concomitant DMARDs and biologicals with MTX. This is probably because patients without

an ALT increase were able to use MTX for a longer period and thus also in the position to be treated with more concomitant drugs and for a longer period if necessary based on the DAS. Cumulative dosage of MTX was significantly higher (2 mg/week) in patients with an increased level of ALT >2x ULN, but this was not clinically significant. The results suggest that in patients with recent onset RA who are treated with MTX in a dynamic DAS-steered strategy, the risk for ALT increases appears to be less than previously reported, and that the monitoring strategies may be re-evaluated.

Influenza

For patients with active rheumatoid arthritis the risk of infections is twice as high as in the general population.[61] A higher state of disease activity[62] as well as the use of antirheumatic drugs[63-65] predispose patients to an increased risk of infections. In **chapter 10** we investigated the risk for influenza in rheumatoid arthritis patients and its association with disease activity and antirheumatic treatment. Influenza is caused by the influenza virus, but in this study there was no procedure to prove the presence of this virus. Instead, we defined influenza based on having at least fever >38ºC, headache, muscle soreness and coughing and/or dyspnoea. In the period between September 2009 and April 2010, 5.9% of all patients with rheumatoid arthritis who visited the rheumatology outpatient clinic reported that they had influenza, which was higher than the prevalence in the general population. Peak incidence was increasing in September and highest in October and November, before the start of the normal influenza season, but in time with the end of the pandemic with H1N1 influenza. Patients using anti-TNFs had a higher risk for influenza, while there was no increased risk for patients using methotrexate or prednisone. Also patients not in clinical remission (DAS <1.6) and patients with a higher BMI reported more influenza. Previously, obesity was found to be a predisposing factor for many types of infections.[66] Although 75% of the patients were vaccinated against influenza, in many cases this occurred after the peak incidence of the H1N1 influenza period. Patients who were vaccinated did not report less influenza than those who were not, but they did report more often milder upper airway infections. Milder upper respiratory tract infections were also reported more often by females, younger patients and patients with previous lung conditions, but they were not associated with use of anti-rheumatic drugs or level of disease activity.

Overall, patients with RA are more prone to influenza and influenza-like symptoms compared to the general population, in particular those patients using anti-TNF and with high disease activity. For those patients, vaccination against influenza should be recommended.

FUTURE PERSPECTIVES AND CONCLUSION

Current treatment strategies, with the initiation of early combination therapy and frequent treatment adjustments ('treat-to-target'), have changed the face of rheumatoid arthritis. Patients have better clinical outcomes and less radiological damage progression, and in some, early improvement and prevention of damage progression means that they achieve remission and can stop the medication. This suggests that with adequate treatment, rheumatoid arthritis may no longer have to be a chronic disabling disease.

Data in this thesis indicate that patients benefit from early effective treatment by regaining functional ability that was compromised by inflammatory activity. As a bonus, the same treatment will also result in less joint damage over time. Although routinely evaluated only on radiographs of small joints in the hands and the feet, bone involvement and bone damage extends to the large joints, and, through bone quality, probably also to the vertebrae. Both locations become clinically relevant several years into the disease course and may have a significant impact on functional ability. Suppression of disease activity appears key to prevent this, and bone mineral density measurements suggest that achieving remission is better than achieving low disease activity. It may be helpful to measure disease activity not only by routine laboratory tests (such as CRP or ESR) and joint evaluations, but also by combining information of several serum biomarkers, for instance in an algorithm such as used in the Multi-Biomarker Disease Activity score.

Several antirheumatic therapies have been associated with an increased risk for infections and liver enzyme elevations and more intensive use of such treatments in the new strategies may be associated with these treatment related side effects. On the other hand, high disease activity in rheumatoid arthritis in itself is a risk factor for infections and adequate suppression of disease activity may ultimately be beneficial. Probably the most effective and safe antirheumatic treatment is started early, and then tapered and discontinued as soon as possible. In a dynamic treatment setting, monitoring for side effects may need to be only temporary. Ideally, patients who have the highest risk for side effects will be identified before treatment is commenced. Personalized treatment involves not only identifying the optimal treatment goal and the optimal treatment, but also the optimal monitoring strategy for possible side effects. It seems likely that in the future more research in autoantibody profiles will be conducted in order to develop more individual treatment strategies.

Conclusion

Patients with early active rheumatoid arthritis benefit most from dynamic treatment strategies where treatment is adjusted based on disease activity ('treat-to-target') and where initial treatment starts with combination therapy including corticosteroids or biologicals. However, there is still no consensus about the optimal treatment goal for an individual patient. For some patients prevention of radiological damage progression is most important, while prevention of functional disability is important for all patients. There may also be patients where evasion of side effects dominates treatment decisions. Initial combination therapy is beneficial in terms of ensuring rapid improvement and preventing later damage and disability, while allowing early tapering and discontinuation of (some of) the medication in order to minimize overtreatment and side effects. Remission rather than low disease activity seems to be the optimal treatment goal. Thus the best ratio in the title of this thesis will be found in patients who achieve drug free remission. It is expected that the treatment of rheumatoid arthritis will further develop in this direction.

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