A joint evaluation of local and systemic disease activity in treated-to-target rheumatoid arthritis

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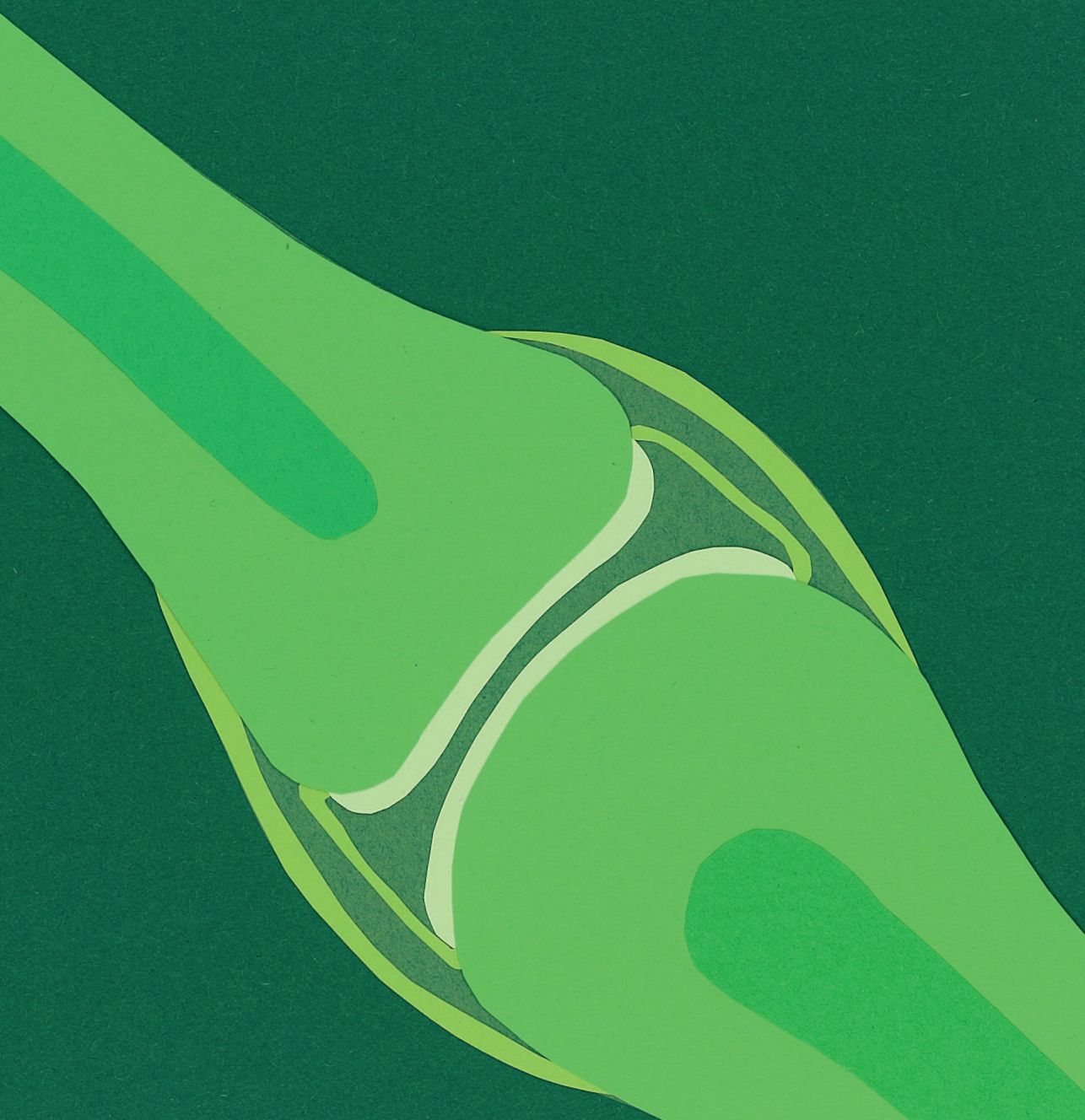
Chapter 8

Summary and discussion



In this thesis, we aimed to assess outcomes of local disease activity in patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) who received treatment to target, and to describe long-term clinical and radiographic outcomes in patients with treated-to-target RA.

Here, I will summarize the findings described in this thesis, and discuss the implications of these findings and the future perspectives following from this.

Summary

Local recurrence of joint inflammation

We found that in patients with RA, clinical joint inflammation, indicated by joint swelling, tended to recur over time in the same joints (**chapter 2**). Joints that were swollen at treatment start had a higher odds for joint swelling during follow-up, and were also more often recurrently swollen (that is, after disappearance of joint swelling) than joints that were not swollen at baseline. This association was also present in the most often affected joints, and the association between baseline and later swelling was stronger within the same joint than between different joints, indicating that local factors play a role, beyond local differences in inflammation susceptibility based on anatomical location. Duration of baseline joint swelling also affected later joint swelling. We found the association between baseline and later local joint swelling in all treatment groups that were studied (sequential monotherapy, step-up combination therapy, initial csDMARD combination therapy with (tapered) prednisone and initial bDMARD/csDMARD combination therapy).

Joints that were more frequently or persistently swollen during follow-up, were shown to have more radiographic joint damage progression after 10 years (**chapter 3**). The association between cumulative joint swelling and local joint damage progression was stronger for joint space narrowing than for erosions. The association between cumulative joint swelling and joint damage progression differed between treatment strategies, with the strongest association in patients treated with sequential monotherapy, and the least strong association in patients treated with initial bDMARD/csDMARD combination therapy. Cumulative joint tenderness without joint swelling was associated with joint damage progression to a lesser extent than joint swelling.

In children with JIA, clinical joint inflammation also had a tendency for local recurrence (**chapter 4**). Although the distribution of joint involvement is different for different types of JIA (RF-negative polyarticular, oligoarticular and

psoriatic JIA), we found this local recurrence in all subtypes. The association between baseline and later joint inflammation was present in all three treatment strategy groups (initial csDMARD combination therapy, initial MTX with prednisone, initial bDMARD/csDMARD combination therapy). Over the 2-year follow-up period, we did not find an association between clinical joint inflammation and radiographic damage.

Long-term outcomes of early treat-to-target strategy trials

Since the implementation of early treatment initiation and treat-to-target therapy in RA, survival of patients with RA has improved.[1, 2] In some studies, including 10-year follow-up analyses of the BeSt study, it has been reported that there was no longer excess mortality in patients who had been treated according to these improved treatment strategies.[3, 4] However, it has been suggested that excess mortality may only become apparent later in the disease course. Therefore, in **chapter 5**, we studied long-term mortality in patients with RA and also in patients with undifferentiated arthritis (UA). These patients had been treated-to-target for respectively 10 and 5 years in the BeSt and IMPROVED studies. We found that, 20 and 13 years after treatment start, excess mortality was present in both trial cohorts. Excess mortality became manifest after more than 10 years and was mainly present in the subgroup of patients who were ACPA positive and smoked. Over the 20-year follow-up period of BeSt, the mean reduction in life expectancy was 10 months. In IMPROVED, the mean reduction in life expectancy was 13 months over 13 years follow-up. Opposed to results from previous studies from before initiation of treat-to-target strategies, the main underlying cause of death was malignancy and not cardiovascular disease. High disease activity tended to be associated with higher mortality.

Clinical and radiographic outcomes of rheumatoid and undifferentiated arthritis on long term were assessed in **chapter 6**. Patients who had been treated-to-target for 10 and 5 years in BeSt and IMPROVED were invited to a long-term follow-up visit 20 and 12 years after treatment start. Most patients were in remission at the follow-up visit, and functional ability was relatively preserved. Physical quality of life was slightly worse than in the general population, but mental quality of life was similar. Despite treat-to-target strategies, radiographic damage progression had occurred in most patients. The degree of radiographic damage progression was limited compared to radiographic results from the pre-treat-to-target era. Damage was mainly characterized by joint space narrowing, and not by erosions, indicating that the progression may have been partially caused by age-related alterations of the joint. Radiographic joint damage differed between patients from different initial treatment strategy arms in BeSt, with less radiographic

damage progression in the bDMARD/csDMARD combination therapy arm. In IMPROVED, no differences in joint damage were found between different treatment groups.

Interstitial lung disease in treated-to-target RA

In **chapter 7**, we described the incidence and prevalence of RA-associated interstitial lung disease (ILD) in hospitals from 5 countries worldwide (The Netherlands, India, Mexico, South Africa, Colombia). The incidence was relatively low (1.6 to 6.6 per 1000 patient years) and differed between the countries, with the highest incidence in South Africa. It is difficult to assess whether these differences are related to variations in genetic and environmental risk factors, disease types or variations in treatment between countries, or that they reflect differences in local screening and diagnostic policies. In a pooled dataset with data from different countries, we assessed the association between RA disease activity and RA-ILD and found, within limited follow-up time, no statistically significant association between RA disease activity and the development of RA-ILD. We did find higher disease activity in patients who had been diagnosed with RA-ILD after the ILD diagnosis, compared to patients with RA but without ILD with the same follow-up duration. There was no clear difference in treatment between patients with and without RA-ILD, both before the ILD diagnosis and afterwards.

Added value of further treatment intensification

To summarize, despite the advantages of early treatment-to-target, we observed excess mortality in a group of patients with RA or UA who had received long-term treatment to target in a trial setting, and saw that in surviving patients, physical functioning and health-related quality of life was not as good as in the general population. Furthermore, joint damage had progressed in these patients, despite treat-to-target therapy. This raises the question whether additional treatment intensification can further improve the outcomes. I consider various options.

Implications of the findings and future perspectives

Potential effects of further treatment intensification on local joint inflammation

In in vitro and in vivo (mice) experiments, several factors potentially influencing the tendency for recurrence of joint inflammation have been studied. One of the studied hypotheses is that of 'tissue priming': joints that have been previously exposed to inflammatory triggers appear to be sensitized, resulting in higher susceptibility to joint inflammation afterwards.[5]

Specifically, synovial fibroblasts might play an important role in this, with acquirement of a more inflammatory phenotype as a result of priming.[5] Another study found that antigen-specific cytotoxic T cells and memory T cells are recruited in the synovium during the initial inflammatory response, reside in the synovium during remission, and expand during an arthritis flare.[6] These synovial fibroblasts and T cells might be specific treatment targets for future therapies. The presence of B cells in the synovial compartment has also been considered to contribute to the chronicity of joint inflammation.[7] Potentially, rapid and sustained suppression of initial joint inflammation can (partially) prevent tissue priming or the recruitment of T or B cells in the synovium, or other local factors that play a role in initial and recurrent joint inflammation processes.

We indeed found an association between the duration of baseline RA joint inflammation and joint inflammation during follow-up in the same joint. However, we observed joint swelling recurrence in all treatment strategy groups, including initial bDMARD/csDMARD combination therapy and csDMARD combination therapy with prednisone, indicating that relatively fast inflammation suppression with current available treatment strategies might not be sufficiently effective in preventing local recurrence.

Differences in local factors between patients may also be used for guiding treatment decisions. For example, treatment stratification based on the level of B cells in the synovium was studied, but so far, the results do not substantiate the implementation of biopsy-guided treatment decisions in clinical practice.[8, 9]

Another option might be not to steer treat-to-target therapy on clinical signs of joint inflammation, but on inflammation detected by imaging. Subclinical joint inflammation on MRI has been found in 27%-66% of the joints that were not swollen on clinical examination, and we cannot rule out the possibility that subclinical inflammation was present between the episodes of clinical inflammation that we used to assess local recurrence.[10] However, previous studies do not show an additional effect of ultrasound-steered DMARD treatment on clinical and radiographic outcomes, compared to a conventional treat-to-target strategy, indicating no added value of steering on eradication of subclinical inflammation on imaging.[11, 12] Nevertheless, treatment intensification in the ultrasound arms was partly accomplished by administering local glucocorticoid injections, so potentially, ultrasound guidance for (local) treatment with a longer treatment effect might still be effective.

Potential effects of further treatment intensification on radiographic damage

If recurrence of joint inflammation can be further prevented, radiographic outcomes will likely also be better, since we showed an association between the frequency of joint inflammation and radiographic damage progression in the same joint.

However, this might not be the only way to limit joint damage progression. Although local recurrence of joint swelling was not reduced in the BeSt treatment arm with initial methotrexate/infliximab combination therapy, we found that cumulative joint swelling was less strongly associated with radiographic damage in the same joint compared to the other treatment strategy arms. In previous studies, a disconnect between disease activity and radiographic joint damage progression has also been described on a patient level in patients who were treated with tumour necrosis factor (TNF) inhibitors.[13-15] In other words, patients who are treated with TNF inhibitors develop less radiographic damage than patients on csDMARD treatment who have the same level of RA disease activity. An explanation for this disconnect might be that there are separate processes leading to clinical signs of inflammation and to joint damage progression, and that TNF inhibitors specifically inhibit the pathway leading to joint damage.

Interestingly, the protective effect of initial infliximab therapy on joint damage seems to persist for a very long time, according to the results of our analyses in which we studied the differences in joint damage progression between the different treatment strategies 20 years after the start of the BeSt study. However, the fact that patients in this group more often stayed on their initial treatment, so probably had better disease activity suppression, might also have contributed to the favourable radiographic results in the methotrexate/infliximab arm after 20 years.[3]

Potential effects of further treatment intensification on mortality

Although survival of patients with RA improved after the introduction of early treat-to-target strategies, we found excess mortality 13 and 20 years after treatment initiation in patients from the IMPROVED and BeSt studies. Excess mortality could only be observed after 10 years since baseline. This was also described in another study with more than 10 years follow-up.[16] This study however was performed before the introduction of treat-to-target therapy. There are several potential explanations for the fact that we still found late excess mortality despite use of improved (with regard to clinical outcomes) treatment strategies. First, residual RA disease activity, despite disease-activity steered treatment, might affect survival negatively. This is supported

by the association we found between the erythrocyte sedimentation rate and mortality, and the finding of a protective effect of drug-free remission on mortality. However, in IMPROVED, which had a stricter treatment target than BeSt (disease activity score (DAS) <1.6 vs DAS ≤2.4), we also found excess mortality, which indicates that a stricter treatment target does not have a sufficiently protective effect on mortality, although the immediate tapering of treatment after achievement of remission might also have played a role. An interesting finding was that cardiovascular disease was less often the primary cause of death than previously observed. This shift in causes of death might have been influenced by better suppression of disease activity, since RA disease activity and cardiovascular disease have previously been shown to be associated.[17] Furthermore, since survival has improved, the shift in death causes might also be explained by the aging of the population and its associated causes of death, such as malignancies.

The fact that we found no statistically significant excess mortality in the BeSt arm starting with methotrexate/infliximab implies that intensification of treatment might be beneficial for patients with RA. However, the difference in mortality with the other treatment arms was not statistically significant, and based on our analyses we cannot determine whether assumed improved survival is due to infliximab itself or to the fact that in practice, treatment was less often tapered, and disease activity therefore better suppressed, in the infliximab arm.

Another explanation for the excess mortality might be that patients with RA may have a higher mortality risk because some risk factors of RA, such as smoking, are also risk factors for other diseases that are associated with reduced survival. Intensified treatment is unlikely to affect the mortality risk associated with these factors. Of course, in case of modifiable risk factors like smoking, other interventions can contribute to better survival. Smoking cessation has been shown to improve survival compared to continued smoking in patients with RA.[18]

It can also not be ruled out that adverse effects of DMARD therapy affect mortality, and that further treatment intensification has a negative effect on survival.

Feasibility of further treatment intensification

In addition to the question whether treatment intensification is effective, we should also consider the feasibility of treatment intensification. For treatment intensification in the sense of stricter treatment targets, this has been investigated by comparing BeSt and IMPROVED. In IMPROVED,

physicians violated the treatment protocol more often if intensification was required than in BeSt, indicating that a stricter treatment target is harder to adhere to.[19] Of the patients of BeSt and IMPROVED who followed similar treatment strategies and had similar disease characteristics, patients with a stricter treatment target (that is, patients from IMPROVED) achieved DAS remission (DAS<1.6) and drug-free remission more often than patients with a less strict treatment target (that is, patients from BeSt).[20] However, there were no statistically significant differences in functional ability and radiographic damage after 5 years.[20] Also in a meta-analysis comparing treatment targets used in different studies, studies aiming at DAS remission indeed had higher percentages of patients in DAS remission than studies aiming at DAS≤2.4, but radiographic and functional outcomes were not different.[21] These results indicate that pursuing stricter treatment targets only has limited effects on long-term clinical outcomes, or that stricter treatment targets should be based on other disease activity measures than currently used.

Alternatively, new therapies might provide additional advantages in long-term RA disease outcomes. These might include targeted synthetic DMARDs, which have not been studied in this thesis and for which no long-term outcomes are available yet, or therapies that still have to be developed.

Conclusion

In this thesis, we showed that joint inflammation has a tendency to recur locally in the same joints in both RA and JIA. In RA, this was associated with more radiographic joint damage. This association was less strong in joints of patients who had been treated with initial methotrexate/infliximab combination therapy, and these patients also had better treatment outcomes in a long-term follow-up study of two treat-to-target trials. In general, radiographic damage and functional disability were mild in patients with RA or UA who were treated in these trials. However, we also observed excess mortality in our study population. Whether clinical outcomes and survival can be further improved cannot be determined based on our results, but potentially better disease activity control, either with adjusted treatment strategies or new therapies, might be beneficial.

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