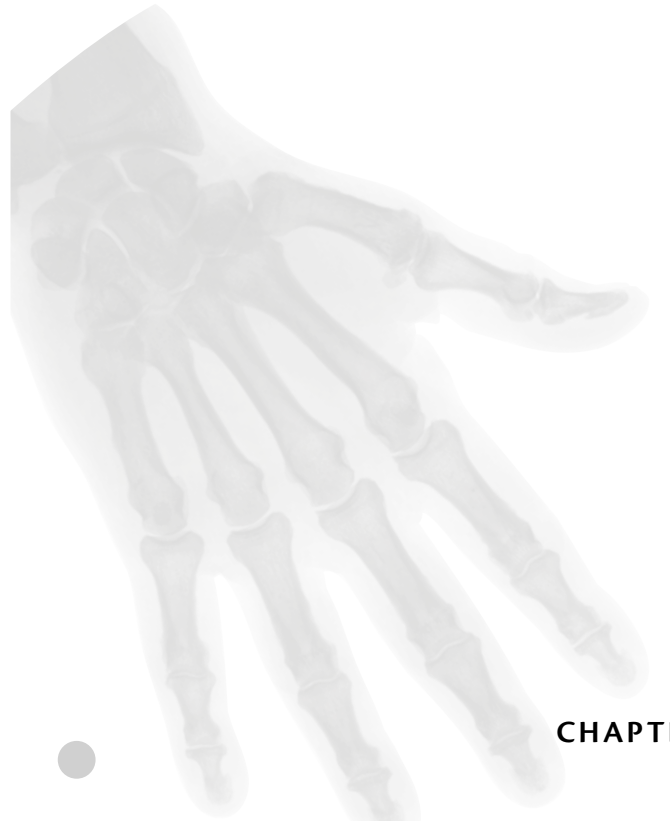

CHAPTER 13

Summary and general discussion

This thesis focuses on treatment strategies and outcome measures in rheumatoid arthritis. In *chapter 1* a general introduction for this thesis is given. Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterised by synovitis, particularly of small joints of hands and feet, although larger joints can be involved as well. Patients with RA often suffer general complaints like fatique and morning stiffness and may suffer extra-articular manifestations. RA is associated with severe morbidity and even mortality if not treated properly. The last decades RA has been evolved from a disease were treatment was aimed at symptom relief towards a disease were treatment is aimed at disease control. Hereby, the outlook of patients diagnosed with RA improved dramatically.[1] The early institution of disease-modifying antirheumatic drugs (DMARDs), combination therapy, the availability of drugs specifically targeting the immune system (biologicals) and tight-controlled treatment, aiming at minimal disease activity have contributed to this improvement and led to a shift in treatment paradigm.[2-4] *Chapter 2* reviews clinical presentation, diagnosis and treatment options of RA patients with an emphasis on the importance of early referral and early effective treatment.

Strategy trials

Randomised double-blind clinical trials to investigate the efficacy of treatment usually have a static design with a head-to-head comparison of different (combination of) drug(s) during a mostly limited duration of follow-up. Although this a valuable and indispensable 'gold standard' design to compare the efficacy of drugs, the translation to clinical practice can hamper. Treating a chronic disease in clinical practice is a dynamic process, with therapy changes in case of insufficient response (treat to target), adverse events or other patient- or drugs related factors. Strategy trials have a dynamic design, which more resembles daily practice. Instead of the emphasis on the static comparison of individual drugs, the emphasis lies on the application of the different treatment options in a continuous, dynamic, more individualized and 'real life' approach. These dynamic trials play a pivotal role in translating the available evidence from RCTs to clinical practice. *Chapter 3* summarizes recent strategy trials in the treatment of rheumatoid arthritis. The BeSt study (acronym for 'Behandel Strategieën'; Dutch for 'treatment strategies'), which is the base of this thesis, is an example of a strategy trial.[5,6]

The BeSt study

In the BeSt study, 508 patients with recent-onset rheumatoid arthritis (less than two years) according to the 1987 American College for Rheumatology (ACR) criteria were randomised into four treatment strategies: 1. sequential monotherapy (n=126), 2. step-up combination therapy (n=121), both starting with methotrexate monotherapy, 3.initial combination therapy with a tapered dose of prednisone (n=133), and 4. initial combination therapy with the tumour necrosis factor (TNF) α inhibitor infliximab (n=128). In each strategy, patients were treated according to a stepwise protocol, all aiming at low disease activity. Every 3 months the disease activity score (DAS) was calculated. If the DAS was 2.4 or lower (i.e. low disease activity) treatment was continued and tapered

to a maintenance dose after 6 months. If the DAS was above 2.4 the next step of the protocol was taken. In total, 20 hospitals in the south-western part of The Netherlands have participated in the BeSt study.[5]

Primary outcomes were functional ability, 3 monthly measured with the health assessment questionnaire (HAQ) and annual joint damage progression assessed on X-rays of hands, wrists and feet. Secondary outcomes were patient-reported outcomes (quality of life) and clinical remission percentages. Analysis of the first two years of follow-up showed an earlier improvement in disease activity, functional ability and quality of life, earlier clinical remission and less radiological damage progression in the initial combination therapy groups compared to the initial monotherapy groups.[7] Due to continuous measurement of disease activity and changes in treatment if disease activity was too high, from one year onwards, clinical parameters were comparable across all groups and stable during 5 years of follow-up *(chapter 4)*. After 5 years the initial combination therapy groups showed less joint damage than the initial monotherapy groups. A detailed analysis of joint damage progression showed that after 5 years of follow-up the lower total joint damage progression in the combination therapy arms compared with the monotherapy groups is based on less progression during the first year of treatment, reflecting earlier clinical improvement. In later years annual progression rates were comparable between the monotherapy and combination therapy arms. There were no major differences in toxicity between the four treatment arms.

Setting a treatment goal and its association with clinical and radiological outcome

Abundant evidence showed the association between disease activity measures, functional ability and joint damage progression, providing a rationale for early reduction of disease activity in rheumatoid arthritis with effective treatment strategies. Early in the disease course functional limitations are mainly determined by active inflammation (largely reversible), whereas with increasing disease duration, joint damage adds to functional limitations (largely irreversible).[8,9]

In the BeSt study treatment was aimed at low disease activity (DAS ≤2.4), which was associated with a mean HAQ of 0.58 after 5 years of follow-up irrespective of initial treatment. To analyse the association between disease activity and functional ability in more detail, in *chapter 5* a longitudinal analysis of disease activity and functional ability was performed. By using interaction terms we analysed whether the association between a change in DAS and a change in HAQ was dependent on follow-up duration and absolute DAS-value. We found that a larger decrease in DAS is associated with a larger decrease in HAQ. This association was dependent on the absolute DAS-level but did not change with follow-up duration. According to the model, a DAS decrease from 2.5 to 1.5 will improve HAQ more than a decrease from 3.5 to 2.5, probably because of more residual disease activity. A matrix was constructed to visualise the findings. These data suggest that striving for the lowest possible disease activity is valuable, in early and in longstanding disease.

The original DAS have been criticised for its complicated tender joint count: the Ritchie articular index.[10] With the RAI 53 joints are scored for tenderness on a graded scale of 0-3 per joint, it uses joint groups of which only the highest tender score per group counts and the joints differ from the 44 joints assessed for swelling. In *chapter 6* we validated three simplified versions of the DAS with simplified tender joint counts to replace the RAI: a variant omitting the grading (DAS 0-1), a variant omitting the grading and the grouping (DAS-TJC53) and a variant omitting the grading and grouping and using only the 44 joints which are assessed with the swollen joint count (DAS-TJC44). We compared these three variants with the original DAS. The correlations between the alternatives and the original DAS is high, and the classification into clinical remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA) using the cut-offs of the original DAS was highly comparable. In addition, the percentages of patients with rapid radiological progression (>5 SHS points in 1 year) in the different disease activity levels showed high agreement across the DAS variants. These results indicate that a simplified DAS variant seems a valid alternative to the original DAS. The DAS-TJC44 may be the most practical because it assesses the same joints for swelling and tenderness.

In addition to changing the tender joint counts, in *chapter 6* we also evaluated the original DAS and its variants using either a patients' global assessment of disease activity (PGA) or of general health (GH), both assessed on a visual analogue scale of 0-100 mm. In literature both versions are used, but it was unknown whether these were interchangeable. Although both VAS scores in individual patients could differ considerably, used as part of a composite score the difference is negligible, probably because of the limited weight of this component in the total score. These results suggests that both can be used, confirming the study by Khan, et al.[11]

After the development of the original DAS, a variety of composite indices to measure disease activity have been published, all with proposed cut-offs for remission, LDA, MDA and HDA. All these composite indices have shown to be related to functionality and joint destruction. No direct of comparison of the indices was made so far and no consensus exists on which index should be used. In *chapter 7* we compared the classification in disease activity levels of 9 often used composite indices and found considerable variation in the proportion of patients in the subsequent levels across the different indices.[12-15] CDAI and SDAI classified more patients in low disease activity and less in remission; DAS28 and DAS28 with CRP had a smaller proportion in LDA and more in remission and MDA. However, all indices showed a 'dose relationship' with the outcomes functional ability and joint damage progression in a remarkably similar way, raising the question of the clinical relevance of the differences in classification.

In addition to the longitudinal association between DAS and HAQ as analysed in *chapter 5*, these data suggest the importance of setting a strict treatment goal, ie remission, because remission is associated with the fewest functional limitations and joint damage progression. This is in line with the EULAR recommendations for the treatment of RA and the recommendations of the international 'Treat to target' initiative in which clinical remission is recommended as treatment goal.[16,17] Unfortunately, a large clinical trial

comparing remission versus low disease activity as treatment goal with the outcomes functional capacity, progression of joint damage and quality of life is lacking until now. Such a trial would provide direct evidence for the (possible) gain of using clinical remission as treatment goal compared with the treatment goal low disease activity.

Remission

In *chapter 7, 13* remission definitions have been compared, including four variants of the 2011 ACR/EULAR remission criteria: clinical practice and clinical trial, with 28/28 as well as 68/66 joint counts.[20] The most stringent remission definition was ACR/EULAR clinical trial remission with 68/66 joint counts classifying the least patients in remission, followed by the other variants of the 2011 ACR/EULAR remission criteria set. From the composite scores the strictest definitions were SDAI remission and CDAI remission, followed by remission defined with the original DAS and his variants. The DAS28 with BSE or CRP classified most patients in remission. The main question is whether the difference in classification, what might be based on relevant residual disease activity in the less stringent definitions, is associated with worse outcome in daily functioning and the occurrence of joint damage progression. With generalised estimating equation (GEE) analyses we analysed the association between all remission definitions, functional ability (measured with HAQ) and joint damage progression (measured with the Sharp-van der Heijde method) on a continuous and on a dichotomous scale. As expected, remission was associated with better functional ability and less joint damage progression according to all definitions. Although the proportions of patients classified as having clinical remission vary considerably between the different definitions, the absolute predicted HAQ and Sharp-van der Heijde progression showed high accordance, as did the estimated probabilities of HAQ >0.5 and SHS progression ≥3.0 in all indices. Although a direct statistical comparison is lacking, the clinical relevance of the differences in HAQ and SHS progression between the different definitions seems limited. This raises questions about the validity of remission definitions, especially the strict definitions. It suggests that the difference between strict and less strict definitions might not be based on clinical relevant residual disease activity, at least not leading to a significant change in daily functioning and joint damage progression.

Which remission definition should be preferred? Since all definitions perform comparable despite considerable differences in classification, there is no clear answer to this question and the answer will largely be based on personal preferences. The 2011 ACR/EULAR remission criteria have to prove value in future research.

How can existing remission definitions be improved? Clinical remission is associated with radiological remission on the group level; however, on individual patient level all available clinical remission criteria allow some residual disease activity associated with joint damage progression *(chapter 7)*. Therefore, parallel to clinical remission, radiological remission should be part of a remission definition, but finding a proper definition is a challenge. Besides a radiological outcome, an ideal remission definition should include a timeline. Real remission is durable and stable over time.

Discontinuing medication

Targeted treatment with a predefined goal with treatment adjustments until the goal is reached is recommended in RA treatment.[17] However, no recommendations are published on what to do if a treatment target is reached. Should medication be continued or is it possible to taper or even complete discontinue treatment? Discontinuation can be beneficial regarding adverse events and costs but, on the downside, may stimulate a relapse of disease with potential harmful consequences. Is it possible to predict which patients have a high risk for a flare of disease? In the *chapters 8 and 9* the discontinuation of infliximab in patients with persistent low disease activity and discontinuation of all drugs in patient in persistent remission has been assessed, respectively.

Discontinuing infliximab in persistent low disease activity

Treatment with a TNF inhibitor combined with methotrexate is effective in the early effective suppression of disease activity and the prevention of joint damage, but is expensive and has a possible risk for adverse events. Therefore, the early discontinuation of TNF blockers might be beneficial. In the BeSt study infliximab was discontinued if patients had low disease activity for at least six months. In *chapter 8* the discontinuation of infliximab is studied in more detail, in patients who initially started infliximab (group 4) as well as in patients starting infliximab after failing at least three conventional DMARDs (groups 1 to 3). In total, 45% of patients treated with infliximab were able to discontinue infliximab. Of those 80% were able to stop for at least one year and 48% had to restart infliximab because of a flare of disease during a median follow-up period of 7.2 years. The amount of joint damage in the year after stopping infliximab was limited, irrespective of the occurrence of a flare. Retreatment of infliximab was successful in 84%. Predictors for a flare of disease were smoking, the presence of shared epitope and long infliximab treatment (≥18 months). These results are largely in line with the limited number of studies on discontinuing TNF inhibitors, although differences in patient characteristics, study designs and requirements for the discontinuation of TNF blockers differed, harming a direct comparison.[21-24] Since even temporarily discontinuing TNF inhibitors can be beneficial with regards to costs and adverse events, the cessation of TNF inhibitors should be considered in individual patients with persistent low disease activity with little risk factors for a flare under strict control of disease activity.

Drug-free remission

With the growing percentages of remission with new effective and early treatment, the question whether treatment should be continued or can be discontinued in patients in long term remission becomes more important. Discontinuation of treatment in clinical remission has rarely been studied in modern treatment approaches.[25] From the beginning of the BeSt study remission percentages were higher than expected beforehand in this population with recently diagnosed active RA. After 5 years, 48% of patients were in clinical remission, defined as DAS <1.6, without differences between the treatment arms (*chapter 4*). Because of the high remission percentages, the BeSt study incorporated discontinuation of treatment in patients in prolonged clinical remission (>6 months) from the third year onwards. The last effective drug was immediately reintroduced in case of losing remission. After 5 years 10-19% of patients were in drug-free remission (completers analysis), for a median duration of 23 months (*chapter 4*). In *chapter 9* drug-free remission is studied in more detail. In total, 23% of all patients achieved drug-free remission during 5 years of follow-up, of whom 51% were still drug free after 5 years follow-up (median 23 months), 46% had to restart treatment because they lost remission, and 3% were lost to follow-up. Predictors for a relapse were the presence of anti-cyclic citrullinated peptide antibodies (anti-CCP), sulfasalazine as last DMARD, low baseline health assessment questionnaire (HAQ) score and high mean DAS until remission. The DAS and its components immediately before discontinuation were not predictive for the occurrence of a flare. After restarting treatment, the majority of patients again achieved clinical remission after 3-6 months. Joint damage progression was slightly higher in the patients who restarted treatment compared to the sustained drug-free remission group. The patients who restarted treatment had an unfavourable risk pattern for joint damage progression: positive anti-CCP and more joint damage at the time of discontinuation.[26] A controlled discontinuation study would be necessary to assess whether the relapses and the small amount of joint damage would have occurred when medication was continued. Such a randomised-controlled stop trial is currently performed in the Netherlands (POEET study), in which TNF inhibitors are discontinued in patients in prolonged clinical remission, while continuing conventional DMARDs like methotrexate. Before the arrival of biologicals, Ten Wolde, et al. performed a double blind placebo-controlled discontinuation study in patients with longstanding disease who were in clinical remission in which all antirheumatic medication was discontinued. There, discontinuation of treatment led to more disease flares.[27] Despite large differences in patient populations, these data suggest that the relapse rate is probably higher than it would have been if medication was continued. On the other hand, the data also suggest that a considerable part of patients would have relapsed irrespective of continuing or discontinuing medication. Taking these factors into consideration, discontinuation of medication can be considered in patients in prolonged remission. Discontinuation should be performed under strict control of disease activity and as a shared decision between patient and the rheumatologist, carefully weighing benefits and risks.

Clinical synovitis versus progression of joint damage

The interrelationship between disease activity, functional ability and progression of joint damage is well-established and forms the basis of current treatment approaches.[8,9,18] Although generally accepted, limited studies assessed the association between clinical signs of synovitis (tenderness, swelling) and progression of joint damage on the individual joint level in a methodological correct manner.[28,29] In *chapter 10*, clinical assessments of tender and swollen joints during year 1 in in patients of the BeSt study were related

to the progression of erosions and joint space narrowing as assessed on radiographs after year 1 in the same joint. Swelling and tenderness were independently associated with progression of joint damage. The associations were comparable strong for erosions, joint space narrowing and total joint damage progression. Although tenderness might be seen as a less specific marker for RA synovitis than a swollen joint, *chapter 10* showed that both swelling and tenderness were independently associated with progression of joint damage with comparable OR, indicating that measuring tenderness has additional value upon measuring swelling alone.
The longer swelling and tenderness is present, the higher the chance for progression. The dose-response relationship was found in the first follow-up year, underlining the importance of early effective targeted treatment. The association was found to be stronger in hands than in feet, probably because of more difficult joint assessments in the feet. Although there is a clear relationship, clinical signs of synovitis explain only a part of the total variability leading to the progression of joint damage. Several known and unknown factors determine the risk for joint progression in the individual joint: patient characteristics, local joint circumstances and treatment. Besides swelling and tenderness, known predictors for joint damage progression like auto-antibodies (anti-CCP and rheumatoid factor), acute phase reactants, age, total baseline joint damage, baseline damage per joint, were also found to be related to progression of erosions and joint space narrowing in the individual joint. Beyond these factors, the presence of swelling and tenderness increases the risk for progression by its odds ratio.
We found that the treatment strategy interacts with the association between clinical signs of synovitis and joint damage progression, both with tenderness and swelling. Analysis per treatment strategy showed that in patients treated with initial combination therapy including infliximab there was no statistically significant association between signs of synovitis and joint damage progression, this in contrast to the findings in the other three treatment arms. These results confirm at joint level a disconnect between clinical inflammation and joint damage progression that has been shown earlier on patient level[30] and underline the importance of the pro-inflammatory cytokine tumour necrosis factor (TNF) alpha in the pathophysiology of joint damage.

Assessing progression of joint damage in clinical practice
Regular assessments of joint damage progression should be part of clinical practice when treatment is evaluated. Irrespective of clinical parameters, treatment change should be considered if patients show joint damage progression on x-rays, which on the long term may lead to functional limitations. Joint damage progression without clinical symptoms might be the only hint of subclinical inflammation indicating that treatment is insufficient. Ideally, joint damage progression should be assessed using a structured scoring method. Used methods as the Sharp-van der Heijde method and Larssen score are comprehensive, time-consuming and require training which hamper the use in clinical practice. In *chapter 11* a comparison between the comprehensive, well-validated Sharp van der Heijde method and the simplified erosion and narrowing score (SENS) is made.

SENS ignores grading of damage per joint, is around three times faster than the Sharp-van der Heijde method and is quicker and easier to learn. The results showed that SENS is a valuable and structured method for assessing joint damage in clinical practice due to its time efficacy. However, SENS is not recommended in research because the method is less sensitive and because grading of damage is disregarded, the discriminative power will be lower.

Cardiovascular disease
The (patho)physiological phenomenon inflammation is thought to play a role in a variety of diseases of which atherosclerosis is an example.[31] Rheumatoid arthritis carries a higher risk for cardiovascular diseases, which is suggested to be comparable to the effect of having diabetes mellitus.[32] Besides a higher prevalence of traditional risk factor in RA, shared inflammatory pathways between RA and atherosclerosis probably contributes to the increased risk. Because of this increased risk, attendance should be paid to traditional risk factors including life style changes and optimal treatment of hypertension, hypercholesterolemia and diabetes mellitus. Additionally, attention should be paid to the role of treatment of RA in relation to cardiovascular disease and its risk factors. *Chapter 12* shows an association between disease activity level and blood pressure. Although small, the association was present for systolic and diastolic blood pressure suggesting that a lower level of inflammatory activity is associated with a more favourable cardiovascular risk pattern. Furthermore, we observed a decrease in systolic and diastolic blood pressure in patients treated with the combination methotrexate and the TNFα inhibitor infliximab; in the other groups no decrease was observed. These results should be interpreted with caution because the BeSt study was not developed to compare blood pressure and observations were based on single blood pressure measurements without a measurement protocol. Nevertheless, in the light of the high burden of cardiovascular disease in rheumatoid arthritis patients this might be a clinical relevant observation.

Early start?
The BeSt study illustrates that with effective treatment early in the disease course, a significant improvement in clinical parameters and limited joint damage progression is realistic in a group of patients with active rheumatoid arthritis. At baseline, all patients fulfilled the 1987 classification criteria for rheumatoid arthritis. The process of developing rheumatoid arthritis can be seen on a timeline from an unknown pathophysiological event at the beginning, auto-antibody responses, towards subclinical inflammation and signs and symptoms of what is called 'RA', to which patients with a genetic predisposition are more susceptible. The 1987 classification criteria incorporated relatively late manifestations of the disease process such as damage and rheumatoid nodules; this means that there is a strong possibility that early RA is not classified as such. Not identifying and treating early RA could result in progression to severe destructive disease. The window-of-opportunity hypothesis suggests the presence of a period of

time somewhere on this timeline in which a longstanding immunological benefit can be expected when the proper treatment is initiated.[33] Withholding treatment until patients fulfil the 1987 criteria for RA, and keeping in mind the growing evidence for the benefit of early effective treatment, the window of opportunity might be (partly) missed. The BeSt study aimed at early treatment, including patients who had less than 2 years of arthritic symptoms, however, since patients were also required to fulfil the 1987 classification criteria, one may argue that many patients did not have 'early RA'. Although in some patients remarkable results were observed, in many disease activity remained smouldering or flared and radiological damage progression continued to increase over time, possibly the result of a relatively late start of treatment. When exactly treatment has to start in patients with (undifferentiated) arthritis in order to achieve a long-lasting benefit and to prevent joint damage progression remains unclear. The PROMPT study shows that anti-CCP positive patients with inflammatory arthritis, not yet fulfilling the 1987 classification criteria, benefit from early treatment with methotrexate with suppression of disease activity and radiological damage progression.[34] However, in most patients the symptoms progressed to '1987 classified RA' after MTX was discontinued showing that early treatment with MTX was insufficient to change the disease course. The most effective early treatment has yet to be determined. To classify RA in an earlier phase of the disease, the 2010 classification criteria for RA were developed with the consequence of encouraging earlier initiation of treatment. Ideally, treatment should start immediately after the occurrence of the first immunological event that in time will lead to the progression of RA, or even better, treatment should prevent that event to happen. To do so, the challenge is to identify and understand pivotal events in the development of inflammatory arthritis. Once identified, the next step is to develop specific targeted treatment in order to prevent these master switches to occur.

Future challenges

To continue the followed road of improving treatment options and thereby improving the outlook and prognosis of recently diagnosed RA patients further unravelling of the pathophysiology, and as mentioned above, identification of the major pivotal events leading to RA is essential. Then we could enter a new era of targeted treatment leading towards cure and/or prevention of the disease.

Until then, the available treatment options should be used in an optimal manner, which is challenging with the growing armamentarium of available therapies. Further implementation of early, aggressive targeted treatment aiming at remission is the first step towards optimising treatment. With the development of treatment recommendations an important start has been made, but still a large gain can be made here. Regular disease activity measurements should be the base of treatment decisions. The development of the 2010 ACR/EULAR criteria for RA made it possible to assess the efficacy of DMARDs and biologicals, alone or in combination, earlier in the disease course in a well-defined group, what will be translated to clinical practice the next decades. Future

research will elucidate whether treatment initiation when these criteria are fulfilled is early enough or whether treatment should be initiated before this stage. Challenging is the development of effective therapeutic strategies in patients who cannot achieve or keep clinical remission with current therapies.

The variety of clinical remission definitions all allow residual disease activity, potentially leading to joint damage progression, providing a rationale for aiming at radiological remission parallel to clinical remission in the future. However, first needs to be proven that radiological remission is treatable and that aiming at radiological remission has additional value in improving patients outcome above aiming at clinical remission.[35] If that is the case, next challenges are the development of radiological remission criteria feasible for clinical practice, preferable combined with a clinical remission definition, to convince clinicians of the necessity of regular structured damage scoring and the implementation into clinical practice by arranging training in simple structured damage scoring systems like the simplified erosion and narrowing score world-wide.

The clinician should continuously weigh the efficacy, side effects, risk for over- and undertreatment and costs of available treatment options in an evidence-based way, which is almost impossible with the massive and growing treatment possibilities. New trials with a dynamic design mimicking clinical practice like BeSt will add to the development of evidence-based strategies that can be incorporated in daily practice and can help the clinician in choosing optimal treatment. The exact role of the newer biologicals in treatment strategies is unclear. Of large value would be a clinical trial with a direct comparison of available biologicals, including TNF inhibitors, in early as well as in more established disease, preferable in a dynamic treatment design. The growing number of eligible drugs would make the inclusion of all candidates into a trial challenging.

In the BeSt study treatment is individualised by making treatment decisions based on disease activity levels of the individual patient. Although partly tailored, all patients followed predefined treatment steps and the decision in all patients was based on the DAS with the cut-offs 2.4 and 1.6, ignoring the development of radiological joint damage progression. Tailor made treatment is necessary not only to prevent over- and undertreatment, but also for keeping health costs manageable. Further development of prediction models, probably by introducing genetic and biological risk factors instead of more clinical characteristics may contribute to more personalised treatment in the future. The difficulties lie in the identification of these important biological characteristics and feasibility for clinical practice.

Conclusion

This thesis describes several clinical aspects of modern RA treatment from the perspective of a randomised controlled trial comparing four different treatment strategies. Starting with combination therapy led to an earlier improvement of clinical characteristics with an advantage on joint damage progression until 5 years of follow-up compared to starting with monotherapy. With the availability of new treatment options, including biologicals, the early aggressive start of treatment and target-steered treat-

ment the outlook for recently diagnosed RA patients improved considerably the past few decades. Where treatment has changed from symptom control to more and more disease control over the past few decades, RA itself appears to have changed, leaving the traditional clinical picture of a chronically progressive, destructive disease. For a majority of patients, suppression of disease activity and radiological damage progression can effectively be achieved and clinical remission has become a realistic treatment goal. Clinical remission without DMARDs, which was found in up to 20% of patients, has become real now, coming close to cure. Further exploration of the biological and immunological background of RA and earlier start of more individualised aggressive treatment may change rheumatoid arthritis into a curable or even preventable disease in the future.

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