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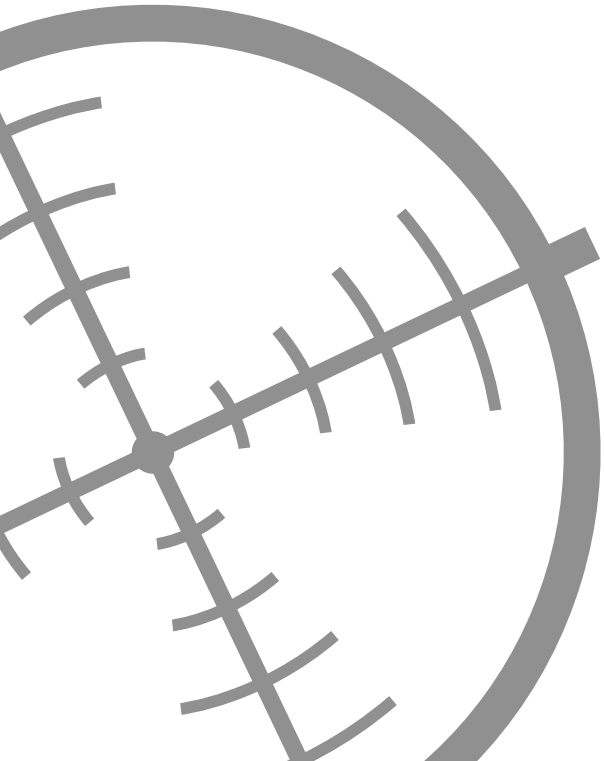
General introduction and outline



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RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disease that most noticeably starts with affecting the joints. With a prevalence of 0.5 to 1.0% and an incidence of 5 to 50 per 100,000 adults in developed countries, both increasing with age, it is a disease with a considerable impact.[1] RA is more prevalent in Northern European and American countries than in Southern countries, and is most common in females (ratio 3:1).[1,2]

The aetiology of RA is not fully understood. It is however estimated that genetic factors cover 50% of the risk for developing RA while smoking is identified as the major environmental factor.[3,4] RA is characterized by chronic inflammation of the synovial joints with infiltration of the synovium by blood-derived cells.[5] By activation of tumor necrosis factor α (TNFα), a key inflammatory cascade is triggered.[6] TNFα stimulates the production of other cytokines such as interleukin 1 and 6, enhances proliferation of T-cells and B-cells, and thereby leads to prolonged inflammation and joint damage.[5,6]

Patients typically present with joint swelling, tenderness and morning stiffness, often accompanied by systemic complaints such as malaise, fatigue and weight loss.[7] Joint swelling due to synovitis occurs most often in the small joints of the feet, hands and wrists, but large joints and later in the disease course the cervical spine can be affected too. In longstanding or untreated disease, extra-articular manifestations may develop. Nodules, Sjögren's syndrome, Raynaud's phenomenon and interstitial lung disease are relatively common, but also vasculitis, pericarditis, polyneuropathy and (epi)scleritis can occur.[8] Besides extra-articular disease, complications of RA are defined. These range from chronic leg ulcers and osteoporotic fractures to ischaemic heart disease and septic arthritis.[8] The increased risk of infections and cardiovascular disease leads to a decreased life expectancy.[9]

> The nomenclature is extracted from the Greek words ῥεύμα (pathogenic, current) and ἀρθρίτις (arthritis). There is some evidence pointing towards prevalence of RA in antiquity based on research in skeletal remains, although several studies show conflicting evidence.[104,105] It is hypothesized that the disease already existed in ancient times, but was rare due to a limited life expectancy.[105] Further reports describe famous patients in later centuries as painters Peter Paul Rubens (1577 – 1640), Pierre-Auguste Renoir (1841 – 1919), Raoul Dufy (1877 – 1953), and cardinal Carlo de'Medici (1595 – 1666).[106–108] Also Christopher Columbus (1451 – 1506) suffered from an arthritic disorder, although it is unclear whether this was of rheumatic origin.[109] The first description of RA was published in 1800, where gout was distinguished from asthenic gout: 'une nouvelle espèce de goutte sous la dénomination de goutte asthénique primitive'.[110] In 1876, the term 'rheumatoid arthritis' was proposed and described as being 'met with in the young and old, rich and poor, and in both sexes' and 'studied in three forms, the acute, chronic, and irregular, the second of which may be subdivided in the general and localized varieties'.[111]

Box 1. History of rheumatoid arthritis

CLASSIFICATION

Diagnosis and classification of rheumatoid arthritis has always been challenging, especially because the pathophysiology of the disease remains unclear. For infectious diseases, positive cultures confirm the diagnosis and malignancies can be diagnosed using pathology.

Since knowledge about the exact aetiology of RA is lacking, classification criteria based on clinical and serological features are used. The first diagnostic criteria were developed by the American Rheumatism Association in 1958, differentiating between definite, probable and possible RA.[10] These were revised in 1987 into classification criteria, in order to improve simplicity and specificity. These criteria aim to distinguish between patients with definite, established RA and patients with a definite other rheumatic disease (Figure 1).[11] In the subsequent decades, the need for early diagnosis and early initiation of treatment triggered and were reinforced by the development of more effective therapies (see below). The 2010 classification criteria were developed in recognition of this process, in order to detect and treat patients with RA in an earlier stage of the disease (Figure 1).[12] The new criteria aim to identify a subset of patients at high risk of chronicity and erosive damage, and are used as a basis to initiate DMARD therapy. While the 1987 criteria tried to improve specificity, the 2010 criteria primarily improve sensitivity. This results in a heterogeneous population, that can also include patients with other rheumatic diseases like psoriatic arthritis, spondyloarthritis or unclassified arthritis. Hence, RA should be considered as a syndrome that can overlap with other rheumatic diseases. This could hamper rheumatologists to choose the most effective

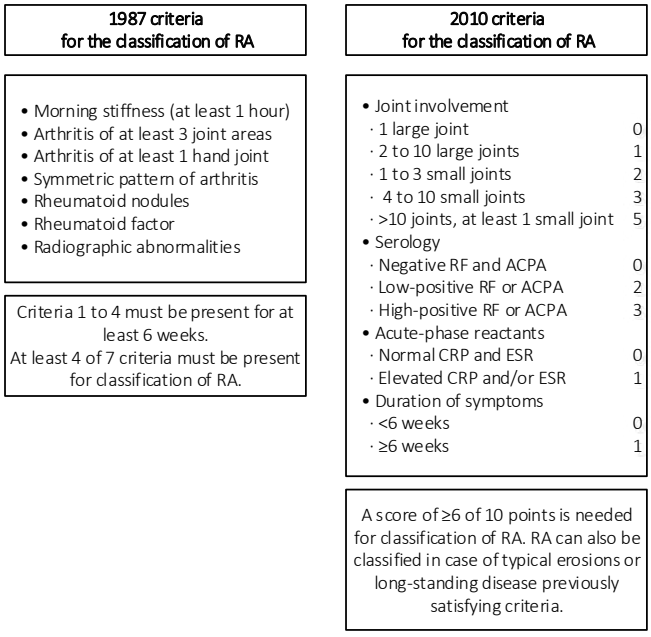

Figure 1. Classification of RA according to the 1987[11] and 2010 criteria.[12]
Notes 2010 criteria. Target population: patients who have at least one joint with definite clinical synovitis, not better explained by another disease. Joint involvement: any swollen or tender joint on examination. Large joint: shoulders, elbows, hips, knees and ankles. Small joint: joints in the hands, wrists and feet. Negative serology: below or equal to upper limit of normal (ULN). Low-positive serology: higher than ULN, less than 3 times ULN. High-positive serology: more than 3 times ULN. Acute-phase reactants: according to local standards. Duration of symptoms: reported by the patient or symptoms of synovitis at the time of assessment.
ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor.

therapy in individual patients. In this thesis, patients are classified according to 1987 criteria for RA, whereby this complex dilemma is averted.

In the 1987 criteria, rheumatoid factor is incorporated as one criterion, but in the 2010 criteria, the presence of autoantibodies gained considerable importance. RA seems to be a clinical syndrome with different disease entities, distinguished by the presence of autoantibodies.[13,14] Rheumatoid factor is the traditional autoantibody in RA, but antibodies directed against citrullinated proteins (ACPA) seem to be more specific and more related to the disease course.[15] It has been suggested that ACPA-positive and ACPA-negative RA are different disease subsets that might have a similar phenotype at disease onset, but have another pathogenesis and response to treatment.[13,14,16]

TREATMENT

Early recognition and early initiation of antirheumatic treatment have improved the outlook for RA patients.[17–19] Not only the timing, but also the pharmacological options for the treatment of RA have changed considerably during the last decades. Current antirheumatic medication can roughly be divided into conventional synthetic disease-modifying antirheumatic drugs (DMARD), biological DMARD and glucocorticoids.

The current guidelines recommend to start with a (combination of) conventional synthetic DMARD (csDMARD) as soon as the diagnosis of RA is made.[20] Methotrexate is the anchor drug in RA treatment and should be part of the initial treatment choice,[21] with sulfasalazine[22] and leflunomide[23,24] as the alternative in case of contraindications.[20] Also hydroxychloroquine[25], azathioprine[26], cyclosporine A[27,28] and gold[28] have shown (variable) clinical efficacy in patients with RA.

Glucocorticoids have proven to be effective, and are preferably combined with a csDMARD.[20,29–32] Despite the strong evidence advocating towards the use of glucocorticoids, concerns of patients and rheumatologists with regard to (long-term) side effects remain,[33,34] although these concerns are not confirmed by published data for low dosages that are usually prescribed.[35]

The first biological DMARD (bDMARD) that were available for patients with RA, were the TNFα-inhibitors. As previously described, TNFα is an important cytokine that stimulates inflammation and by depleting TNFα, inflammatory activity can be suppressed. Nowadays, five anti-TNFα agents are proven to be effective and registered: infliximab,[36,37] adalimumab,[38–40] etanercept,[41,42] certolizumab pegol[43,44] and golimumab.[45,46] Later, bDMARD with other modes of action were demonstrated to be effective in RA: tocilizumab (interleukin 6-receptor antagonist),[47] rituximab (anti-CD20, B-cell depleting agent),[48] abatacept (binds CD80 and CD86 to inhibit T-cell co-stimulation)[49] and anakinra (interleukin 1-receptor antagonist).[50]

The guidelines for the management of RA state that bDMARD treatment should be initiated differently in patients with a poor prognosis and a favourable prognosis. In patients with a poor prognosis, a bDMARD should be started after failure on the initial csDMARD therapy

(with or without glucocorticoids). In patients with a favourable prognosis, after failure on the initial csDMARD therapy, another csDMARD should be considered before adding or switching to a bDMARD.[20] This recommendation has been adapted from the 2010 guidelines, stating that patients with a poor and a favourable prognosis also needed a different initial treatment.[51]

The approach of patients with newly diagnosed RA made a U-turn. In the past, patients used to be treated with only non-steroidal anti-inflammatory drugs to control symptoms, and csDMARD were reserved until later stages of the disease, after the start of joint destruction. Nowadays patients receive csDMARD treatment immediately after diagnosis to suppress symptoms as well as to prevent joint damage.[52] Starting with combination therapy has proven to result in superior efficacy compared to initial monotherapy.[30,53–55] This combination may comprise a csDMARD, usually methotrexate,[56] in combination with one or more other csDMARD, glucocorticoids or a bDMARD, and results in earlier improvement of functional ability and less radiographic progression.[53–55,57]

Besides early treatment initiation, adoption of a treat-to-target approach has resulted in better outcomes than routine care.[58,59] According to this strategy, treatment is intensified as long as the predefined target (usually based on a composite score) is not achieved. This ties in with the concept of tight control which promotes that rheumatologists assess disease activity at regular visits with relatively short intervals to check whether or not the treatment target is achieved. Although recommended to adopt in daily practice,[20] it still appears to be challenging to implement this strategy in daily practice.[60–62] Conceivable reasons might be that performing a composite score is time consuming and does not reflect actual disease activity in some situations.

As the treat-to-target strategy in clinical trials results in a large proportion of patients achieving the treatment target, the question was raised whether it would be possible to taper and maybe even discontinue medication in these patients. Studies with tapering regimens in case of achieving and maintaining the target showed that some RA patients are able to stop their antirheumatic treatment after a good response to therapy.[63–67]

One might expect that with the improvement of treatment strategies and accompanied effective suppression of inflammatory activity, the former excess mortality in RA patients would improve. Increased mortality rates were attributed to persistent inflammation and a higher risk of infections.[9] However, conflicting results were published last years, from increasing mortality rates to decreasing mortality rates over the last decades.[68–70]

OUTCOME MEASURES

Disease activity can be measured using several composite scores. One of the most comprehensive composite scores is the original disease activity score (DAS), based on swelling in 44 joints, tenderness in 53 joints (Ritchie articular index),[71] erythrocyte sedimentation rate (ESR) and patient's assessment of global health on a visual analogue scale (VAS) from 0 (best)

to 100 millimetre (worst).[72,73] Clinically relevant cut-offs have been established: DAS <1.6 is generally considered to represent clinical remission and DAS ≤2.4 denotes low disease activity.[73,74] The DAS28 is a simplified version of the original DAS that excludes several joints, most notably all joints of the ankles and feet, resulting in a 28-joint count for swelling and tenderness.[75] Other modified scores to measure disease activity are the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI).[76,77] The potential of biomarkers has been investigated, because it might be desirable to avoid physical examination in some situations, or to increase reliability of disease activity measurement. This led to the development of a multi-biomarker disease activity (MBDA) score, based on twelve serum biomarkers.[78] The MBDA score shows a correlation with the DAS28,[79] but to implement this score in daily practice, it is of value to study whether it also associates with other important disease outcomes, such as radiographic progression.

Disease activity in patients with RA can fluctuate over time, reflecting the relapsing and remitting character of the disease. Besides periods in which the disease is (relatively) indolent, also periods with an increase of symptoms and higher disease activity might occur. These periods are generally referred to as 'flares'. As this phenomenon is difficult to capture, a definition of flares is still in development.[80–82] It is however determined that disease flares are associated with worsening of patient-reported outcomes and, if registered, should be followed by treatment intensification.[81,83–85] Recently, a definition of flare based on the DAS28 has been proposed and validated, that met the above mentioned criteria.[84] Since it is believed that some flares may resolve spontaneously, intensifying treatment at a time of a (captured) flare may constitute overtreatment. In contrast, mean disease activity over time may be affected by flares and result in worse long-term outcomes, which would provide a rationale for treatment adjustment following each registered flare.

Chronic inflammation in the joint can lead to local damage, such as joint space narrowing and bone erosions. Evaluation of joint damage on plain radiographs of hands and feet is traditionally a major outcome in RA.[86] As Sharp proposed this principle in 1971 and van der Heijde modified this scoring method by expanding assessment of the hands with assessment of the feet, this method is referred to as the Sharp/ van der Heijde score (SHS).[86,87] Bone erosions are scored in 16 areas in the hands and 6 in the feet. No abnormalities (score 0), discrete erosions (score 1), larger erosions (score 2 if less than half of the bone is affected; score 3 if more than half of the bone is affected) and complete collapse (score 5) can be scored. In case more than one lesion per joint is observed, scores are summed up to a maximum of 5 per joint in the hands and 10 per joint in the feet. Joint space narrowing is scored in 15 areas in the hands and 6 in the feet.[86] A normal joint space width (score 0), focal or doubtful (score 1), generalized (score 2 if more than half of the original space is left; score 3 if less than half of the original joint space is left), subluxation (score 3) and bony ankylosis or complete luxation (both score 4) can be scored. In total, the SHS ranges from 0 to 448. Radiographic joint damage progression is defined as the increase in SHS between two time points. Two readers assess the X-rays of hands and feet independently, in chronological or

random order, and the mean score of the two readers is used.[88]

To handle missing follow-up data on radiographic progression in clinical trials, two imputation methods are frequently used.[89,90] With linear extrapolation, observed values are extrapolated beyond the last observation. At least two observations are required to apply this imputation method and a linear increase in joint damage is assumed.[89,90] Last observation carried forward (LOCF) entails the imputation of the last observed value for each future missing score. This conservative method assumes a halt of SHS progression after loss to follow-up, which is not a realistic reflection of the disease course.[91] In placebo-controlled clinical trials, patients tend to drop out more often in the placebo arm than in the treatment arm. Linear extrapolation is sometimes criticized because it might overestimate actual radiographic progression, and thereby overestimate the efficacy of the medication under study. In that case, LOCF would be an appropriate, conservative alternative. However, validation studies for linear extrapolation and LOCF are lacking.

Both disease activity and radiographic damage (progression) have a narrow relationship with functional ability.[92–98] All can be measured reliably with validated scores, but physical functioning is best related to the experience of the patient. Functional ability is measured with the health assessment questionnaire (HAQ).[99] This questionnaire inventories eight dimensions of daily activities, such as the ability to get dressed or the strength of grip. Possible answers range from 'effortless' to 'unable' and the total HAQ score ranges from 0 (best) to 3 (worst). Another patient-reported outcome is health-related quality of life (HRQoL), which can be measured using the short form-36 (SF-36).[100] With 36 questions focussing on eight domains, physical and mental health is inventoried. The SF-36 is standardized based on a the reference population in the same country and ranges from 0 (worst) to 100 (best).[101]

BEST STUDY

In the 1990s several reports had been published concluding that combination therapy with two or three csDMARD and corticosteroids or with a csDMARD and a TNFα-inhibitor were more effective than csDMARD monotherapy.[36,53,54,57,102] However, it remained unclear whether this implied that all patients should start with combination therapy, or that reserving combination therapy for patients who did not respond to csDMARD monotherapy was just as effective and safe. To answer this question, in 2000 the BeSt study was initiated with the aim to identify the best initial treatment choice and the most effective subsequent treatment steps. BeSt is a Dutch acronym for 'Behandel Strategieën', treatment strategies. Between 2000 and 2002, this multicentre randomized clinical trial enrolled 508 patients with early, active rheumatoid arthritis according to the 1987 criteria for RA (Figure 1).[11] Patients were randomized to one of four treatment strategies: sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone and initial combination therapy with infliximab (Figure 2). To enable comparisons between the four treatment strategy arms, treatment adjustments had to be made at uniform time points, using the same method to evaluate treatment efficacy,

Figure 2. Treatment steps in the BeSt study.
AZA, azathioprine 2-3mg/ kg/ day; CSA, cyclosporin A 2.5mg/ kg/ day; Depomedrol, 3 gifts of 120mg in week 1, 4 and 8; Gold 50mg/ week; HCQ, hydroxychloroquine 200mg/ day, IFX, infliximab, dosages once per 8 weeks; Leflunomide 20mg/ day; MTX, methotrexate, dosages per week; Pred, prednisone 7.5mg/ day unless indicated otherwise; SSA, sulphasalazine 2000mg/ day.

and with the same threshold to trigger a change in medication. Therefore, in each strategy arm, every three months, the effect of medication was evaluated, with low disease activity, defined as DAS ≤2.4 as the chosen target of therapy efficacy.[73] In case DAS was >2.4, the next treatment step was taken (Figure 2). When DAS was ≤2.4 for at least six months, combination therapy was tapered to monotherapy, and monotherapy was tapered to a maintenance dose. Then, when the DAS was again <1.6 for six months, medication was discontinued. As soon as DAS increased to >2.4 or ≥1.6, medication was intensified or restarted, respectively. In patients who earlier had a disease flare after tapering, a second attempt to taper medication could be made if once again the DAS was ≤2.4 for at least six months. For a third tapering attempt the DAS had to be <1.6 for at least six months. After restarting medication, a second attempt of discontinuation could be made from the fifth year of follow-up onwards when the DAS had been <1.6 during at least one year. A third attempt to discontinue medication was left to a joint decision between the patient and the rheumatologist. The BeSt study is unique in continuing the treatment approach as described above for the full ten years of the study duration.

During the first year in the BeSt study, patients randomized to the initial combination therapy arms (including either prednisone or infliximab) showed an earlier clinical response with improvement of functional ability and achieving clinical remission (DAS <1.6)[74] than patients randomized to initial monotherapy (both groups starting with methotrexate).[55] By the end of year one, patients treated with initial combination therapy also had less joint damage progression than patients treated with initial monotherapy.[55] Following the treat-to-target strategy, with multiple treatment adjustments for patients who did not achieve the target, during year 2 to year 5, the good clinical response was maintained and initial differences between the groups did not remain, although patients who started with combination therapy still benefitted with less radiographic progression.[103] Data on ten year follow-up should demonstrate whether this difference in joint damage remains and whether the initial improvement in functional ability can be maintained over time.

OUTLINE OF THIS THESIS

With modern treatment strategies in rheumatoid arthritis, many opportunities have been created, but also new questions have raised. On a group level, early initiation of a combination therapy followed by targeted treatment is the preferred treatment. However, whether this is the optimal strategy for each individual patient is still unclear. Therefore, we set out to identify the optimal initial treatment choice and subsequent treatment step as recommended by the current guideline for patients with a poor or a favourable prognostic profile, based on their disease characteristics at baseline (chapter 2). Subsequently, we concentrate on methods to monitor patients over time. The potential of the novel multi-biomarker disease activity score as a monitoring method is explored, by studying the association between the MBDA score and radiographic progression in the subsequent year (chapter 3). Radiographic joint damage

progression assessed by the Sharp/ van der Heijde score is an important method to monitor treatment effects in RA patients. Unfortunately, missing radiographs are not an exception and therefore, we need proper imputation methods. The performance of linear extrapolation and last observation carried forward as imputation methods is studied and both methods are compared to truly observed radiographic data (chapter 4).

Thereafter, we focus on the long-term outcomes of targeted treatment. The effects of four dynamic treatment strategies in the BeSt study on disease activity, functioning, radiographic progression, toxicity and survival are evaluated during ten years of targeted treatment (chapter 5). Even though most patients achieve low disease activity or remission with this strategy, disease activity flares still occur. These flares trigger treatment adjustment in case of targeted treatment, and this might result in overtreatment in case flares would spontaneously resolve. To weigh these pros and cons, we aim to determine whether these disease flares cause burden at that moment and on the long-term (chapter 6). Then, we return to the topic of tailored treatment choices for patients with different prognostic profiles. A lot of attention has been drawn to ACPA-positive patients because they appear to have a more severe disease course. However, the best treatment strategy in patients with ACPA-negative rheumatoid arthritis is not yet revealed (chapter 7).

Targeted treatment is a breakthrough in the management of patients with rheumatoid arthritis. However, it is a demanding treatment strategy to implement in busy daily practice, for example because the joint counts included in most composite scores are time-consuming and not always represent disease activity according to the opinion of the rheumatologist. Evaluating adherence to the treat-to-target protocol of the BeSt study, the opinion of rheumatologists about the performance of the DAS and reasons to deviate from the protocol could learn us more about the feasibility of targeted treatment (chapter 8). Also for patients, a treat-to-target approach requires a considerable effort. In the BeSt study visits are scheduled regularly, and patients need to be willing to adjust medication based on the DAS. Motives of patients to continue participation in such an intensive ten year follow-up trial and risk factors for early study termination may help us to improve the rates of study completers in future studies (chapter 9). Outside a trial, this situation might be completely different. Patients who do not participate in a study might not be aware of the current opportunities of tapering and discontinuing medication and might also be more reluctant to change their medication regularly based on a composite score. With qualitative research using interviews, the knowledge and opinion of patients can be explored (chapter 10).

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