Treatment strategies in recent-onset rheumatoid arthritis : the best study

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Chapter 1

General introduction

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RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory disease with both articular and extra-articular manifestations affecting approximately 1% of the general population world wide. The disease has a relapsing remitting character resulting in progressive joint destruction and loss of function over time. The onset of symptoms may be acute or insidious with symptoms peaking in days or, more frequently, in weeks to months. Initial symptoms include fatigue, malaise, morning stiffness, pain and swelling of joints, most commonly affecting the small joints first in a more or less symmetrical pattern.

The first convincing description of rheumatoid arthritis is found in the text of the dissertation presented in 1800 by Augustin Jacob Landré-Beauvais (1). He describes a distinct entity of the disease known since Hippocrates as gout. In contrast to gout, Landré-Beauvais notices that the disease he calls 'goutte asthénique primitive' (primary asthenic gout) occurs more in females, and in feeble spasmodic subjects. The disease is characterised by a pain that is less sharp than in gout, but often lasts longer, relapses are frequent and usually in joints that have been afflicted on several occasions one can find extremely tender deformities, swelling of the bones, ulcers in the joint surfaces and more or less extensive suppuration. Sir Alfred Garrod first introduced the term rheumatoid arthritis in 1876 (2), which also included polyarticular osteoarthritis and a number of seronegative arthritides. Paleopathologic studies have identified bone erosions consistent with rheumatoid arthritis in skeletons dating as far back as 6500 years ago in a circumscribed area of the Mississipi Basin (3).

TREATMENT

In his dissertation in 1800, Landré-Beauvais breaks with the doctrine of bloodletting, which was until then common practice for the treatment of 'gout' (1). He states that the weakness produced by bloodletting would prolong the disease and recommends a more gentle approach by giving patients fortifying foods, soft and warm clothes, aromatic and steam baths, to avoid humid dwelling places, to use only mild sudorifics and tonics and he mentions that narcotics and antispasmodic agents can be given more freely than in ordinary gout. The modern history of Non-steroidal-Antiinflammatory Drugs started in 1829 with the identification of the active ingredient of willow bark, salicylic acid, by Leroux. In 1897 acetylsalicylic acid, which was less irritating to the stomach, was synthesized by Hoffman and/or Eichengrün (4). After the introduction of this compound into medicine as aspirin in 1899, it has been used extensively to relieve symptoms in patients with various forms of arthritis.

Antirheumatic drugs

Several drugs have been introduced for the treatment of patients with rheumatoid arthritis. An overview of the most commonly used antirheumatic drugs is given here.

In the early 1900s, the development of new antirheumatic therapies evolved around the theory that rheumatoid arthritis might initially be triggered by an infection. After the discovery that gold salts could inhibit the growth of tubercle bacilli in vitro by Koch in 1890, Jacques Forestier introduced these agents in 1929 for the treatment of rheumatoid arthritis (5). The use of gold has declined since the 1990s, parallel with the emergence of methotrexate, which is more convenient because of its oral administration and its superior longterm cumulative tolerability (6).

In the early 1940s, Nanna Svartz synthesized sulphasalazine from the anti-inflammatory agent salicylic acid and the antibiotic sulphonamide (7). She reported favourable results in 63% of over 400 patients with rheumatoid polyarthritis. After the publication of an unfavourable trial in 1948 (8) the interest in the drug declined until it was rediscovered in the early 1980s. Although methotrexate has replaced sulphasalazine as the drug of first choice (9), it is still widely used alone or in combination with other drugs.

Antimalarials were first derived from the Peruvian bark and the active agents were isolated by Pelletier and Caventau in 1820. The first description of successful treatment of patients with a rheumatoid disease, lupus, comes from J.P. Payne (10). Since the 1950s the use of antimalarials in the treatment of rheumatoid arthritis has become widespead. The most widely used antimalarial today is hydroxychloroquine. Its clinical efficacy has been demonstrated in several trials (11;12), but it is one of the least potent antirheumatic drugs (13) and there are no convincing data that hydroxychloroquine could slow the progression of joint damage (14). In patients with active disease, hydroxychloroquine has been used successfully as an adjunct to combination therapy (15-20).

The efficacy of azathioprine as a disease modifying drug for the treatment of patients with rheumatoid arthritis was published first in 1969 (21). However, because of the high risk to benefit ratio there is no evidence to recommend the use of azathioprine over other disease modifying antirheumatic drugs for the treatment of rheumatoid arthritis (22).

Cyclosporine has been used to reduce solid organ allograft rejection for many years before it was introduced for the treatment of patients with rheumatoid arthritis. As monotherapy, it has no advantage over more established antirheumatic drugs. In patients with active disease, adding of cyclosporine to methotrexate could provide an additional benefit over methotrexate alone (23-26).

The first studies on low dose methotrexate in patients with rheumatoid arthritis date from the early 1960s. Since the 1980s, its is popularity gradually increased due to its favourable efficacy and toxicity profile (27). In addition, in a meta-analysis methotrexate had a significantly lower discontinuation rate than other disease modifying antirheumatic drugs (DMARDs) (28), although it should be noted that leflunomide and TNF-inhibitors were not included in this analysis. Finally, methotrexate can be combined successfully with biologics. These observations have lead to the European League Against Rheumatism (EULAR) recommendation to start with methotrexate as first DMARD in patients with recent onset disease at risk of persistent or erosive disease, with leflunomide and sulphasalazine as best alternatives (29). Leflunomide, a reversible inhibitor of de novo pyrimidine synthesis, was first introduced in the late 1990s. It has proven to be at least as effective as methotrexate and sulphasalazine in several trials (30-34). Five year follow-up

data demonstrated continued efficacy and safety (35).

Glucocorticoids

In 1949, Philip Hench, published a case of a patient with rheumatoid arthritis who improved dramatically after the administration of cortisone. The unprecedented rapid relief of symptoms by corticosteroids was considered so important that Hench and his colleagues were awarded with the Nobel prise in Physiology or Medicine in 1950 (36). However, the use of these agents declined dramatically in the 1980s after the recognition of serious side effects after more prolonged use. The place and role of corticosteroids in the treatment of patients with rheumatoid arthritis have been debated since. A recent cochrane review of literature between 1966 and 2005 demonstrated that glucocorticoids in addition to standard therapy substantially reduce the rate of erosion progression in patients with rheumatoid arthritis, although longterm safety remains a concern (37). In line with this review, the recent EULAR recommendations hold the recommendation to consider systemic glucocorticoid therapy as a (mainly temporary) adjunct to the DMARD strategy (29). In patients with recent onset rheumatoid arthritis, the efficacy of glucocorticoids has not been formerly investigated.

Treatment strategies

Until the early 1980s, the management of patients with rheumatoid arthritis could be described as a pyramid, with non-steroidal anti-inflammatory agents for all patients at the base of the treatment pyramid and the assumed more toxic disease modifying antirheumatic drugs (DMARDs) reserved for the subgroup of patients showing a progressive destructive disease course. The top of the pyramid represented combination therapy for the most severe cases. Several findings resulted in the abandonment of the pyramidal approach in the 1980s (38). First, it was recognized that long-term outcomes of the majority of patients with rheumatoid arthritis were poor, with severe joint destruction, disability and increased mortalitity (39-41). Second, it became clear that joint destruction already started early in the course of disease (42) and that DMARD therapy is more effective if started earlier (43-46). Third, DMARDs appeared to be less toxic than previously assumed (47), and finally, early treatment with DMARDs was shown to be effective in suppressing joint damage progression. These insights led to a new therapeutic strategy in the nineties referred to as the 'sawtooth' strategy', with earlier, continuous and serial use of DMARDs, substituting one DMARD for another or combining DMARDs when response to the previous drug(s) starts to decline (48). Although outcomes appeared better than with the old approach (49;50), progression of joint damage could not be halted and long lasting remission was still rare (51).

Rheumatologists started to combine different anti-rheumatic drugs, although the first results were disappointing, with only modest advantage and more toxicity. A meta-analysis of studies of combination therapy published in 1994 by Felson failed to

support the concept of their benefit (52). The initial negative perception turned into a much more positive one towards the end of the nineties. The efficacy and toxicity of combination therapy in patients with recent onset rheumatoid arthritis are outlined in chapter 2. Several combinations have proven superiority over monotherapy, although concerns have been raised about confounding factors in some trials, such as the use of glucocorticoids only in the combination arm and the choice for a less potent DMARD in the monotherapy group, which could have been responsible for the superiority of combination therapy (53).

TNF-antagonists

Technical developments and better understanding of the disease process led to the development of monoclonal antibodies against a key cytokine in rheumatoid arthritis, the proinflammatory cytokine tumor necrosis factor-alpha, TNF. Infliximab, a chimeric monoclonal antibody composed of human constant and murine variable regions, was the first TNF-antagonist to be introduced, and demonstrated to be highly effective in combination with methotrexate in suppressing signs and symptoms of inflammation and in reducing joint damage progression in patients with active rheumatoid arthritis despite DMARD therapy (54). In a subanalysis of this study, the additional efficacy of infliximab appeared greater in patients with early rheumatoid arthritis (55). Since then several trials demonstrated the superior efficacy of methotrexate and infliximab over methotrexate alone in patients with early rheumatoid arthritis (56-58). Remarkably, baseline predictors of poor prognosis in patients treated with methotrexate monotherapy were no longer correlated with poor outcome in patients treated with the combination of methotrexate and infliximab (58;59).

Other TNF-inhibitors that were introduced appear to have comparable clinical and radiographic efficacy (60). In patients with active rheumatoid arthritis despite DMARD therapy, the combination of etanercept, a recombinant human soluble TNFα-receptor fusion protein, and methotrexate was superior to monotherapy of either drugs (61). In patients with early rheumatoid arthritis not previously treated with methotrexate, etanercept monotherapy resulted in better suppression of joint damage progression than methotrexate after 2 years (62). The combination of adalimumab, a recombinant fully human IgG1 monoclonal TNF antibody, and methotrexate was more effective and resulted in less joint damage progression than methotrexate monotherapy in patients with longstanding rheumatoid arthritis (63;64) and adalimumab monotherapy was clinically more effective than methotrexate monotherapy in a 26 week trial (65). In patients with early rheumatoid arthritis the combination of methotrexate and adalimumab was superior to the treatment with either drug alone (66).

MONITORING OF CLINICAL RESPONSE

Because the pathogenesis of rheumatoid arthritis is still unknown, antirheumatic

therapies focus on non-specific suppression of disease activity and functional ability. In 1980, Fries presented a questionnaire for self-administration to assess disability in patients with rheumatoid arthritis (67). This filled the need for a more objective tool for evaluating the grade of disability in patients with rheumatoid arthritis and for comparing various groups of rheumatoid arthritis patients. In 1984, a Dutch version of this Health Assessment Questionnaire (HAQ) was validated for use in the Netherlands (68). In the past, many disease activity variables have been used to evaluate the efficacy of antirheumatic agents. However, in a study evaluating various aspects of validity of single and composite variables used to measure disease activity, many single variables showed to have low validity and the Disease Activity Score (DAS) turned out to be one of the most valid variables to measure disease activity (69-71). The DAS is a composite measure of the Ritchie articular index (RAI), a swollen joint count including 44 joints (swollen44), the erythrocyte sedimentation rate (ESR) and an assessment of the patient's general health on a visual analogue scale (GH):

DAS = 0.54*sqrt(RAI) + 0.065*(swollen44) + 0.33*Ln(ESR) + 0.0072*GH

Later, the DAS28, based on the 28 joint count for tenderness and swelling, has been developed (72):

DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * GH

Fluctuations in disease activity score appear to be related to changes in radiographic progression (73) and the DAS is a sensitive discriminator between patients with high and low disease activity and between active and placebo treated patient groups (74).

In addition to disease activity, the response of individual patients is an important measurement in clinical trials. Based on the DAS, the EULAR response criteria have been developed, including both the relevant change in disease activity since the start of treatment and the disease activity attained during follow-up (75). Three categories of responders are defined: good, moderate and non-responders.

Figure 1. European League Against Rheumatism response criteria based on the Disease Activity Score

	Improvement >1.2	Improvement ≤1.2 and >0.6	Improvement ≤0.6
DAS ≤2.4	Good response		
2.4 < DAS ≤3.7		Moderate response	
DAS >3.7			No response

Another valid definition of the response of individual patients in clinical trials is given by the American College of Rheumotology (ACR) criteria for improvement. The ACR20 criteria define improvement for clinical trial patients as 20% improvement in tender and swollen joint counts and 20% improvement in at least 3 of the following 5 ACR core set measures: pain, patient and physician global assessments, self-assessed physical disability, and acute phase reactant (76). There is a high level of agreement between the

EULAR and ACR reponse criteria and their validity appears to be equivalent (77).

In a setting where treatment is left to the discretion of the treating physician, systematic monitoring of disease activity in rheumatoid arthritis may lead to more changes in DMARD treatment, resulting in a larger number of patients with low disease activity (78). In addition, intensive management with tight disease control has shown to result in better suppression of disease activity and less progression of radiographic joint damage than routine management (79). The availability of such a monitoring tool as the DAS and the finding that higher preset goals can be achieved, have raised a new awareness that better suppression of RA is possible.

MONITORING OF RADIOGRAPHIC DAMAGE

Over the years several scoring methods for assessing joint damage progression have been developed. The most well known are the Larsen and Sharp methods and their modifications (80-84). All methods produce sufficient intra- and inter-reliability. The Sharp score and modification are the most sensitive to detect changes over time, but are more time consuming than the Larsen score and its modification (85). In patients with early rheumatoid arthritis, the Sharp-van der Heijde score shows better reliability and less measurement error than the Larsen score (86).

Sharp developed a scoring method to assess joint erosions and joint space narrowing in the hands (83). Van der Heijde adapted the scoring method of the hands and added a scoring method for the feet, because erosive changes are frequently more pronounced in the feet (84;87). This modified Sharp score, or Sharp-van der Heijde score, assesses erosions in 16 areas of the hands and in 6 areas of the feet and joint space narrowing in 15 areas of the hands and in 6 areas of the feet. In the hands, the maximal score per area is 5 for erosions and 4 for joint space narrowing, and in the feet, the maximum score per area is 10 for erosions and 4 for joint space narrowing. Thus, the maximum erosion score of all joints in both hands is 160 and in both feet 120, and the maximum joint space narrowing score of all joints in both hands is 120 and in both feet 48. Summing of the absolute scores of the hands and the feet results in a maximum score of 448. Progression of joint damage can be expressed as the mean and median change over time at a group level. However, radiographic data are highly skewed, with most patients showing no or minimal progression. Thus, valuable information can be added when the percentage of patients with no progression is reported. First the smallest detectable difference (SDD) has been suggested as a clinically relevant cut-off level with a value greater than the measurement error (88). However, the SDD expresses the smallest difference between two independently obtained measures that can be interpreted as real, while radiographic joint damage progression is usually based on the simultaneous assessment of a series of films. Therefore, the smallest detectable change (SDC) has been proposed as the cut-off level to determine the amount of progression that is reliably detectable above the measurement error (89).

Another important issue is in which order films should be scored to measure

progression. Scoring films in chronological order is the most sensitive to change, but it cannot be excluded that it overestimates the progression of joint damage (90). On the other hand, when scoring films paired, in random time order, negative progression, i.e. healing of erosions, could be detected. Both the one and two year follow-up results of the TEMPO trial suggest that therapy induced repair may be possible on a group level (61;91).

THE BEST STUDY

Despite all new therapeutic options, it is still unclear how and when a drug, or combinations of drugs should be introduced over time in patients with newly diagnosed rheumatoid arthritis. Previous studies focussed on the comparison of one drug or combination with another drug or combination. More relevant for clinical practice is what consecutive therapeutic steps should be taken when disease activity if insufficiently suppressed, and, provided the immediate treatment goal is clear, which strategy results in the best long term outcomes, with the least side effects, and the most favourable cost-effectiveness profile. Should all patients be treated initially with a combination of antirheumatic drugs or biologic agents, or can they be reserved for patients who fail on initial monotherapy? There are concerns about the long-term safety of more aggressive approaches, especially about infections and malignancies in TNF-antagonists and about cardiovascular toxicity in long-term prednisone treatment. TNF-antagonists seem to be associated with a higher chance of infectious complications (92;93). There is controversy about the risk for lymphomas in patients treated with TNF-antagonists (92-95). Data on the development of lymphomas are difficult to interpret because of the higher lymphoma incidence in patients with rheumatoid arthritis (96). Finally, financial restrictions preclude treatment of newly diagnosed rheumatoid arthritis patients with the expensive TNF-antagonists in many countries.

Against this background, the BeSt study (acronym for Behandel-Strategieën, i.e. Treatment Strategies) was designed by a group of Dutch Rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR). In this study, patients with recent onset rheumatoid arthritis were randomly allocated to one of the following treatment strategies: sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with prednisone (group 3) or initial combination therapy with infliximab (group 4) (Figure 2).

For patients failing on their medication, the treatment protocol prescribed a number of subsequent treatment steps. The decision whether or not to adjust medication was made every 3 months based on the DAS, aiming at a value of ≤2.4. To avoid bias, the DAS was calculated by a research nurse who remained blinded for the allocated treatment group during the entire study period. If the DAS was >2.4 (insufficient response), the treating physician immediately adjusted therapy by proceeding to the next step in the allocated treatment group. If the DAS was ≤2.4 for at least 6 months, medication was gradually tapered until one drug remained in a maintenance dose.

Along with the DAS calculations, the research nurses collected data on clinical efficacy and safety. Radiographs of hands, wrists and feet were made at baseline, 1 and 2 year follow-up and scored independently by 2 trained physicians, in random order, and masked for patient identity and date.

OUTLINE OF THE THESIS

Chapter 2 describes the background against which the BeSt study was designed. It outlines the history of the treatment of patients with rheumatoid arthritis over the last decades and reviews all controlled clinical trials on combination therapy in patients with rheumatoid arthritis, published in 1999 or 2000. Despite the growing number of treatment options, the timing and make-up of combinations is left unanswered. In chapter 3 and 4, respectively, the one and two year clinical and radiographic outcomes of the comparison of the four treatment strategies of the BeSt study are presented.

Because of the small differences in outcomes between the treatment groups after 2 years, it was hypothesized that this could be the result of the intense monitoring of treatment effect and the standardized therapy aiming for low disease activity. In chapter 5, the comparison of DAS-driven therapy of the BeSt study and routine care is presented. For the implementation of new therapeutic approaches, it is important to understand patients' likes and dislikes, which can be strong and widespread. Chapter 6 describes the results of a questionnaire on the subject of patient preferences in patients enrolled in the BeSt study. Before initiation of the BeSt study, several combinations of drugs had proven superiority over monotherapy in patients with recent onset rheumatoid arthritis. Nevertheless, in daily practice many rheumatologists still start treatment with a single agent. In chapter 7, patient characteristics that might influence rheumatologists in their choice for a single drug or a combination of drugs have been investigated. Finally, the direct and indirect medical costs involved in different treatment strategies are an important issue for health insurance companies. The results of the health economics analysis of the BeSt study are given in chapter 8.

Figure 2. The four treatment strategies compared in the BeSt study

SEQUENTIAL MONOTHERAPY	STEP-UP COMBINATION THERAPY	INITIAL COMBINATION THERAPY WITH PREDNISONE	INITIAL COMBINATION THERAPY WITH INFLIXIMAB
MTX 15mg/wk	MTX 15mg/wk	MTX 7,5mg/wk + SSA 1000mg bid + prednisone 60 -> 7.5mg/day in 7 wks	MTX 25mg/wk + infliximab 3mg/kg/8 wks
↓	↓	↓	↓
MTX 25mg/wk	MTX 25mg/wk	MTX 25mg/wk + SSA 1000mg bid + prednisone 7.5mg/day	MTX 25mg/wk + infliximab 6mg/kg/8 wks
			↓
↓	↓	↓	MTX 25mg/wk + infliximab 7.5mg/kg/8 wks
SSA 1000mg bid	MTX 25mg/wk + SSA 1000mg bid	MTX 25mg/wk + CSA 2.5mg/kg/day + prednisone 7.5mg/day	↓
			MTX 25mg/wk + infliximab 10mg/kg/8 wks
↓	↓	↓	↓
leflunomide 20mg/day	MTX 25mg/wk + SSA 1000mg bid + HCQ 200mg bid	MTX 25mg/wk + infliximab 3mg/kg/8 wks	SSA 1000mg bid
↓		↓	↓
MTX 25mg/wk + infliximab 3mg/kg/8 wks	MTX 25mg/wk + SSA 1000mg bid + HCQ 200mg bid + prednisone 7.5mg/day	MTX 25mg/wk + infliximab 6mg/kg/8 wks	leflunomide 20mg/day
		↓	
↓	↓	MTX 25mg/wk + infliximab 7.5mg/kg/8 wks	↓
MTX 25mg/wk + infliximab 6mg/kg/8 wks	MTX 25mg/wk + infliximab 3mg/kg/8 wks	↓	MTX 25mg/wk + CSA 2.5mg/kg/day + prednisone 7.5mg/day
↓		MTX 25mg/wk + infliximab 10mg/kg/8 wks	

MTX 25mg/wk + infliximab 7.5mg/kg/8 wks	↓	↓	↓
↓	MTX 25mg/wk + infliximab 6mg/kg/8 wks	leflunomide 20mg/day	gold 50mg/wk + 3 gifts depomedrol 120mg (week 1, 4 and 8)
MTX 25mg/wk + infliximab 10mg/kg/8 wks	↓		
↓	MTX 25mg/wk + infliximab 7.5mg/kg/8 wks	↓	
gold 50mg/wk + 3 gifts depomedrol 120mg (week 1, 4 and 8)	↓	gold 50mg/wk + 3 gifts depomedrol 120mg (week 1, 4 and 8)	↓
	MTX 25mg/wk + infliximab 10mg/kg/8 wks		
	↓		
↓	MTX 25mg/wk + CSA 2.5mg/kg/day + prednisone 7.5mg/day	↓	AZA 2-3mg/kg/day + prednisone 7.5mg/day
	↓		
MTX 25mg/wk + CSA 2.5mg/kg/day + prednisone 7.5mg/day	leflunomide 20mg/day	AZA 2-3mg/kg/day + prednisone 7.5mg/day	
↓	↓		
AZA 2-3mg/kg/day + prednisone 7.5mg/day	gold 50mg/wk + 3 gifts depomedrol 120mg (week 1, 4 and 8)		

MTX=methotrexate, SSA=sulphasalazine, CSA=cyclosporin A, AZA=azathioprine, HCQ=hydroxychloroquine.

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