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

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Chapter 5

DAS-driven therapy versus routine care in patients with recent onset active rheumatoid arthritis

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ABSTRACT

Objectives. To compare the efficacy of disease activity score (DAS)-driven therapy and routine care in patients with recent-onset rheumatoid arthritis.

Methods. Patients with recent-onset rheumatoid arthritis receiving traditional antirheumatic therapy were selected from either the BeSt study (1), a randomized controlled trial comparing different treatment strategies (group A) or 2 Early Arthritis Clinics (group B). In group A, systematic DAS-driven treatment adjustments aimed to achieve low disease activity ($DAS \leq 2.4$). In group B, treatment was left to the discretion of the treating physician. We evaluated functional ability (HAQ), disease activity score (DAS28) and Sharp/van der Heijde radiographic score (SHS).

Results. At baseline, patients in group A ($n=234$) and group B ($n=201$) had comparable demographic characteristics and a mean HAQ of 1.4. Group A had a longer median disease duration than group B (0.5 vs 0.4 year, $p=0.016$), higher mean DAS28 (6.1 vs 5.6, $p<0.001$), more rheumatoid factor positive patients (66% vs 42%, $p<0.001$) and more erosive patients (71% vs 53%, $p<0.001$). After 1 year, the HAQ improvement was 0.7 vs 0.5 ($p=0.029$), and the percentage in remission ($DAS28<2.6$) 31% vs 18% ($p<0.005$) in groups A and B, respectively. In group A, median SHS progression was 7.0 expected and 2.0 observed. In group B, SHS progression was 4.4 expected and 1.0 observed.

Conclusions. In patients with recent onset rheumatoid arthritis receiving traditional therapy, systematic DAS-driven therapy results in better clinical improvement than routine care and in a trend towards better suppression of the expected rate of joint damage progression.

INTRODUCTION

In patients with recent-onset rheumatoid arthritis, initial combination therapy with disease modifying antirheumatic drugs or biologics (2-10) has proven superiority over initial monotherapy in improving clinical and radiographic outcomes. In the recently performed BeSt study (1), four different treatment strategies were compared in a setting of tight disease control. Patients treated with initial combination therapy with either prednisone or infliximab had a more rapid clinical response than patients treated with sequential monotherapy or step-up to combination therapy. After 1 year, changes in the physical function and the percentage of patients in clinical remission were comparable for all treatment groups. To achieve this, treatment had to be adjusted more often and for more patients in the initial monotherapy groups than in the initial combination therapy groups. We hypothesized that the systematic measurements of disease activity with adjustments to therapy according to a fixed protocol aiming at a disease activity score (DAS) ≤ 2.4 (11) are the reasons for the remarkable improvement in the initial monotherapy groups after 1 year of follow-up.

To investigate this further, we compared the results of the patients receiving sequential monotherapy or step up to combination therapy in the BeSt trial (1) with the results of similar RA patients who were treated outside of the BeSt trial, and managed with routine, i.e. non-DAS-driven, therapy.

METHODS

Patients

All patients fulfilled the American College of Rheumatology (ACR) 1987 criteria for rheumatoid arthritis (12). Group A consisted of patients participating in the BeSt study, who were treated with the traditional strategies, i.e. sequential monotherapy (group 1) or step-up combination therapy (group 2). Selection criteria were as follows: age ≥ 18 years, a disease duration ≤ 2 years, $\geq 6/66$ swollen joints, $\geq 6/68$ tender joints, and either an erythrocyte sedimentation rate (ESR) ≥ 28 mm/hr or a global health score ≥ 20 mm on a visual analogue scale (VAS) of 0-100 mm (0=best, 100=worst). Patients in the BeSt study were derived from 2 university and 18 peripheral hospitals in the Western part of the Netherlands between April 2000 and August 2002. Group B consisted of all patients from the databases of the Early Arthritis Clinic of Leiden University Medical Center (LUMC) and the Jan van Breemen Institute (JBI) in Amsterdam, who were diagnosed with rheumatoid arthritis and met the inclusion criteria of the BeSt study (see above). During the inclusion period of the BeSt study, all eligible patients were enrolled in this study. For group B, patients from the period before (January 1998 - March 2000) and after the BeSt study (August 2002 - December 2004) were selected.

Only patients with baseline and 1-year follow-up data of the Dutch version of the health assessment questionnaire (HAQ) (13), Sharp-van der Heijde score (SHS) for radiographic joint damage (14), or both, were included in this comparison.

Treatment

In group A, treatment adjustments were standardized and based on the DAS, obtained every 3 months, with the goal to achieve low disease activity ($\text{DAS} \leq 2.4$) (15). Patients assigned to sequential monotherapy started treatment with methotrexate, which, in case of a persistent $\text{DAS} > 2.4$, was substituted subsequently by sulphasalazine, leflunomide, and methotrexate with infliximab. If the DAS was ≤ 2.4 for at least 6 months, medication was tapered to the last established drug at a maintenance dose. Patients assigned to step-up combination also started treatment with methotrexate alone, followed, in the case of a persistent $\text{DAS} > 2.4$, subsequently by methotrexate with sulphasalazine, methotrexate with sulphasalazine and hydroxychloroquine, methotrexate with sulphasalazine, hydroxychloroquine and prednisone, and methotrexate with infliximab. If the DAS was ≤ 2.4 for at least 6 months, medication was tapered, last added drug first, until monotherapy in maintenance dose remained. Parenteral corticosteroids were not allowed and low dose oral corticosteroids were allowed only as described in the treatment protocol for the step-up combination group. A detailed description of the protocol has been published previously (1).

In group B, treatment including the use of corticosteroids and biologics was left to the discretion of the treating physician.

Outcomes

In both treatment groups, assessments were made by research nurses every 3 months during the entire follow-up period. The primary clinical endpoint was functional ability, measured by the HAQ, with higher scores indicating more severe loss of physical function (13). The secondary clinical endpoint was the mean disease activity score in 28 joints (DAS_{28}) (16) and the remission percentage defined as $\text{DAS}_{28} < 2.6$. The primary radiographic endpoint was the change from baseline to 1 year in the total SHS, ranging from 0-448 (14). Radiographs of hands, wrists and feet, at baseline and at 1-year follow-up, were scored independently by two readers (JV and YG) blinded to the patient's identity, treatment group and sequence of the films. The mean score of the two readers was used for the analysis. The intra-observer coefficients were 0.84 and 0.87 and the inter-observer coefficient was 0.96. Erosive disease was defined as a mean erosion score above 0.5. Progression of joint damage was defined as a change in total SHS greater than the smallest detectable change (SDC) (17), which was 4.10. The predicted joint damage progression during the first year was extrapolated by dividing the baseline total SHS by the symptom duration. This extrapolation has been described previously in a study using the Larsen score for joint damage progression (18). Suppression of joint damage progression was defined as the median observed minus the expected progression.

Statistical analysis

All available data were used for the analyses. Measurements with a Gaussian distribution are expressed as mean and standard deviation (SD), and measurements with a non-

Gaussian distribution are expressed as median and interquartile range (IQR). Outcomes of patients in groups A and B were compared, using the Student's T-test, Mann-Whitney U test and chi-square test where appropriate.

RESULTS

A total of 435 patients with recent-onset, active rheumatoid arthritis were selected (234 in group A, 201 in group B). In group B, 121 patients were selected from the period before initiation of the BeSt study and 80 patients were selected from the period after the BeSt study. HAQ scores were available for 228 patients (97%) in group A and 192 patients (96%) in group B, DAS28 scores were available for 232 patients (99%) in group A and 166 patients (83%) in group B, and baseline SHS was available in 229 patients (98%) in group A and 191 patients (95%) in group B.

Data of all other demographic and disease characteristics were available in over 98% of patients. Patients for whom data on DAS28 were missing had a lower median baseline SHS than patients in whom these data were complete (1.5 versus 3.0, $p=0.011$). There were no other differences in baseline characteristics between patients with missing and complete data.

At baseline, the average age of patients was 54 years, 72% were female, the mean HAQ was 1.4, the mean DAS28 was 5.9 and the median SHS was 3.0. Patients in group A had a longer median disease duration than patients in group B (0.5 versus 0.4 year, $p=0.016$), a higher mean DAS28 (6.1 versus 5.6, $p<0.001$) and a higher median ESR (39 versus 31 mm/hr, $p=0.033$). More patients in group A were rheumatoid factor positive (66% versus 42%, $p<0.001$) and more had erosive disease (71% versus 53%, $p<0.001$) when compared with patients in group B (Table 1).

Table 1. Baseline demographic and disease characteristics.

Characteristic	All patients n=435	DAS-driven therapy n=234	Routine care n=201
Age - yr*	54 ±14	54 ±13	54 ±15
Female sex - no. (%)	72	70	73
Symptom duration - yr†	0.4 (0.3-0.8)	0.5 (0.3-1.0)	0.4 (0.3-0.6)‡
Rheumatoid factor positive - no. (%)	55	66	42‡
Erythrocyte sedimentation rate - mm/hr†	35 (21-54)	39 (22-58)	31 (20-51)‡
Disease Activity Score in 28 joints*	5.9 ±1.0	6.1 ±1.0	5.7 ±1.0‡
Health Assessment Questionnaire*	1.4 ±0.7	1.4 ±0.7	1.4 ±0.7
Total Sharp-van der Heijde score†	3.0 (1.0-6.9)	4.0 (1.5-8.5)	2.0 (0.5-5.0) ‡
Erosive - no. (%)	63	71	53‡
Predicted radiographic progression rate†	5.7 (1.4-16.9)	7.0 (2.0-20.0)	4.4 (0.9-13.2) ‡

*Mean ±standard deviation; †Median (interquartile range); ‡p-value <0.05 for comparison between groups A and B.

Clinical outcomes

Overall, clinical outcomes had improved after 1 year. The mean HAQ improvement was 0.6, the mean DAS28 improvement was 2.4 and the mean ESR decrease was 15mm/hr (Table 2). Despite higher baseline scores, patients in group A had better clinical outcomes after 1 year of follow-up than patients in group B. The mean HAQ improvement was 0.7 in group A versus 0.5 in group B ($p=0.029$) (Figure 1A), the mean DAS28 improvement was 2.7 in group A versus 1.9 in group B ($p<0.001$) (Figure 1B) and the median ESR improvement was 19 mm/hr in group A versus 13mm/hr in group B ($p=0.011$). The percentage of patients in clinical remission (DAS28 <2.6) after 1 year was 31% in group A versus 18% in group B ($p=0.005$).

For the subgroup of patients from LUMC and JBI, patients treated with DAS-driven therapy had better clinical outcomes, but due to the small sample size, no statistically significant differences were observed (data not shown).

Table 2. Change in patient outcomes during 1-year follow-up.

	All patients n=435	DAS-driven therapy n=234	Routine care n=201	P Value
Health Assessment Questionnaire*	-0.6 \pm 0.7	-0.7 \pm 0.7	-0.5 \pm 0.7	0.029
Disease Activity Score in 28 joints*	-2.4 \pm 1.5	-2.7 \pm 1.5	-1.9 \pm 1.5	<0.001
Erythrocyte sedimentation rate – mm/hr†	-15 (-5 to -32)	-19 (-6 to -37)	-13 (-3 to -28)	0.011
Total Sharp/van der Heijde score†	1.5 (0.0 to 5.5)	2.0 (0.0 to 7.0)	1.0 (0.0 to 3.5)	0.001

*Mean \pm standard deviation; †Median (interquartile range)

Radiographic outcomes

Radiographs of hands, wrists and feet of both baseline and 1 year follow-up for 410 patients (94%) were available for analysis (224 patients in group A and 186 patients in group B). Based on the SHS score at baseline and the duration of symptoms at baseline, the expected progression of radiographic joint damage was calculated for patients in both groups. In group A, the expected progression after 1 year was 7.0, whereas the observed progression was 2.0. In group B, the expected progression was 4.4, whereas the observed progression was 1.0 ($p<0.001$ for expected progression, $p=0.006$ for observed progression) (Figure 2). The larger difference between the expected progression and observed progression in group A suggests that the suppression of joint damage progression was better in this group than in group B, although this was not statistically significant ($p=0.126$). At baseline, significantly more patients in group A had erosive disease (group A 71%, group B 53%; $p<0.001$). After 1 year, the difference in percentage of patients with erosive disease was less distinct (group A 81%, group B 74%; $p=0.091$). The number of patients who progressed from non-erosive to erosive disease was 27 out of 65 patients (42%) in group A and 40 out of 88 patients (46%) in group B ($p=0.629$).

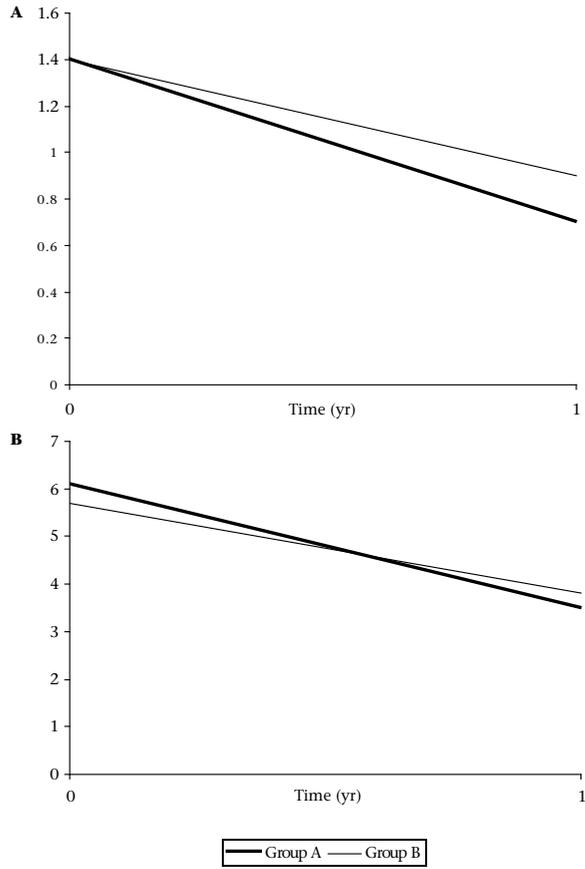


Figure 1. Mean Health assessment questionnaire and DAS28 scores of the patients with DAS-driven therapy (group A) and routine care (group B).

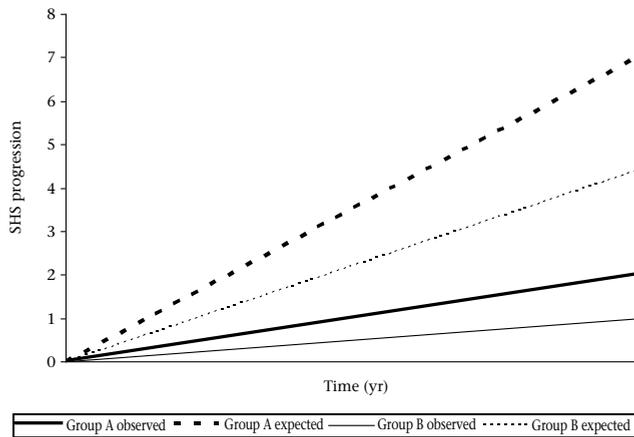


Figure 2. Expected and observed progression of the Sharp-van der Heijde score for radiographic joint damage.

Treatment

During the first year, more patients in group A than in group B had received DMARD therapy (100% vs 89%). The mean number of DMARDs per patient was 2.1 in group A and 1.5 in group B. In group A, all patients started with methotrexate. As dictated by the protocol, patients in group A switched medication if the DAS was >2.4 , corresponding with a DAS28 >3.6 . The following antirheumatic drugs were prescribed during the first year: sulphasalazine in 58% of patients, leflunomide in 20%, antimalarials in 15%, low dose prednisone in 7%, and infliximab in 11% of patients. In group B, methotrexate had been prescribed in 54% of patients, sulphasalazine in 32%, prednisone in 21%, antimalarials in 19%, cyclosporin A in 3%, leflunomide in 1%, gold in 1%, etanercept in 1%, and adalimumab in 1% of patients.

DISCUSSION

This comparison of clinical and radiological outcomes in patients with recent-onset rheumatoid arthritis receiving traditional antirheumatic therapy shows that patients benefit from systematic monitoring of disease activity and standardized therapy adjustments compared with routine care. DAS-driven therapy adjustments result in significantly better clinical outcomes than routine management and in a trend towards better suppression of the expected rate of joint damage progression. These results are consistent with previous studies, which demonstrated that intensive management is more effective than routine care (19) and that adherence to treatment guidelines improves outcome (20).

Our observations are the result of comparing treatments for patients with recent-onset rheumatoid arthritis in the BeSt study (initial monotherapy with antirheumatic drugs) with a cohort of patients receiving routine therapy. We selected patients who would have met the inclusion criteria of the BeSt study within a period of 2 years before and after the inclusion period of the BeSt study from the Early Arthritis Clinics databases of the LUMC and the JBI, which were the main contributors of patients for the BeSt study. Nevertheless, when we compared the baseline characteristics, patients in the routine care group had a milder disease at baseline with fewer patients testing positive for rheumatoid factor, a lower disease activity and less radiographic joint damage than the patients in the BeSt study. The differences in baseline demographic and disease characteristics between patients in the BeSt study and patients in the routine care group were smaller when only patients included in the LUMC and JBI were analyzed, suggesting selection bias in the BeSt study of patients with worse disease characteristics, which appears to be most prominent in the other participating (peripheral) centers.

A second important difference between group A and group B is the medication received. Despite the fact that both the LUMC and the JBI are specialized centers for patients with rheumatoid arthritis, patients in the routine care group received methotrexate less often, which is now considered to be the anchor drug in RA treatment (21). In part, this may be explained by milder disease characteristics in the routine group at the time of diagnosis.

On the other hand, oral prednisone was prescribed more often, and low dose steroids are effective in suppressing the rate of joint damage progression (22-24). Over time, novel insights might have influenced treatment choices in the routine care group, but the number of patients treated before and after the inclusion period of the BeSt study was too small to find significant differences in drug prescription patterns.

In our opinion, the differences between the two groups only increases the strength of the observation that, despite a worse prognosis, patients treated in the BeSt study with DAS-driven therapy show more clinical improvement than patients receiving routine care, who had a better initial prognosis and more often received oral corticosteroids.

Consistent with these observations, the radiographic outcomes show a clear trend towards a benefit from DAS-driven treatment. In patients from the BeSt study the expected rate of joint damage progression after 1 year, based on linear extrapolation of baseline damage, was better suppressed than in patients in the routine care group, who had a lower expected damage progression rate. It is conceivable that DAS-driven treatment is indeed more effective in suppressing joint damage progression. The fact that we did not find a statistically significant difference between the two groups might be explained by differences in disease severity at presentation and drug prescription, with milder disease and more oral prednisone in the routine management group.

We conclude that systematic DAS-driven therapy adjustment in itself has a beneficial effect in securing better improvement of clinical outcomes and shows a trend towards better suppression of the rate of joint damage progression.

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