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

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Chapter 7

Dutch rheumatologists prefer monotherapy as initial treatment strategy for patients with recent onset rheumatoid arthritis

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ABSTRACT

Objectives. To determine what rheumatologists in the BeSt study (1) prefer as initial treatment strategy for patients with recent onset rheumatoid arthritis and which patient and disease characteristics influence their choice.

Methods. All recruiting rheumatologists of the BeSt study, a randomized controlled trial comparing different treatment strategies, were asked at inclusion (2000-2002) whether or not they agreed with the allocated treatment strategy and if not, what treatment strategy they would chose. Treatment groups were: (1) sequential monotherapy, starting with methotrexate; (2) step-up combination therapy, starting with methotrexate; (3) initial combination therapy with methotrexate, sulphasalazine and high dose tapered prednisone; (4) initial combination therapy with methotrexate and infliximab. We evaluated whether baseline patient and disease characteristics influenced the rheumatologists' preference for a certain treatment strategy.

Results. Rheumatologists agreed with the allocated treatment strategy in 88%, 90%, 51% and 38% of patients in groups 1-4, respectively (overall, P<0.001). Sequential monotherapy was preferred in respectively 42% and 48% of patients allocated to initial combination therapy with prednisone or infliximab. Patients for whom rheumatologists preferred initial combination therapy had a higher ESR than patients for whom rheumatologists preferred initial monotherapy (median ESR 49 vs 35; OR 1.71 (1.09-2.79) for upper vs lower quartile), a higher BMI (27 vs 25; OR 1.71 (1.07-2.72) for upper vs lower quartile), and more often were rheumatoid factor positive (87% vs 60%; OR 4.37 (1.42-13.45)).

Conclusion. Rheumatologists tend to be conservative and prefer initial monotherapy in most patients with recent onset, active rheumatoid arthritis. A preference for combination therapy is especially associated with a positive rheumatoid factor.

INTRODUCTION

Due to rapidly changing insights, physicians have had to adjust their therapeutic strategy for the treatment of patients with recent onset rheumatoid arthritis many times over the last decades. Only 2 decades ago, therapy rested on the use of non-steroidal anti-inflammatory agents. Since then, a gradual increase in the use of disease modifying antirheumatic drugs is observed (2-6). Methotrexate has become increasingly popular as a first line agent (7-9)and has replaced sulphasalazine as a first agent (10). The concept of diagnosing and treating rheumatoid arthritis early seems to be accepted by a large proportion of the rheumatologic community (11). In the last decade, new therapeutic options including combinations of disease modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF) inhibitors have become available. In a meta-analysis on efficacy and toxicity of combination therapy, methotrexate plus sulphasalazine and/or anti-malarials and methotrexate plus TNF inhibitors showed to have favourable benefit/risk ratios (12) However, partly due to costs (13) and concerns about long term side effects, in current clinical practice combination therapy is not commonly first choice as initial therapy.

In the BeSt study, four different treatment strategies in patients with recent onset active rheumatoid arthritis were compared. To evaluate the preference of rheumatologists for one of the treatment groups, rheumatologists were asked by questionnaire, at the time of inclusion of each patient, whether or not they agreed with the allocated treatment group, and if not, which strategy they would prefer. We evaluated whether there was a relation between the rheumatologist's preference for a certain treatment group and the baseline patient and disease characteristics.

METHODS

Design

Within the setting of a randomized controlled trial comparing four different treatment strategies in patients with recent onset rheumatoid arthritis (the BeSt study[1]), rheumatologists were asked by questionnaire at the time of enrolment whether or not they agreed with the treatment strategy their patient was allocated to, and if not, what they would chose as initial therapy. We investigated whether there was a relation between the preferred treatment and the baseline characteristics of the patient involved. Furthermore, we compared the answers to the questionnaire with the physician's assessment of the patient's disease activity on a visual analogue scale.

Treatment

In the BeSt study, 508 patients were randomized to receive one of four treatment strategies: sequential monotherapy (group 1), step-up combination therapy (group 2), initial

combination therapy with high dose tapered prednisone (group 3) or initial combination therapy with infliximab (group 4). In case of an insufficient clinical response (DAS >2.4) or intolerable side effects, patients proceeded to subsequent treatment steps as dictated by the treatment protocol. A detailed description of the protocol has been published previously(1).

Questionnaire

All rheumatologists were asked to complete a questionnaire at the time of enrolment of their patient. All questionnaires were collected by the research nurses and returned to the authors. The first question was whether or not the rheumatologist agreed with the allocated treatment strategy. The options were: (1) agree with the allocated strategy; (2) disagree with the allocated strategy; (3) no opinion. The next question was: If you disagree, which treatment would you have started for this patient? (free text).

Patient and disease characteristics

The following baseline patient and disease characteristics were analyzed in relation to the rheumatologists' treatment preference: sex, age, body mass index (BMI), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), hemoglobin (Hb), erosive disease at baseline, total Sharp/van der Heijde score for radiographic joint damage, swollen joint count (SJC), Ritchie articular index (RAI), DAS, patient's assessment of global health on a visual analogue scale (VAS) ranging from 0-100mm, and symptom duration.

To detect whether preferences changed during the 2.5 years inclusion period, a separate analysis was performed for first hundred patients included (April 2000 – Januari 2001) and the last hundred patients included (March to August 2002).

Statistical analysis

All completed questionnaires were used for the analyses. Where appropriate, analyses were performed using an independent-sample's T test, a Mann-Whitney U, or a Chi square test. Erosive disease was defined as a mean erosion score above 0.5, as measured by the Sharp-van der Heijde score for radiographic joint damage.

Binary logistic regression analysis was performed to determine which baseline patient and disease characteristics influenced the preference of rheumatologistis for monotherapy or combination therapy. Odds ratios with 95% confidence intervals were calculated for the characteristics with the largest impact on treatment preference.

RESULTS

All rheumatologists and trainee rheumatologists who recruited and enrolled patients in the BeSt trial were asked fill in the questionnaire on treatment preferences for each enrolled patient. The questionnaire was completed and returned for 93 out of 126 (74%)

patients in the sequential monotherapy group, 89 out of 121 (74%) patients in the step-up combination group, 96 out of 133 (72%) patients in the initial combination group with prednisone, and for 125 out of 128 (98%) patients in the initial combination group with infliximab. Baseline and disease characteristics of patients for whom the questionnaire was returned were similar to those for whom the questionnaire was not returned, except for a slightly lower mean DAS (4.4 versus 4.6; P=0.045), a higher haemoglobin (8.0 versus 7.7; P=0.027) and fewer painful joints (13 versus 14 ;P=0.028). There were no significant differences in baseline characteristics between the four treatment groups.

Overall, rheumatologist agreed with the allocated treatment strategy in 256 patients (64%). Rheumatologists agreed significantly more often with the allocated treatment when patients were randomized to receive sequential monotherapy or step-up combination therapy than when patients were randomized to receive initial combination therapy with either prednisone or infliximab (agreed in 88%, 90%, 51% and 38% of patients in groups 1 through 4, respectively; overall P<0.001) (Table 1). When rheumatologists disagreed with allocation to sequential monotherapy or step-up combination therapy, they most often preferred combination therapy with prednisone as initial treatment (in 9% and 8% of patients, respectively). When rheumatologists disagreed with allocation to initial combination therapy with prednisone or infliximab, they most often preferred sequential monotherapy as initial treatment (in 43% and 48% of patients, respectively) (Table 1).

Table 1. Results of the questionnaire reporting whether or not rheumatologists agreed with the allocated treatment strategy*.

	Sequential monotherapy (n=91)	Step-up combination therapy (n=89)	Intial combination with prednisone (n=97)	Initial combination with infliximab (n=123)
Agree	82 (88)	80 (90)	49 (51)	48 (38)
Disagree	8 (9)	9 (10)	45 (47)	70 (56)
-prefer monotherapy	-	1 (1)	41 (43)	60 (48)
-prefer combination with prednisone	8 (9)	7 (8)	3 (3) †	9 (7)
-prefer combination without prednisone	-	1 (1)	1 (1)	1 (1)
No opinion	3 (3)	-	2 (2)	7 (6)

*Number (percentage) of patients; †rheumatologists preferred a different combination of antirheumatic drugs including prednisone.

Baseline patient and disease characteristics of patients in whom the rheumatologists agreed and disagreed with the allocated treatment were comparable for most parameters. Differences between patients in whom rheumatologists agreed and disagreed with the allocated treatment group were statistically significant for age in the sequential monotherapy group (agreed 55 years, disagree 42 years; P=0.004), for the VAS global health in the step-up combination group (agree 51, disagree 65; P=0.021) and for the number of painful joints in the combination group with prednisone (agree 16, disagree 13; P=0.021).

When comparing the patient and disease characteristics of patients in whom the rheumatologist had an explicite preferrence for either monotherapy or combinationtherapy, several differences were noticed. Patients for whom combination therapy was preferred had a higher ESR (median ESR 49 vs 35; P=0.003), a higher BMI (27 vs 25; P=0.011), and more often were rheumatoid factor positive (87% vs 60%; P=0.012) (Table 2). The higher DAS, a composite measure of ESR, swollen joint count, painful joint count and VAS global health, in patients in whom combination therapy is preferred, can be ascribed to the higher ESR. The physician's assessment of the patient's disease activity on a VAS was higher when combination therapy was preferred (62 versus 51; P=0.004) (Table 2).

Table 2. Patient and disease characteristics for the patients in whom rheumatologists disagreed with the allocated treatment strategy and preferred another initial treatment strategy.

Baseline variables	Preferred initial monotherapy N=102	Preferred initial combination therapy N=30	P-value
Age - yr*	54 ±15	51 ±13	0.319
Female sex, no (%)	68 (67)	17 (57)	0.430
Body mass index*	25 ±3	27 ±4	0.011
Rheumatoid factor positive, no (%)	61 (60)	26 (87)	0.012
Symptom duration - wk†	25 (14-57)	18 (12-33)	0.093
Erythrocyte sedimentation rate - mmhr†	35 (19-47)	49 (33-81)	0.003
Hemoglobin*	8.0 ±0.8	7.7 ±1.2	0.202
Swollen joints†	12 (9-17)	15 (8-21)	0.183
Painful joints†	12 (8-16)	14 (8-20)	0.163
Disease activity score*	4.2 ±0.7	4.7 ±1.0	0.016
HAQ*	1.3 ±0.7	1.5 ±0.7	0.142
VAS pain*	53 ±23	55 ±21	0.702
VAS disease activity*	60 ±22	60 ±24	0.885
VAS global health*	54 ±21	58 ±21	0.409
VAS physician*	51 ±18	62 ±16	0.004
Total Sharp/van der Heijde score†	3.5 (1.5-7.5)	3.5 (1.3-8.0)	0.982
Erosive disease, no (%)	75 (75)	19 (68)	0.587

*Mean ± standard deviation; †median (interquartile range)

Table 3. Odds Ratios with 95% Confidence Interval for the explicit preference of rheumatologists for initial combination therapy over initial monotherapy.

Baseline variables	Odds Ratio	95% Confidence Interval
Erythrocyte sedimentation - mm/hr		
<19.5 (lower quartile)	1.00	
>56 (upper quartile)	1.74	1.09-2.79
Body mass index		
<23.1 (lower quartile)	1.00	
>27.9 (upper quartile)	1.71	1.07-2.72
Rheumatoid factor		
negative	1.00	
positive	4.37	1.42-13.45

The odds ratio for the preference for combination therapy over monotherapy was 1.74 (1.09-2.79) for an ESR above 56 (upper quartile) versus an ESR below 19.5 (lower quartile), the odds ratio was 1.71 (1.07-2.72) for a BMI above 27.9 (upper quartile) versus a BMI below 23.1 (lower quartile), and the odds ratio was 4.37 (1.42-13.45) for a positive versus a negative rheumatoid factor (Table 3).

There were no significant changes in the rheumatologists' preferences for the different treatment strategies over time (data not shown).

DISCUSSION

While recruiting their patients into a study to determine which of four different treatment strategies is most effective in patients with recent onset, active RA, between March 2000 and August 2002 Dutch rheumatologists expressed their preference for sequential monotherapy or step-up combination therapy over initial combination therapy with either high dose tapered prednisone or infliximab. In 88% to 90% of patients allocated to either one of the initial monotherapies rheumatologists agreed with the allocated treatment group, whereas in 43%-48% of patients allocated to either one of the initial combination therapies rheumatologists expressed their preference for initial monotherapy. This preference to start with a single drug is in line with other published reports on prescribing trends in patients with recent onset RA, that also showed that the majority of patients start with a single antirheumatic drug (8;10).

Rheumatologists most often disagreed with the allocated treatment group in patients who were to receive initial combination therapy with infliximab, and if they preferred combination therapy over monotherapy, they never choose initial combination therapy with infliximab. This can be explained by the current standard of care in The Netherlands, where TNF-antagonists are only reimbursed for patients failing on at least two conventional antirheumatic drugs. In addition, at the time the questionnaires were filled in, data on the efficacy of TNF-antagonists in patients with recent onset RA were scarce.

The superior efficacy of initial combination therapy with methotrexate, sulphasalazine and a tapered high dose of prednisone over sulphasalazine was already established at the time of this study (14). Interestingly, although several rheumatologists in our study had previously participated in the COBRA trial, we still noticed a preference for monotherapy over combination therapy. The preference for initial combination therapy was weakly associated with a high ESR and BMI and strongly associated with a positive rheumatoid factor.

In conclusion, despite new therapeutic options and evidence for greater efficacy of combination therapy in patients with recent onset RA, rheumatologists in majority are conservative in their treatment choice and prefer to start with a single antirheumatic drug, except in some rheumatoid factor positive patients with high indices of inflammation. For the successful implementation of new paradigms in the treatment of patients with RA this conservatism requires special attention.

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