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

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Chapter 4

Comparison of treatment strategies in early rheumatoid arthritis

A randomized trial

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Ann Intern Med 2007;146:406-15.

ABSTRACT

Background. In patients with early rheumatoid arthritis, initial combination therapies provide earlier clinical improvement and less progression of joint damage after 1 year compared with initial monotherapies (as demonstrated in the BeSt study).

Objective. To evaluate whether the initial clinical and radiographic efficacy of combination therapies could be maintained during the second year of follow-up in patients with early rheumatoid arthritis.

Design. Randomized, controlled clinical trial with blinded assessors.

Setting. 18 peripheral and 2 university medical centers in The Netherlands.

Patients. 508 patients with early active rheumatoid arthritis.

Intervention. Sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), or initial combination therapy with infliximab (group 4). Trimonthly treatment adjustments were made to achieve low disease activity.

Measurements. Primary end points were functional ability (Health Assessment Questionnaire) and Sharp-van der Heijde Score for radiographic joint damage.

Results. Groups 3 and 4 had more rapid clinical improvement during the first year; all groups improved further to a mean functional ability score of 0.6 (overall, $P = 0.257$) and 42% were in remission (overall, $P = 0.690$) at the end of the second year. Progression of joint damage remained better suppressed in groups 3 and 4 (median scores of 2.0, 2.0, 1.0, and 1.0 in groups 1, 2, 3, and 4, respectively [$P = 0.004$]). After 2 years, 33%, 31%, 36%, and 53% in groups 1 through 4, respectively, were receiving single-drug therapy for initial treatment. There were no significant differences in toxicity.

Limitations. Patients and physicians were aware of the allocated group, and the assessors were blinded.

Conclusions. Currently available antirheumatic drugs can be highly effective in patients with early rheumatoid arthritis in a setting of tight disease control. Initial combination therapies seem to provide earlier clinical improvement and less progression of joint damage, but all treatment strategies eventually showed similar clinical improvements. In addition, combination therapy can be withdrawn successfully and less treatment adjustments are needed than with initial monotherapies.

INTRODUCTION

Over the last few years, the outcome for patients with rheumatoid arthritis has improved considerably (1). Combinations of disease modifying antirheumatic drugs (DMARDs) with corticosteroids and DMARDs with the new tumor necrosis factor-α antagonists seem to suppress the inflammatory process more effectively than single-drug therapy in patients with early (2-11) and established (12-15) disease. This results in less progression of radiographic joint damage and better preservation of physical function compared with single-drug therapy. More recently, tight control of disease activity has been shown to improve outcome (16), and there are indications that outcome is related to adherence to treatment guidelines (17). Whether combination therapy with DMARDs, corticosteroids, or tumor necrosis factor antagonists should be considered for initial treatment in all patients with rheumatoid arthritis or whether such therapy should be reserved for patients who do not respond to monotherapy is unknown. Therefore, the BeSt study (8) evaluated the efficacy of 4 of the most frequently used treatment strategies in a head-to-head comparison: sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with infliximab (group 4). Treatment adjustments were made every 3 months in patients with an insufficient response or a continued good response. During the first year of treatment, initial combination therapy for groups 3 and 4 resulted in more rapid clinical improvement and less progression of joint damage compared with initial monotherapy for groups 1 and 2. In the second year, response to therapy continued to be tightly monitored. Treatment adjustments were made according to the protocol. We evaluated whether the initial clinical and radiographic outcomes could be maintained and what treatment adjustments were needed in each group.

METHODS

Patients

Rheumatologists participating in the Foundation for Applied Rheumatology Research in 18 peripheral and 2 university hospitals in the western part of the Netherlands designed and conducted the BeSt study. Between April 2000 and August 2002, we recruited patients with early rheumatoid arthritis who fulfilled the American College of Rheumatology (ACR) 1987 criteria for rheumatoid arthritis (18). Patients were 18 years of age or older; had a disease duration of 2 years of less; had active disease with at least 6 of 66 swollen joints and at least 6 of 68 tender joints; and had an erythrocyte sedimentation rate of 28 mm/hr or greater or a global health score of 20 mm or more (on a visual analog scale of 0 mm [best] to 100 mm [worst]). Patient enrollment criteria have been described in detail previously (8). The Medical Ethics Committee at each participating center approved the study protocol, and all patients gave written informed consent before inclusion.

Treatment protocol

Patients were allocated to 1 of 4 treatment groups by variable block randomization (9-13), which was stratified per center. Treatment groups were sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with infliximab (group 4). For patients who did not respond to medication, the protocol prescribed many subsequent steps. The decision of whether to adjust medication was made every 3 months on the basis of the disease activity score (19), a continuous measure consisting of the Ritchie articular index and number of swollen joints in a 44-joint count, erythrocyte sedimentation rate, and global health as measured on a visual analog scale. A disease activity score of 2.4 or less indicates low disease activity (20). A research nurse who remained blinded for the allocated treatment group during the study period calculated the score. If the disease activity score was greater than 2.4 (insufficient response), the treating physician immediately adjusted therapy by proceeding to the next step in the allocated treatment group. If the disease activity score was 2.4 or less for at least 6 months, medication was gradually withdrawn until 1 drug remained in a maintenance dose.

Patients in group 1 started with methotrexate, followed subsequentially by sulphasalazine, leflunomide, methotrexate with infliximab, gold with methylprednisolone (intramuscular), methotrexate with cyclosporine A and prednisone, and azathioprine with prednisone. Patients in group 2 started with methotrexate, followed subsequently by methotrexate with sulphasalazine, methotrexate with sulphasalazine and hydroxychloroquine, methotrexate with sulphasalazine, hydroxychloroquine and prednisone, methotrexate with infliximab, methotrexate with cyclosporine A and prednisone, leflunomide, and azathioprine with prednisone. Patients in group 3 started with the combination of methotrexate, sulphasalazine, and tapered high-dose prednisone (2), followed subsequently by methotrexate with cyclosporine A and prednisone, methotrexate with infliximab, leflunomide, gold with methylprednisolone, and azathioprine with prednisone. Patients in group 4 started with the combination of methotrexate and infliximab, followed subsequently by sulphasalazine, leflunomide, methotrexate with cyclosporine A and prednisone, gold with methylprednisolone, and azathioprine with prednisone. In addition to the regular trimonthly assessments, we calculated additional disease activity scores every 8 weeks in all patients who were treated with infliximab in the week before infusion. On the basis of these scores, we decided whether to increase of taper the dosage. The treatment protocol and dose regimen have been described in detail previously (8).

We permitted concomitant treatment with nonsteroidal anti-inflammatory drugs and intra-articular injections with corticosteroids and did not allow other parenteral corticosteroids. We allowed DMARDs or oral corticosteroids only as dictated by the treatment protocol. All patients received folic acid, 1 mg per day, during treatment with methotrexate.

Study end points and assessments

The primary efficacy end point was functional ability, as measured by the Dutch Health Assessment Questionnaire. Higher scores indicated more severe loss of physical function (21). Secondary efficacy end points were 20% and 70% improvement according to the ACR (ACR20 and ACR70, respectively) response criteria (22) and clinical remission, defined as a disease activity score less than 1.6 (23). Assessments were done every 3 months by blinded research nurses, who were trained at study onset and every 6 months thereafter to maintain consistency. Two study physicians ensured adherence to the protocol every 3 months. All protocol deviations were recorded. Patients were not informed about study outcomes until the end of the second year of follow-up.

The primary radiographic end point was the change in the total Sharp-van der Heijde score for joint damage, which ranged from 0 to 448, over 2 years (24). Two trained readers independently scored the radiographs of hands, wrists and feet at baseline and at the 2-year follow-up. The patient's identity, treatment group, and sequence of the films in sets were masked to the readers (JV and YG). We used the mean score of the 2 readers for the analysis. The intra-observer coefficients were 0.90 and 0.91, and the interobserver coefficient was 0.94. Erosive disease was defined as a mean erosion score greater than 0.5.

Toxicity

We performed physical examination and laboratory tests and recorded all adverse events at all visits. If necessary, the treating physician adjusted the patient's medication as outlined previously. Serious adverse events were defined as an adverse reaction resulting in any of the following outcomes: a life-threatening condition or death, substantial or permanent disability, malignant disease, hospitalization or prolongation of hospitalization, or a congenital abnormality or birth defect.

Before beginning infliximab therapy, all patients were evaluated for tuberculosis with a purified protein derivative skin test and chest radiography. In the beginning of 2002, congestive heart failure was added as a contraindication for treatment with infliximab. Previously enrolled patients with heart failure - functional classes I, II, III, and IV concomitant congestive heart failure, as defined by the New York Heart Association- who had already received infliximab continued this therapy and were closely monitored (25). If these patients' conditions seemed to be worsening, treatment with infliximab was discontinued, Worsening was defined as every transition to a higher functional class.

Statistical analysis

We needed a sample size of 468 patients (117 per group) to ascertain 80% power to detect a difference of at least 0.2 in the Health Assessment Questionnaire score. This was set as a clinically relevant difference with a 5% significance level and adjustment for multiple comparisons between groups, assuming a SD of 0.45. The sample size also ensured greater than 80% power to detect a difference of 20% or greater in the change in score for

radiographic joint damage. We performed intention-to-treat analyses. When appropriate, we analyzed outcomes with a 1-way analysis of variance (post hoc, least significant difference test for primary outcomes and Tukey test for secondary outcomes to correct for multiple comparisons), Kruskal-Wallis test (post hoc Mann-Whitney U test), and chi-square test.

We performed longitudinal data analysis of the primary outcomes with linear mixed-effects models with therapy group, time, and their interaction as fixed effects and center as a random effect. We did not make parametric assumptions regarding the change in pattern over time. Because all measurements were done at fixed times, we considered, in addition to the center as the random effect, different association models for the covariance structure between the repeated measures of the primary outcomes and used the structure with the lowest Akaike information criterion value. We found that the Health Assessment Questionnaire (HAQ) score was a first-order, autoregressive model with heterogeneous variances and that the Sharp-van der Heijde score for radiographic joint damage was an unstructured covariance matrix. We investigated the baseline variables of sex, age, body mass index, rheumatoid factor positivity, disease activity score, HAQ score, and total Sharp-van der Heijde score for radiographic joint damage separately as fixed covariates for potential effect modifiers and confounders potentials and their interactions with time and therapy group in the mixed-effects model.

Role of the funding sources

This study was funded by a grant from the Dutch College of Health Insurances (College voor zorgverzekeringen). Schering-Plough, B.V. and Centocor, Inc. provided additional funding and supplied the medication for patients in group 4. The funding sources had no role in study design; collection, analyses, and interpretation of all data; writing the article; and the decision to submit the manuscript for publication.

RESULTS

We randomly assigned a total of 508 patients to receive sequential monotherapy (group 1, $n = 126$), step-up combination therapy (group 2, $n = 121$), initial combination therapy with prednisone (group 3, $n = 133$), or initial combination therapy with infliximab (group 4, $n = 128$) (Figure 1). At baseline, the groups were balanced with respect to the demographic and disease characteristics (Table 1). Enrolled patients had a median disease duration of 23 weeks (interquartile range, 14 to 53 weeks) and had active disease with mean disease activity and HAQ scores of 4.4 (SD, 0.9) and 1.4 (SD, 0.7), respectively. Seventy-two percent of patients had joint erosions at baseline. Over time, 27 patients who were equally distributed across the treatment groups ($P = 0.474$) were lost to follow-up: 12 withdrew consent (7 declined follow-up, 4 discontinued all medications despite having no adverse events, and 1 moved from the area), 7 had a revised diagnosis, 1 discontinued treatment because of an adverse event, 4 died, and 3 were lost to follow-up for other reasons (2 were admitted to a nursing home and 1 wanted to become pregnant)

(Figure 1). Furthermore, 12 (10%), 11 (9%), 14 (11%), and 6 (5%) patients in groups 1, 2, 3, and 4, respectively ($P = 0.343$), did not adhere to the treatment protocol but were included in the intention-to-treat analysis.

Table 1. Baseline Characteristics *

Characteristic	Sequential monotherapy (Group 1)	Step-up combination therapy (Group 2)	Initial combination with prednisone (Group 3)	Initial combination with infliximab (Group 4)
Mean age (SD), *y*	54 (13)	54 (13)	55 (14)	54 (14)
Women, *n (%)*	86 (68)	87 (72)	88 (66)	85 (66)
Median time from diagnosis (IQR), *wk*	2 (1-5)	2 (1-4)	2 (1-4)	3 (1-5)
Median symptom duration (IQR), *wk*	23 (14-54)	26 (14-56)	23 (15-53)	23 (13-46)
Rheumatoid factor positive – *n (%)*	84 (67)	77 (64)	86 (65)	82 (64)
Mean disease activity score (SD)	4.5 (0.9)	4.5 (0.8)	4.4 (0.9)	4.3 (0.9)
Mean health assessment questionnaire score (SD)	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.7)
Total Sharp-van der Heijde score				
Mean (SD)	7.3 (9.5)	6.3 (6.9)	5.9 (6.5)	7.0 (10.0)
Median (IQR)	3.5 (1.5-9.5)	5.0 (1.5-8.1)	3.5 (1.5-8.5)	4.0 (1.5-8.5)
Erosion score				
Mean (SD)	4.1 (6.2)	3.5 (4.3)	3.3 (4.3)	3.9 (5.8)
Median (IQR)	2.0 (0.5-4.5)	2.0 (0.5-4.5)	2.0 (0.5-4.5)	2.0 (0.5-5.0)
Narrowing score				
Mean (SD)	3.2 (4.9)	2.8 (3.2)	2.6 (3.2)	3.1 (5.2)
Median (IQR)	1.0 (0.0-4.0)	2.0 (0.0-4.5)	1.5 (0.0-4.0)	1.5 (0.0-3.5)
Erosive diseae, *n (%)*	89 (72)	82 (70)	93 (71)	93 (73)

*Baseline radiographs were available for 123, 118, 131, and 127 patients in groups 1, 2, 3 and 4, respectively. There were 126, 121, 133, and 128 patients in groups 1 to 4, respectively. IQR = interquartile range.

Therapy

Seventy-nine percent of patients in all groups achieved the predefined goal of low disease activity (disease activity score ≤ 2.4) (overall, $P = 0.554$). To accomplish this goal, more patients in groups 1 and 2 required treatment adjustments than in groups 3 and 4 (67%, 69%, 42%, and 28%, respectively) (Figure 2). Most patients in groups 3 and 4 who responded well to the initial combination of drugs were eventually maintained on only 1 drug. Thus, at the 2-year follow-up, 33%, 31%, 36%, and 53% of patients in groups 1 through 4, respectively, were taking a single drug as initial treatment. At the same time, 27%, 7%, 13%, and 18% of patients, respectively, received the combination of methotrexate and infliximab, which could be given to patients who were not responding to their medication no earlier than 12 months in group 1, 15 months in group 2, and 9 months in group 3 as dictated by the treatment protocol.

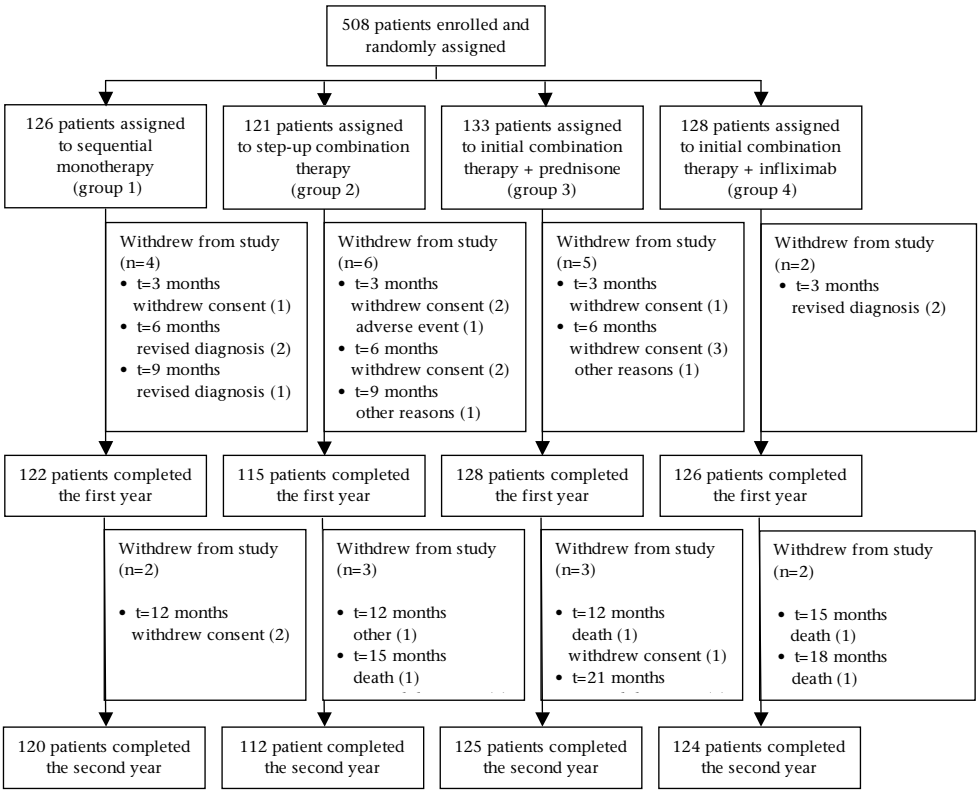


Figure 1. Study flow diagram.
Revised diagnoses in the first year were paraneoplastic arthritis, gout, systemic lupus erythematosus, mixed connective tissue disease, Henoch Schonlein purpura. Revised diagnoses in the second year were gout and sclerodermia. Causes of death were cerebrovascular accident (group 2), ovarian cancer (group 3), myocardial infarction (group 4) and disseminated tuberculosis (group 4).

Clinical efficacy

During the first year of treatment, patients in groups 3 and 4 regained physical function, as measured by the HAQ, substantially earlier than patients in groups 1 and 2 (9). During the second year, physical function improved further in all groups, resulting in a 2-year change in scores of 0.7, 0.8, 0.9, and 0.9 in groups 1 through 4, respectively (mean overall change, 0.6, [$P = 0.257$]) (Table 2). The percentage of patients in clinical remission increased from 31% after the first year to 42% after the second year (overall at 2 years, $P = 0.690$) (Figure 3). A total of 22%, 21%, 28%, and 40% of patients in groups 1 through 4, respectively, achieved a continued low disease activity score (≤ 2.4 from 6 to 24 months).

Radiographic efficacy

Radiographs of the hands, wrists, and feet at baseline and at 2 year follow-up of 455 patients were available for analysis (111 [88%] in group 1, 105 [87%] in group 2, 123 [92%] in group 3, and 116 [91%] in group 4). The treatment groups had similar baseline radiographic joint damage (Table 1).

The patients in groups 3 and 4 had less progression of radiographic joint damage than that of those in groups 1 and 2. The median increase in total Sharp-van der Heijde score was 2.0, 2.0, 1.0, and 1.0 in groups 1 through 4, respectively (group 1 vs. 2, P = 0.850; group 1 vs. 3, P = 0.043; group 1 vs. 4, P = 0.014; group 2 vs. 3, P = 0.006; group 2 vs. group 4, P = 0.004; group 3 vs. 4, P = 0.798) (Table 2). Fewer patients in groups 3 and 4 had severe progression of the total Sharp-van der Heijde score compared with those in groups 1 and 2. An increase in total Sharp-van der Heijde score of more than 20 points in 2 years was seen in 18 patients, 7 patients, 1 patient, and 1 patient in groups 1 through 4 respectively (Figure 4).

Mixed-model analysis

In the mixed-model analysis, groups 3 and 4 had significantly better HAQ scores over time than those of groups 1 and 2, and group 4 had better scores than those of group 3 (all pairwise comparisons between groups 1 or 2 and groups 3 or 4, $P < 0.001$; group 3 vs. group 4, P = 0.021; and group 1 vs. group 2, P = 0.573). Groups 3 and 4 also had less progression of the Sharp-van der Heijde score for radiographic joint damage over time than groups 1 and 2, and group 2 had less progression than group 1 (group 1 vs. group 2, P = 0.044; group 1 vs. groups 3 and 4, $P < 0.001$; group 2 vs. group 3, P = 0.008; group 2 vs. group 4, P = 0.009; group 3 vs. group 4, P = 0.734). We found an association among HAQ scores, sex, baseline disease activity score, and body mass index and an association between the Sharp-van der Heijde scores and age. None of these potential effect-modifying variables significantly changed outcomes.

Adverse events

Overall, 210 (41%) patients and 193 (38%) patients had at least 1 adverse event in the first and second year, respectively. The mean number of adverse events per patient was 1.9 (SD, 1.2) in the first year and 1.8 (SD, 1.2) in the second year. Most adverse events were classified as mild to moderate and lead to discontinuation or dose reduction of antirheumatic drugs in less than 11% of patients. Gastrointestinal adverse events were the most frequently reported events during the 2 years of follow-up . During the second year of follow-up, 14 (12%), 11 (9%), 12 (9%), and 15 (12%) patients in groups 1 through 4, respectively, had mild to moderate gastrointestinal events, including elevated liver enzyme levels. At least 5% of patients of groups 1 through 4 had other

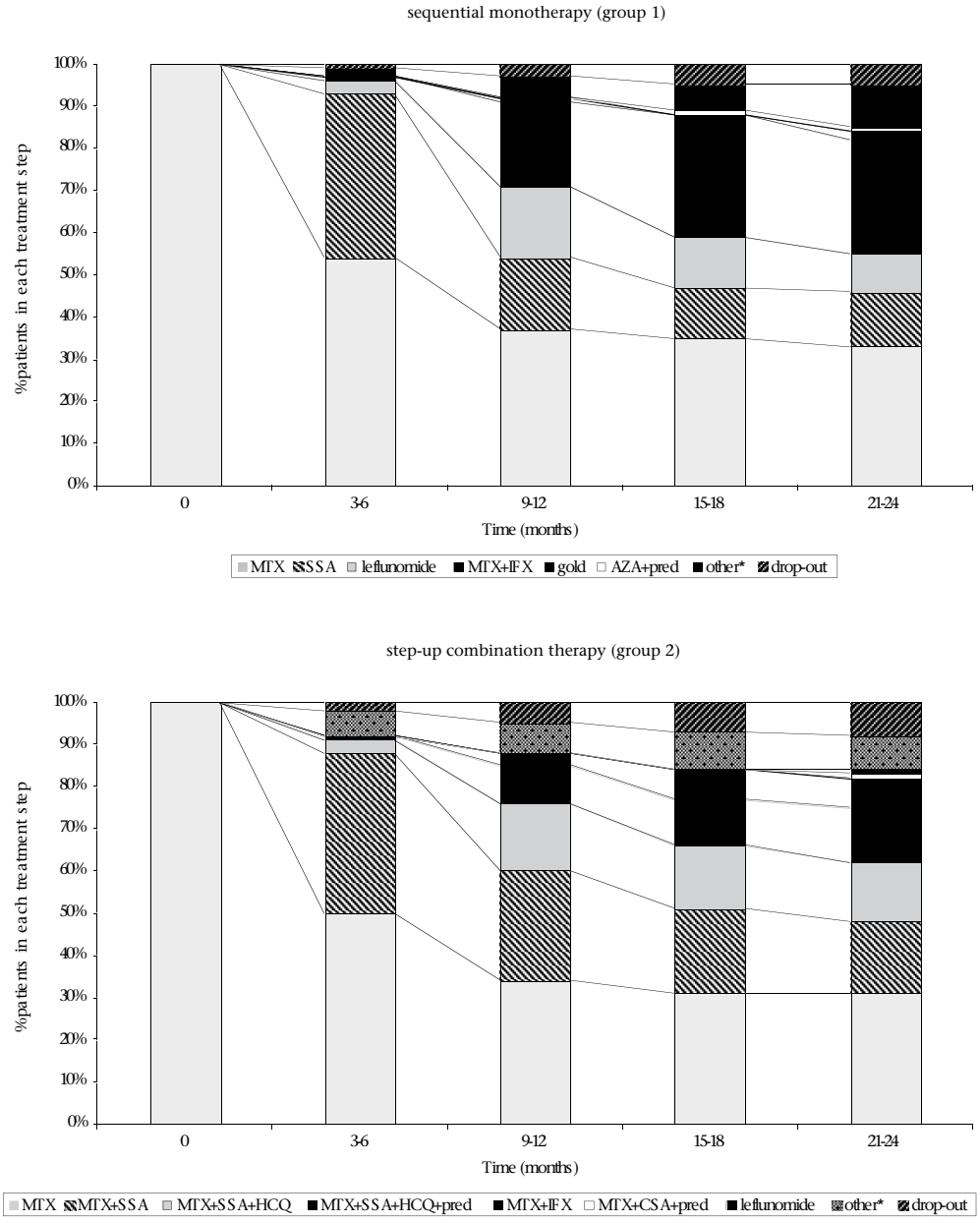
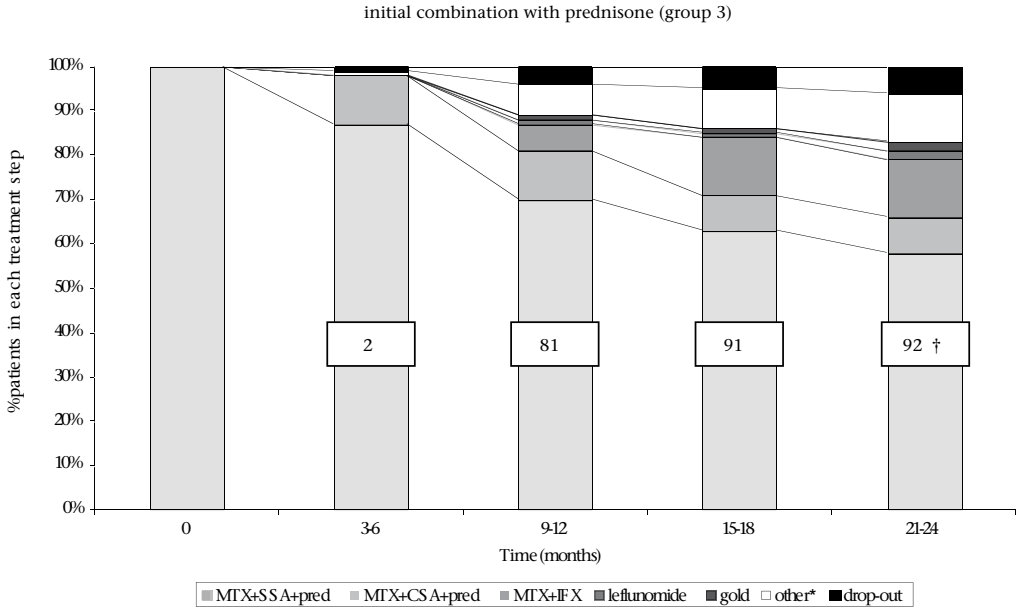
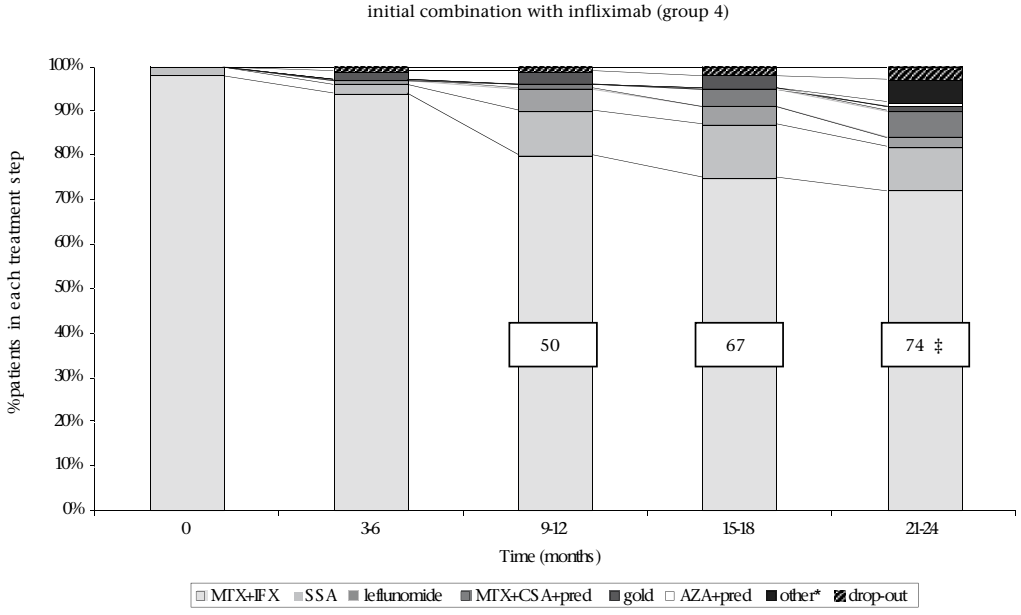
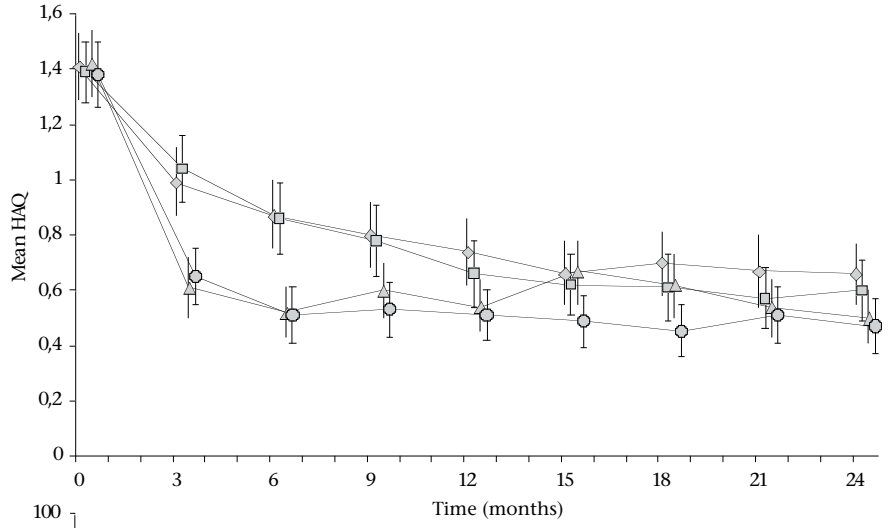


Figure 2. Treatment of patients during the second year of follow-up.
*Percentage of patients that lost adherence to the treatment protocol. †Percentage of patients in the initial combination treatment group who discontinued prednisone (pred), because of a sustained disease activity score ≤ 2.4;





‡Percentage of patients in the initial combination treatment group who discontinued infliximab (IFX), because of a sustained disease activity score ≤ 2 .4.
MTX=methotrexate, SSA=sulphasalazine, HCQ=hydroxychloroquine, CSA=cyclosporine A, AZA=azathioprine.


Mean HAQ
1,6
1,4
1,2
1
0,8
0,6
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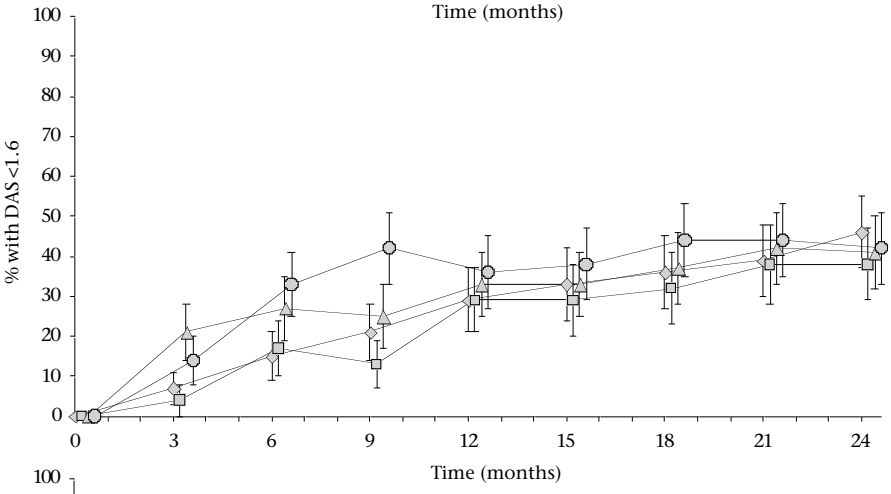
0,2
0
0
3
6
9
12
15
18
21
24
Time (months)


% with DAS <1.6
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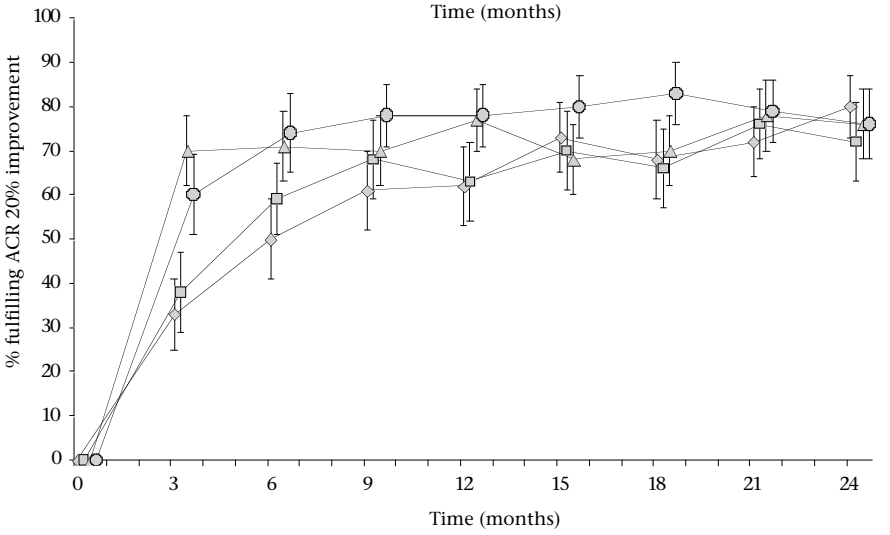
Time (months)


% fulfilling ACR 20% improvement
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Time (months)

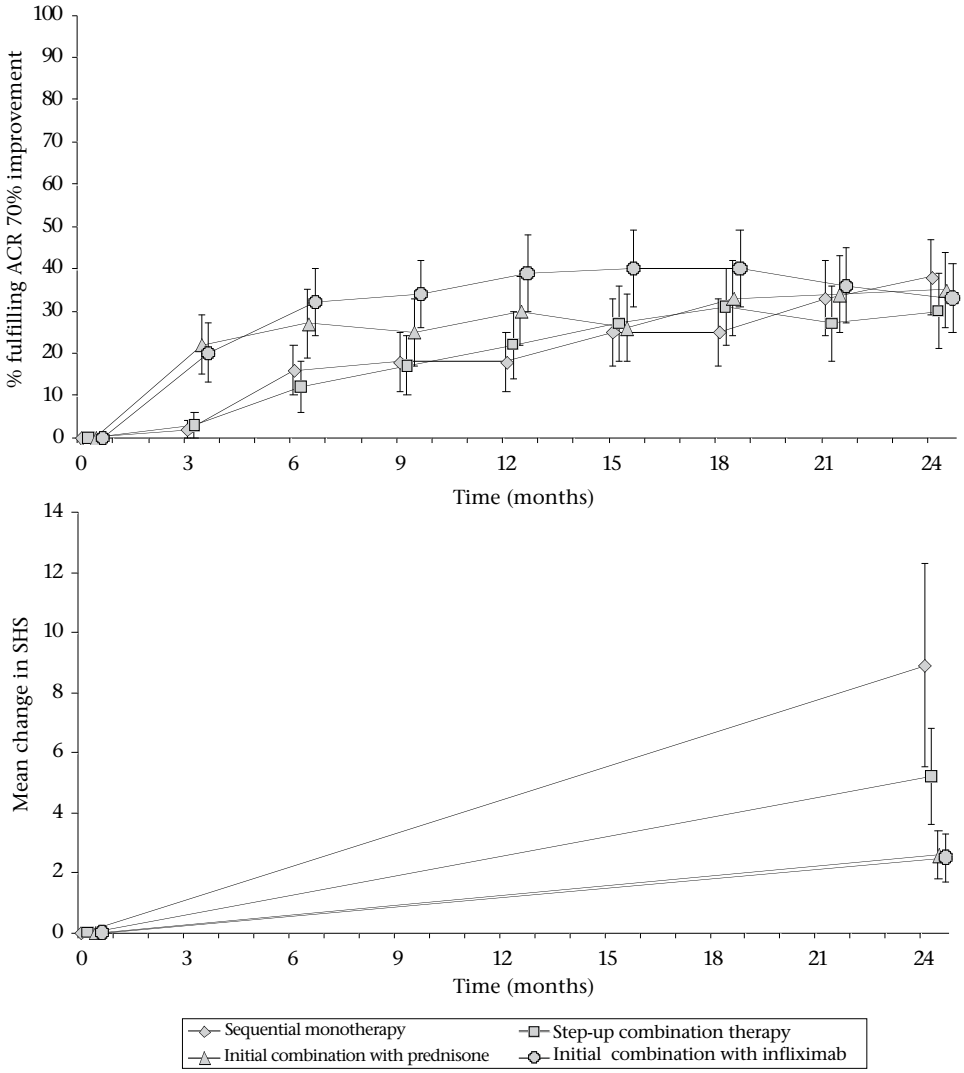

Figure 3. Clinical and radiographic efficacy outcomes during 2 years of follow-up.
The error-bars indicate the 95% confidence intervals. HAQ=Health Assessment Questionnaire. A disease activity score (DAS) <1.6 indicated clinical remission; ACR20 and ACR70 indicated 20% and 70% improvement, respectively, according to the American College of Rheumatology (ACR) criteria. SHS = Sharp-van der Heijde score for radiographic joint damage.

Table 2. Primary patient outcomes during 2 years of follow-up*

Mean improvement in health assessment questionnaire compared with baseline (SD)					
	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab	P Value
3 months	0.4 (0.6)	0.3 (0.6)	0.8 (0.7)	0.7 (0.6)	<0.001†
6 months	0.5 (0.7)	0.5 (0.7)	0.9 (0.7)	0.8 (0.6)	<0.001†
9 months	0.6 (0.7)	0.6 (0.7)	0.8 (0.7)	0.8 (0.6)	0.010†
12 months	0.7 (0.7)	0.7 (0.7)	0.9 (0.7)	0.9 (0.7)	0.031‡
15 months	0.7 (0.7)	0.8 (0.7)	0.7 (0.8)	0.9 (0.7)	0.299
18 months	0.7 (0.7)	0.8 (0.7)	0.8 (0.8)	0.9 (0.7)	0.255
21 months	0.7 (0.7)	0.8 (0.7)	0.8 (0.7)	0.9 (0.7)	0.220
24 months	0.7 (0.7)	0.8 (0.7)	0.9 (0.7)	0.9 (0.7)	0.257
Progression of Sharp-van der Heijde score compared with baseline					
Total score					
Mean (SD)	9.0 (17.9)	5.2 (8.1)	2.6 (4.5)	2.5 (4.6)	0.005†
Median (IQR)	2.0 (0.0-8.6)	2.0 (0.3-7.0)	1.0 (0.0-2.5)	1.0 (0.0-3.0)	
Erosion score					
Mean (SD)	4.7 (9.0)	3.1 (5.0)	1.1 (2.2)	1.3 (2.7)	<0.001†
Median (IQR)	1.5 (0.0-5.6)	1.0 (0.0-5.3)	0.5 (0.0-2.0)	0.5 (0.0-2.0)	
Narrowing score					
Mean (SD)	4.3 (9.8)	2.1 (3.8)	1.5 (3.2)	1.2 (2.9)	0.072
Median (IQR)	0.0 (0.0-3.5)	0.5 (0.0-3.0)	0.0 (0.0-1.5)	0.0 (0.0-1.5)	

*IQR = interquartile range; † $P < 0.050$ for all comparisons between groups 1 and 2 versus groups 3 and 4; ‡ $P < 0.050$ for group 1 versus groups 3 and 4.

mild adverse events, including skin rash or other mild dermal or mucosal events in 12 (10%), 10 (8%), 15 (11%), and 7 (6%) patients, respectively; infections in 10 (8%), 10 (8%), 10 (8%), and 13 (10%) patients, respectively; and cardiovascular events 5 (4%), 5 (4%), 9 (7%), and 8 (6%) patients, respectively. In the second year, we observed 3 reactions to infliximab infusions (1 in group 1 and 2 in group 3). One infusion reaction in group 3 resulted in the patient being hospitalized overnight for observation of mild dyspnea and facial redness.

Serious adverse events were reported in 8, 9, 17, and 6 patients in groups 1 through 4, respectively, during the first year. A detailed description of these events has been published previously (9). During the second year, 56 serious adverse events were reported (16 events [13 patients] in group 1, 10 events [10 patients] in group 2, 17 events [11 patients] in group 3, and 13 events [8 patients] in group 4). In group 1, serious adverse events included (hospitalization for) atrial fibrillation, myocardial infarction, coronary artery bypass surgery, syncope, pyelonephritis, viral infection, perforated gastric ulcer, pleural effusion, ovarian cyst, methotrexate intoxication, malaise, and depressive symptoms in 1 patient each, and pneumonia in 1 patient, *Legionella* pneumonia in 1 patient, and malignant disease--basal-cell carcinoma and renal-cell carcinoma—in 1 patient each. In group 2, serious adverse events included (hospitalization for) pacemaker implantation, pneumonia, symptomatic gallstone

disease, surgery for carpal tunnel syndrome, complicated calcaneal fracture, uterus extirpation, and malignant prostate cancer in 1 patient each and placement of total hip prostheses in 2 patients. One patient in group 2 died because of a cerebrovascular event. In group 3, serious adverse events included (hospitalization for) implantation of intracardiac device, syncope due to aortic valve dysfunction, limb amputation due to occlusion of femoral artery, pyelonephritis, viral infection, oral infectious ulcer, interstitial lung disease with respiratory failure, dyspnea during infliximab infusion, retinal hemorrhage, scleroderma, active rheumatoid arthritis, and 1 malignant, ovarian cancer (which resulted in death) in 1 patient each and placement of total hip prostheses in 2 patients. One patient had 2 retinal detachments. In group 4, serious adverse events included (hospitalization for) myocardial infarction, unstable angina pectoris, septic arthritis, gastrointestinal bleeding, cholecystectomy, placement of total knee prosthesis, placement of elbow prosthesis, active rheumatoid arthritis, and basal-cell carcinoma in 1 patient each. One patient had 4 episodes of disseminated tuberculosis. In group 4, 1 patient died of myocardial infarction and 1 died of disseminated tuberculosis. The patient who died from tuberculosis had positive results on purified protein derivative skin test (12-mm nodule) and an adhesive intrapulmonary lesion on the baseline chest radiograph. Six months of isoniazid prophylaxis was given, as recommended by the local guidelines at that time. One year after discontinuation of isoniazid therapy, while receiving methotrexate, 25 mg/week, and infliximab, 10mg/kg, every 8 weeks, the patient received a diagnosis of meningitis tuberculosa, pulmonary *Aspergillus* infection, and mucocutaneous herpes simplex virus 2 infection (26). After a complicated disease course and several readmissions to the hospital, the patient died of septicemia with diffuse coagulation disorder and liver failure 7 months later.

DISCUSSION

The BeSt study has shown that a remarkable improvement of clinical signs and symptoms in patients with recent-onset rheumatoid arthritis can be achieved by using currently available drugs when treatment adjustments are made systematically and according to disease activity measurements. In all 4 treatment strategies studied, 29% to 36% of patients achieved clinical remission (disease activity score < 1.6) after the first year of therapy, which increased to 38% to 46% after the second year. Seventy-nine percent of patients achieved the goal of low disease activity (disease activity score ≤ 2.4) after 2 years. In addition, functional ability improved and progression of joint damage was suppressed effectively with all treatment strategies. Compared with previous trials reporting a median Sharp-van der Heijde score progression of 3.2 to 12 over 1.5 to 2 years for patients with early rheumatoid arthritis who receive monotherapy (2,6,12), we observed the median progression of 2.0 in our groups with initial monotherapy (groups 1 and 2), suggesting effective suppression in these patients. Because of consequent monitoring and adjustment of medications, which

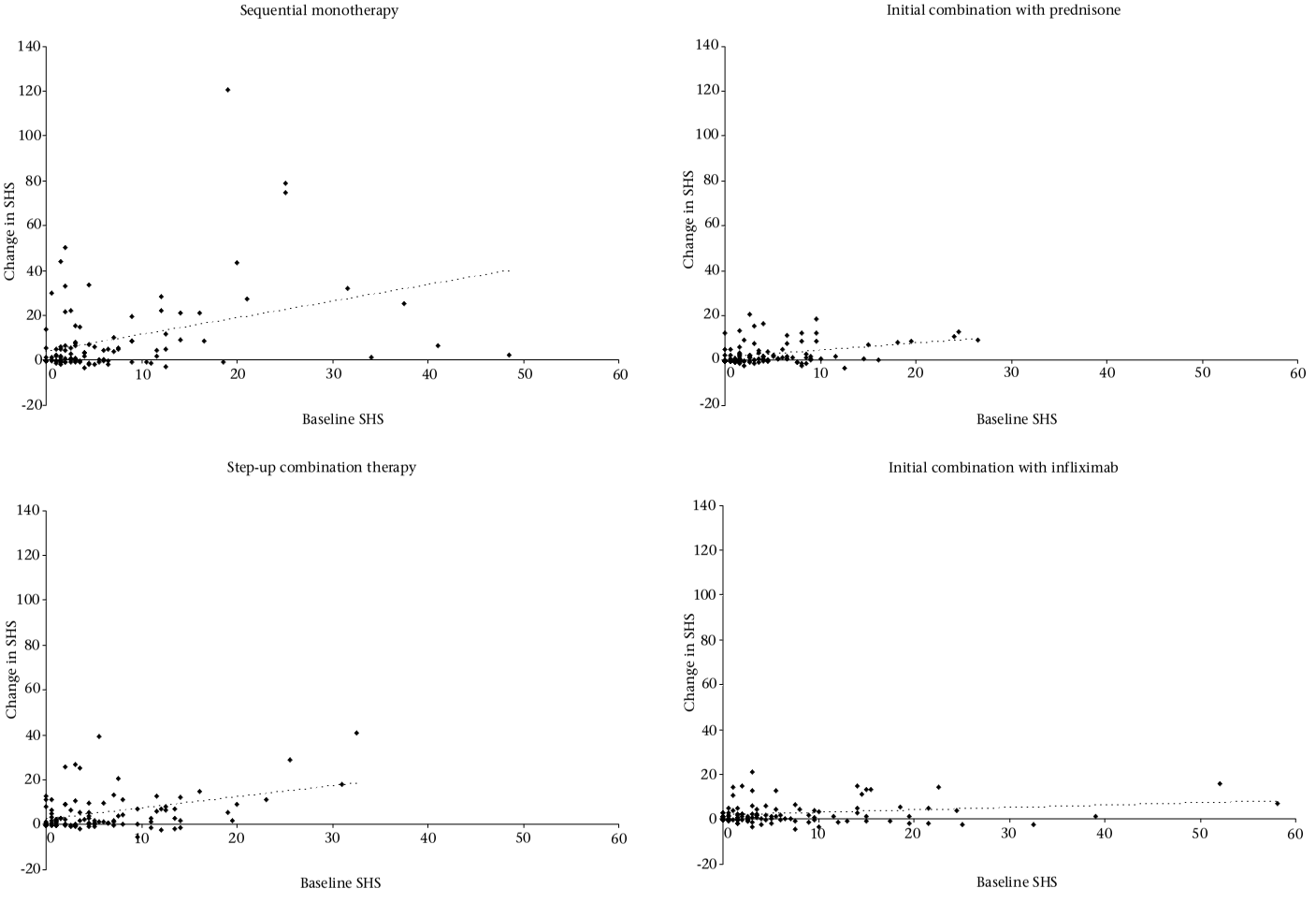

Figure 4. Median change by baseline total Sharp-van der Heijde score (SHS) for the 4 treatment groups. The dotted lines are regression lines.

is more dynamic than in current daily practice, patients in groups 1 and 2 achieved almost the same improvement in disease activity and functional ability after 2 years as those who started with combination therapy (groups 3 and 4). Medication had to be adjusted more often in patients in groups 1 and 2 than in patients in groups 3 and 4 to achieve this improvement. As a result, even more patients in the initial combination groups were successfully treated with monotherapy than those who were treated with initial monotherapy after 2 years.

During the first year of treatment, patients in groups 3 and 4 achieved lower levels of disease activity than did those in groups 1 and 2. Patients in groups 3 and 4 also had less radiographic progression of joint damage after 2 years. In particular, severe progression was seen less often in groups 3 and 4 than in groups 1 and 2 despite the high baseline Sharp-van der Heijde score (median, 4) and erosion percentage (72%). The traditionally observed linear association between baseline damage and progression of damage over time was seen in group 1, was less acute in group 2, and was not seen in groups 3 and 4. One may argue the significance of the differences in disease outcomes between the initial combination therapy strategies and the strategies starting with initial monotherapy when tight disease control is applied. We conclude that the difference in disease activity during the first year is clinically relevant and will probably have an economic impact. Patients with active disease are known to discontinue working, and the success of reintegration into the workforce is inversely related to the duration of sick leave (27). The clinical relevance of the difference in joint damage progression is less clear. The small difference observed has not translated into differences in functional capacity. In the years after the 2-year observation period, tight disease control in the patients with initial monotherapy may lead physicians to prescribe combination therapy. Further progression of joint damage, similar to that observed in patients who started treatment with combination therapy, would be suppressed. However, intense suppression of rheumatoid arthritis activity as early as possible may result in more mild disease and less joint destruction. Long-term follow-up of our patient groups with respect to functional and radiographic outcomes will provide more insight.

The therapeutic advantage of initial combination therapy is not counterbalanced with increased toxicity. Vigilance in recognizing and treating serious infections is necessary, as demonstrated by the case of 1 patient in our study. The risk of reactivation of tuberculosis in patients who start tumor necrosis factor-α blocking therapies warrants screening and treatment for tuberculosis according to local guidelines.

On the basis of these results, we recommend that physicians increase their targets regarding suppression of disease activity and prevention of joint damage in patients with recent-onset rheumatoid arthritis. With intensive and objective monitoring of disease activity and adjustments of therapy, low disease activity is a realistic goal that can be achieved with all treatment strategies. Initial combination treatment with tapered high-dose prednisone, methotrexate and sulphasalazine, or infliximab and methotrexate seems to be the best choice to rapidly achieve this goal in patients with active rheumatoid arthritis of recent onset.

Acknowledgments

The authors thank the following participants of the Foundation for Applied Rheumatology Research for their contribution to the design and the conduct of the study: M.H.W. de Bois MD, Medical Center Haaglanden, The Hague; G. Collée MD, Medical Center Haaglanden, The Hague; A.H. Gerards MD, Vlietland Hospital, Schiedam; B.A.M. Grillet MD, De Honte Hospital, Terneuzen; J.H.L.M. van Groenendael MD, Franciscus Hospital, Roosendaal; K.H. Han MD, Medical Center Rijnmond Zuid, Rotterdam; H.M.J. Hulsmans MD, Haga Hospital, The Hague; M.H. de Jager MD, Albert Schweitzer Hospital, Dordrecht; M.V. van Krugten MD, Walcheren Hospital, Vlissingen; H. van der Leeden (retired); W.F. Lems MD, Slotervaart Hospital, Amsterdam; M.F. van Lieshout-Zuidema MD, Spaarne Hospital, Hoofddorp; A. Linssen MD, Kennemer Gasthuis, Haarlem; P.A.H.M. van der Lubbe MD, Vlietland Hospital, Schiedam; H.K. Markusse (deceased); H.K. Ronday MD, Haga Hospital, The Hague; D. van Schaardenburg MD, VU Medical Center, Amsterdam and Jan van Breemen Institute, Amsterdam; P.E.H. Seys MD, Lievensberg Hospital, Bergen op Zoom; R.M. van Soesbergen (retired); I. Speyer MD, Bronovo Hospital, The Hague; J.P. Terwiel MD, Spaarne Hospital, Hoofddorp; A.E. Voskuyl MD, VU Medical Center, Amsterdam; M.L. Westedt MD, Bronovo Hospital, The Hague; S. ten Wolde MD, Kennemer Gasthuis, Haarlem.

Grant support

A government grant of the Dutch College of Health Insurance Companies was provided, with additional grants of Schering-Plough B.V. and Centocor, Inc. who also supplied infliximab study medication for patients in group 4.

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