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Clinical and Radiographic Outcomes of Four Different Treatment Strategies in Patients With Early Rheumatoid Arthritis (the BeSt Study)

A Randomized, Controlled Trial

Y. P. M. Goekoop-Ruiterman,[1] J. K. de Vries-Bouwstra,[2] C. F. Allaart,[1] D. van Zeben,[3] P. J. S. M. Kerstens,[4] J. M. W. Hazes,[5] A. H. Zwinderman,[6] H. K. Ronday,[7] K. H. Han,[8] M. L. Westedt,[9] A. H. Gerards,[10] J. H. L. M. van Groenendael,[11] W. F. Lems,[12] M. V. van Krugten,[13] F. C. Breedveld,[1] and B. A. C. Dijkmans[14]

Objective. **Several treatment strategies have proven value in the amelioration of rheumatoid arthritis (RA), but the optimal strategy for preventing long-term joint damage and functional decline is unclear. We undertook this study to compare clinical and radiographic outcomes of 4 different treatment strategies, with intense monitoring in all patients.**

Methods. **In a multicenter, randomized clinical trial, 508 patients were allocated to 1 of 4 treatment strategies: sequential disease-modifying antirheumatic drug monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with the tumor necrosis factor antagonist infliximab (group 4). Treatment adjustments were made every 3 months in an effort to obtain low disease activity (a Disease Activity Score in 44 joints of ≤2.4).**

Results. **Initial combination therapy including either prednisone (group 3) or infliximab (group 4) resulted in earlier functional improvement than did sequential monotherapy (group 1) and step-up combination therapy (group 2), with mean scores at 3 months on the Dutch version of the Health Assessment Questionnaire (D-HAQ) of 1.0 in groups 1 and 2 and 0.6 in groups 3 and 4 ($P < 0.001$). After 1 year, mean D-HAQ scores were 0.7 in groups 1 and 2 and 0.5 in groups 3 and 4 ($P = 0.009$). The median increases in total Sharp/Van der Heijde radiographic joint score were 2.0, 2.5, 1.0, and 0.5 in groups 1–4, respectively ($P < 0.001$). There were no significant differences in the number of adverse events and withdrawals between the groups.**

Conclusion. **In patients with early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy.**

Over the last 2 decades, the treatment of patients with rheumatoid arthritis (RA) has changed considerably. Currently, the goal of therapy is not only symptom

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[1]Y. P. M. Goekoop-Ruiterman, MD, C. F. Allaart, MD, F. C. Breedveld, MD: Leiden University Medical Center, Leiden, The Netherlands; [2]J. K. de Vries-Bouwstra, MD: VU Medical Center, Amsterdam, The Netherlands; [3]D. van Zeben, MD: Sint Franciscus Gasthuis, Rotterdam, The Netherlands; [4]P. J. S. M. Kerstens, MD: Jan van Breemen Institute, Amsterdam, The Netherlands; [5]J. M. W. Hazes, MD: Erasmus Medical Center, Rotterdam, The Netherlands; [6]A. H. Zwinderman, MD: Academic Medical Center, Amsterdam, The Netherlands; [7]H. K. Ronday, MD: Haga Hospital, The Hague, The Netherlands; [8]K. H. Han, MD: Medical Center Rijnmond-Zuid, Rotterdam, The Netherlands; [9]M. L. Westedt, MD: Bronovo Hospital, The Hague, The Netherlands; [10]A. H. Gerards, MD: Vlietland Hospital, Schiedam, The Netherlands; [11]J. H. L. M. van Groenendael, MD: Franciscus Hospital, Roosendaal, The Netherlands; [12]W. F. Lems, MD: Slotervaart Hospital, Amsterdam, The Netherlands; [13]M. V. van Krugten, MD: Walcheren Hospital, Vlissingen, The Netherlands; [14]B. A. C. Dijkmans, MD: VU Medical Center, and Jan van Breemen Institute, Amsterdam, The Netherlands.

Drs. Goekoop-Ruiterman and de Vries-Bouwstra contributed equally to this work.

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Address correspondence and reprint requests to Y. P. M. Goekoop-Ruiterman, MD, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: y.p.m.goekoop@lumc.nl.

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relief, but in particular the prevention of long-term structural damage and functional decline. To this end, an increasing number of effective disease-modifying antirheumatic drugs (DMARDs) as well as biologic agents have been developed and have demonstrated clinical value in randomized clinical trials. It has become clear that treatment should start early and must be maintained without interruption to reduce the occurrence of irreversible joint damage (1–8). Furthermore, several combinations of DMARDs as well as tumor necrosis factor (TNF) antagonists have shown superiority to DMARD monotherapy in patients with early (9–17) and longstanding (18–22) RA. Finally, intensive monitoring of disease activity and adjusting DMARD use accordingly has resulted in improved outcomes (23). However, the increase in therapeutic options has left unanswered the question of what the optimal therapeutic strategy is in patients presenting with RA.

The BeSt (Dutch acronym for Behandel-Strategieën, "treatment strategies") study is a multicenter, randomized clinical trial in which we compared the clinical and radiographic outcomes of 4 different treatment strategies: 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 the TNF antagonist infliximab (group 4). The common goal in all strategies was to reduce disease activity rapidly and persistently by tight monitoring and immediate adjustment of therapy in the case of an insufficient response. Here we present the results of the first year of followup.

PATIENTS AND METHODS

Patients. The BeSt study was designed and conducted by rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR) in 18 peripheral and 2 university hospitals in the Western part of The Netherlands. The Medical Ethics Committee at each participating center approved the study protocol, and all patients gave written informed consent before inclusion. Patients with early RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria (24), were recruited between April 2000 and August 2002. Patients had to have a disease duration of ≤2 years, be age ≥18 years, and have active disease with ≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either an erythrocyte sedimentation rate (ESR) ≥28 mm/hour or a global health score of ≥20 mm on a 0–100-mm visual analog scale, where 0 = best and 100 = worst. Exclusion criteria included previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental drug, a malignancy within the last 5 years, bone marrow hypoplasia, a serum aspartate aminotransferase or alanine aminotransferase (ALT) level >3 times the upper limit of normal, a serum creatinine level >150 μmoles/liter or an estimated creatinine clearance <75 ml/minute, diabetes mellitus, alcohol or drug abuse, concurrent pregnancy, wish to conceive during the study period, or inadequate contraception.

Treatment allocation and intervention. Patients were allocated to 1 of 4 treatment groups by variable block (9–13) randomization, stratified per center. Closed envelopes containing the patient study number, the allocated treatment group, and preprinted prescriptions for the allocated treatment were distributed and stored by ascending stratified randomization number in the participating centers. After receiving authorization by telephone from the study coordinator, the local rheumatologists enrolled eligible patients.

Patients received 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). For all groups, the treatment protocol described a number of subsequent treatment steps for patients whose medication failed. The decision of whether to adjust medication was made every 3 months based on the Disease Activity Score in 44 joints (DAS_{44}), which was calculated by a research nurse who remained blinded to the allocated treatment group during the entire study period. If the patient did not reach a DAS_{44} of ≤2.4, the treating physician immediately adjusted therapy by proceeding to the next step in the allocated treatment group. If the clinical response was consistently adequate (DAS_{44} of ≤2.4 for at least 6 months), medication was gradually tapered until 1 drug remained at a maintenance dose. The DAS_{44} cutoff level of 2.4 was chosen because observational studies have shown that rheumatologists are generally satisfied with the treatment results and do not intensify therapy if the DAS_{44} is ≤2.4 (25,26).

The patients assigned to sequential monotherapy (group 1) started with 15 mg/week methotrexate (MTX), which was increased to 25–30 mg/week if the DAS_{44} was >2.4. Subsequent steps for patients with an insufficient response were sulfasalazine (SSZ) monotherapy, leflunomide monotherapy, MTX with infliximab, gold with methylprednisolone, and, finally, MTX with cyclosporin A (CSA) and prednisone.

The patients assigned to step-up combination therapy (group 2) also started with 15 mg/week MTX, which was increased to 25–30 mg/week if the DAS_{44} was >2.4. If response to therapy was still insufficient, SSZ was added, followed by the addition of hydroxychloroquine (HCQ) and then by prednisone. Patients whose disease failed to respond to the combination of these 4 drugs subsequently switched to MTX with infliximab, MTX with CSA and prednisone, and, finally, to leflunomide.

The patients assigned to initial combination therapy with prednisone (group 3) started with the combination of 7.5 mg/week MTX, 2,000 mg/day SSZ, and 60 mg/day prednisone (the last of which was tapered in 7 weeks to 7.5 mg/day). In the case of a DAS_{44} of >2.4, MTX was augmented to 25–30 mg/week, and if the response was still insufficient, the combination was replaced subsequently by the combination of MTX with CSA and prednisone, followed by MTX with infliximab, leflunomide monotherapy, gold with methylprednisolone, and, finally, by azathioprine (AZA) with prednisone. In the case of a persistent DAS_{44} of ≤2.4, first prednisone was tapered to zero after 28 weeks, and then MTX was tapered to zero after 40 weeks.

The patients assigned to the initial combination with infliximab started with 25–30 mg/week MTX with 3 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. After 3 months, the dose of infliximab was increased to 6 mg/kg/every 8 weeks if the DAS_{44} was >2.4. Extra DAS_{44} calculations for dose adjustments were performed every 8 weeks within 1 week before the next infusion of infliximab. If the DAS_{44} was >2.4, the dose of the next infusion was increased to 7.5 mg/kg/every 8 weeks and finally to 10 mg/kg/every 8 weeks. If patients still had a DAS_{44} of >2.4 while receiving MTX with 10 mg/kg infliximab, medication was subsequently switched to SSZ, then to leflunomide, then to the combination of MTX, CSA, and prednisone, then to gold with methylprednisolone, and, finally, to AZA with prednisone. In the case of a persistent good response (DAS_{44} of ≤2.4 for at least 6 months), the dose of infliximab was reduced (from 10 to 7.5, 6, and then 3 mg/kg) every next infusion until stopped.

An overlap period of 1 month was used when switching from 1 single DMARD to the next. Unless otherwise specified, the doses of the different drugs were as follows: for MTX, 25–30 mg/week (oral or subcutaneous); for SSZ, 2,000–3,000 mg/day; for leflunomide, 20 mg/day; for HCQ, 400 mg/day; for prednisone, 7.5 mg/day; for CSA, 2.5 mg/kg/day; for gold, 50 mg/week (intramuscular) with 120 mg methylprednisolone (intramuscular) at weeks 0, 4, and 8; for AZA, 2–3 mg/kg/day; and, for infliximab, 3–10 mg/kg/every 8 weeks (intravenous), as described above in greater detail for group 4.

In all groups, if the clinical response was consistently adequate (DAS_{44} of ≤2.4 for at least 6 months), drugs were tapered to monotherapy at a maintenance dose, which was 10 mg/week for MTX, 2,000 mg/day for SSZ, 10 mg every other day for leflunomide, 50 mg every other week for gold, or 2 mg/kg/day for AZA. Prednisone and infliximab were always the first drugs to be tapered to a dose of zero. If disease activity flared (DAS_{44} >2.4) after tapering a drug, the last effective dose was reintroduced. In all groups, prednisone could be reintroduced only once: if, after a second discontinuation, the DAS_{44} increased again to >2.4, then the next step in the protocol was taken. Infliximab could be discontinued only once; after reintroduction, it could be tapered again, but only to a maintenance dose of 3 mg/kg/every 8 weeks. If side effects occurred, the responsible drug was reduced to the lowest tolerated dose. If a drug was not tolerated at all or contraindicated, patients receiving monotherapy proceeded to the next step in the allocated treatment group, and patients receiving combination therapy proceeded with the other drug(s) of the combination.

Contraindications for treatment with infliximab included the following: a known allergy to murine proteins, a chronic infectious disease, serious infections which occurred within the last 3 months, opportunistic infections which occurred within the last 6 months, a neurologic or cerebral disease, a lymphoproliferative disease, active tuberculosis (TB) within the last 2 years, and evidence of an old or latent TB infection for which latent TB therapy (isoniazid [INH]–based therapy or another regimen recommended by local experts) was not instituted prior to infliximab therapy. Prior to infliximab therapy, all patients were evaluated for TB with a purified protein derivative skin test and a chest radiograph. At the beginning of 2002, heart failure was added as a contraindication for treatment with infliximab. Previously enrolled patients with heart failure who had already received infliximab continued therapy and were closely monitored.

Concomitant treatment with nonsteroidal antiinflammatory drugs and intraarticular injections with corticosteroids were permitted. Other parenteral corticosteroids were not allowed. The use of DMARDs or oral corticosteroids was only permitted as dictated by the treatment protocol. All patients received 1 mg/day folic acid during treatment with MTX.

Assessment of end points. Every 3 months, assessments were performed by a research nurse who was blinded to the allocated treatment group. Primary end points were functional ability, measured by the Dutch version of the Health Assessment Questionnaire (D-HAQ) (27), and radiographic joint damage according to the modified Sharp/Van der Heijde score (SHS), with a range of 0–448 (28), assessed on radiographs of the hands and feet obtained at baseline and after 1 year of followup. Higher D-HAQ scores indicate poorer function. All radiographs were read by 2 trained assessors who were blinded to the patient's identity, treatment center, and date of radiograph and who scored the radiographs paired, in random order, and independently. The intraobserver coefficients were 0.93 and 0.94, and the interobserver coefficient was 0.93. The mean score of the 2 assessors was used for the analysis. A patient was classified as having erosive disease if the mean erosion score was >0.5. Progression of radiographic joint damage was defined as a change in radiographic score greater than the smallest detectable difference (SDD), as well as by a change (in the total ragiographic score) >0.5 (29,30). The SDD was 5.92, 3.76, and 3.75 for total SHS, erosion score, and joint space narrowing score, respectively. Secondary end points were 20%, 50%, and 70% improvement according to the ACR response criteria (31) and clinical remission, defined as a DAS_{44} of <1.6 (32).

To maintain uniformity in scoring and assessment quality, all research nurses were trained at study initiation and every 6 months thereafter. Two trial physicians verified adherence to the protocol every 3 months. All protocol deviations were recorded.

Toxicity. At each control visit, the following laboratory tests were performed: ESR, complete blood cell count, and serum levels of ALT, gamma glutamyl transpeptidase, bilirubin, lactate dehydrogenase, creatinine, electrolytes, and glucose. The treating physician recorded all adverse events (AEs) and serious AEs and, if necessary, made treatment adjustments in accordance with the protocol. Serious AEs were defined as any adverse reaction resulting in any of the following outcomes: a life-threatening condition or death, a significant or permanent disability, a malignancy, hospitalization or prolongation of hospitalization, a congenital abnormality, or a birth defect.

Statistical analysis. A total sample size of 468 patients (117 per group) was needed to obtain 80% power to detect a difference of at least 0.2 in the D-HAQ score, which was set as a clinically relevant difference, with a 5% significance level and adjusting for multiple comparisons between groups, assuming an SD of 0.45. This sample size also ensured >80% power to detect a difference of ≥20% in the change score of radiographic damage as measured by the SHS.

All outcomes were calculated in an intention-to-treat (ITT) analysis using all available data. Measures with a Gaussian distribution, expressed as the mean and SD, were analyzed

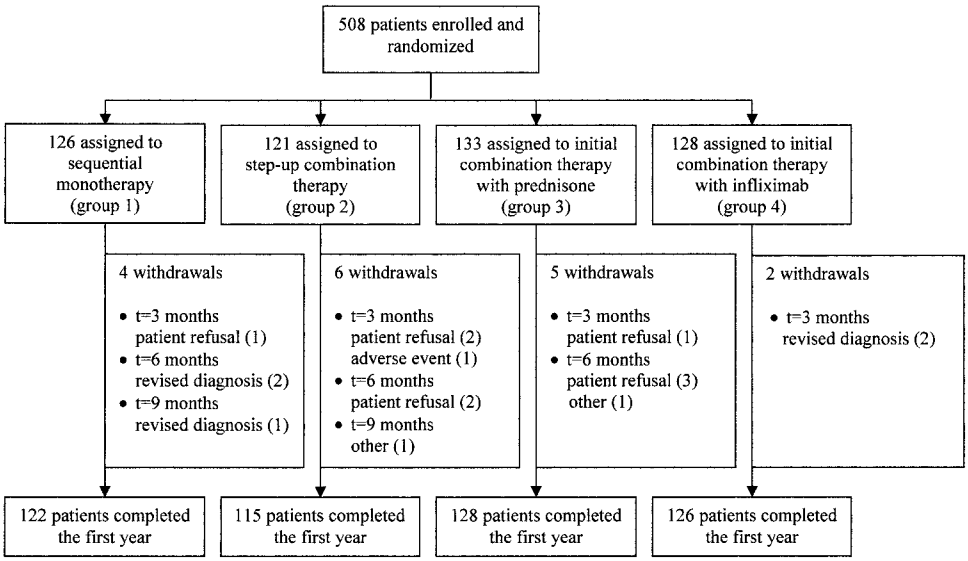

Figure 1. Study profile. Revised diagnoses were paraneoplastic arthritis, gout, systemic lupus erythematosus, mixed connective tissue disease, and Henoch-Schönlein purpura. See Patients and Methods for description of treatment groups.

using a one-way analysis of variance. In the case of an overall significant difference between the groups, a post hoc least significant difference test was performed for the primary outcomes, and Tukey's honestly significant difference test was used for the secondary outcomes to correct for multiple testing. Outcome measurements with a non-Gaussian distribution, expressed as the median and interquartile range (IQR), were analyzed by the Kruskal-Wallis test. Pairwise comparisons between groups were performed using the Mann-Whitney U test. For the SHS, the change scores were reported both as the mean and as the median. Categorical variables such as sex and rheumatoid factor (RF) positivity were compared between treatment groups using the chi-square test. A subgroup analysis of the progression of radiographic joint damage was performed in patients who either did or did not have erosive disease at baseline.

RESULTS

Five hundred eight patients were included and randomly assigned to 1 of 4 treatment groups: 126 patients were assigned to sequential monotherapy

Table 1. Baseline demographic and disease characteristics*

	Treatment group			
	Sequential monotherapy (n = 126)	Step-up combination therapy (n = 121)	Initial combination with prednisone (n = 133)	Initial combination with infliximab (n = 128)
Age, mean ± SD years	54 ± 13	54 ± 13	55 ± 14	54 ± 14
Women, no. (%)	86 (68)	86 (71)	86 (65)	85 (66)
Time from diagnosis to inclusion, median weeks (IQR)	2 (1–5)	2 (1–4)	2 (1–4)	3 (1–5)
Symptom duration, median weeks (IQR)	23 (14–54)	26 (14–56)	23 (15–53)	23 (13–46)
Previous antimalarial therapy, no. (%)	9 (7)	13 (11)	10 (8)	11 (9)
IgM rheumatoid factor positive, no. (%)	84 (67)	77 (64)	86 (65)	82 (64)
DAS_{44}, mean ± SD	4.5 ± 0.9	4.5 ± 0.8	4.4 ± 0.9	4.3 ± 0.9
D-HAQ score, 0–3 scale, mean ± SD	1.4 ± 0.7	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.7
Total SHS, 0–448 scale, median (IQR)/ mean ± SD	3.5 (1.5–9.5)/7.3 ± 9.5	5.0 (1.5–8.1)/6.3 ± 6.9	3.5 (1.5–8.5)/5.9 ± 6.5	4.0 (1.5–8.5)/7.0 ± 10.0
Erosion score, 0–280 scale, median (IQR)/mean ± SD	2.0 (0.5–4.5)/4.1 ± 6.2	2.0 (0.5–4.5)/3.5 ± 4.3	2.0 (0.5–4.5)/3.3 ± 4.3	2.0 (0.5–5.0)/3.9 ± 5.8
Joint space narrowing score, 0–168 scale, median (IQR)/mean ± SD	1.0 (0.0–4.0)/3.2 ± 4.9	2.0 (0.0–4.5)/2.8 ± 3.2	1.5 (0.0–4.0)/2.6 ± 3.2	1.5 (0.0–3.5)/3.1 ± 5.2
Erosions on hand/foot radiograph, no. (%)	89 (72)	82 (70)	93 (71)	93 (73)

* IQR = interquartile range; DAS_{44} = Disease Activity Score in 44 joints; D-HAQ = Dutch version of the Health Assessment Questionnaire; SHS = modified Sharp/Van der Heijde score. See Patients and Methods for description of treatment groups.

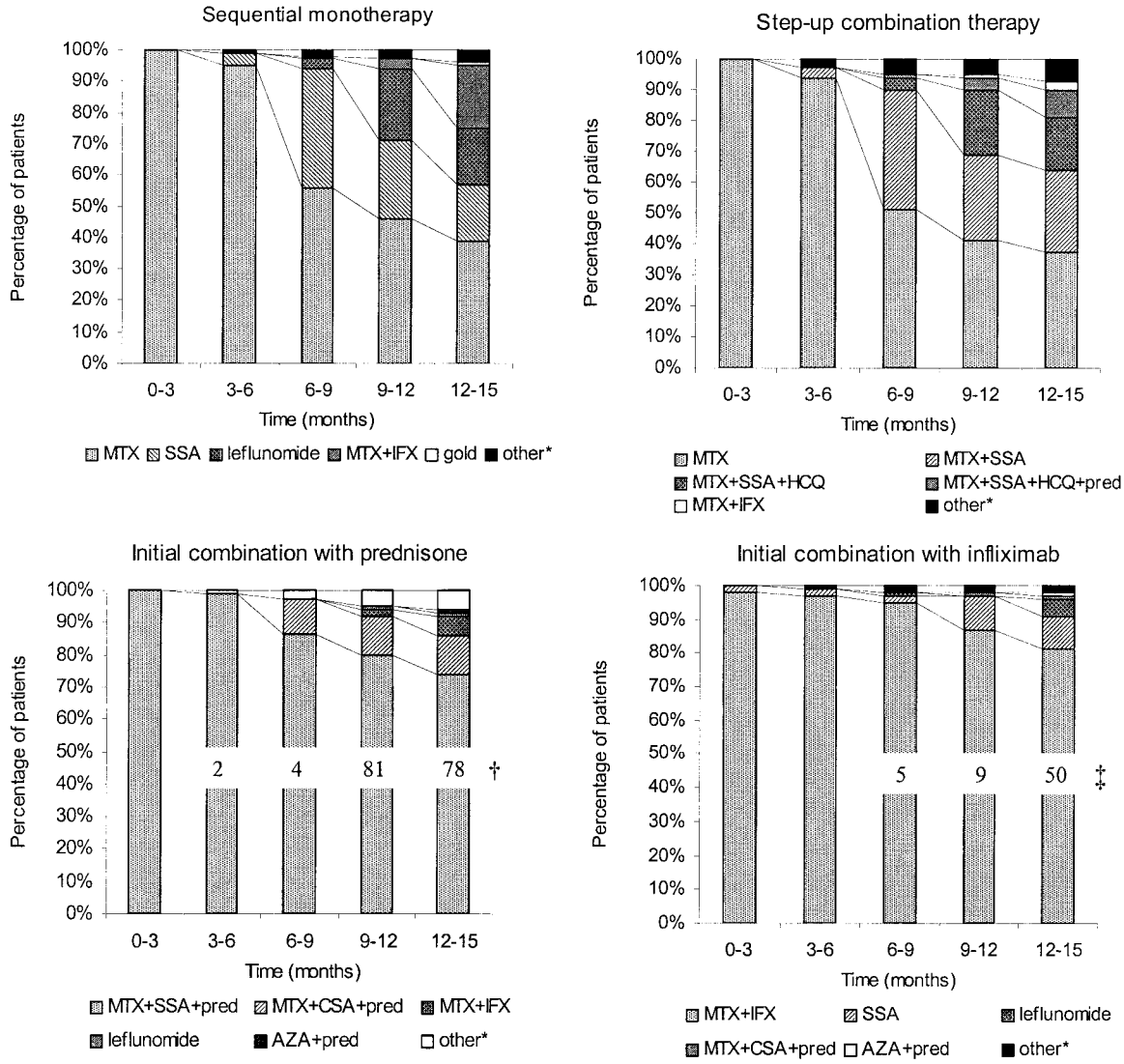

Figure 2. Treatment of patients during the first year of followup. ∗ = percentage of patients treated outside the treatment protocol. † = percentage of patients who discontinued prednisone because of a sustained Disease Activity Score in 44 joints (DAS_{44}) of ≤2.4. ‡ = percentage of patients who discontinued infliximab because of a sustained DAS_{44} of ≤2.4. MTX = methotrexate; SSA = sulfasalazine; IFX = infliximab; HCQ = hydroxychloroquine; pred = prednisone; CSA = cyclosporin A; AZA = azathioprine. See Patients and Methods for description of treatment groups.

(group 1), 121 patients to step-up combination therapy (group 2), 133 patients to initial combination therapy including prednisone (group 3), and 128 patients to initial combination therapy including infliximab (group 4). Seventeen patients dropped out (4, 6, 5, and 2 patients in groups 1–4, respectively) (Figure 1). Twenty-four patients (5%) discontinued adherence to the protocol because of noncompliance (5, 8, 8, and 3 patients in groups 1–4, respectively), but these patients were not lost to followup, and all available data were included in the ITT analysis.

There were no statistically significant differences in the demographic and baseline disease characteristics of the 4 groups (Table 1). The study population consisted of patients with very early RA, with a median duration between diagnosis and inclusion of 2 weeks (IQR 1–5) and a median duration of symptoms of 23 weeks (IQR 14–53). All patients had active disease with a mean ± SD DAS_{44} of 4.4 ± 0.9, and 72% of the patients had erosive disease at baseline.

Two patients with latent TB in group 4 refused concomitant treatment with INH. By mistake, these patients started with the next treatment step (SSZ) instead of MTX monotherapy. Two patients were ex-

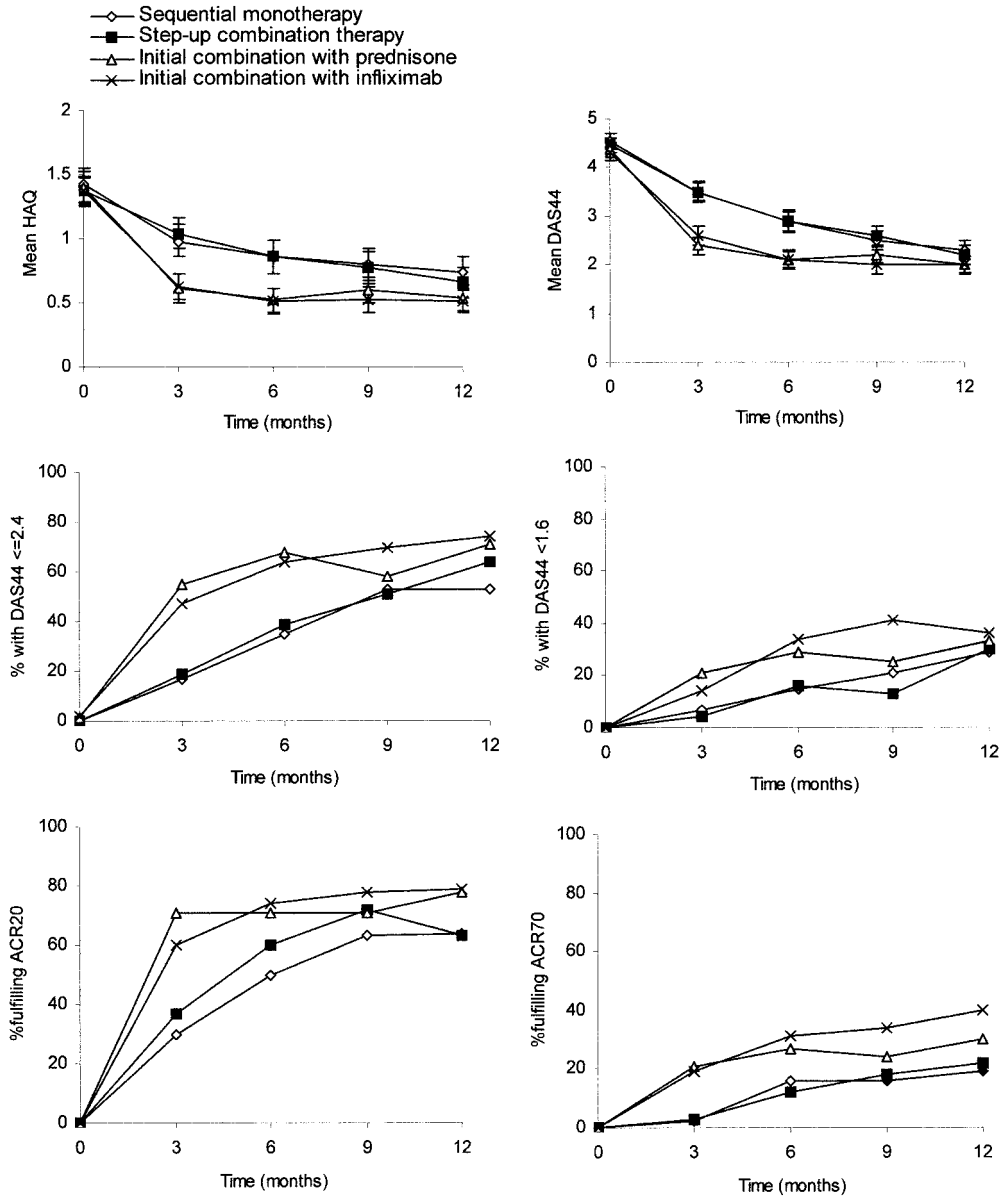

Figure 3. Clinical outcomes. Error bars indicate 95% confidence intervals. HAQ = Dutch version of the Health Assessment Questionnaire; DAS_{44} = Disease Activity Score in 44 joints (a DAS_{44} of ≤2.4 indicates adequate clinical response; a DAS_{44} of <1.6 indicates clinical remission); ACR20 = 20% improvement according to the American College of Rheumatology response criteria. See Patients and Methods for description of treatment groups.

cluded from treatment with infliximab (1 because of a history of untreated TB accompanied by a lesion on a chest radiograph and 1 because of cardiac failure) and started with MTX monotherapy according to the treatment protocol. All 4 patients were analyzed for treatment in group 4 according to the ITT principle.

The goal in each treatment group was to reach and sustain a DAS_{44} of ≤2.4, indicating low disease activity. After 1 year, this goal was reached by 63 of 118 patients (53%), 72 of 112 patients (64%), 87 of 122 patients (71%), and 89 of 121 patients (74%) in groups 1–4, respectively ($P = 0.004$ for group 1 versus group 3; $P = 0.001$ for group 1 versus group 4; P not significant [NS] for other comparisons). More patients in groups 3 and 4 than in groups 1 and 2 remained at the initial stage of treatment because of a sustained DAS_{44} of ≤2.4 (48 [39%], 43 [37%], 94 [73%], and 102 [81%] of the patients in groups 1–4, respectively) (Figure 2). Of these

Table 2. Primary outcomes of the BeSt study*

	Treatment group				
	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab	*P*
D-HAQ score, mean ± SD					
Baseline	1.4 ± 0.7	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	NS
3 months	1.0 ± 0.7	1.0 ± 0.6	0.6 ± 0.6	0.6 ± 0.6	<0.001†
6 months	0.9 ± 0.7	0.9 ± 0.7	0.5 ± 0.5	0.5 ± 0.5	<0.001†
9 months	0.8 ± 0.7	0.8 ± 0.7	0.6 ± 0.6	0.5 ± 0.6	0.001†
12 months	0.7 ± 0.7	0.7 ± 0.6	0.5 ± 0.5	0.5 ± 0.5	0.009‡
Progression of radiographic joint damage, median (IQR)/mean ± SD					
Total SHS, 0–448 scale	2.0 (0.0–7.4)/7.1 ± 15.4	2.5 (0.0–6.0)/4.3 ± 6.5	1.0 (0.0–2.5)/2.0 ± 3.6	0.5 (0.0–2.3)/1.3 ± 4.0	<0.001†
Erosion score, 0–280 scale	1.0 (0.0–3.9)/3.5 ± 8.2	1.0 (0.0–4.0)/2.6 ± 4.7	0.5 (0.0–1.4)/0.9 ± 1.9	0.0 (0.0–1.5)/0.7 ± 2.1	<0.001†
Joint space narrowing score, 0–168 scale	1.0 (0.0–3.8)/3.6 ± 8.4	0.0 (0.0–2.4)/1.6 ± 2.9	0.0 (0.0–1.9)/1.0 ± 2.4	0.0 (0.0–1.0)/0.6 ± 2.6	<0.001§

* BeSt = Behandel-Strategieën ("treatment strategies"); NS = not significant (see Table 1 for other definitions). See Patients and Methods for description of treatment groups.
† $P < 0.05$, groups 1 and 2 versus groups 3 and 4.
‡ $P < 0.05$, group 1 versus groups 3 and 4.
§ $P < 0.05$, group 1 versus groups 3 and 4 and group 2 versus group 4.

patients, 78% in group 3 had stopped prednisone and 50% in group 4 had stopped infliximab because of a persistent DAS_{44} of ≤2.4 (Figure 2). The number of patients who had received intraarticular steroids at least once was 28 (22%), 32 (26%), 10 (8%), and 17 (13%) in groups 1–4, respectively ($P < 0.001$).

Clinical outcomes. Patients treated with initial combination therapy with either prednisone (group 3) or infliximab (group 4) had more rapid functional improvement than patients treated with sequential monotherapy (group 1) or step-up combination therapy (group 2) (Figure 3 and Table 2). The mean D-HAQ score at 3 months was 1.0 in groups 1 and 2 and 0.6 in groups 3 and 4 ($P < 0.001$ for groups 1 and 2 versus groups 3 and 4; *P* NS for other comparisons). After 1 year, the differences in D-HAQ scores between the groups were smaller, with mean D-HAQ scores of 0.7 in groups 1 and 2 and of 0.5 in groups 3 and 4 ($P = 0.010$ for group 1 versus group 3; $P = 0.003$ for group 1 versus group 4; *P* NS for other comparisons). Thirty-two percent of all patients had clinical remission of their disease (DAS_{44} of <1.6) after the first year of followup (overall $P = 0.690$) (Figure 3). Clinical improvement, as defined by the ACR response criteria, was reached earlier and by more patients in groups 3 and 4 than in groups 1 and 2 (Figure 3).

Radiographic outcomes. At baseline, 499 radiographs were assessed (123, 118, 131, and 127 in groups 1–4, respectively). The treatment groups were similar at baseline with respect to the number of erosions, joint space narrowing, and total SHS (Table 1). Radiographs obtained at baseline and at 1 year of followup were available for 467 patients. Compared with patients with baseline and followup radiographs, the 32 patients without followup radiographs (including the 17 patients who withdrew) had a higher total SHS with more erosions at baseline, but did not differ in baseline joint space narrowing, age, sex, RF positivity, D-HAQ score, DAS_{44}, and ESR, and patients were equally distributed over the 4 treatment groups (data not shown).

In the first year of followup, patients treated with initial combination therapy including prednisone (group 3) or infliximab (group 4) had less progression of radiographic joint damage than did patients treated with sequential monotherapy (group 1) or step-up combination therapy (group 2) (Table 2). The median increases in the total SHS were 2.0, 2.5, 1.0, and 0.5 in groups 1–4, respectively ($P = 0.003$ for group 1 versus group 3; $P < 0.001$ for group 1 versus group 4; $P = 0.007$ for group 2 versus group 3; $P < 0.001$ for group 2 versus group 4) (Table 2).

The number of patients without progression of radiographic joint damage was higher in groups 3 and 4 than in groups 1 and 2 (Figure 4). No progression of the total SHS (greater than the SDD) was observed in 76 of 114 patients (67%), 82 of 112 patients (73%), 104 of 120 patients (87%), and 113 of 121 patients (93%) in groups 1–4, respectively ($P < 0.001$ for group 1 versus groups 3 and 4; $P = 0.010$ for group 2 versus group 3; $P < 0.001$ for group 2 versus group 4; *P* NS for other comparisons). Improvement of the total SHS (greater than the SDD)

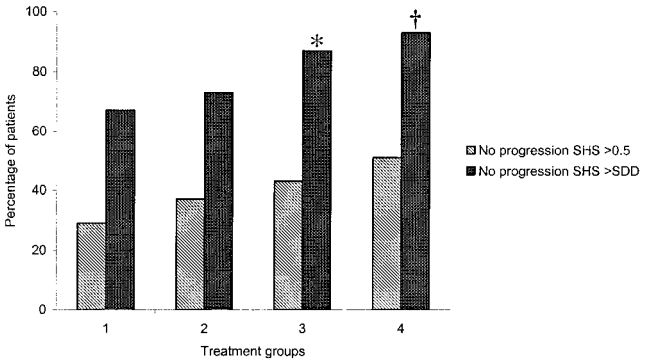

Figure 4. Percentage of patients without progression of radiographic joint damage. 1 = sequential monotherapy; 2 = step-up combination therapy; 3 = initial combination therapy with prednisone; 4 = initial combination therapy with infliximab (see Patients and Methods for description of treatment groups). * = $P < 0.001$ versus group 1 and $P = 0.010$ versus group 2. † = $P < 0.001$ versus groups 1 and 2. SHS = modified Sharp/Van der Heijde score; SDD = smallest detectable difference.

was seen in 1 patient each in groups 1, 3, and 4. Of all patients with nonerosive disease at baseline, 9 of 31 (29%) in group 1, 18 of 34 (53%) in group 2, 14 of 37 (38%) in group 3, and 5 of 34 (15%) in group 4 progressed to erosive disease ($P = 0.050$ for group 1 versus group 2; $P = 0.001$ for group 2 versus group 4; $P = 0.028$ for group 3 versus group 4; P NS for other comparisons).

AEs. A total of 41% of all patients experienced ≥1 AEs: 54 (43%), 57 (47%), 49 (37%), and 50 (39%) of the patients in groups 1–4, respectively (overall $P = 0.367$). Gastrointestinal symptoms were most frequently reported and were observed in 20 (16%), 18 (15%), 11 (8%), and 14 (11%) of the patients in groups 1–4, respectively. Skin rash or other mild dermal or mucosal events were reported in 12 (10%), 15 (12%), 12 (9%), and 8 (6%) of the patients in groups 1–4, respectively. Infections, mainly upper respiratory tract infections, were reported in 5 (4%), 8 (7%), 10 (8%), and 10 (8%) of the patients in groups 1–4, respectively, and cardiovascular events were reported in 3 (2%), 2 (2%), 8 (6%), and 2 (2%) of the patients in groups 1–4, respectively. Ten patients in group 4 had a mild-to-moderate infusion reaction during treatment with infliximab. Infliximab was discontinued in these patients. Nine patients in group 4 had latent TB and received concomitant INH prior to the initiation of infliximab therapy. No cases of TB or opportunistic infections were reported.

There were 8, 9, 17, and 6 serious AEs reported in groups 1–4, respectively ($P = 0.438$ for comparison of the number of patients with serious AEs between the treatment groups). In group 1, patients were hospitalized for the following reasons: 1 for hypertension, 1 for transient ischemic attack, 1 for pulmonary embolism, 1 for pneumonia, 1 for herpes simplex encephalitis, 1 for a hip prosthesis operation, 1 for fever associated with SSZ, and 1 for active arthritis with revision of diagnosis to gout. In group 2, patients were hospitalized for the following reasons: 1 for a peripheral bypass operation, 1 for pacemaker implantation, 1 for a prolapsed vertebral disk, 1 for neuropathy, 1 for a hip prosthesis operation, 1 for diffuse peritonitis, and 2 for exacerbations of RA, and there was 1 malignancy (bladder carcinoma). In group 3, patients were hospitalized for the following reasons: 3 for myocardial infarction, 1 for heart failure, 1 for oral herpes simplex infection, 1 for hip fracture, 1 for hip pain, 1 for granulocytopenia, 1 for a urinary tract stone, 1 for temporal arteritis, 2 for exacerbation of RA, 1 for excision of benign microcalcifications viewed on mammography, and 2 for appendectomy, and there were 2 malignancies (1 breast cancer and 1 lymphoma). Finally, in group 4, patients were hospitalized for the following reasons: 1 for transient cardiac ischemia, 1 for pulmonary embolism, 1 for peripheral vascular disease, 1 for pneumonia, 1 for septic arthritis, and 1 for MTX pneumonitis.

DISCUSSION

In the BeSt study, the clinical and radiographic efficacies of 4 different treatment strategies for early RA were compared in the search for the optimal strategy to prevent long-term joint damage and functional decline. Initial combination therapy including either prednisone (group 3) or infliximab (group 4) resulted in earlier functional improvement compared with sequential monotherapy (group 1) and step-up combination therapy (group 2). By the end of the first year, there was a marked improvement in all groups, with 32% of all patients having clinical remission of their disease (DAS_{44} of <1.6). Presumably, this result after 1 year was due to close monitoring with immediate treatment adjustments made in all patients who had a DAS_{44} >2.4. To achieve an adequate clinical response (DAS_{44} ≤2.4), medications were altered more often in groups 1 and 2 than in groups 3 and 4. The absence of a difference between groups 1 and 2 confirms observations that the combination of SSZ and MTX has no additive therapeutic effect (33,34) and suggests that with these 2 drugs, adding is not better than switching.

The 4 treatment strategies that were compared in the BeSt study are the most frequently used and discussed strategies. The group 1 strategy reflects conventional therapy in combination with tight disease control,

which has recently been demonstrated to be more effective than routine care (23). The group 2 strategy was designed because the case for step-up combination therapy has not yet been proven. We chose to step up to the combination of MTX, SSZ, and HCQ with prednisone, which has been proven effective in previous studies (10,12,18). The group 3 strategy is designed according to the COBRA (Combinatietherapie Bij Reumatoïde Artritis) trial (9), and the group 4 strategy is considered to be the most aggressive strategy, with rapid dose increments of MTX in combination with the biologic agent infliximab. To minimize the risk of bias of the open design, all outcome measurements were assessed by trained research nurses who were blinded to the allocated treatment strategy during the entire study period, and the end points were chosen to allow for the least possible subjectivity of interpretation.

There were no statistically significant differences in the frequency of toxic effects and in the number of withdrawals between the 4 treatment groups. The difference in the progression of radiographic joint damage between the patients in groups 3 and 4 and the patients in groups 1 and 2 was statistically significant after 1 year of followup. From a clinical perspective, however, these differences were small. On the one hand, in >40% of the patients in groups 1 and 2, a sustained adequate suppression of disease activity was achieved with MTX monotherapy, which is an indication that a large proportion of patients would be overtreated if all patients were to start with initial combination therapy. On the other hand, the patients in groups 3 and 4 had the benefit of a more rapid relief of symptoms and improvement of physical function. In addition, there is the possibility that effective suppression of disease activity during the early phases of the disease may ameliorate the long-term joint damage and poor physical function and, ideally, even induce true clinical remission without the need for DMARD treatment.

The followup of the COBRA study showed that the rate of progression of joint damage remained lower in the combination therapy group for up to 4 years after the initial 56-week controlled intervention period (11). The same was seen in the early RA trial, in which patients treated with etanercept monotherapy had a more rapid clinical response and less progression of joint damage than patients treated with MTX (16). From this perspective, starting therapy with a single DMARD would be a missed opportunity in a considerable number of patients. The results of the long-term followup of the BeSt study, which includes analyses of joint destruction, physical function, and cost-effectiveness, should clarify this issue. Furthermore, we hope to identify clinical and serologic parameters as well as genetic variations that can identify those patients who will benefit most from initial combination therapy.

In conclusion, during the first year of followup, patients with newly diagnosed RA who received initial combination therapy with either prednisone or infliximab had earlier functional improvement, with less progression of radiographic joint damage and fewer side effects than in patients who received sequential monotherapy or step-up combination therapy.

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