Treatment of Recent-Onset Rheumatoid Arthritis: Lessons from the BeSt Study

CORNELIA F. ALLAART, FERDINAND C. BREEDVELD, and BEN A.C. DIJKMANS

ABSTRACT. ***Objective***. To determine the efficacy, toxicity, utilities, and costs of 4 treatment strategies for patients with recent-onset rheumatoid arthritis (RA).

Methods. 508 patients with recent-onset active RA [mean Disease Activity Score (DAS) 4.4, mean Health Assessment Questionnaire score 1.4] were randomized into 4 strategy groups: (1) sequential monotherapy; (2) step-up to combination therapy [both starting with methotrexate (MTX)]; (3) initial combination therapy with MTX, sulfasalazine, and prednisone; (4) initial combination therapy with MTX and infliximab. Treatment adjustments were based on 3-monthly calculations of the DAS (target DAS ≤ 2.4), by research nurses who were blinded to the strategy group. They also collected data on treatment toxicity, functional ability, costs, and utilities. Yearly anonymized radiographs of hands and feet were scored in random order by 2 independent physicians, using the Sharp/van der Heijde score.

Results. Functional ability improved significantly earlier in Groups 3 and 4 than in Groups 1 and 2, but was comparable among the groups at the end of the first year of treatment. Radiographic joint damage progression was significantly lower in Groups 3 and 4 than in Groups 1 and 2, but low in all groups compared to other RA populations, probably due to DAS-driven treatment adjustments in all groups. More patients in Groups 3 and 4 than in Groups 1 and 2 achieved clinical remission (DAS 1.6), and patients who achieved early continued remission in Groups 3 and 4 had significantly less joint damage progression than those who achieved the same in Groups 1 and 2. More patients could taper and stop all antirheumatic drugs and still retained remission in Group 4 (17% at t = 3 years) than in the other groups (10%, 5%, 9%, respectively). Toxicity was comparable between groups. Quality of life measures were significantly higher in Group 4 than in the other groups, but costs of treatment were also the highest in Group 4. Depending on the method used, higher productivity in Group 4 compensated for the higher medical costs.

Conclusion. In patients with recent-onset RA, initial combination therapy including prednisone or infliximab results in earlier clinical improvement and less joint damage progression than initial monotherapy. Initial treatment with infliximab resulted in the highest quality of life, highest productivity, and highest medical costs. DAS-driven treatment adjustments were effective to suppress disease activity and damage progression in all groups. (J Rheumatol 2007;34 Suppl 80:25-33)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TREATMENT COMBINATION DRUG THERAPY
DISEASE ACTIVITY

INTRODUCTION

In the last decade a revolution has occurred in the treatment of rheumatoid arthritis (RA). New insights into the inflammatory process of the disease have stimulated the development of new drugs, and new monitoring tools have enabled rheumatologists to optimize the results of treatment. Although studies have demonstrated benefits of one drug or a combination of drugs over another, it remained unclear how to position the available antirheumatic drugs over the course of time in this chronic disease in daily practice. Against this background, Dutch rheumatologists from 20 hospitals in the southwestern part of The Netherlands, participating in research in the Foundation for Applied Rheumatology Research, designed a study in patients with recently diagnosed RA, to establish which of 4 commonly used treatment strategies results in the best outcomes in terms of functional ability and radiological damage.

The BeSt Study

The BeSt study (Behandel Strategieën, i.e., Treatment Strategies), initially intended as a 2 year followup study, started in March 2000 and included 508 patients until August 2002. Once diagnosed with RA according to the American College of Rheumatology 1987 revised criteria, patients (≥ 18 years of age, at least 6 of 68 tender joints and 6 of 66 swollen joints, and either erythrocyte sedi-

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mentation rate (ESR) > 28 mm/h or visual analog scale (VAS) for global health > 20 mm, as described[1]) were randomized into 4 treatment strategy groups:

Group 1: Sequential monotherapy, starting with methotrexate (MTX), next steps sulfasalazine, leflunomide, MTX + infliximab, gold, MTX + cyclosporine + prednisone, azathioprine + prednisone;

Group 2: Step up combination therapy, starting with MTX, next steps add sulfasalazine, then hydroxychloroquine, then prednisone, next switch to MTX + infliximab, MTX + cyclosporine + prednisone, leflunomide, gold, azathioprine + prednisone;

Group 3: Initial combination therapy with prednisone, starting with MTX + sulfasalazine + a tapered high dose of prednisone, next step MTX + cyclosporine + prednisone, next MTX + infliximab, leflunomide, gold, azathioprine + prednisone;

Group 4: Initial combination therapy with infliximab, starting with MTX + infliximab, next steps sulfasalazine, leflunomide, MTX + cyclosporine + prednisone, gold, azathioprine + prednisone.

To follow daily practice, the study design was dynamic over time. Patients moved through the steps of their assigned strategy depending on their clinical response: in case of insufficient response (DAS based on a 44-joint count, DAS > 2.4[2,3]), they started the next treatment step, either increasing the dosage of the current drug or adding or moving on to the next drug, and in case of consistent good response, drugs were tapered (in reverse order) in number and dosages, until the last remaining drug could be tapered to maintenance dose. If the disease flared, the last effective dose or combination was restarted. Prednisone and infliximab were always tapered to nil. To avoid prolonged use, prednisone was restarted only once. Infliximab could be stopped only once and was tapered to maintenance dose if reintroduced after a flare.

To determine who had insufficient response or who could taper and stop, every 3 months all patients were evaluated by research nurses who were blinded for the assigned strategy. With the result of a calculated DAS in hand, the patients went to the rheumatologist, who adjusted the medication accordingly: if DAS was > 2.4, the next step in the protocol was taken; if DAS was ≤ 2.4 the treatment was continued; and if DAS was ≤ 2.4 for at least 6 consecutive months treatment was tapered. Yearly radiographs of hands and feet were scored in random order by 2 independent readers blinded to patient identity and assigned strategy, according to the Sharp/van der Heijde method[4].

The First 2 Years

Clinical outcomes, functional ability, and quality of life all improved earlier in the patients who started with initial combination therapy, either with prednisone or with infliximab (Figure 1)[1,5]. After 12 months, there were no longer significant differences between the groups.

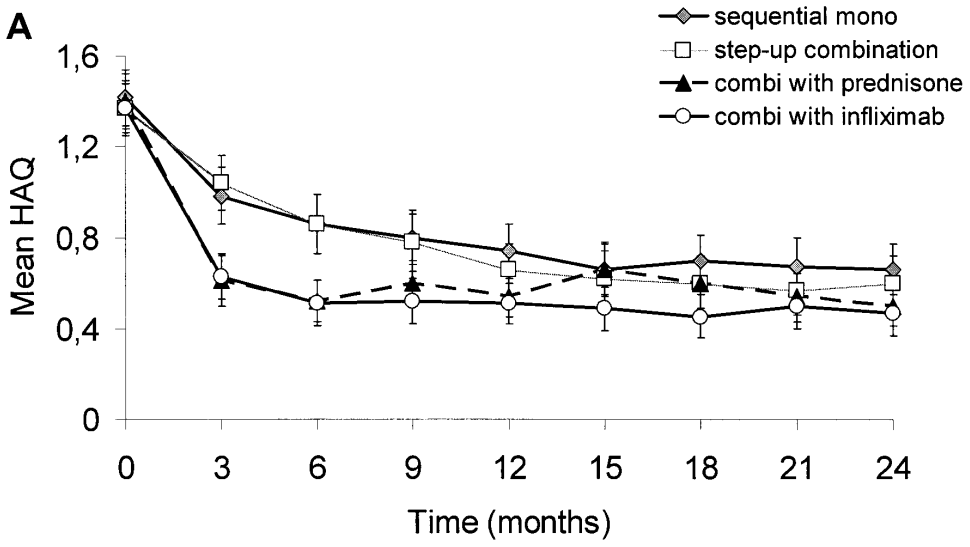

Figure 1A. Improvement in functional ability as measured by the Health Assessment Questionnaire (HAQ).

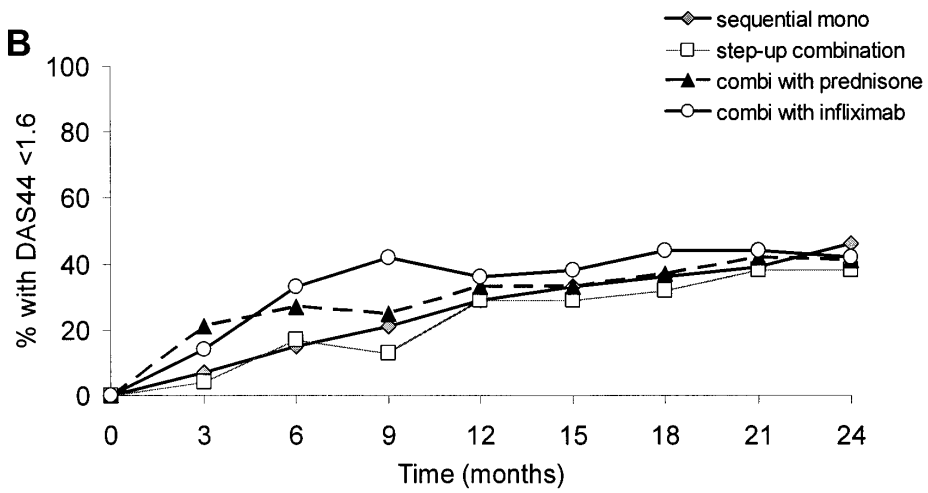

Figure 1B. Percentages of patients in clinical remission (DAS < 1.6) over time.

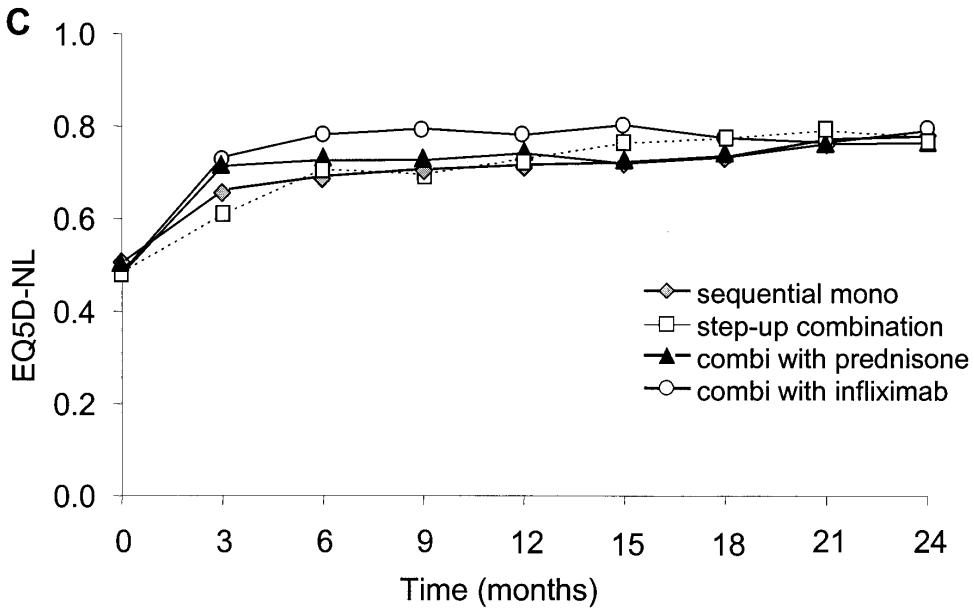

Figure 1C. Quality of life over time, by EuroQol. Data in Figure 1 have been published in part in Arthritis & Rheumatism[1] and Annals of Internal Medicine[20].

This was probably due to therapy adjustments in case of insufficient clinical response, which occurred more often in the initial monotherapy group and the step-up to combination-therapy group. As a result of these adjustments, at the end of the second year, 68% of patients in Group 1 and Group 2 had discontinued their first treatment, MTX monotherapy, and moved on to the next treatment steps (Figure 2). Subanalysis of these 2 "initial monotherapy groups" revealed 2 other findings: (1) after failure taking MTX, switching to or adding sulfasalazine had results that were similar in terms of efficacy and toxicity; and (2) the efficacy of switching to or adding other conventional disease modifying antirheumatic drugs (DMARD) after failure on initial MTX monotherapy

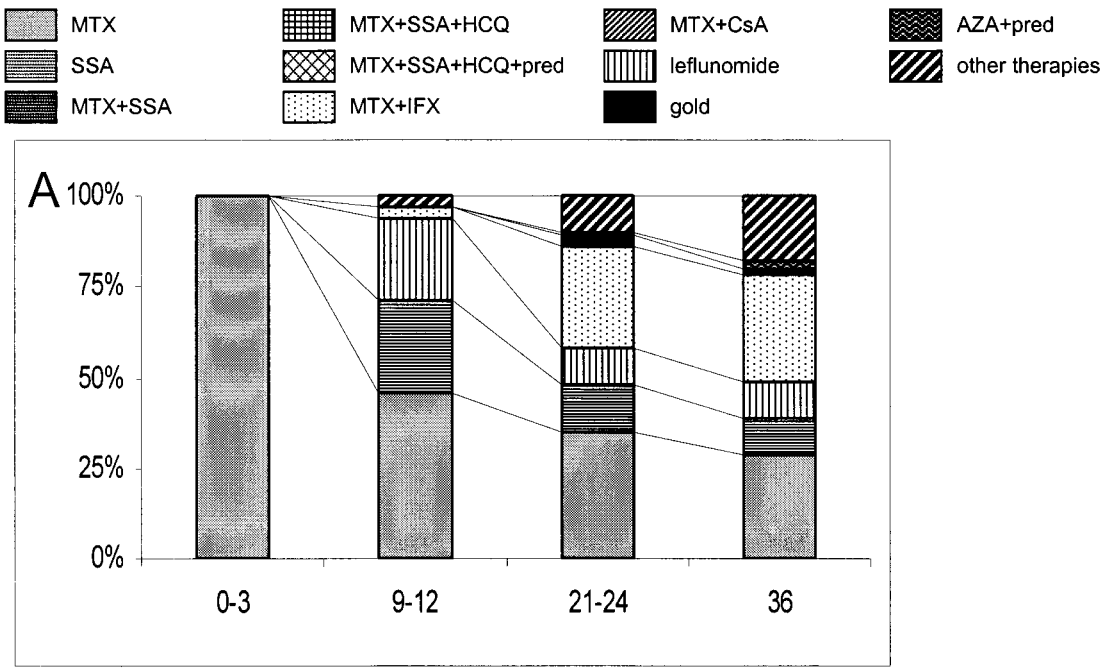

Figure 2A. Changes in medication over time in sequential monotherapy.

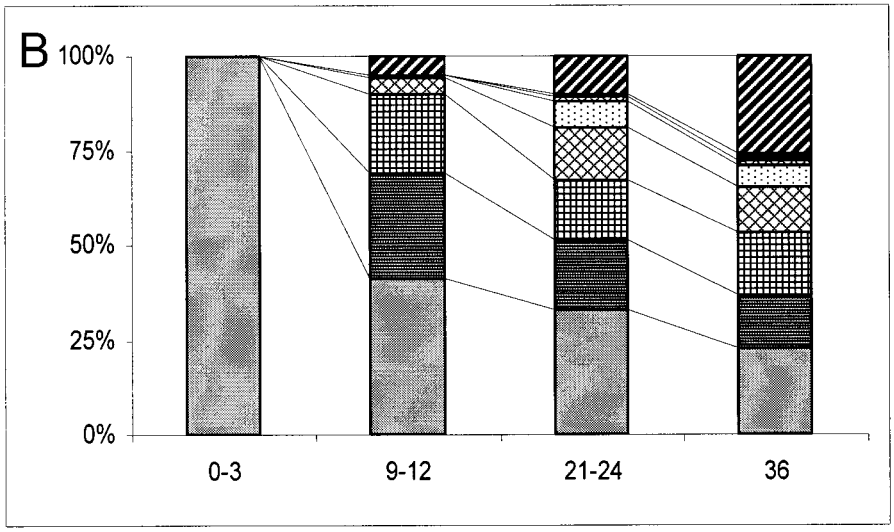

Figure 2B. Changes in medication over time in step-up to combination therapy.

was disappointing, if one was aiming to achieve a good clinical response, defined as DAS ≤ 2.4[6].

Radiological evaluations showed good suppression of joint damage progression in all groups, taking into consideration that at baseline all patients had very active disease [mean DAS 4.4, mean Health Assessment Questionnaire (HAQ) 1.4], and that 65% were rheumatoid factor (RF)-positive and already 72% of patients showed some erosions. After one year, patients treated with sequential monotherapy and step-up to combination therapy had a median progression score of 2 compared to a median progression score of 0.5 in the patients treated with initial combination therapy with either prednisone or infliximab[1]. The overall low progression score is possibly a result of the DAS-adjusted treatment. Previous trials comparing the efficacy of initial combination therapy with prednisone[5] or a tumor necrosis factor-blocker[8-11] to that of initial monotherapy did not adjust the medication

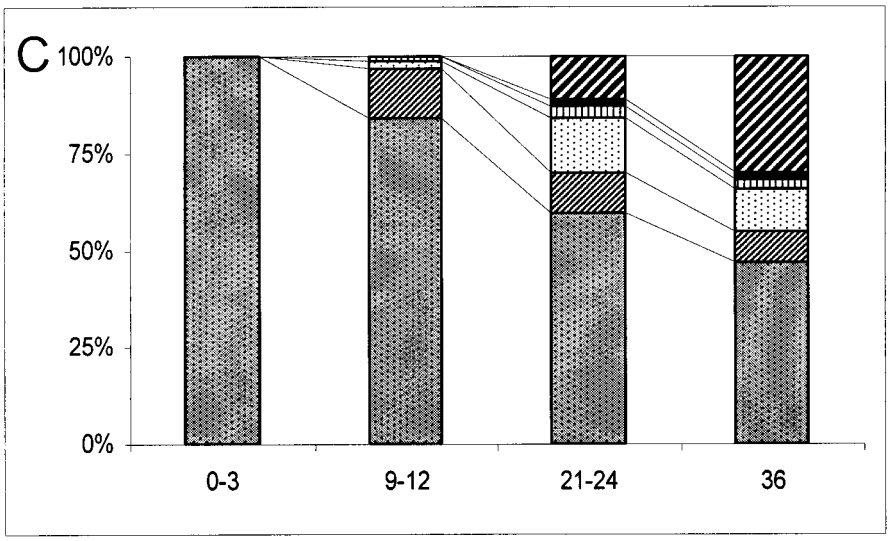

Figure 2C. Changes in medication over time in initial combination therapy including prednisone.

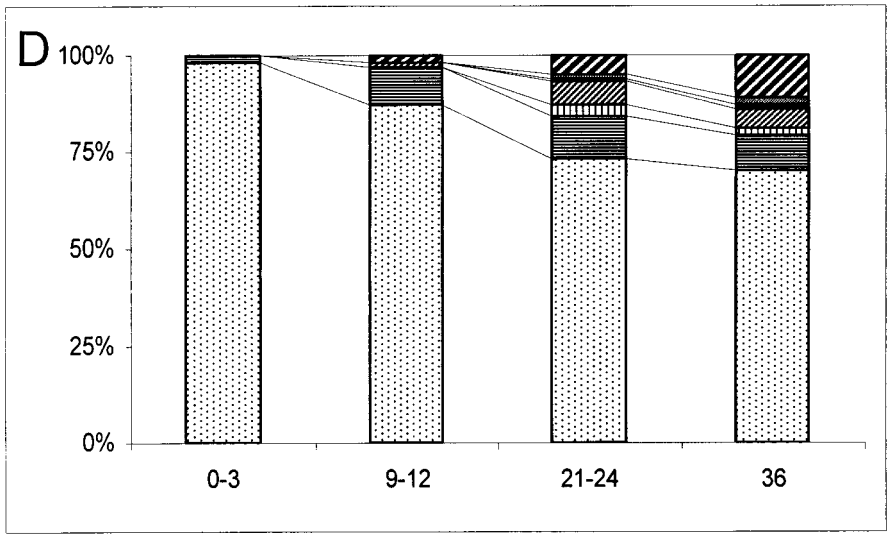

Figure 2D. Changes in medication over time in initial combination therapy including infliximab. Data in Figure 2 have been published in part in Arthritis & Rheumatism[1] and Annals of Internal Medicine[20].

in case of clinically insufficient response and observed higher progression rates in the initial monotherapy arms than we found in the BeSt study. However, the TICORA study[12] also had a DAS-driven design, including the use of corticosteroids, and still showed joint damage progression of median 4.5 units in the intensive-therapy group versus median 8.5 units in the routine-therapy group. To investigate this further, lacking a "non-DAS-adjusted" control group in the BeSt study itself, we tried to compose a control group from the early arthritis databases of the 2 major contributors to the BeSt population, the Leiden University Medical Center and the Free University (VU) Medical Center in Amsterdam. From these databases we selected patients who were diagnosed with RA in the 2 years before and after the inclusion period of the BeSt study, and who would have been eligible for participation in the BeSt study based on their clinical presentation. They were treated according to the insights of their treating

Table 1. Changes in patient outcomes during one year followup in Groups 1 and 2 of the BeSt trial (DAS-adjusted conventional DMARD therapy) and a non-DAS-adjusted control group.

	All Patients	DAS-based Routine Therapy	Management	p
Health Assessment Questionnaire*	−0.6 ± −0.7	−0.7 ± −0.7	−0.5 ± −0.7	0.029
Disease Activity Score in 28 joints*	−2.4 ± -1.5	−2.7 ± 1.5	−1.9 ± 1.5	<0.001
Erythrocyte sedimentation rate, mm/h†	−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 ± standard deviation; † median (interquartile range).

rheumatologists, without a fixed treatment protocol and not adjusted by regular DAS measurements. Although on more detailed examination the patients in this "control group" appeared to have milder disease at baseline, with a lower ESR, lower percentage RF-positive, and lower percentage already erosive at baseline, we found that after one year of treatment the clinical outcomes of the patients in the "control group" were statistically significantly worse than those of patients treated only with conventional DMARD in Groups 1 and 2 in the BeSt study. The radiological outcomes were still better than in the BeSt patients, but compared against the predicted radiological progression, based on the symptom duration and amount of damage at baseline, the benefits of DAS-adjusted treatment were again clear (Table 1)[13].

Implementation of 3-monthly DAS calculations and DAS-driven treatment adjustments for all patients may have practical and economic drawbacks in daily practice. We calculated that once DAS ≤ 2.4 was achieved (after which the medication remained unchanged in the BeSt study), the likelihood of the next DAS being ≤ 2.4 again was 74% — regardless of the treatment received, the timing of the first DAS ≤ 2.4, or the fact that this DAS was achieved after an intermittent disease flare. The likelihood to achieve a second consecutive DAS ≤ 2.4 (after which medication was tapered in the BeSt study) was even greater, and also after a DAS < 1.6, the chance of low disease activity in the next 3 or 6 months was high. For practical purposes this could indicate that one should start measuring and making adjustments according to the DAS every 3 months (or possibly even more often) as long as RA is active, but one could be more flexible once low disease activity is achieved[14].

Meanwhile, as the followup period in the BeSt study increased, the differences in radiological outcomes remained significant over time. This was all the more remarkable since in the dynamics of the study, many patients who originally started on conventional monotherapy had now progressed to treatment with MTX + infliximab after failure on previous steps, and patients who had originally started on combination therapy had discontinued and tapered to monotherapy maintenance dose because of continued good response. To investigate whether there were specific effects of these drug combinations that went beyond inducing an earlier reduction in disease activity, we performed a subanalysis of patients in all 4 groups who had achieved clinical remission (defined as DAS < 1.6) early (from 6 months) and who maintained this throughout the first 2 years of the study (once a DAS ≥ 1.6 but ≤ 2.4 was allowed). Besides finding that this was achieved twice as often in the initial combination-therapy groups, we observed that the patients in continuous remission on initial combination therapy had significantly less joint damage progression than the patients in continuous remission on initial monotherapy, despite the fact that in the combination-therapy groups (after 8 months, on average) prednisone or infliximab had been permanently discontinued[15].

The BeSt study included the largest cohort of patients who, after achieving a good response, have discontinued treatment with infliximab. It is also the only study where systematic dose increases of infliximab were employed in order to obtain a good response, before then trying to taper again. Although previous studies have shown no significant benefit of a dosage of 5 or 10 mg/kg over 3 mg/kg[16], we found that in a regimen of DAS-driven treatment adjustments, 30 of 77 patients first needed a dose-increase of infliximab (up to 10 mg/kg) before a good response was achieved and infliximab could then be tapered and finally stopped. The need for a higher infliximab dose to achieve a good response was not associated with a higher relapse rate after discontinuation of infliximab — indeed, none of these patients relapsed. Twenty-five percent (30/120) of patients who were treated with initial infliximab did not achieve a good response, despite dose increases up to 10 mg/kg (given twice). Most of these patients also failed on consecutive therapies[17].

The 67/120 (56%) patients who discontinued infliximab and maintained a good response also tapered MTX, to an average of 12 mg/week. This percentage of success taking MTX is significantly higher than in the initial monotherapy groups, where 32% still had a good response after 2 years, having tapered to (on average) 11 mg/week.

The 10 patients (8%) who had to restart infliximab because of an increase in DAS to > 2.4 after discontinuation all restarted within 4 months, and none showed an allergic reaction. All achieved a DAS ≤ 2.4 again, although some only after a dose increase.

Reviewing baseline characteristics and results of laboratory tests, we tried to identify predictors for a good radiological outcome. After including ESR, symptom duration, HLA-DR4, RF status, and erosions at baseline in a multiple regression analysis, we found that none of the factors traditionally associated with worse outcomes predicted high damage progression, but that the only significant risk determinant appeared to be the treatment group allocation: initial combination therapy resulted in significantly less joint damage progression than initial monotherapy[18].

In a subanalysis in patients who had shown consistent clinical failure (i.e., DAS > 2.4 from 6 to 24 months' followup, once ≤ 2.4 but > 1.6 allowed), patients treated with initial combination therapy did not show less joint damage progression than patients treated with initial monotherapy. This is in contrast to the subanalysis of the ATTRACT study[19], but there, patients who failed on infliximab still continued the drug, whereas in the BeSt study, after 9 months on average, such patients discontinued infliximab (or prednisone) and moved to the next treatment step. Still, patients in the BeSt study who clinically failed initial combination therapy appeared to benefit in achieving better functional ability than patients who failed initial monotherapy [median HAQ 1.5 (IQR 1.0–1.8) compared to 1.0 (IQR 0.8–1.5); p = 0.02][15].

Toxicity in terms of adverse events and serious adverse events was comparable between the 4 strategy groups. A hint of more serious adverse events in Group 3 could to a large extent be attributed to patients who had (repeated?) hospitalizations for problems unrelated to either RA or the treatment received. In the initial combination-therapy groups, a few more serious infections were reported than in the initial-monotherapy groups. In part this may be due to overdiagnosis based on assumed risk associations, but on the other hand these may also have led to preventing minor infections becoming serious[20].

The cost-utility evaluation of the BeSt study was based on monitoring of treatment steps, and on 3-monthly quality of life questionnaires and diaries on costs of healthcare and work absenteeism that were completed by the patients. Quality of life improved significantly earlier in Groups 3 and 4 than in Groups 1 and 2. Over 2 years, average quality of life as measured by the EuroQol and the Short Form-36 was significantly higher in the initial combination-therapy groups than in the initial monotherapy groups, and significantly higher in patients treated with initial infliximab than in patients treated with initial prednisone [1.41, 1.42, 1.44, and 1.52, respectively, for the EQ5D-NL (p ≤ 0.05 for Group 4 vs Groups 1-3); and 1.38, 1.38, 1.39, and 1.44 for the SF6D (p ≤ 0.05 for Group 4 vs Groups 1-3)]. Better quality of life was associated with more productivity: on average over the entire sample, a decrease of 0.1 on utility was accompanied by a decrease of 2 working hours per week. As a result, productivity was higher in patients in Group 4. In the medical-cost categories there were significantly higher costs of study medication (in particular infliximab) in Group 4 (p ≤ 0.05 Group 4 vs Groups 1-3) and lower costs of non-study medication in Group 4 (p ≤ 0.05 Group 4 vs Group 1). Total medical costs were estimated at € 10,792, € 7,288, € 7,809, and € 23,761, respectively, in Groups 1-4 (p ≤ 0.05 for all comparisons, except Group 2 vs Group 3). Whether the higher productivity compensated for the higher medical costs depends on the method used to calculate the overall societal cost. The friction-cost method takes the perspective of the employer and considers as loss only those hours that fall in a period of at most 6 months that the employer needs to adjust to the new situation. The human-capital method takes the perspective of the patient and considers each hour not worked as a loss. Using the friction-cost method, overall societal costs were estimated at € 19,905, € 15,926, € 17,810, and € 28,547 (p ≤ 0.05 Group 4 vs Groups 1-3). The cost-utility ratio for Group 4 versus Group 3 was estimated at € 121,000 per quality-adusted life-year [QALY (95% CI € 34,000 to € 1,660,000 per QALY)]. Using the human-capital method instead of the friction-cost method, the savings on productivity costs in Group 4 largely compensated for the extra medical costs[5].

During followup, the discontinuation of infliximab by protocol, either in case of success or in case of failure, reduced the costs of initial infliximab therapy considerably, whereas the costs of infliximab in the other groups increased over time with the introduction of the drug in those who failed previous treatments. Based on previous observations in patients who started and then discontinued infliximab after failing other therapies, it is unlikely that many of the "late starters" will be able to discontinue infliximab as in the initial treatment group, but this is still speculative. Nor can it be predicted how long the "infliximab-free" period will last in those who previously discontinued it. During the next years, we will continue to follow all patients and the cost-utility analysis will be repeated.

The Next Years

The results of the first 2 years of the BeSt study encouraged us to adapt the treatment protocol for the next years, introducing the possibility of discontinuing all antirheumatic drugs once the patient had been in clinical remission (DAS < 1.6) for at least 6 months after tapering to monotherapy in maintenance dose. If the DAS

increases to ≥ 1.6, the last discontinued drug is restarted; if the DAS then increases to > 2.4 the dose is increased; and then, if necessary, the next drug or combination of drugs is reintroduced. In case of repeated remission for at least 6 months, all medication is tapered and stopped again, with the exception of infliximab, which is to be kept in maintenance dose.

This adaptation of the protocol resulted in followup of a large number of patients who were in clinical remission without any therapy. In Group 1, 11% of patients could discontinue all medication and were still in remission at t = 3 years; in Group 2 this was 6%; in Group 3, 7%; and in Group 4, 16% ($p < 0.05$ for Group 4 vs Groups 2 and 3). In Group 4, over time 14 patients had restarted infliximab because of an increase of the DAS > 2.4. Ten of these patients restarted in the first year, shortly after discontinuation of infliximab; 4 restarted in the third year, 19, 20, 25, and 27 months, respectively, after discontinuation of infliximab. Having restarted, all again regained a good response, and none experienced an allergic reaction[21].

After 3 years of treatment, radiological damage progression remained low in all groups, and was significantly lower in the initial combination-therapy groups than in the initial monotherapy groups. The median increase in total Sharp/van der Heijde score after 3 years was 3.8, 3.0, 1.8, and 1.5 in Groups 1 through 4, respectively (Group 1 vs 2: $p = 0.518$; Group 1 vs 3: $p = 0.007$; Group 1 vs 4: $p < 0.001$; Group 2 vs 4: $p = 0.004$; other comparisons $p > 0.05$). Joint damage progression > smallest detectable change was observed in 44%, 43%, 29%, and 25% of patients in Groups 1-4, and an increase in total Sharp/van der Heijde score of more than 20 points in 3 years was seen in 17, 9, 4, and 3 patients in Groups 1-4, respectively (Figure 3).

In the coming years, the 3-monthly evaluations will continue to determine the duration of drug-free remission, and to monitor further changes in the medication in relation to functional ability and quality of life. Yearly radiographs of hands and feet will establish whether clinical remission with or without medication translates to radiological remission. Cost-utility analyses are scheduled for t = 5 years and t = 10 years. Thus, the BeSt study will continue to register the effects of the new approach to treatment of recent-onset RA.

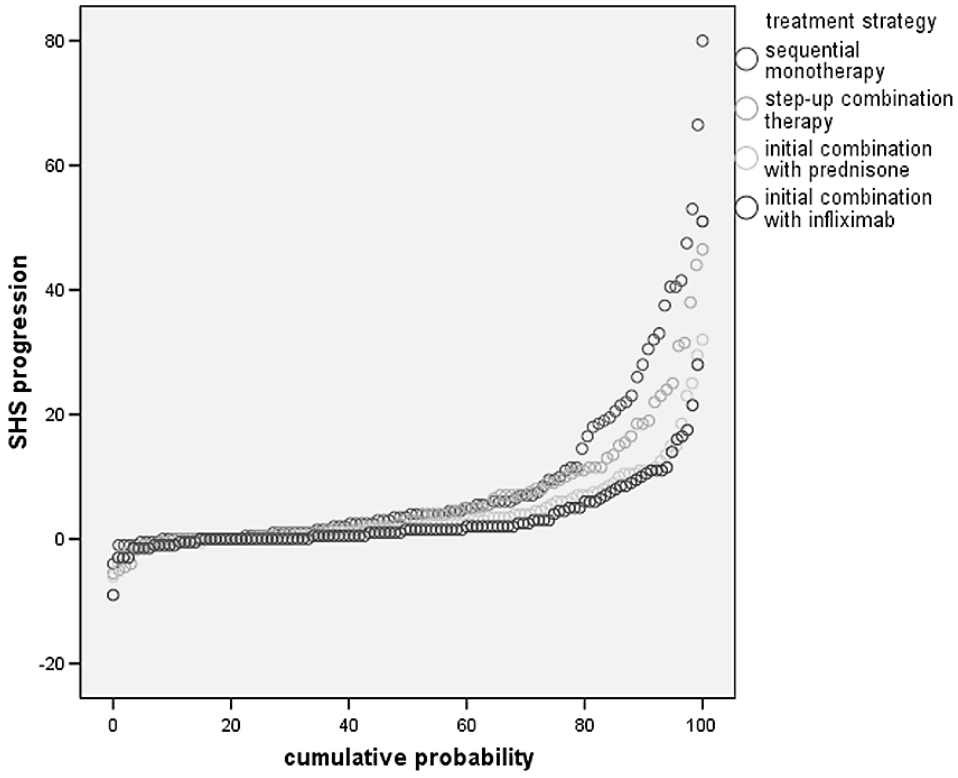

Figure 3. Cumulative probability distribution of total Sharp score over 3 years of treatment with sequential monotherapy, step-up combination therapy, initial combination therapy including prednisone, or initial combination therapy including infliximab.

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