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Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial

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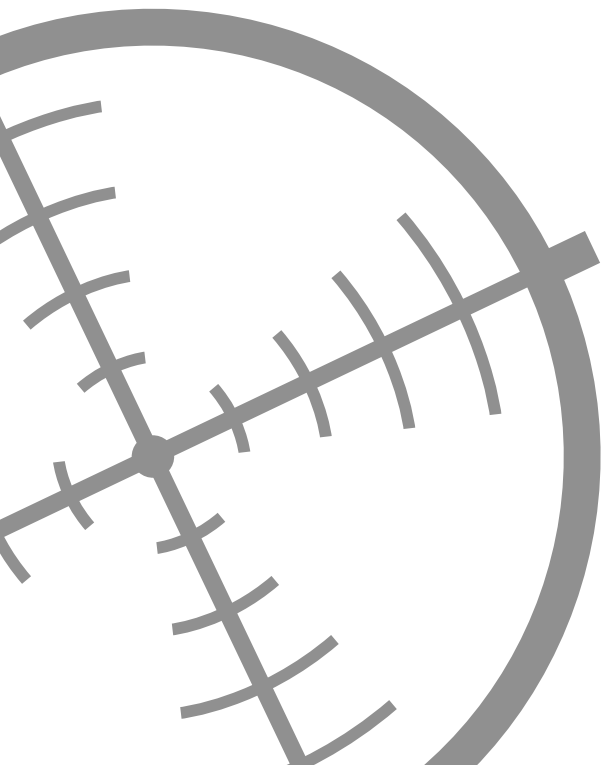

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ABSTRACT

Background

In patients with rheumatoid arthritis (RA), treat-to-target therapy is effective. However, long-term results of continued targeted treatment are lacking.

Objective

To evaluate long-term outcomes in patients with recent-onset RA after ten years of targeted treatment in 4 treatment strategy arms (BeSt study).

Design

Long-term follow-up randomized trial.

Setting

The Netherlands.

Patients

508 patients with recent-onset, active RA.

Intervention

Sequential monotherapy (strategy arm 1), step-up combination therapy (strategy arm 2), initial combination with prednisone (strategy arm 3), initial combination with infliximab (strategy arm 4), all followed by targeted treatment aiming at low disease activity.

Measurements

Functional ability (health assessment questionnaire) and radiographic progression (Sharp/van der Heijde score) were primary endpoints. Survival in the BeSt population was compared to the general population with the Standardized Mortality Ratio (SMR).

Results

195/508 (38%) of patients dropped out of the study (28% in arm 4 versus 40-45% in arms 1 to 3). At year 10, mean (SD) HAQ was 0.57 (0.56), 53% was in remission, and 14% in drug-free remission, without differences between the strategy arms. Over ten years, mean HAQ was 0.69, 0.72, 0.64 and 0.58 in strategy arm 1 to 4, respectively (differences not clinically relevant, p=0.030 for strategy arm 2 versus 4, other comparisons not significant). Ten-year radiographic progression was low in all strategy arms (median progression 2.0). Over time, small differences in joint damage showed an advantage for strategy arm 4 (p=0.045).
SMR was 1.16 (95% CI 0.92 – 1.46), based on 72 observed and 62 expected deaths, with similar survival rates among the strategy arms (p=0.81).

Limitations

Drop-out rate varied by strategy arm.

Conclusions

In early RA patients, initial (temporary) combination therapy results in more rapid clinical improvement, and targeted treatment determines long-term outcomes. (Drug-free) Remission, with prevention of functional deterioration and clinically relevant radiographic damage, and normalized survival are realistic outcomes.

INTRODUCTION

Suppression of inflammation in patients with rheumatoid arthritis (RA) is associated with clinical improvement and prevention of radiographic joint damage. Rapid suppression of inflammation can be achieved with initial combination therapy including synthetic disease-modifying antirheumatic drugs (DMARD) and corticosteroids or a tumor necrosis factor alpha (TNFα) inhibitor.[1–7] In addition, tightly controlled targeted treatment, i.e. frequent measurements of disease activity, with treatment adjustments aiming to achieve a predefined target, results in better outcomes than 'routine' care.[8,9]

The BeSt study integrated a treat-to-target concept to achieve low disease activity (defined as disease activity score (DAS) ≤2.4) with a comparison of four dynamic treatment strategies. Patients with early, active RA were randomized to sequential monotherapy, step-up combination therapy or initial combination therapy including either prednisone or an anti-TNFα agent (infliximab). Based on three-monthly measurements of disease activity, medication was intensified in case of DAS >2.4 and tapered in case of a persistent DAS ≤2.4. The study compared the clinical, radiographic and toxicity outcomes of these strategies over time. Here we report on the outcomes during ten years of follow-up.

PATIENTS AND METHODS

Study design

The randomized, multicenter, assessor-blind BeSt (Dutch acronym for treatment strategies) study was designed by Dutch rheumatologists to determine in which order available antirheumatic medication could best be used to treat patients with newly diagnosed RA, aiming at low disease activity, over a period of ten years.[2] The original study protocol and the amendments for study extension after 2 and 5 years were approved by the medical ethics committees of all participating hospitals. All patients gave written informed consent.

508 patients with recent-onset, active rheumatoid arthritis according to the revised 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis,[10] with a symptom duration of less than 2 years and aged ≥18 were recruited in 18 non-university hospitals and 2 university hospitals in the Netherlands between 2000 and 2002. Exclusion criteria encompassed contraindications to the antirheumatic medication used in the study protocol. Details are described in Supplementary File 1 and have been published previously.[2,11]

Randomization and interventions

Patients were allocated to one of four dynamic treatment strategies by variable block randomization, stratified per center: 1. sequential monotherapy, 2. step-up combination therapy (both starting with methotrexate monotherapy), 3. initial combination with methotrexate, sulphasalazine and prednisone, 4. initial combination with methotrexate and infliximab. For all randomization arms, subsequent treatment adjustments were specified in

the study protocol for patients with an inadequate response (Supplementary Figure 1). Over ten years, treatment response was measured every three months using the disease activity score (DAS),[12] based on a swollen joint count in 44 joints, a tender joint count in 53 joints (Ritchie articular index),[13] erythrocyte sedimentation rate (ESR) and patient's assessment of global health on a visual analogue scale (VAS, 0 to 100 mm).[12] A DAS ≤2.4, indicating low disease activity,[14] was set as the treatment goal in this study. Treatment was intensified (medication change or dose increase, according to the treatment strategy) each study visit when a DAS >2.4 was measured. In case of a continued good response (DAS ≤2.4), medication was tapered to a maintenance dose and eventually (if DAS remained <1.6, defined DAS-remission)[15] to drug-free remission (DFR) (details in Supplementary File 2).

Study endpoints

Planning and content of the study visits every three months did not change during all phases of ten years follow-up. Functional ability was measured every three months with the health assessment questionnaire (HAQ, range 0 [best] to 3 [worst])[16]. Joint damage progression was evaluated on annual conventional radiographs of hands and feet using the modified Sharp/van der Heijde score (SHS, range 0 [best] to 448 [worst]).[17] All obtained radiographs from baseline to year ten were scored by two independent blinded readers in one session in random time order. The intraclass correlation coefficient (95% confidence interval, 95% CI) between the two readers was 0.96 (0.95 – 0.97). The mean score of the two readers was used for the analysis.

Adverse events (AE), either reported during three-monthly visits or apparent in continued three-monthly laboratory assessments, and serious adverse events (SAE), which also included death during follow-up, were recorded during the trial. For patients who had dropped out, life/death status up to year ten from inclusion was obtained from the hospital of inclusion, the general practitioner or the municipality of residence of the patient. Patients who emigrated and could not be traced thereafter, were censored from the date of emigration (n=6). One patient could not be localized after loss to follow-up and was also censored from the last moment of contact. Survival data of the general Dutch population were acquired from the Central Bureau for Statistics Netherlands.

Statistical analysis

For each analysis, patients were analyzed in the treatment strategy arm of allocation at baseline, regardless of the number of treatment steps that were taken during follow-up. Time to drop-out was compared between the treatment strategies with the log-rank test. HAQ, low disease activity (LDA), DAS-remission, DFR, SHS and initial treatment step at year ten (intention-to-treat and completer analyses) were compared between the randomizations arms using the Kruskal-Wallis, independent *t*-test, analysis of variance or χ^2-test as appropriate. Multiple imputation, creating ten datasets, was used for missing data on DAS based on a linear regression model fitting observed DAS, HAQ, randomization arm, age, gender, anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), SHS and treatment step. A

generalized linear model was used to estimate the percentages of low disease activity and remission at year 10, and to compare these outcomes between the strategy arms. HAQ over time was analyzed using a linear mixed model, taking into account repeated measurements, with a Toeplitz covariance type, under the assumption of equally spaced visits (scheduled three-monthly). Time was entered as continuous variable, treatment and its interaction term as independent variables. Observed radiographic progression (based on the SHS) was compared among the treatment strategy arms with a Kruskal-Wallis test and was depicted in a cumulative probability plot. Radiographic progression over time was analyzed using GEE due to the skewed nature of these outcomes and to account for the repeated measurements within individuals over time. Missing data were handled with weighing under a 'missing at random' (MAR) framework. Weights per patient per year were found by using a logistic regression analysis including determinants based on biological plausibility and literature (see Supplementary File 3). Survival in the study population was compared to the general population (matched by gender, age, calendar year) using the standardized mortality ratio (SMR): observed/ expected deaths, and the 95% confidence interval: exp (ln (SMR) ± 1.96 * 1/√(observed)). Kaplan-Meier curves and the log-rank test were used to compare survival rates between the treatment strategies. Cox regression analysis was used to identify possible predictors for death. Predictors for the univariable model were selected based on literature and biological plausibility, and for the multivariable model based on significance in the univariable model and biological plausibility (see Supplementary File 3). Stata version 13 (StataCorp LP, Texas, USA) was used to calculate the SMR. IBM SPSS Statistics version 20 (IBM Corporation, New York ,USA) was used for all other analyses. Details are given in Supplementary File 3.[18,19]

RESULTS

Baseline characteristics were comparable among 508 patients randomized to four strategy arms (Table 1, Supplementary Figure 2). Patients had a short symptom duration (median 23 weeks), high disease activity (mean DAS 4.4) and reduced functional ability (mean HAQ 1.4). During ten years of follow-up, 195/508 patients (38%) dropped out of the study (Supplementary Figure 2), least often in strategy arm 4 (p=0.031). Of these, 77 patients (39%) were in clinical remission (DAS <1.6) at the time they left the study, with a median (IQR) duration of 18 (3 – 35) months. Of the 313 patients (292 with a DAS available) who completed ten years follow-up, 238/292 (82%) had low disease activity (DAS ≤2.4) and 154/292 (53%) were in DAS-remission (47 in drug-free remission), without statistically significant differences across the treatment arms.

Time to response

During the first year, the treatment target of DAS ≤2.4 was achieved earlier after initial combination therapy in strategy arms 3 and 4 than in arm 1 and 2 (Figure 3; Supplementary Figure 3A). Figure 3 and Supplementary Figure 3B show that patients allocated to initial

Table 1. Patient and disease characteristics at baseline.

	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab
	n=126	n=121	n=133	n=128
Age (years), mean (SD)	54 (13)	54 (13)	55 (14)	54 (14)
Female, n (%)	85 (68)	87 (72)	88 (66)	83 (65)
Symptom duration (weeks), median (IQR)	23 (14 – 54)	26 (14 – 56)	23 (15 – 53)	23 (13 – 46)
DAS, mean (SD)	4.5 (0.9)	4.5 (0.8)	4.4 (0.9)	4.3 (0.9)
HAQ, mean (SD)	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.7)
RF positive, n (%)	84 (67)	77 (64)	86 (65)	82 (64)
ACPA positive, n (%)	80 (64)	69 (57)	68 (51)	83 (65)
Erosive disease, n (%)*	89 (72)	82 (70)	93 (71)	93 (73)

ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; IQR, interquartile range; HAQ, health assessment questionnaire (range 0 – 3); RF, IgM rheumatoid factor; SD, standard deviation.
*Erosive disease denotes the presence of doro: >0.5 bone erosion on conventional radiographs of hands and feet.

combination therapy also achieve remission somewhat earlier. In subsequent years, continued targeted treatment resulted in similar levels of disease activity in all strategy arms. At year ten, 84%, 76%, 83% and 84% of patients in arm 1 to 4 were estimated to have DAS ≤2.4 (after multiple imputation, p<0.001). Remission percentages (DAS <1.6) over time increased to estimations of 51%, 49%, 53% and 53% in strategy arm 1 to 4, respectively (p=0.042). In strategy arm 1 to 4, 11, 11, 12 and 13 patients were in drug-free remission at year ten (observed data, p=0.60) with a median duration of 25, 75, 38 and 68 months, respectively (p=0.27). During follow-up, 34/126 patients (27%), 29/121 patients (24%), 29/133 patients (22%), 37/128 patients (29%) had ever achieved DFR (observed data, p=0.57).

Treatment

After ten years of treat-to-target therapy aiming at DAS ≤2.4, the majority of patients had proceeded to the next treatment step (Figure 2 and Supplementary Figure 1 and 2), using an estimated median (IQR) number of antirheumatic medications of 4 (2 – 6); 4 (2 – 6); 5 (3 – 6); 3 (2 – 6) per 10 patient years in strategy arm 1 to 4, respectively. Only 21/126 patients (17%) in strategy arm 1, 13/121 patients (11%) in strategy arm 2, 33/133 patients (25%) in strategy arm 3 and 52/128 patients (41%) in strategy arm 4 were still on the initial treatment step, with most patients in arms 3 and 4 having been able to taper initial combination therapy to monotherapy or drug-free remission (Figure 2C and 2D). Twenty-three of 92 (25%) completers in strategy arm 4 still used or had restarted infliximab at year ten, while of completers in strategy arm 1 to 3, 14/76 (18%), 8/67 (12%) and 10/78 (13%), respectively, had switched to infliximab at year ten (overall comparison strategy arms 1 to 4 p=0.184; p=0.037 for strategy arm 2 versus strategy arm 4; p=0.048 for strategy arm 3 versus strategy arm 4). The treatment protocol did not allow prolonged use of prednisone, and only 3, 8, 8 and 8 patients in strategy arm 1 to 4, respectively, used prednisone at year ten.

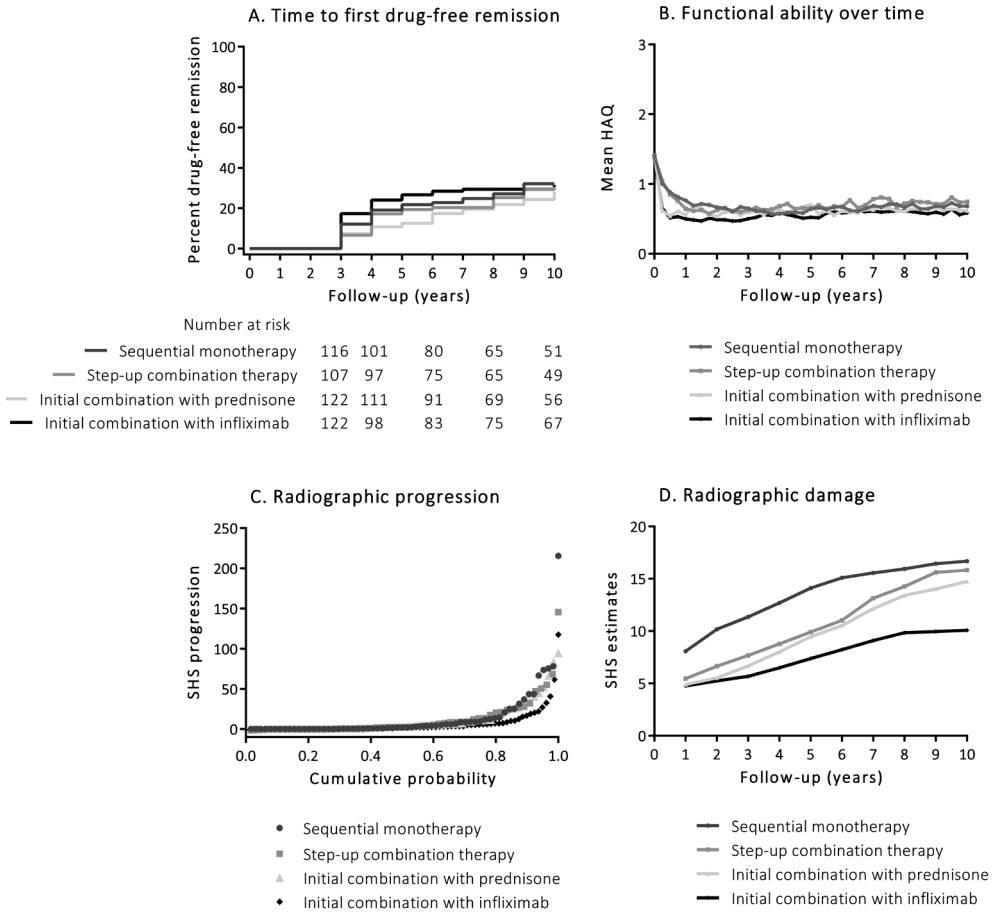

Figure 1. (A) Time to achieve drug-free remission (raw data), (B) Mean functional ability over time (based on estimates of a linear mixed model), (C) Cumulative probability plot (raw data of completers), (D) Estimated radiographic damage (weighted generalized estimating equation), during/ after ten years of targeted treatment, with multiple medication adjustments when low disease activity was not achieved or maintained, for the four treatment strategies.
Note (Figure 1A): Log-rank test: p=0.69.
Note (Figure 1C): This plot is a cumulative frequency distribution that orders the data from the lowest through the highest value per strategy arm, and plots each individual value with a dot. The figure is based on all observed radiographs during the trial. The changes from baseline were used to find the cumulative probabilities by treatment strategy. [36,37]
Note (Figure 1D): Depiction of SHS estimates over time for the total BeSt population, as a result of the weighted generalized estimating equation.
HAQ, health assessment questionnaire; SHS, Sharp/ van der Heijde score.

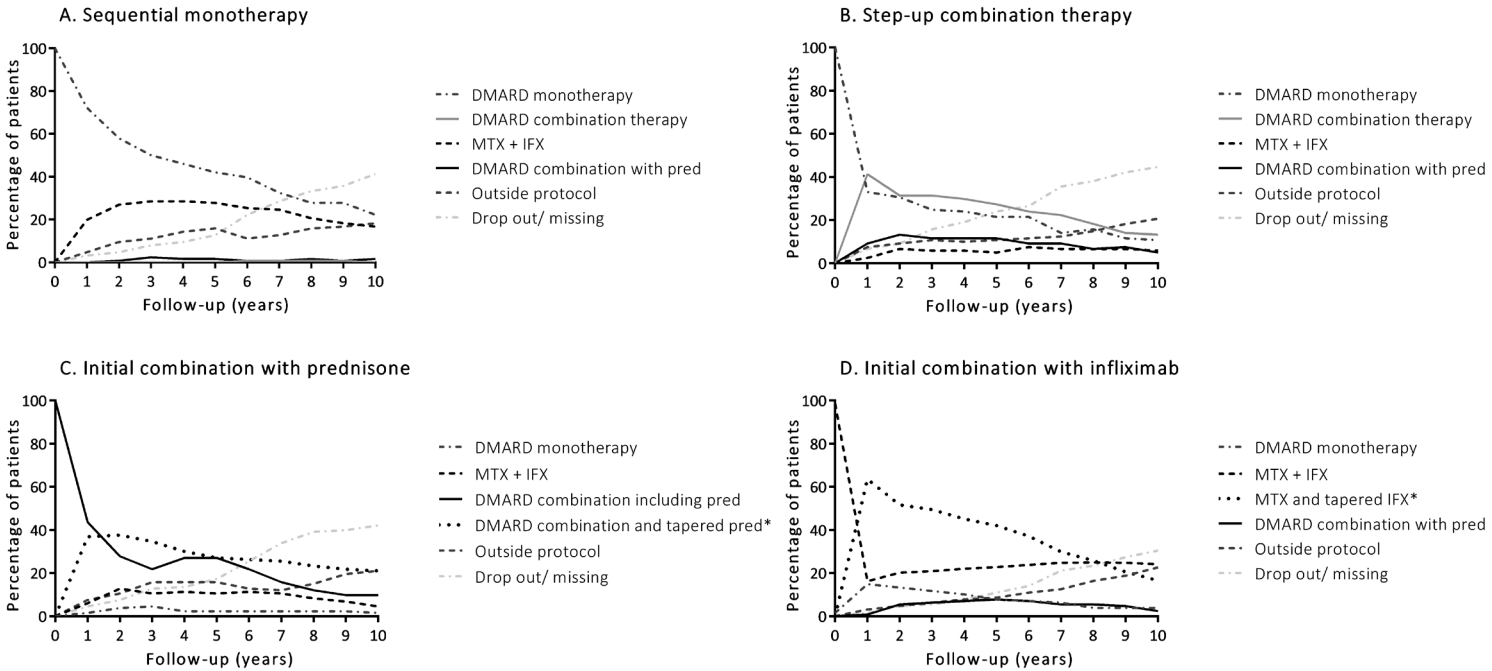

Figure 2. Percentages of patients on various treatment steps over time for patients allocated to (A) sequential monotherapy, (B) step-up combination therapy, (C) initial combination with prednisone and (D) initial combination with infliximab.
*These lines in strategy arm 3 and 4 depict the number of patients on the initial treatment step who have tapered to monotherapy or discontinued all medication.
Note 1: Outside protocol denotes patients who, although continuing DAS ≤2.4 steered treatment, did not use medications of the sort and/or at the time required in the protocol.
Note 2: Comparison of patients still on the initial treatment step at year ten: p<0.001 for strategy arm 1 versus strategy arm 4; p<0.001 for strategy arm 2 versus strategy arm 4; p=0.002 for strategy arm 2 versus strategy arm 3; p=0.038 for strategy arm 3 versus strategy arm 4; other comparisons not significant.
Note 3: 47 patients in drug-free remission at year 10 achieved this (i.e. achieved and maintained remission allowing to taper to drug-free) on the following treatment steps: methotrexate monotherapy, 13/47 (28%) (for all the initial treatment step in strategy arm 1 and 2); methotrexate and infliximab, 11 (23%) (for all the initial treatment step in strategy arm 4); methotrexate, sulphasalazine and prednisone, 8 (17%) (for all the initial treatment step in strategy arm 3); methotrexate with sulphasalazine, 4 (9%); sulphasalazine monotherapy, 2 (4%); leflunomide monotherapy, 2 (4%); methotrexate, ciclosporin A with prednisone, 2 (4%); methotrexate with sulphasalazine and hydroxychloroquine, 1 (2%); azathioprine with prednisone, 1 (2%); outside protocol, 3 (6%).
DMARD, disease-modifying antirheumatic drug; IFX, infliximab; MTX, methotrexate.

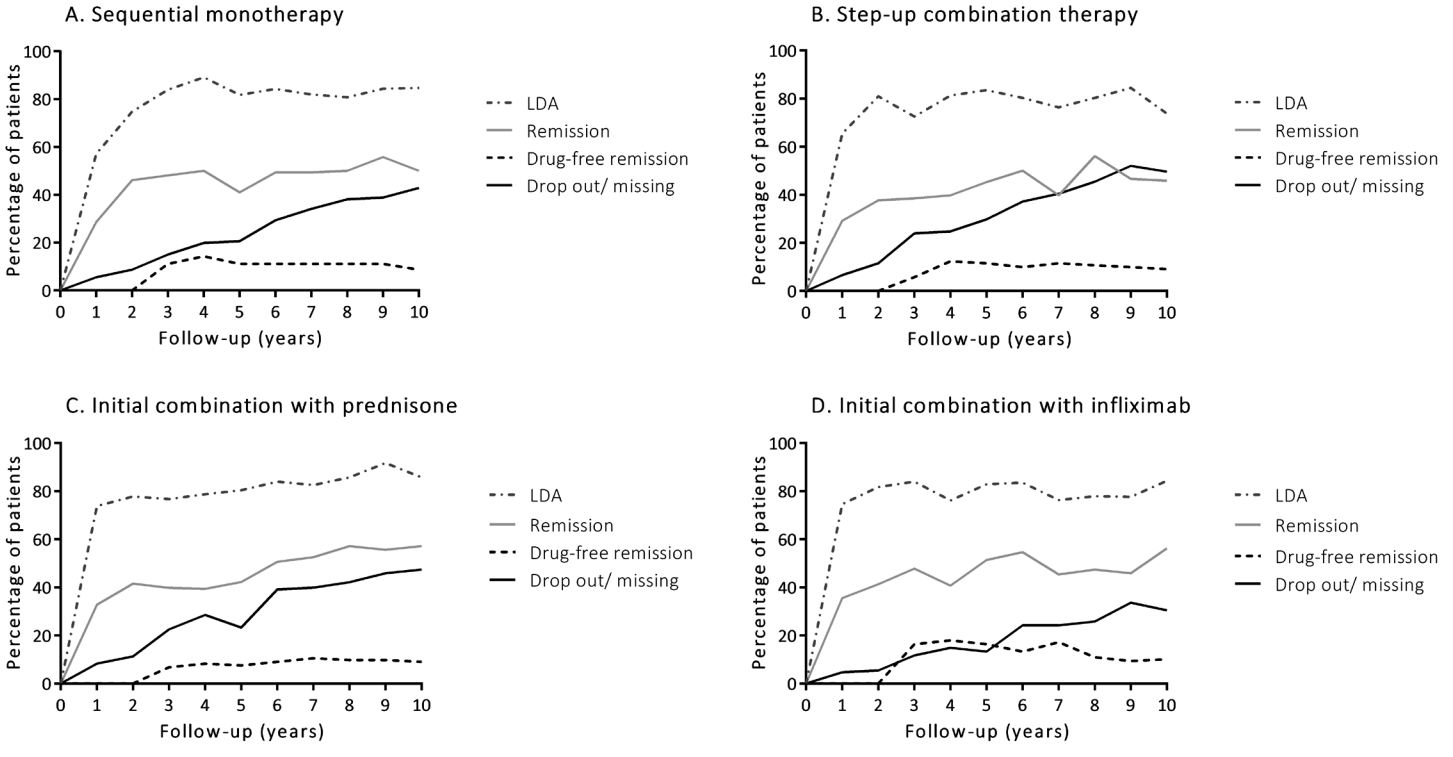

Figure 3. Patient disposition over time (observed data, showing the percentage of total number of patients included, not of total number of patients with data available at that timepoint) for patients allocated to (A) sequential monotherapy, (B) step-up combination therapy, (C) initial combination with prednisone and (D) initial combination with infliximab. LDA, low disease activity (defined as DAS ≤2.4).

Functional ability

During the first year, functional ability improved earlier in patients allocated to the initial combination therapy strategy arms compared to patients treated with initial monotherapy (Figure 1B). In subsequent years, representing the effect of continued targeted treatment, HAQ remained stable with mean values over time of 0.69, 0.72, 0.64 and 0.58 in strategy arm 1 to 4, respectively (LMM, p=0.030 for arm 2 versus 4; differences not clinically relevant;[20] other comparisons not significant).

Joint damage

After ten years of targeted treatment, median (IQR) joint damage progression (measured with the SHS) in patients who completed follow-up was low: 2.0 (0.0 – 11.0) in strategy arm 1, 2.5 (0.0 – 13.5) in strategy arm 2, 3.0 (0.3 – 11.3) in strategy arm 3 and 1.5 (0.0 – 6.0) in strategy arm 4 (completer analysis; p=0.39) (Figure 1C). SHS estimates at year 10 were 16.7, 15.8, 14.7 and 10.1 in strategy arm 1 to 4, respectively (weighted GEE, p=0.050 for strategy arm 1 versus 4; p=0.049 for strategy arm 2 versus 4; p>0.10 for other comparisons) (Figure 1D). The mean estimated SHS progression over time for strategy arm 1 to 4 was 13.6, 10.8, 9.9 and 7.7, respectively (weighted GEE, p=0.045 for overall comparison; p=0.018 for strategy arm 1 versus 4; p=0.053 for strategy arm 2 versus 4; p=0.093 for strategy arm 3 versus 4; p>0.10 for other comparisons).

Toxicity

During ten year follow-up 3,109 AE in 453/508 patients (89%) were reported (74 AE per 100 patient years), equally distributed among the strategy arms (p=0.159) (Supplementary Table 2). Infectious AE were the most common subtype (no difference in occurrence of infectious AE between the strategy arms: p=0.158).Numerically, more cardiovascular events occurred in strategy arm 3, including a higher prevalence of hypertension in these patients (Supplementary Table 2), and less gastrointestinal events during the first study period.
486 SAE were recorded in 240/508 patients (47%) (12 SAE per 100 patient years). In year 1-2 there appear to be more SAE in strategy arm 3, but over time frequencies of SAE vary without significant differences between the strategy arms (p=0.47) (Table 2). Seventy-two patients died during follow-up, 16 in strategy arm 1, 15 in arm 2, 21 in arm 3 and 20 in arm 4. The causes of death could only be obtained in 39 of these 72 patients (Table 2). Of three patients who died of an infectious cause in arm 4, two were on infliximab 10 mg/kg/8 weeks. The other patient stopped infliximab almost 9 years before death. Of three patients who died of an infectious cause in arm 1, two had never used infliximab and one had used infliximab but discontinued a year before death.

Survival

In 501/508 patients (99%) life/death status could be obtained. Six of 7 patients with missing life/death status emigrated after a mean (SD) follow-up duration of 4.2 (3.0) years. The seventh patient was lost to follow-up after 4.4 years and was censored at that time. Mean

(SD) age at baseline of these 7 patients was 47 (10) years and three of them were female, compared to a mean (SD) age at baseline of the total BeSt population of 54 (14) years with 67% females.

In total, 72 patients died before the end of ten year follow-up at a mean (SD) age of 75 (10) years. The SMR for the total BeSt population was 1.16 (95% CI 0.92 – 1.46), based on 72 observed and 62 expected deaths. Comparing the general population to each treatment strategy resulted in SMR (95% CI) of 1.00 (0.61 – 1.64), 1.02 (0.61 – 1.69), 1.30 (0.85 – 1.99) and 1.32 (0.85 – 2.04) in strategy arm 1 to 4, respectively. Within the BeSt population, no difference in survival was observed between the treatment strategies (p=0.81) (Figure 4).

Age, male gender, smoking and HAQ at baseline were independently associated with an increased risk of mortality (Supplementary Table 3). Disease activity over time was also associated with increased mortality (HR 1.44, 95% CI 1.10 – 1.90).

Table 2. Serious adverse events and deaths per study period.

SAE per 100 patient years	**Year 1 - 2**	**Year 3 - 5**	**Year 6 - 10**	**After drop out**
Sequential monotherapy	9.8	12.7	13.2	***NA***
Step-up combination therapy	8.2	11.4	10.9	***NA***
Initial combination with prednisone	13.6	10.5	12.1	***NA***
Initial combination with infliximab	6.3	12.2	13.4	***NA***
Deaths				
Sequential monotherapy	0	3	5	8
Step-up combination therapy	1	2	5	7
Initial combination with prednisone	1	1	7	12
Initial combination with infliximab	2	2	10	6
Causes of death				
Sequential monotherapy		1 inf, 1 mal, 1 CVD	2 inf, 1 mal, 2 other/unkown	***NA***
Step-up combination therapy	1 CVD	1 mal, 1 CVD	2 mal, 1 CVD, 2 other/unkown	***NA***
Initial combination with prednisone	1 mal	1 CVD	1 inf, 4 mal, 1 CVD, 1 other/unkown	***NA***
Initial combination with infliximab	1 inf, 1 CVD	1 inf, 1 CVD	1 inf, 4 mal, 2 CVD, 3 other/unkown	*NA*

CVD, cardiovascular disease; inf, infectious disease; NA, not available; mal, malignancy.

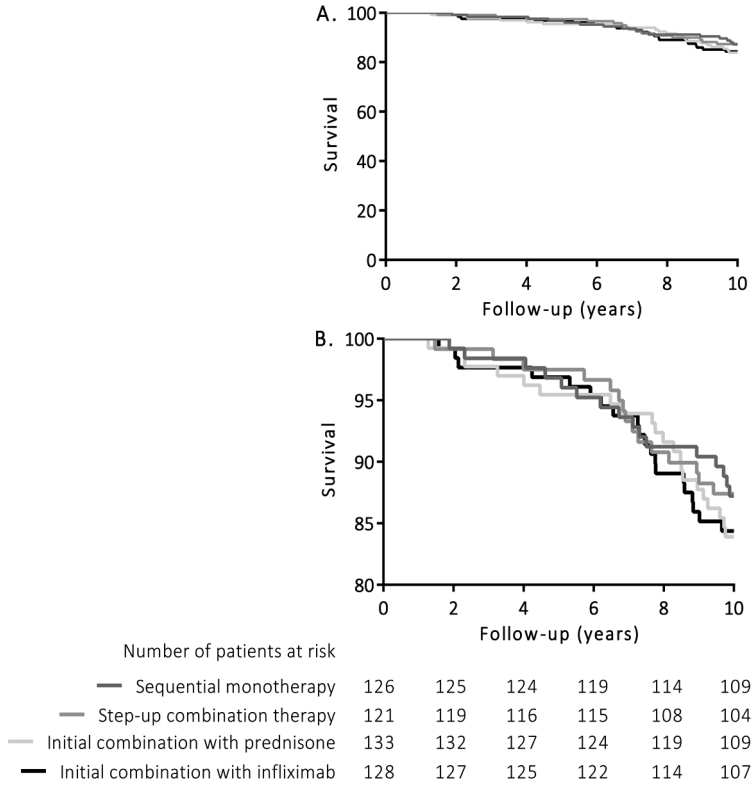

Figure 4. Survival curves per treatment strategy (B, with an y-axis ranging from 80 to 100%, is an enlargement of A, with an y-axis ranging from 0 to 100%).
Note: log-rank test: p=0.81.

DISCUSSION

In the BeSt study, after ten years of protocolled treatment targeted at low disease activity in patients with early, active rheumatoid arthritis (ACR 1987 criteria)[10], there is persistent efficiently suppressed disease activity, good functional ability and limited joint damage progression in most patients, and overall survival is comparable to that of the general Dutch population.

This study was designed in the late 1990s to determine in which order available antirheumatic therapies should be given to achieve the best clinical outcomes and the least radiographic progression. Four treatment strategies were compared, in all of which over 10 years of follow-up a treat-to-target strategy was maintained. It is clear that earlier clinical improvement was achieved in patients who started with a combination of methotrexate, sulphasalazine and prednisone (strategy arm 3) or with methotrexate and infliximab (arm 4) rather than with initial methotrexate monotherapy in arms 1 and 2.[2,11] After this important difference,

at year ten (or even at year one), it appears that all four treat-to-target strategies were equally effective in preventing functional disability and radiographic progression. As long as the target of DAS ≤2.4 was not achieved, the protocol dictated treatment adjustments in all arms involving the same established antirheumatic drugs, although not always in the same order. As a result, most patients who started with monotherapy proceeded to some type of combination therapy. Once a DAS of ≤2.4 was achieved for ≥6 consecutive months patients were required to taper medication, even to nil if sustained remission was achieved. Most patients in the initial combination therapy arms thus tapered to monotherapy.

Both initial combination therapies appear to have principally similar results although numerically, radiographic progression was lowest and functional ability was highest over time in strategy arm 4. Infliximab is expensive and currently in most countries as initial treatment it is not reimbursed. Nevertheless, in an earlier analysis we have shown that the initial costs of treatment decrease when infliximab is tapered and discontinued, and may be compensated elsewhere.[21] Toxicity was comparable among the strategy arms, although numerically there were more early SAE in arm 3 and there appeared to be more infection-related deaths in arm 4 and 1 (where many patients proceeded to use infliximab). However, a causal effect between treatment and adverse events could not be determined. The fact that we found no statistically significant differences in overall survival between the four treatment arms, suggests that (the level of) suppression of disease activity contributes more to better survival than initial and over time use of specific drugs. Although we could not prove this hypothesis with our data, we found an association between higher disease activity over time and increased mortality. On the contrast (and in contrast with previous reports), [22,23] no increased risk for mortality was demonstrated in patients with autoantibodies. This is in line with a previous finding in the BeSt study that RF and ACPA positivity (except in arm 1)[24] were not associated with inferior clinical response to treatment.[25] Non-modifiable factors as male gender and a higher age, and functional disability at baseline, and also smoking (defined as current smoking at baseline, a potentially modifiable risk factor) and disease activity over time were independent predictors for increased mortality. Thus, possibly related to effective suppression of inflammation with current therapies, patients with RA seem to become more and more similar to the general population when it comes to outcomes such as survival. It is still possible that excess mortality will emerge after ten years of disease duration,[26] although in previous studies it was described already in the first decade of the disease.[22,27,28]

Survival may also have been influenced by trial in- and exclusion criteria of the study. On the one hand, due to the administration of anti-TNFα in one randomization arm, patients with severe comorbidity (e.g., recent malignancies, recurrent infections) were excluded. On the other hand, patients with active, mostly autoantibody positive and already erosive RA were included. Despite these possible selection effects, our results confirm the finding of normalized survival rates in RA patients from a previous study based on the follow-up of unselected patients in the Leiden Early Arthritis Cohort.[27]

The BeSt study helped change the outlook for new generations of patients. Although patients

had active, severe disease at inclusion, many achieved the treatment goal of low disease activity, and even clinical remission, allowing tapering of medication. Thus, initial combination therapy in most patients was effectively 'bridging therapy'. Not just low disease activity, but DAS-remission may be a realistic treatment target, as also suggested by the outcomes of more recent remission steered studies,[1,7,29–32], and current guidelines even recommend more stringent definitions of remission as the optimal treatment target.[33,34] However, continued treatment adjustments in patients who achieved low disease activity but not yet remission may lead to relative overtreatment. Hence, further research is needed to focus on optimal treatment targets in subgroups of patients, finding a balance between disease suppression and the amount of medication.

Of course the BeSt study has limitations. It covers only 10 years in a disease that may last many decades. With 38% drop out over ten years, results of the completers analyses should be interpreted carefully. The more sophisticated methods used as mixed models and weighted GEE might provide more reliable results. Patients who dropped out were older and had a higher HAQ at baseline, which might result in an underestimation of HAQ levels (thus, an overestimation of treatment effect) during the later phase of follow-up. Lacking a non-targeted-treatment arm we cannot confirm, as shown in the TICORA study,[8] that DAS ≤2.4 steered treatment is superior to interview-based treatment. As we aimed to monitor the effect of the order of medications rather than the effect of individual therapies, we cannot compare medications head-to-head, or link side effects to specific drugs. The study started in 2000 and we never changed the protocol, except for the introduction of tapering to drug-free remission. Our results could have been different had we included, for example, newer (combinations of) drugs, more stringent treatment targets, other tapering regimens, or patients with RA according to new classification criteria.[35]

In conclusion, the BeSt study has shown that rapid clinical response, DAS-remission, effective suppression of joint damage progression, sustained functional ability, tapering and discontinuation of medication, and normal survival are realistic options for patients with recent-onset rheumatoid arthritis. Treating patients with (temporary) initial combination therapy results in early improvement, while independent of initial treatment choice, continued treat-to-target therapy is important to ensure continued good results over time. New therapies and combinations of therapies can be tested and used in similar strategy trials, combined with further efforts to shorten the time to diagnosis and treatment initiation and to define the optimal treatment target. Then, more improvements in the outcomes of patients with rheumatoid arthritis may be on the horizon.

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SUPPLEMENTARY MATERIAL

Supplementary file 1. Inclusion and exclusion criteria

Inclusion criteria: Symptom duration less than 2 years, age ≥18, at least 6 of 66 swollen joints, at least 6 of 68 tender joints, and an erythrocyte sedimentation rate (ESR) of at least 28 mm/ hour or a visual analogue scale of global health of at least 20 mm (on a scale from 0 [best] to 100 mm [worst]).

Exclusion criteria: previous treatment with disease-modifying antirheumatic drugs other than antimalarials, concomitant medication with an experimental drug, a malignancy within the last five years, bone marrow hypoplasia, a serum aspartate aminotransferase or alanine aminotransferase level >3 times the upper limit of normal, a serum creatinine level >150 µmoles/ liter or an estimated creatinine clearance <75 ml/ minute, uncontrolled diabetes mellitus, alcohol or drug abuse, concurrent pregnancy, wish to conceive pregnancy during the study period, or inadequate anticonception.

Supplementary file 2. Tapering regimens

If the DAS was ≤2.4 during ≥6 months, medication was tapered to a maintenance dose. From year three, if patients achieved remission (defined as a DAS <1.6)[15] during ≥6 months while on maintenance dose, the last medication was discontinued (resulting in drug-free remission, DFR), but restarted if at a later study visit the DAS was ≥1.6. For a second attempt to taper medication to a maintenance dose again the DAS had to be ≤2.4 for ≥6 months. For a third tapering attempt the DAS had to be <1.6 for ≥6 months. A second attempt at achieving drug-free remission could be made from year 5 onwards if the DAS was <1.6 during ≥1 year. A third attempt to discontinue medication was left to a joint decision between the patient and the physician. Details on the subsequent treatment steps per strategy were reported previously.[2,11]

Supplementary file 3. Statistical methods

Weighted GEE to analyse radiographic progression

Because of a very skewed distribution, radiographic damage scores over time were analyzed using a weighted generalized estimating equation (GEE) approach with identity link function. Ordinary (unweighted) GEE assumes missing values to be 'completely at random', which is not applicable to our data. Weighted GEE, taking into account the probability of observing the outcome for each patient, is valid under the less stringent assumption of 'missing at random'. The probabilities of observing were estimated with a logistic regression analysis including an extensive set of determinants based on biological plausibility and literature: age, age squared, gender, strategy arm, education, follow-up year, functional ability, the trend of functional ability (decreasing or increasing), disease activity, serious adverse events, adverse events, joint damage and drug-free remission. By weighing the patients for each year of follow-up, based on the observed values, we aimed to compose a population that

was representative across all ten years of follow-up. In the GEE model SHS per year was entered as outcome variable, and treatment strategy, time as categorical and its interaction with treatment strategy as determinants. This resulted in estimated radiographic damage scores over time in the four treatment strategy arms.

Cox regression analysis

Cox regression analysis was used to identify possible predictors for death. To avoid immortal time bias,[39] only baseline characteristics were entered in this analysis. Based on biological plausibility and literature, the following risk factors were assessed:[32,34,35,37] randomization arm, age, gender, smoking status, disease activity score, functional ability, C-reactive protein, ESR, body mass index, IgM rheumatoid factor (RF) positivity, anti-citrullinated protein antibody positivity, bone erosions (defined by the SHS)[18], cardiovascular disease (CVD), diabetes mellitus and malignancy in the medical history (>5 years ago, according to the exclusion criteria). Disease activity over time was also evaluated as a risk factor for increased mortality. The proportional hazards assumption was tested in two ways. For categorical determinants, log minus log plots were made and checked for parallelism.[40–42] All plots showed parallel curves. In addition, for all determinants time-by-covariate interaction was tested.[40–42] None of the variables showed a significant interaction with time. Predictors with a p value <0.10 in the univariable Cox regression analysis, were selected for the multivariable Cox regression analysis, where a p value <0.05 was considered statistically significant. In addition, the following predictors based on biological plausibility were included in the multivariable model: age, gender, smoking, ESR and medical history of a malignancy or CVD. The selection of these variables was verified performing a multivariate Cox regression model in which all studied predictors were entered, and by performing a multivariate Cox regression model with all studied predictors and the backward selection procedure.[43] All methods led to the same selection of predictors. To study the predictive value of disease activity over time, a Cox regression analysis with a time dependent covariate was used. As this analysis cannot handle missing values, missing data were imputed using multiple imputation (see Statistical Analysis section in the main text).

Causes of death

Fischer's exact test and Chi-Square test were used to compare the causes of death between treatment strategies.

Supplementary Table 1. Percentages of patients on various treatment steps over time by treatment strategy (completers analysis).

Sequential monotherapy	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
On protocol treatment											
DMARD monotherapy	100.0	72.2	57.9	50.0	46.0	42.1	39.7	32.5	27.8	27.8	22.2
DMARD combination	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.8	0.8	0.8	0.0
MTX + IFX	0.0	19.8	27.0	28.6	28.6	27.8	25.4	24.6	20.6	18.3	16.7
DMARD combination including prednisone	0.0	0.0	0.8	2.4	1.6	1.6	0.8	0.8	1.6	0.8	1.6
Outside protocol treatment	0.0	4.8	9.5	11.1	14.3	15.9	11.1	12.7	15.9	16.7	18.3
Drop out/ missing	0.0	3.2	4.8	7.9	9.5	12.7	22.2	28.6	33.3	35.7	41.3
Low disease activity*	0.0	57.1	74.8	84.0	89.1	81.8	84.3	81.9	80.8	84.4	84.7
Remission*	0.0	28.6	46.1	48.1	50.0	41.0	49.4	49.4	50.0	55.8	50.0
Drug-free remission*	0.0	0.0	0.0	11.1	14.3	11.1	11.1	11.1	11.1	11.1	8.7
Step-up combination therapy											
On protocol treatment											
DMARD monotherapy	100.0	33.1	30.6	24.8	24.0	21.5	21.5	14.0	15.7	11.6	10.7
DMARD combination	0.0	41.3	31.4	31.4	29.8	27.3	24.0	22.3	18.2	14.0	13.2
MTX + IFX	0.0	2.5	6.6	5.8	5.8	5.0	7.4	6.6	6.6	6.6	5.8
DMARD combination including prednisone	0.0	9.1	13.2	11.6	11.6	11.6	9.1	9.1	6.6	7.4	5.0
Outside protocol treatment	0.0	7.4	9.1	10.7	9.9	10.7	11.6	12.4	14.9	18.2	20.7
Drop out/ missing	0.0	6.6	9.1	15.7	19.0	24.0	26.4	35.5	38.0	42.1	44.6
Low disease activity*	0.0	65.5	81.0	72.5	81.3	83.5	80.3	76.4	80.3	84.5	73.8
Remission*	0.0	29.2	37.7	38.5	39.8	45.3	50.0	39.8	56.1	46.6	45.9
Drug-free remission*	0.0	0.0	0.0	5.8	12.4	11.6	9.9	11.6	10.7	9.9	9.1

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Initial combination with prednisone											
On protocol treatment											
DMARD monotherapy	0.0	1.5	3.8	4.5	2.3	2.3	2.3	2.3	2.3	2.3	1.5
DMARD combination	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MTX + IFX	0.0	6.0	12.8	10.5	11.3	10.5	11.3	10.5	8.3	6.8	4.5
DMARD combination including prednisone	100.0	43.6	27.8	21.8	27.1	27.1	21.8	15.8	12.0	9.8	9.8
DMARD combination including prednisone (tapered)†	0.0	36.8	37.6	34.6	30.1	27.1	26.3	25.6	23.3	21.8	21.1
Outside protocol treatment	0.0	7.5	10.5	15.8	15.8	15.8	12.8	12.0	15.0	19.5	21.1
Drop out/ missing	0.0	4.5	7.5	12.8	13.5	17.3	25.6	33.8	39.1	39.8	42.1
Low disease activity*	0.0	73.8	77.8	76.7	78.7	80.4	84.0	82.5	85.7	91.7	85.7
Remission*	0.0	32.8	41.5	39.8	39.4	42.2	50.6	52.5	57.1	55.6	57.1
Drug-free remission*	0.0	0.0	0.0	6.8	8.3	7.5	9.0	10.5	9.8	9.8	9.0
Initial combination with infliximab											
On protocol treatment											
DMARD monotherapy	1.6	14.8	13.3	11.7	10.2	7.8	7.0	6.3	3.9	3.9	3.9
DMARD combination	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MTX + IFX	98.4	16.2	20.2	20.9	22.0	22.8	23.8	24.8	25.0	24.8	24.1
MTX and tapered IFX†	0.0	63.5	51.7	49.4	45.1	42.0	37.1	29.9	25.8	20.5	16.5
DMARD combination including prednisone	0.0	0.8	5.5	6.3	7.0	7.8	7.0	5.5	5.5	4.7	2.3
Outside protocol treatment	0.0	3.1	4.7	6.3	7.8	8.6	10.9	12.5	16.4	18.8	22.7
Drop out/ missing	0.0	1.6	4.7	5.5	7.8	10.9	14.1	21.1	23.4	27.3	30.5
Low disease activity*	0.0	74.6	81.7	83.9	76.1	82.9	83.5	76.3	77.9	77.6	84.3
Remission*	0.0	35.5	41.3	47.8	40.7	51.4	54.6	45.4	47.4	45.9	56.2
Drug-free remission*	0.0	0.0	0.0	16.4	18.0	16.4	13.3	17.2	10.9	9.4	10.2

† Percentage indicates the proportion of patients on the initial combination treatment step who tapered to monotherapy or discontinued all medication

* All patients are also counted in an 'on protocol treatment step' or an 'outside protocol treatment step', as the study was monitored this way.

DMARD, disease-modifying antirheumatic drug; IFX, infliximab; MTX, methotrexate.

Supplementary table 2. Adverse events per 100 patient years by treatment strategy and by study period.

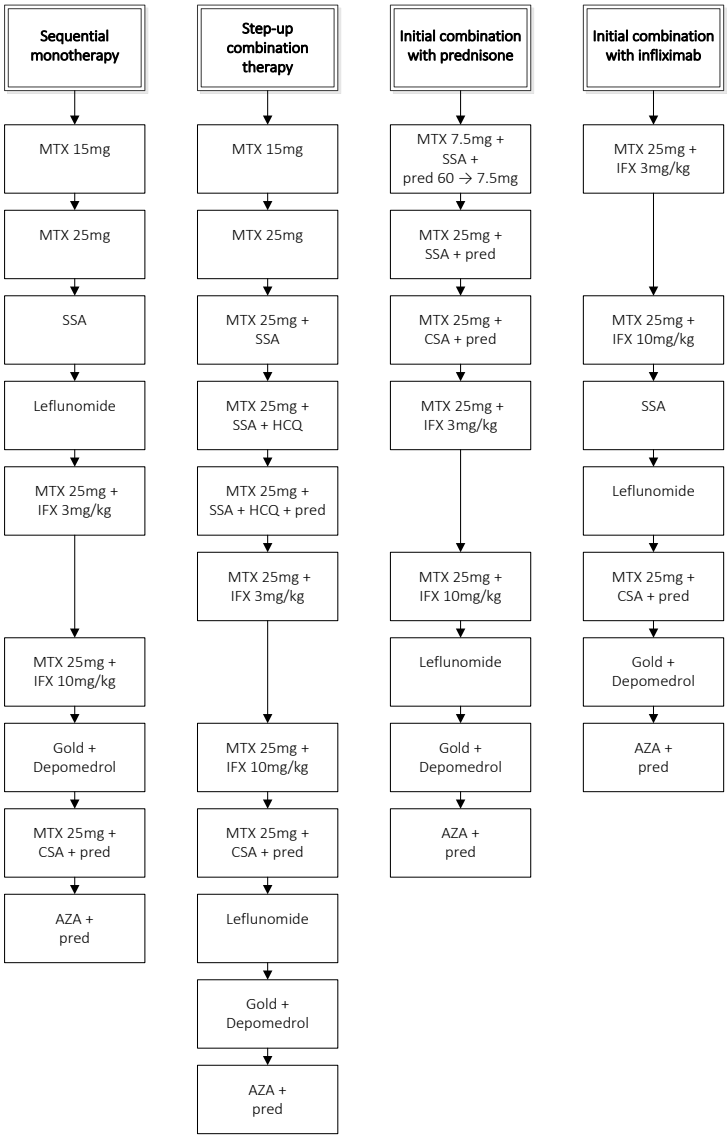
		Year 1 - 2	Year 3 - 5	Year 6 - 10
Sequential monotherapy	CVD	2.9	2.6	5.5
	Pulm	4.9	3.2	4.0
	GI	24.1	7.5	9.0
	NP	10.2	3.5	4.2
	Skin	12.7	6.9	3.3
	Infec	8.6	18.5	26.1
	Other	9.8	17.0	28.5
Step-up combination therapy	CVD	3.0	4.1	6.4
	Pulm	1.3	1.6	4.2
	GI	25.3	7.6	4.2
	NP	9.0	4.8	4.0
	Skin	12.0	7.0	5.9
	Infec	10.3	25.1	23.2
	Other	21.0	19.0	25.9
Initial combination with prednisone	CVD	7.0	5.5	7.8
	Pulm	1.9	1.4	2.4
	GI	10.9	10.2	7.3
	NP	9.7	1.7	4.7
	Skin	12.1	7.2	5.6
	Infec	8.6	14.1	26.5
	Other	17.9	19.9	27.8
Initial combination with infliximab	CVD	5.2	3.3	5.7
	Pulm	4.0	2.8	5.2
	GI	21.0	7.8	6.7
	NP	5.6	5.8	4.8
	Skin	8.3	5.5	6.9
	Infec	14.3	19.1	27.3
	Other	12.7	16.3	35.0

AE, adverse event; CVD, cardiovascular disease (mainly hypertension); GI, gastrointestinal (mainly nausea/ emesis, increased liver enzymes); haem, hematological; infec, infectious (mainly upper and lower respiratory tract infections, gastroenteritis, skin/mucosal infections and urinary tract); metabol, metabolic, NP, neuropsychiatric; pulm, pulmonary; skin, skin and mucous membranes; urogen, urogenital.

Supplementary Table 3. Results of the multivariable Cox regression model with death as outcome.

	Adjusted HR	95% CI
Age (years) at baseline	1.13	1.10 – 1.16
Male	1.82	1.08 – 3.06
Smoking at baseline	5.26	3.12 – 8.89
Baseline HAQ	1.92	1.31 – 2.82
Baseline ESR	0.997	0.99 – 1.01
Erosions at baseline	1.80	0.87 – 3.74
CVD in medical history	1.30	0.76 – 2.22
Malignancy in medical history	1.24	0.49 – 3.13

95% CI, 95% confidence interval; CVD, cardiovascular disease; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HR, hazard ratio, adjusted for the other variables noted in the table.

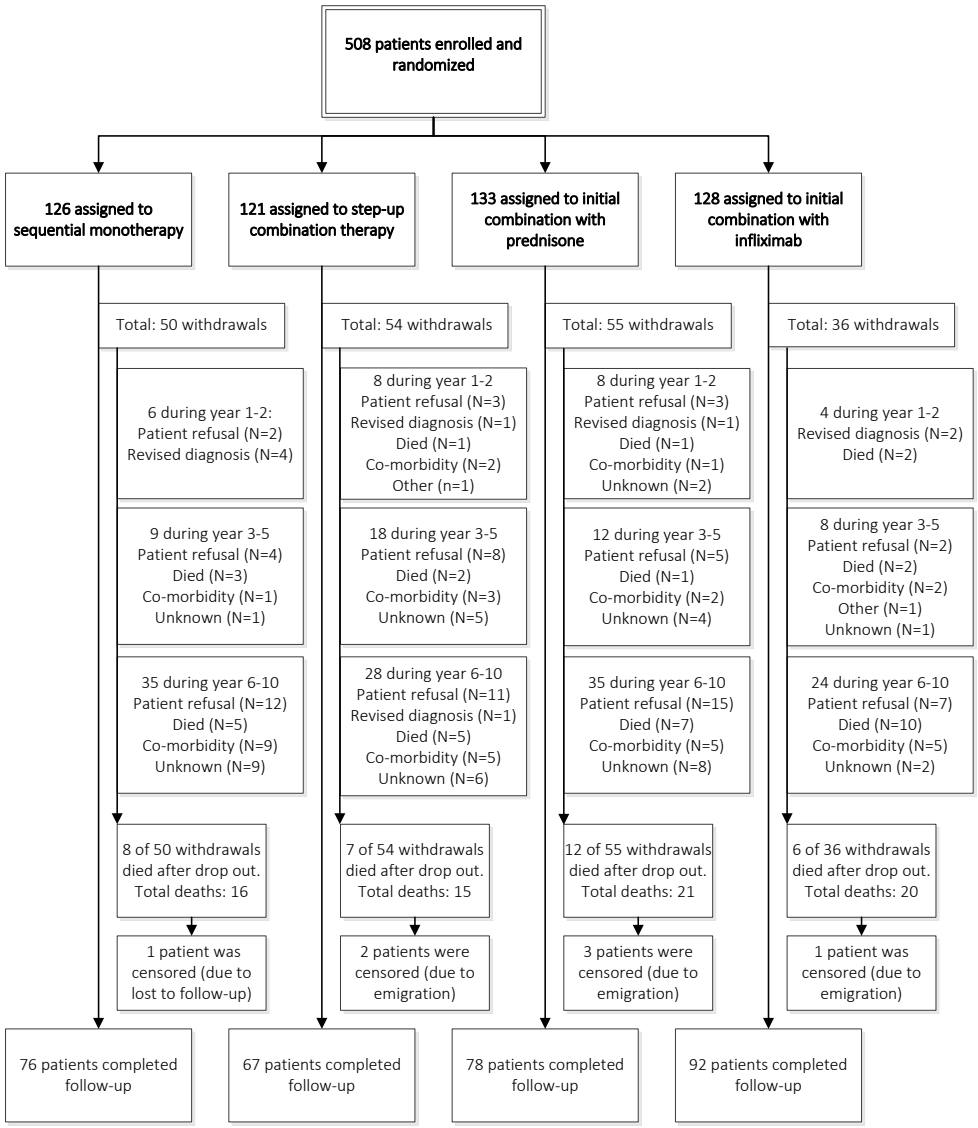


Supplementary Figure 1. Flow diagram of the treatment strategies, showing required treatment intensification steps as long as three-monthly measured DAS remained >2.4.

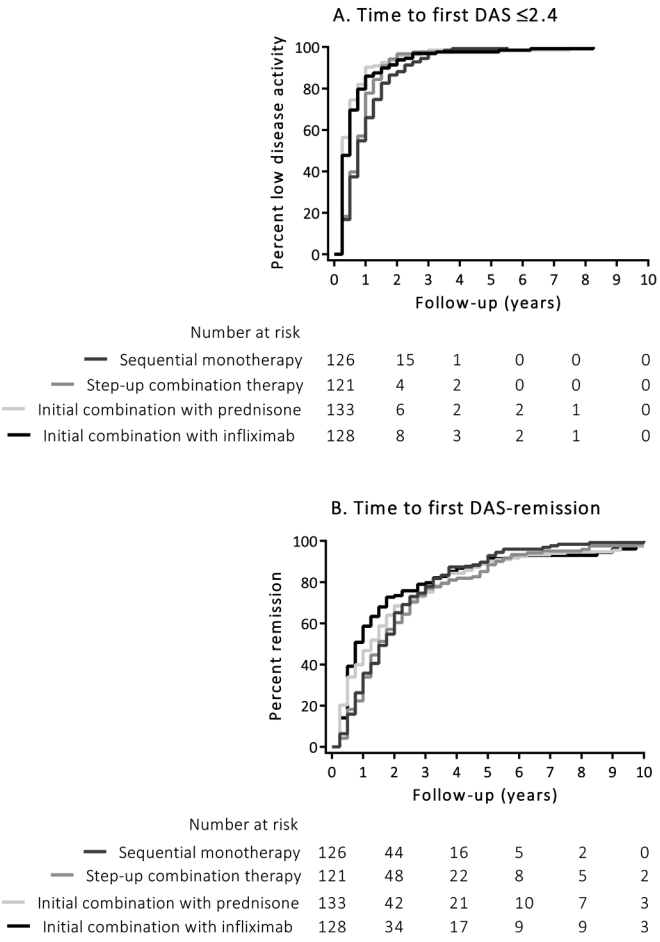
Note 1: In all strategy arms, different patients may progress from one treatment step to the next over different time intervals, depending on individual DAS results at the three-monthly observations.

Note 2: Patients on infliximab (dosed at 8–weekly intervals) had additional DAS measurements one week before each next infusion. That DAS dictated if the infliximab dose would need to be increased. Infliximab dose started with 3 mg/kg and, if DAS >2.4, was stepwise be increased to 6 mg/kg, 7.5 mg/kg and finally 10 mg/kg (always rounded to the nearest hundred). Tapering of the dose could go in reverse order if three-monthly DAS calculations were ≤2.4 for at least 6 consecutive months.

AZA, azathioprine 2-3mg/kg/day; CSA, ciclosporin A 2.5mg/kg/day; Depomedrol, 3 gifts of 120mg in week 1, 4 and 8; Gold 50mg/week; HCQ, hydroxychloroquine 200mg/day, IFX, infliximab, dosages once per 8 weeks; Leflunomide 20mg/day; MTX, methotrexate, dosages per week; Pred, prednisone 7.5mg/day unless indicated otherwise; SSA, sulphasalazine 2000mg/day.



Supplementary Figure 2. Study flow diagram.



Supplementary Figure 3. (A) Time to first low disease activity and (B) time to first remission, both based on an imputed dataset.
Note (Supplementary Figure 3A): log-rank test p<0.001.
Note (Supplementary Figure 3B): log-rank test p=0.36.
DAS, disease activity score.