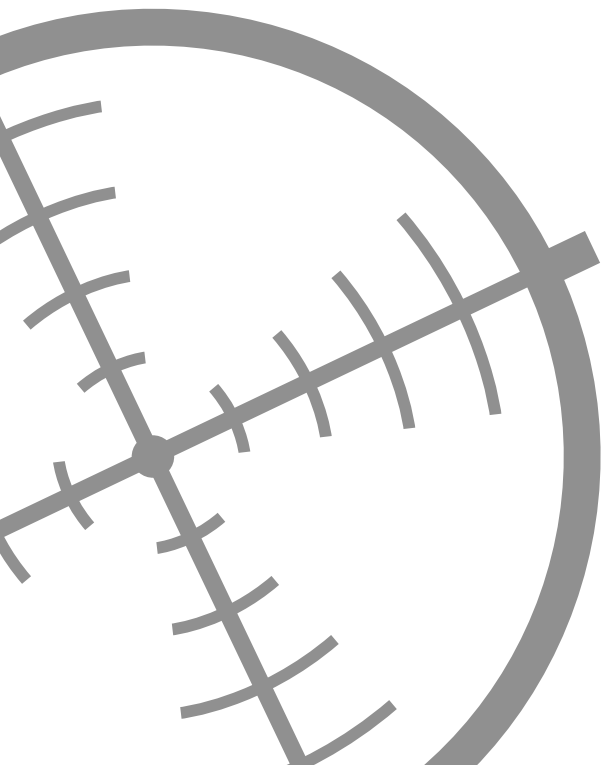
6

Effectiveness of four dynamic treatment strategies in patients with anti-citrullinated protein antibody-negative rheumatoid arthritis – a randomised trial

Gülşah Akdemir*
Iris Markusse*
Linda Dirven
Naghmeh Riyazi
Margreet Steup-Beekman
Pit Kerstens
Willem Lems
Tom Huizinga
Renée Allaart

*both authors contributed equally



Submitted

ABSTRACT

Objective

To determine the most effective treatment strategy among anti-citrullinated protein antibody (ACPA) negative early rheumatoid arthritis patients.

Methods

In the BeSt study, 184 ACPA-negative patients were randomized to 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Treatment was targeted at disease activity score (DAS) ≤2.4. Early response and 10-year outcomes were compared between the four strategy-arms in ACPA-negative patients.

Results

ACPA-negative patients achieved more short-term functional improvement on initial combination therapy than on monotherapy (at month 3 mean health assessment questionnaire [HAQ] 0.71 versus 0.98, p=0.006; at month 6 0.59 versus 0.87, p=0.004). Functional ability over time was comparable between the strategy arms (p=0.551) with a mean HAQ of 0.6 at year 10 (p=0.580 for comparison across the strategy arms). 10-year radiographic progression was negligible (median 0.5) and comparable between the 4 strategy arms (p=0.082). At year 10, remission was achieved by 11/40 (28%), 9/45 (20%), 17/56 (30%) and 17/43 patients (40%) in strategy arms 1 to 4, respectively (p=0.434). Over time similar remission percentages were achieved in all strategy arms (p=0.815). 18%, 16%, 20% and 21% in strategy arms 1 to 4 (p=0.742) were in drug-free remission at year 10, with a median duration of 60 months across the arms.

Conclusions

Initial combination therapy with methotrexate, sulfasalazine and prednisone, or methotrexate and infliximab, is the most effective treatment strategy for ACPA-negative patients, resulting in earlier functional improvement than initial methotrexate monotherapy. After 10 years of targeted treatment, in all strategy arms favourable clinical outcomes were achieved and radiographic progression was limited.

INTRODUCTION

In patients with rheumatoid arthritis (RA), presence of anti-citrullinated protein antibodies (ACPA) is associated with worse clinical and radiographic outcomes, compared to ACPA-negative RA.[1–6] It has been proposed that ACPA-negative RA is another disease entity than ACPA-positive RA[7–9] and therefore requires a different treatment approach.[10] However, it is not clear which treatment strategy, in particular which initial treatment choice, is most effective in ACPA-negative RA patients. ACPA-negative patients have been suggested to not require combination therapy,[10] not benefit from corticosteroids [10] but respond better to anti-tumor necrosis factor alpha (anti-TNFα) agents than ACPA-positive patients.[11–13]

In the BeSt study, recent-onset active RA patients were included and treated without ACPA status being known. Patients were randomized to one of four dynamic treatment strategies, all aiming to achieve low disease activity (disease activity score: DAS ≤2.4). In a previous analysis of the BeSt study we found that there were no significant differences in clinical response between ACPA-negative and ACPA-positive patients.[6] Here, we aim to determine in further detail what the most effective treatment strategy is for ACPA-negative patients. We investigated which treatment strategy resulted in the most rapid clinical response and the most favourable long-term clinical and radiographic outcomes for ACPA-negative patients.

PATIENTS AND METHODS

Study design

The BeSt study (Dutch acronym for treatment strategies), a multicentre randomized clinical trial, enrolled 508 patients to compare four dynamic treatment strategies in patients with recent-onset, active RA according to the 1987 revised American College of Rheumatology (ACR) criteria.[14] More study details were previously published.[15,16] The medical ethics committees of all participating centers approved the study protocol and all patients gave written informed consent.

Patients were randomized to: 1. sequential monotherapy, 2. step-up combination therapy, 3. initial combination with prednisone, 4. initial combination with infliximab. Strategy arm 1 and 2 both started with methotrexate (MTX) monotherapy. In strategy arm 3, patients started with MTX, sulfasalazine (SSA) and prednisone, and in strategy arm 4, patients received MTX and infliximab. Every three months disease activity scores (DAS) were measured. Treatment was targeted at low disease activity (DAS ≤2.4). If low disease activity was not achieved, the next treatment step was taken. In case the DAS was ≤2.4 for ≥6 months, medication was tapered to a maintenance dose. If the DAS was then <1.6 for ≥6 months, medication was discontinued. As soon as DAS was ≥1.6, medication was restarted, and further treatment steps were taken if DAS was >2.4 at a later visit.

ACPA were not determined at baseline, but afterwards in available serum samples using the anti-cyclic citrullinated peptide (anti-CCP2) test. ACPA status was determined in 484 patients;

for the remaining 24 patients no serum sample was available. ACPA status did not influence treatment instructions according to the study protocol. For the current post hoc-analysis, results of the four treatment strategies were compared within ACPA-negative patients.

Study endpoints

Primary outcomes were functional ability and radiographic joint damage progression. Functional ability was measured three-monthly with the health assessment questionnaire (HAQ, range 0 – 3).[17] Radiographic joint damage was assessed on radiographs of hands and feet, using the Sharp/ van der Heijde score (SHS, range 0 – 448).[18] Radiographs were obtained yearly and were assessed in one session by two trained readers, blinded for patient identity, strategy arm and time order. Progression as a continuous measure was defined as an increase in SHS between two subsequent time points. Absence of progression was defined as <0.5 units increase in SHS and presence as ≥0.5 units increase in SHS.

DAS-remission percentages (defined as DAS <1.6)[19], drug-free remission (DFR) percentages, toxicity and treatment response were secondary outcomes in this study. Toxicity included all reported (serious) adverse events ((S)AE). Treatment response to initial monotherapy and initial combination therapy were described for year 1 and 2 of follow-up. Treatment response was defined as success or failure on a specific treatment step. Success was defined as achieving and maintaining a DAS ≤2.4 and failure was defined as a persistent DAS >2.4 or discontinuation of medication due to toxicity.

Early response was defined based on rapid improvement in functional ability and the percentage of DAS-remission during the first year of follow-up. Radiographic progression during the first year was compared among the strategy arms. Long-term effect of the strategy arms was assessed with the primary and secondary outcomes over and at year 10.

Statistical analysis

Baseline characteristics and outcomes after 10 years were compared between the different treatment arms by the χ2 test, independent *t* test and ANOVA, as appropriate. For the non-Gaussian distributed outcomes the Kruskal-Wallis test or Mann-Whitney ***U*** test were used.

HAQ was compared at 3, 6, 9 and 12 months between the initial monotherapy arms (arm 1 and 2 combined) and the initial combination therapy arms (arm 3 and 4 combined) with an independent *t* test. Furthermore, HAQ was longitudinally analysed with linear mixed models (LMM) with treatment group, time and its interaction term as determinants. This analysis was performed twice: once at 1 year follow-up (0 – 1 year) to determine early response, the second at the ten year follow-up (0 – 10 year) to determine long-term outcomes. Generalized linear mixed models (GLMM) were used to determine whether there was a difference in DAS-remission percentages between the four treatment strategies. Treatment group, time and its interaction term were entered as determinants. This analysis was also performed twice; for 0 – 1 year and for 0 – 10 year follow-up. The dropout rates were compared between the different treatment groups using Kaplan-Meier curves. Responses to the first, second and third treatment step in strategy arms 1 and 2, expressed as drug survival, were shown in

Kaplan-Meier curves.
SHS progression during the first year was compared with a Kruskal-Wallis test. SHS progression over ten years was depicted in a cumulative probability plot, stratified for treatment strategy. SHS progression over time was analysed using a GLMM with SHS progression as binary outcome (defined as delta ≥0.5 units per year yes/no). Treatment strategy, time and its interaction were entered as determinants.
On the one hand, the power calculation of the BeSt study was based on the total study population, and we here only include a subpopulation (184 of 508). On the other hand, we performed multiple comparisons. These effects indicate that the p values should be interpreted in opposite directions. Therefore, we decided to adjust for neither of the effects

RESULTS

Baseline characteristics for 184 ACPA-negative patients (of 508 patients included in the BeSt study) were similar in the strategy arms with a high disease activity (mean [SD] DAS 4.6 [0.9]) and impaired functional ability (mean [SD] HAQ 1.5 [0.7]) (Table 1). During ten years follow-up, 71/184 patients (39%) dropped out of the study, equally distributed among the strategy arms (p=0.738).

Table 1. Baseline characteristics.

	Sequential monotherapy	**Step-up combination therapy**	**Initial combination with prednisone**	**Initial combination with infliximab**
	n=40	**n=45**	**n=56**	**n=43**
Age (years), mean (SD)	56 (15)	53 (15)	57 (13)	53 (16)
Female, n (%)	30 (75)	36 (80)	38 (68)	32 (74)
Symptom duration (weeks), median (IQR)	19 (12 – 41)	30 (16 – 52)	22 (11 – 41)	19 (13 – 31)
DAS, mean (SD)	4.6 (0.9)	4.7 (0.8)	4.5 (0.8)	4.6 (1.0)
HAQ, mean (SD)	1.5 (0.7)	1.4 (0.5)	1.5 (0.6)	1.5 (0.8)
RF positive, n (%)	12 (30)	12 (27)	22 (39)	13 (30)
Erosive disease, n (%)	27 (68)	28 (62)	36 (64)	28 (65)
Smoker, n (%)	14 (35)	11 (24)	16 (29)	10 (23)

DAS, disease activity score; HAQ, health assessment questionnaire (range 0 – 3); IQR, interquartile range; RF, IgM rheumatoid factor; SD, standard deviation.

Early response

During the first year, functional ability improved earlier in patients treated with initial combination therapy (arm 3 and 4) than in patients treated with initial monotherapy (arm 1 and 2) (Figure 1A). After 3 months mean HAQ was 0.98 in the monotherapy arms versus 0.71 (p=0.006) in the combination therapy arms and after 6 months 0.87 versus 0.59 (p=0.004). Probably as a result of continued DAS ≤2.4 targeted treatment, from 9

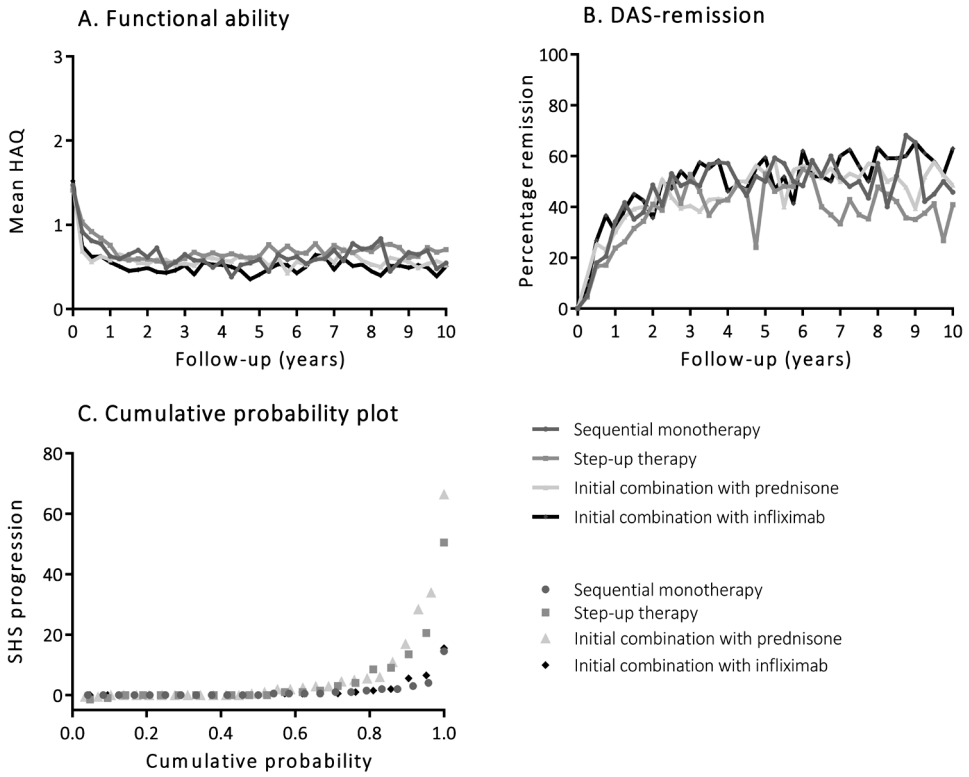


Figure 1. (A) Functional ability, (B) DAS-remission percentages and (C) probability plot of radiographic joint damage progression from baseline to year 10 (completer analysis).
Notes Figure 1B: DAS-remission was defined as disease activity score (DAS) <1.6.[19] Percentages reflect the number of patients in DAS-remission as part of the completers. More patients missed the visits before the yearly visits at year 5 and 10, because they were running behind on their schedule. Low attendance make the DAS-remission percentages at these visits difficult to interpret. Mean disease activity did not show this decrease (data not shown).
Notes Figure 1C: Patients in strategy arm 1 and 4 had numerically less progression compared to strategy arm 2 and 3, although not statistically significant (p=0.639). In strategy arm 1 and 4 patients with progression (defined as ≥0.5 SHS) had moderate disease activity during early visits (mean DAS [SD] 2.99 [1.14] at 3 months and 2.45 [1.13] at 6 months) and 46% was rheumatoid factor (RF) positive. In strategy arm 2 and 3 patients with progression (defined as ≥0.5 SHS) had also moderate disease activity at early visits (mean DAS [SD] 2.99 [1.16] at 3 months and 2.46 [1.14] at 6 months) and 42% was RF-positive.
HAQ, health assessment questionnaire (range 0 – 3); SHS, Sharp/ van der Heijde score.

months of follow-up onwards, no differences in functional ability were found between the strategy arms. At 9 months, mean HAQ was 0.81 versus 0.63 (p=0.067) and at year 1, 0.69 versus 0.57 (p=0.195), in the monotherapy and combination therapy arms, respectively. Over the first year of follow-up, patients in strategy arm 3 had a better level of functioning than patients in strategy arm 2 (mean HAQ 0.62 versus 0.88, respectively, p=0.027; other comparisons non-significant).

During the first year, higher percentages of DAS-remission (DAS<1.6) were found in strategy arms 3 and 4 than in strategy arms 1 and 2, although not significantly different (Figure 1B): after 3 months 5% in the monotherapy arms compared to 11% in the combination therapy arms achieved DAS-remission (p=0.119); after 6 months 17% versus 25% (p=0.161); after 9 months 18% versus 27% (p=0.116) and after 1 year 27% versus 29% (p=0.833). Over the first year, no differences were found between the four strategy arms (p=0.472).
Radiographic progression during year 1 was low as expected, with median (IQR) progression scores of 0 (0 – 0), 0 (0 – 1), 0 (0 – 1) and 0 (0 – 0.5) in strategy arms 1 to 4, respectively (p=0.259).

Long-term outcomes

At year ten, mean (SD) DAS has decreased from 4.6 (0.9) at baseline to 1.6 (0.8) and HAQ from 1.5 (0.7) to 0.6 (0.6) (more details in Table 2). Over ten years time, no differences in clinical outcomes were found. Functional ability was similar among the four strategy arms (p=0.551) (Figure 1A). The same was true for DAS-remission percentages (p=0.851) (Figure 1B).
During ten years, drug-free remission was ever achieved by 16/40 (40%), 15/45 (33%), 20/56 (36%) and 21/43 patients (49%) in strategy arms 1 to 4, respectively (p=0.453). In 5/16, 4/15, 6/20 and 7/21 patients in strategy arms 1 to 4, respectively (p=0.993), DFR was lost during follow-up. Of these patients 4/5, 3/4, 2/6 and 3/7 patients in strategy arms 1 to 4, respectively (p=0.704) achieved clinical DAS-remission again, with a median (IQR) of 1.0 (0.3 – 3.5) years since loss of DFR. Only 1 patient in strategy arm 3 and 2 patients in strategy arm 4 achieved DFR after restart of medication. Table 2 shows DFR percentages at year 10.

Table 2. Clinical and radiographic outcomes in the different strategy arms at year 10.

	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab	p value
	n=40	n=45	n=56	n=43	
Drop out, n (%)	14 (35)	20 (44)	21 (38)	16 (37)	0.738
DAS, mean (SD)	1.7 (0.9)	1.8 (0.8)	1.6 (0.8)	1.4 (0.8)	0.431
HAQ, mean (SD)	0.5 (0.5)	0.7 (0.7)	0.5 (0.5)	0.5 (0.5)	0.580
DAS-remission, n (%)	11 (28)	9 (20)	17 (30)	17 (40)	0.434
Drug-free remission, n (%)	7 (18)	7 (16)	11 (20)	9 (21)	0.742
On initial treatment step, n (%)	10 (25)	7 (16)	18 (32)	15 (35)	0.161
Use of infliximab, n (%)	3 (8)	3 (7)	4 (7)	4 (9)	0.978
Use of prednisone, n (%)	0 (0)	0 (0)	3 (5)	2 (5)	0.226
SHS progression, year 0-10 median (IQR)	0.3 (0 – 1.4)	0 (0 – 6.3)	1.0 (0 – 5.3)	0 (0 – 1.3)	0.639
SHS progression ≥5 units, n (%)	1 (3)	5 (11)	8 (14)	3 (7)	0.132
SHS progression ≥10 units, n (%)	1 (3)	3 (7)	5 (9)	1 (2)	0.324

DAS, disease activity score; HAQ, health assessment questionnaire (range 0 – 3); SHS, Sharp/ van der Heijde score; IQR, interquartile range; SD, standard deviation.

Median (IQR) total SHS progression after 10 years of targeted treatment was low and similar between the four treatment groups in the study completers (p=0.639) (Table 2). Figure 1C shows the cumulative probability of SHS progression per strategy arm in ACPA-negative patients who completed follow-up. Over time, based on a generalized linear mixed model that takes into account all included patients, no difference in SHS progression (defined as delta ≥0.5 units per year) was found between the randomization strategy arms: with strategy arm 1 as reference, odds ratios (95% confidence interval) were 1.98 (0.60 – 6.47) for arm 2, 2.89 (0.96 – 8.72) for arm 3 and 1.66 (0.50 – 5.47) for arm 4 (p=0.082).

Response to initial monotherapy

Response to initial monotherapy in strategy arms 1 and 2 was explored during year 1 and 2. Eighteen out of 84 patients (21%) achieved the treatment target of low disease activity after three months, but 64/84 patients (76%) failed to respond to initial MTX monotherapy (and had to increase MTX dose according to the study protocol). Two patients stopped MTX because of an AE (nausea and headache) (Figure 2A). At 6 months, 39/84 patients (46%) achieved a DAS ≤2.4 on MTX monotherapy. Thirty six patients failed due to a DAS >2.4 (despite MTX dose increase at 3 months) and 2 patients failed due to an AE (not specified).
The second treatment step was taken in 46/84 patients: switching to (in strategy arm 1) or adding (in strategy arm 2) SSA. In 9/46 patients (20%) a DAS ≤2.4 was achieved on this step (Figure 2B). Failure on SSA therapy occurred in 33/46 patients because of a DAS >2.4 and in 4/46 patients because of an AE (skin/mucous, infection, nausea and malaise).
In total, 35/84 patients continued to the third treatment step during 2 years of follow-up: switching to leflunomide monotherapy (in strategy arm 1) or adding hydroxychloroquine to MTX and SSA (in strategy arm 2). In 9/35 patients (26%) a DAS ≤2.4 was achieved (Figure 2C). During 2 years of follow-up, 21/35 patients (60%) continued to the next treatment step due to a DAS >2.4. Five patients failed due to an AE (3 times gastro-intestinal, malaise and

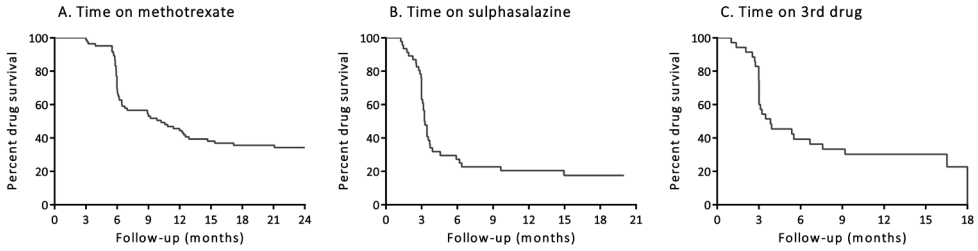


Figure 2. Kaplan-Meier Curves showing drug survival in strategy arms 1 and 2.
(A) Initial methotrexate monotherapy, n=84, (B) Switching to sulphasalazine monotherapy in strategy arm 1, adding sulphasalazine to methotrexate in strategy arm 2, n=46, (C) Switching to leflunomide monotherapy in strategy arm 1, adding hydroxychloroquine to methotrexate and sulphasalazine in strategy arm 2, n=35.
Note: Discontinuation of drugs is due to insufficient response, toxicity or other reasons. The lines indicate the percentage of patients in strategy arm 1 and 2 that are treated according to the concerned treatment step.

skin/mucous). For all patients who failed due to DAS >2.4 on each treatment step, the DAS components are denoted in Table 3.

After 1 year, 7/40 patients (18%) in strategy arm 1 continued to combination therapy (MTX and infliximab). During year 2, two additional patients continued to combination therapy. In strategy arm 2, 24/45 patients (53%) used combination therapy (MTX and SSA, step 3 in the study protocol) at the end of year 1. During year 2, only one more patient failed on monotherapy and continued to combination therapy. The difference in percentages combination therapy between strategy arms 1 and 2 can be explained by the design of the protocol: in strategy arm 1, the first option to receive combination therapy was the 3rd step after initial MTX treatment, while it was already the 2nd step in strategy arm 2.

Table 3. Components of the disease activity score in patients who failed on the treatment steps in strategy arms 1 and 2, both starting with methotrexate monotherapy.

	Failure to MTX at 3 months ***15 mg weekly*** **n=64**	**Failure to MTX at 6 months** ***25 mg weekly*** **n=36**	**Failure on SSA at 9 months** **n=33**	**Failure on step 3 at 12 months** **n=21**
SJC	9 (4 – 14)	9 (4 – 12)	6 (2 – 10)	4 (3 – 11)
TJC	11 (7 – 16)	12 (8 – 17)	9 (5 – 17)	10 (7 – 16)
ESR	22 (12 – 32)	20 (13 – 29)	20 (14 – 41)	21 (12 – 24)
VAS	37 (20 – 51)	47 (26 – 55)	48 (25 – 69)	40 (20 – 65)

Numbers indicate median (interquartile range).
ESR, erythrocyte sedimentation rate; MTX, methotrexate monotherapy; SJC, 44 swollen joint count; SSA, sulfasalazine (switching to SSA monotherapy in strategy arm 1, adding SSA to MTX in strategy arm 2); Step 3, leflunomide in strategy arm 1, adding hydroxychloroquine to MTX and SSA in strategy arm 2; TJC, 53 tender joint count (Ritchie articular index); VAS, patient's assessment of global health on a visual analogue scale (range 0 – 100 mm).

Response to initial combination therapy

By the end of year 1, in strategy arm 3 (MTX, SSA and prednisone) 18/56 patients (32%) had tapered combination therapy to monotherapy of which 3 restarted with MTX during the second year. In strategy arm 4, 17/43 patients (40%) had discontinued infliximab. One of them restarted infliximab during the second year. For more detailed treatment responses to initial combination therapy during 2 year follow-up (strategy arms 3 and 4) flowcharts are shown in the supplementary file (Supplementary Figure 1 and 2).

Toxicity

During ten years of follow-up in total 1,265 adverse events (AE) were reported in 36/40, 39/45, 55/56 and 41/43 patients in strategy arms 1 to 4, respectively (p=0.113). The most common AE in all groups were upper airway infections, elevated liver enzymes, nausea and other gastro-intestinal complaints. SAE were reported in 25/40, 29/45, 27/56, and 22/43 patients in strategy arms 1 to 4, respectively (p=0.300) (Table 4). Ten patients died during the

study; one in strategy arm 1, four in strategy arm 2, one in strategy arm 3 and four in strategy arm 4 (p=0.220) (details in Table 4). (S)AE during year 1, when most patients in strategy arms 3 and 4 were still on combination therapy, are reported in Table 4.

Table 4. Number of reported adverse events and serious adverse events.

	Sequential monotherapy	Step-up combination therapy	Initial combination with prednisone	Initial combination with infliximab	p value
	n=40	n=45	n=56	n= 43	
0 – 1 year follow-up					
AE, n*	31	51	41	34	0.414
SAE, n*	3	3	6	1	0.400
0 – 10 year follow-up					
Total AE, n*	293	292	368	312	0.872
Patients with AE, n (%)	36	39	55	41	0.113
Total SAE, n*	50	33	60	43	0.183
Patients with SAE, n (%)	25 (63)	19 (42)	27 (48)	22 (51)	0.300
Patients with serious infection, n (%)	9 (23)	5 (11)	5 (9)	3 (7)	0.124
Patients with malignancy, n (%)	3 (8)	2 (4)	8 (14)	6 (14)	0.310
Deceased, n**	1	4	1	4	0.220

*More events per patient possible.

** Causes of death, group 1: 1 ischemic colon after complicated diverticulitis surgery; group 2: 1 lung carcinoma, 1 stomach cancer, 2 unknown; group 3: 1 lung carcinoma; group 4: 1 esophagus carcinoma, 1 cardiac arrest, 1 lung carcinoma, 1 unknown.

AE, adverse event; SAE, serious adverse event.

DISCUSSION

Previous literature suggests that ACPA-negative and ACPA-positive RA patients may represent two different disease entities, which may require different treatment strategies.[7–10] On the one hand, as ACPA-negative patients are less likely to develop joint damage and more likely to achieve drug-free remission,[2,5,6,20] they may not need intensive treatment. On the other hand, the clinical response to DMARD monotherapy in daily practice fails in roughly 50% of the patients.[21] In the PROMPT study, we showed that methotrexate was as effective as placebo in ACPA-negative probable RA patients.[22] To establish the best initial treatment strategy in ACPA-negative RA patients, we performed the current analysis in the BeSt study. Based on our results, all four strategy arms starting with either monotherapy or combination therapy have a comparable long-term effectiveness, with the only difference that an earlier functional improvement was achieved following initial combination therapy with the option to taper to monotherapy. Radiographic progression was generally low as expected in ACPA-negative

patients and after ten years of targeted treatment without difference between the strategy arms.

These results expand on our previous report that showed no significant differences in clinical response between ACPA-positive and ACPA-negative patients in the BeSt study.[6] Initial combination therapy appears to result in earlier clinical response in both groups of patients, and during subsequent treatment adjustments targeted at low disease activity (DAS ≤2.4), clinical outcomes are roughly similar from month 9 of follow-up onwards. The only differences that we found are more radiographic damage progression in the ACPA-positive patients and more drug-free remission in the ACPA-negative patients.[6]

In ACPA-positive and ACPA-negative patients, treatment choices depend on positive effects that one aims to achieve, in relation to possible negative effects. If treatment aims mainly at preventing long-term debilitating joint damage, one may argue that ACPA-negative patients require less intensive treatment and maybe a less stringent treatment target, than ACPA-positive patients. Likewise ACPA-positive patients may require more intensive treatment and possibly a more stringent treatment target. If rapid relief of symptoms is the aim of initiating treatment, then initial combination therapy has the highest success rate. In the BeSt study, all patients were selected on having active RA, with ≥6/66 swollen and ≥6/68 painful joints and either an ESR >28 mm/hr or a high VAS (≥20 mm) of global health. At baseline, ACPA-negative patients had an even slightly higher DAS and more severe functional disability than ACPA-positive patients.[6] Compared to the 1987 criteria used in the BeSt study, the 2010 criteria instigate that primarily ACPA-negative patients with high tender and swollen joint counts will be classified as having RA.

Rapid symptom relief, associated with less work disability[23] is an important treatment target. We have shown that only the minority of ACPA-negative patients respond to MTX monotherapy (despite a dose increase after three months), and that in case of failure, the response to SSA is even poorer. DAS components revealed a substantial inflammatory element in these failing patients. In contrast, a rapid decrease in disease activity is observed following initial combination therapy, with accompanied improvement in functional ability. These results point towards the favourable effects of initial combination therapy in patients with ACPA-negative RA. Registration of AEs and SAEs during the BeSt study did not show more toxicity in the initial combination strategy arms than in the initial monotherapy arms.[16] This may be related to the fact that after a rapid improvement, tapering and discontinuation was often possible: tapering at the earliest possibility of prednisone in strategy arm 3 (at week 28) was possible in 66% of patients, and 32% subsequently tapered to SSA monotherapy. In strategy arm 4 discontinuation of infliximab to MTX monotherapy (by protocol possible first at month 9) occurred in 33% of patients, and after 12 months in 40%. To meet concerns on possible adverse effects of high-dose corticosteroids, although not objectified in this trial, more recent studies have shown that the initial dose of prednisone may not need to be as high and as was used in the COBRA trial[24] and subsequently in the BeSt study to achieve similar rapid suppression of disease activity.[25–27]

In conclusion, for ACPA-negative RA patients, initial combination therapy with methotrexate and either sulfasalazine plus prednisone, or infliximab is the most effective treatment strategy. It results in earlier functional improvement, without additional adverse events, than initial methotrexate monotherapy. We suggest that treatment of all patients with early and active RA should focus on rapid relief of symptoms, and that there is no reason to weigh the initial treatment choice based on the presence of ACPA.

REFERENCES

1 Bas S, Genevay S, Meyer O, et al. Anti-cyclic citrullinated peptide antibodies, IgM and IgA rheumatoid factors in the diagnosis and prognosis of rheumatoid arthritis. ***Rheumatology*** 2003;42:677–80.

2 De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, Verpoort KN, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. ***Arthritis Rheum*** 2008;58:1293–8.

3 Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. ***Ann Rheum Dis*** 2005;64:196–201.

4 Meyer O, Labarre C, Dougados M, et al. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. ***Ann Rheum Dis*** 2003;62:120–6.

5 Rönnelid J, Wick MC, Lampa J, et al. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. ***Ann Rheum Dis*** 2005;64:1744–9.

6 Van den Broek M, Dirven L, Klarenbeek NB, et al. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. ***Ann Rheum Dis*** 2012;71:245–8.

7 Daha NA, Toes REM. Rheumatoid arthritis: Are ACPA-positive and ACPA-negative RA the same disease? ***Nat Rev Rheumatol*** 2011;7:202–3.

8 Klareskog L, Rönnelid J, Lundberg K, et al. Immunity to Citrullinated Proteins in Rheumatoid Arthritis. ***Annu Rev Immunol*** 2008;26:651–75.

9 Van der Helm-van Mil A, Huizinga TWJ. Advances in the genetics of rheumatoid arthritis point to subclassification into distinct disease subsets. ***Arthritis Res Ther*** 2008;10:205.

10 Seegobin SD, Ma MH, Dahanayake C, et al. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. ***Arthritis Res Ther*** 2014;16:R13.

11 Canhão H, Rodrigues AM, Mourão AF, et al. Comparative effectiveness and predictors of response to tumour necrosis factor inhibitor therapies in rheumatoid arthritis. ***Rheumatology*** 2012;51:2020–6.

12 Fisher BA, Plant D, Lundberg K, et al. Heterogeneity of Anticitrullinated Peptide Antibodies and Response to Anti-Tumor Necrosis Factor Agents in Rheumatoid Arthritis. ***J Rheumatol*** 2012;39:929–32.

13 Potter C, Hyrich KL, Tracey A, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. ***Ann Rheum Dis*** 2009;68:69–74.

14 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. ***Arthritis Rheum*** 1988;31:315–24.

15 Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. ***Arthritis Rheum*** 2005;52:3381–90.

16 Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. ***Ann Rheum Dis*** 2011;70:1039–46.

17 Siegert CE, Vleming LJ, Vandenbroucke JP, et al. Measurement of disability in Dutch rheumatoid arthritis patients. ***Clin Rheumatol*** 1984;3:305–9.

18 Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. ***J Rheumatol*** 1999;26:743–5.

19 Prevoo MLL, van Gestel AM, van 't Hof MA, et al. Remission in a Prospective Study of Patients with Rheumatoid Arthritis. American Rheumatism Association Preliminary Remission Criteria in Relation to the Disease Activity Score. ***Rheumatology*** 1996;35:1101–5.

20 Van der Woude D, Young A, Jayakumar K, et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug–free remission in rheumatoid arthritis: Results from two large early arthritis cohorts. ***Arthritis Rheum*** 2009;60:2262–71.

21 Wessels JAM, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. ***Arthritis Rheum*** 2007;56:1765–75.

22 Van Dongen H, van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: A double-blind, randomized, placebo-controlled trial. ***Arthritis Rheum*** 2007;56:1424–32.

23 Croon EM de, Sluiter JK, Nijssen TF, et al. Predictive factors of work disability in rheumatoid arthritis: a systematic literature review. ***Ann Rheum Dis*** 2004;63:1362–7.

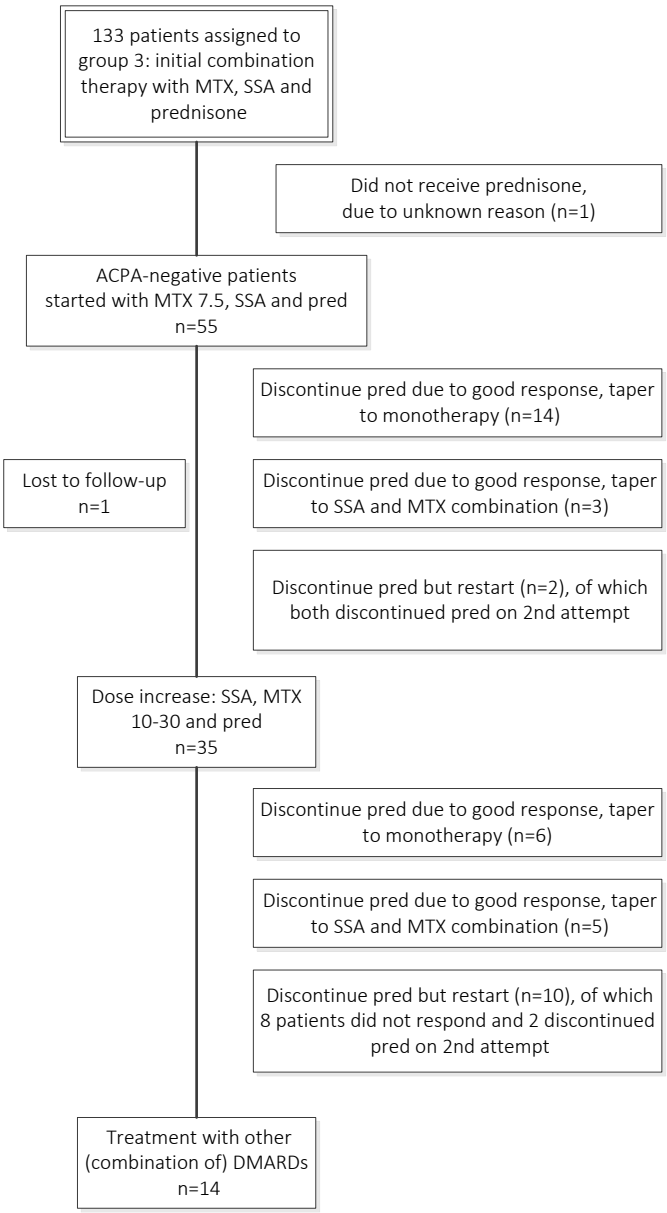
24 Pincus T, Cutolo M. Clinical trials documenting the efficacy of low-dose glucocorticoids in rheumatoid arthritis. ***Neuroimmunomodulation*** 2015;22:46–50.

25 Jong PH de, Hazes JM, Barendregt PJ, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. ***Ann Rheum Dis*** 2013;72:72–8.

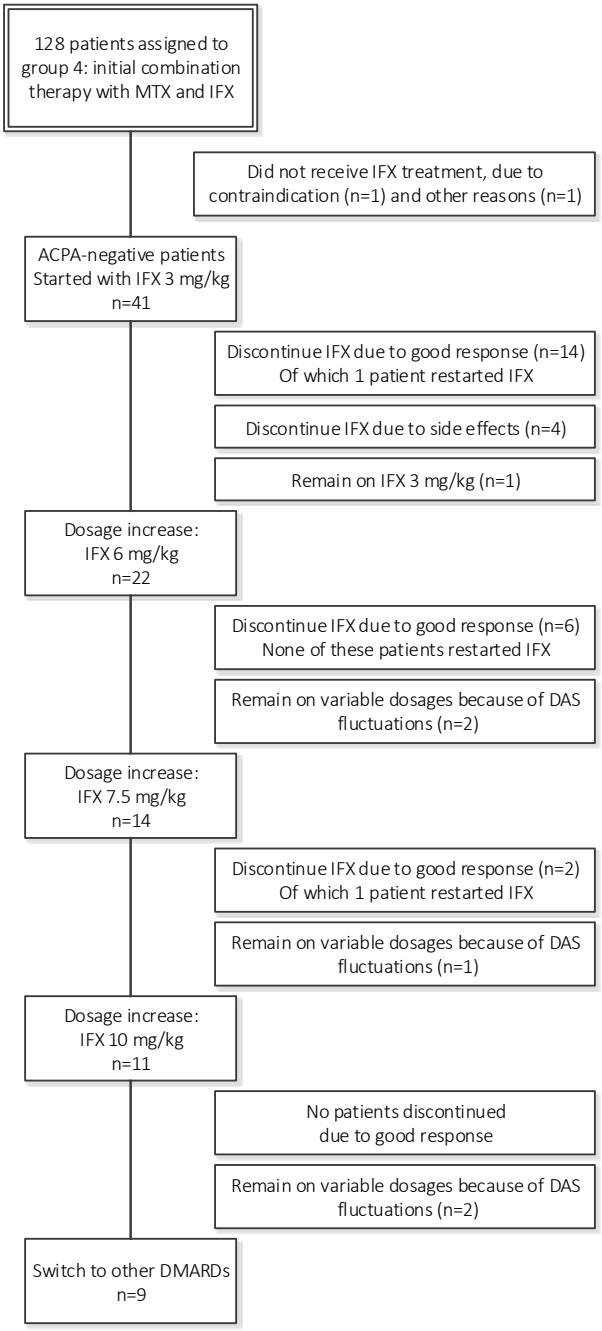
26 Den Uyl D, ter Wee M, Boers M, et al. A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. ***Ann Rheum Dis*** 2014;73:1071–8.

27 Ter Wee MM, den Uyl D, Boers M, et al. Intensive combination treatment regimens, including prednisolone, are effective in treating patients with early rheumatoid arthritis regardless of additional etanercept: 1-year results of the COBRA-light open-label, randomised, non-inferiority trial. ***Ann Rheum Dis*** 2014;74:1233–40.

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Flowchart of randomization arm 3 (initial combination with methotrexate, sulphasalazine and prednisone) during year 1 and 2 of follow-up.
ACPA, anti-citrullinated protein antibodies; DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; pred, prednisone; SSA, sulphasalazine.



Supplementary Figure 2: Flowchart of randomization arm 4 (initial combination with methotrexate and infliximab) during year 1 and 2 of follow-up.
ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; DMARD, disease-modifying antirheumatic drugs; IFX, infliximab; MTX, methotrexate.

6