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Rheumatoid arthritis patients with continued low disease activity have similar outcomes over 10 years, regardless of initial therapy

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Abstract

Objectives. To compare 10-year disease outcomes of RA patients who have continuous low disease activity and are on MTX with or without initial combination therapy with infliximab or prednisone and SSZ.

Methods. Recent-onset RA patients from the Behandel Strategieen (BeSt) (Dutch acronym for Treatment Strategies) study with 10 years of follow-up were analysed. Treatment was tightly controlled, targeted at DAS $\leqslant$ 2.4. The selected patients had low disease activity from 6 months until 10 years and therefore did not intensify treatment. Patients were grouped into those receiving MTX monotherapy and those receiving initial combination therapy. Between-group differences over time were compared, using (generalized) linear mixed model analyses, for the outcomes DAS, HAQ, ESR, visual analogue scale patient global health, percentage of patients in (drug-free) remission and percentage of patients with Sharp/van der Heijde score progression $\geqslant$5.

Results. At 10 years, 28/247 (11%) patients on MTX monotherapy (some tapered to drug free) had continued DAS $\leqslant$ 2.4 compared with 68/261 (26%) patients on combination therapy (all tapered to monotherapy or drug free). No between-group differences in continuous responders were found over time, except for a higher percentage of patients in drug-free remission after MTX monotherapy. Significant group–time interactions were found for DAS, ESR and visual analogue scale patient global health, but the results seem clinically negligible.

Conclusion. More patients achieved continuous low disease activity on initial prednisone or infliximab combination therapy than on initial MTX monotherapy, but there appeared to be no additional benefits. Regardless of induction therapy, patients with continuous low disease activity have similar long-term outcomes, with only a higher proportion of patients in drug-free remission after MTX monotherapy.

Key words: rheumatoid arthritis, long-term outcomes, treatment, disease activity, methotrexate, combination therapy

CLINICAL SCIENCE

Rheumatology key messages

- More RA patients achieve continuous low disease activity on combination therapy compared with those on MTX monotherapy.
- RA patients with continuous low disease activity had no additional benefit from initial combination therapy.

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Introduction

Earlier initiation of treatment, targeted treatment and the use of DMARDs have led to great improvements in the treatment of RA [1, 2]. Current guidelines recommend the use of MTX as (part of) the first treatment of RA [3]. Although MTX can be highly effective in reducing disease activity, 50–75% of early RA patients do not achieve

low disease activity within 3–6 months after initiation of MTX monotherapy in dosages of 20–25 mg/week [3–6]. Previous studies have shown that combination therapy including CSs or a biologic DMARD is more efficacious than MTX monotherapy [7–10], with more patients reaching early low disease activity or even remission when starting combination therapy including CSs or a TNF-blocker. However, it remains to be determined whether patients who have an early good response to combination therapy also have better long-term outcomes than patients who have an early good response to MTX monotherapy. For instance, radiologic damage progression may be better suppressed in patients on combination therapy, since for infliximab and other TNF-inhibitors as well as for prednisone it has been suggested that there may be a 'disconnect' between clinical and radiologic outcomes. Thus, in patients who have insufficient clinical improvement on these medications, there may still be prevention of radiologic damage progression [11–13]. According to the 'window of opportunity' theory, earlier suppression of inflammation by using initial prednisone or infliximab combination therapy may prevent chronicity of inflammation, resulting in achieving long-term remission and drug-free remission more readily than by using MTX monotherapy with slightly delayed clinical response.

Therefore, we hypothesized that compared with patients who have a good clinical response on MTX monotherapy, patients who have a good clinical response on initial combination therapy with prednisone or infliximab may have superior disease outcomes during 10 years of follow-up.

Methods

Data from the Behandel Strategieen (BeSt) (Dutch acronym for Treatment Strategies) study were used. The BeSt study is a multicentre randomized trial (Dutch trial registry, NTR262 and NTR265) with 10 years of follow-up, in which 508 recent-onset RA patients (1987 ACR criteria [14]) were included. Patients were recruited between April 2000 and August 2002 and randomized into one of four treatment strategies: sequential monotherapy, step-up combination therapy, initial combination therapy with prednisone or initial combination therapy with infliximab. Patients were treated to target based on 3-monthly calculations of the DAS in 44/53 joints [15]. Treatment was intensified or changed according to treatment protocol if DAS $>$ 2.4. Patients in the sequential monotherapy and step-up combination therapy groups initiated 15 mg/week MTX. If DAS was $\leqslant$2.4 for at least 6 consecutive months, MTX was tapered to 10 mg/week. Patients in the initial combination therapy with prednisone group initially received 7.5 mg/week MTX + 2000 mg/day SSZ + 60 mg/day prednisone (prednisone was tapered to 7.5 mg/day in 7 weeks). In these three groups, MTX could be increased to 25–30 mg/week in the case of DAS being $\geqslant$2.4. If DAS remained $\leqslant$2.4 from week 28, prednisone was tapered and stopped, and from week 40 the MTX dose was tapered and stopped, until SSZ monotherapy remained. From year 3, if patients who had tapered to MTX 10 mg/week monotherapy or SSZ monotherapy and who were in DAS-remission (DAS $<$ 1.6) for at least 6 consecutive months, the last DMARD was tapered to null, but restarted when DAS was $>$1.6. Patients randomized to initial combination therapy with infliximab started with 25 mg/week MTX + 3 mg/kg infliximab. In this group, infliximab could be increased to 6 mg/kg/8 weeks (but not higher in this subgroup, because of the requirement to have DAS $\leqslant$ 2.4 from month 6). Tapering to 3 mg/kg/8 weeks occurred if DAS was $\leqslant$2.4 for at least 6 months, and ultimately with persistent DAS $\leqslant$ 2.4, infliximab was stopped. Then, if DAS remained $\leqslant$2.4, MTX could also be tapered, by the same schedule as described above.

At baseline, extensive patient characteristics and disease measures were recorded. Every 3 months clinical outcomes were measured. At baseline and for each following year, radiographs of the hands and feet were made and assessed according to the Sharp/van der Heijde score (SHS) [16]. The Medical Ethical Committees of all participating centres approved the study protocol, and all patients gave written informed consent. A more detailed description of the BeSt study has been previously published [7]. This analysis did not require additional approval.

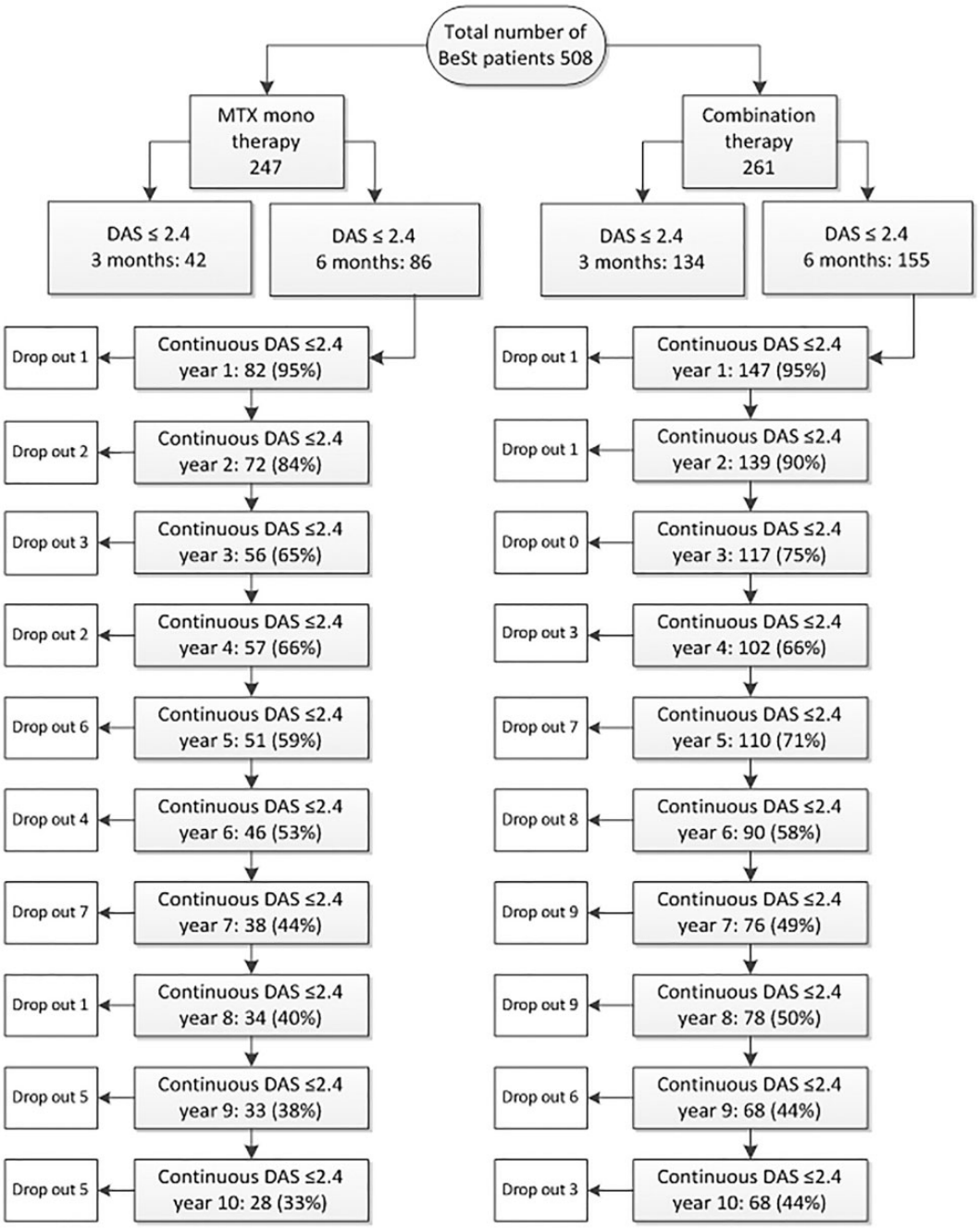
For the present study, patients (responders) from all four randomization arms were selected if they had continuous DAS $\leqslant$ 2.4 from 6 months until the final visit at 10 years. This included patients who at 3 months increased MTX to 25 mg/week because the DAS was still $>$2.4. Patients were divided into two groups: MTX monotherapy responders (in randomization arms 1 and 2) and combination therapy responders (in randomization arms 3 and 4). Although the medications used in combination with MTX in groups 3 and 4 differed, previous results from the BeSt study showed that both groups had equal outcomes over time. Therefore, these arms were combined for this analysis [17].

Between-group differences at baseline were compared using *t*-tests, Mann–Whitney U tests or Chi-square tests, as appropriate. Between-group differences over time were compared for the outcomes with respect to DAS, ESR, patient global health [visual analogue scale (VAS) 0–100, 100 worst score], HAQ, percentage of patients in remission and in drug-free remission, and percentage of patients with SHS progression $\geqslant$5. For continuous, normally distributed outcomes, linear mixed model (LMM) analyses with an unstructured covariance matrix were performed, estimated using restricted maximum likelihood, to compare groups over time. For continuous, non–normally distributed outcomes and for dichotomous outcomes, generalized linear mixed model (GLMM) analyses with an unstructured covariance matrix using adaptive Gauss–Hermite quadrature were performed to compare groups over time. All analyses were performed using Stata SE version 14 (StataCorp LP). A $P < 0.05$ was considered statistically significant.

Results

In Fig. 1, the flow chart of patients initiating MTX monotherapy or combination therapy and responding to initial treatment over 10 years is displayed. Of the 247 patients who initiated MTX monotherapy, 86 (34.8%) patients had a DAS of $\leqslant$2.4 on MTX monotherapy at 6 months (43 had

Fig. 1 Flowchart of patients with continuous DAS ⩽ 2.4 from 6 months until the end of follow-up



increased the MTX dose to 25 mg/week at month 3). Of these 86 patients, 36 dropped out, 22 changed therapy because of a DAS of >2.4 and 28 (11.3% of initial 247, 32.9% of initial responders) kept responding to MTX monotherapy, with a DAS of ⩽2.4 until year 10. Of the 261 patients who initiated combination therapy, 155 (59.4%) patients had a DAS of ⩽2.4 on initial therapy at 6 months (21/133 in arm 3 had increased the MTX dose to 25 mg/weeks and 22/128 in arm 4 had increased the infliximab dose to 6 mg/kg/8 weeks at month 3). Of these 155 patients, 47 dropped out, 40 changed therapy because of a DAS of >2.4 and 68 (26.1% of the initial 261, 43.9% of initial responders) remained on the initial treatment step until year 10, which means by protocol they had tapered the initial combination therapy to monotherapy. The baseline characteristics of MTX monotherapy

continuous responders and initial combination therapy continuous responders are shown in Table 1. Among MTX monotherapy responders, there were fewer ACPA-positive patients (ACPA-positive 46% *vs* 54%, $P = 0.477$), with shorter symptom duration at baseline (14.0 *vs* 28.3 weeks, $P = 0.004$) and a slightly lower SHS score (median 0 *vs* 2.5, $P = 0.014$) than combination therapy responders. In Fig. 2, the DAS, ESR, VAS patient global health, HAQ, percentage of patients in remission and in drug-free remission and the percentage of patients with a SHS progression of $\geqslant 5$ are displayed for MTX monotherapy continuous responders and for initial combination-therapy continuous responders over 10 years of follow-up. Both groups show similar results over time for HAQ, DAS, ESR, VAS patient and global health and and similar SHS progression (Fig. 2A–D and G). There seem to be higher remission and drug-free remission rates in the MTX monotherapy responders than in the combination therapy responders (Fig. 2E and F). These potential differences were tested with a LMM or a GLMM, as appropriate. In Table 2, the results of the LMM and GLMM analyses are shown. For all outcomes an improvement over time was seen, regardless of initial treatment group. For the outcomes DAS, ESR and VAS patient global health (Table 2), a small positive interaction between the treatment group and time was seen. The results indicate slightly worse DAS, ESR and VAS patient global health with increasing time for the initial combination therapy responders compared with the MTX monotherapy responders, but the effects seem to be very small. For the outcomes HAQ, percentage SHS progression of $\geqslant 5$ and percentage of patients in remission and drug-free remission, no interaction was observed. The percentage of patients in remission was not statistically significantly different between the two groups, although a trend could be observed towards a higher percentage of patients in remission in the MTX monotherapy group. The percentage of patients in drug-free remission was higher in the MTX monotherapy group. The same LMM and GLMM analyses were repeated, with an additional adjustment for symptom duration at baseline, since median symptom duration differed between groups (Table 1) and was thought to be a potential confounder. However, this did not lead to a relevant change in the results (Table 1; supplementary Tables S1 and S2, available at *Rheumatology* Online). Also, additional adjustment for baseline SHS did not change the results (Table 2; supplementary Tables S1 and S2, available at *Rheumatology* Online).

Discussion

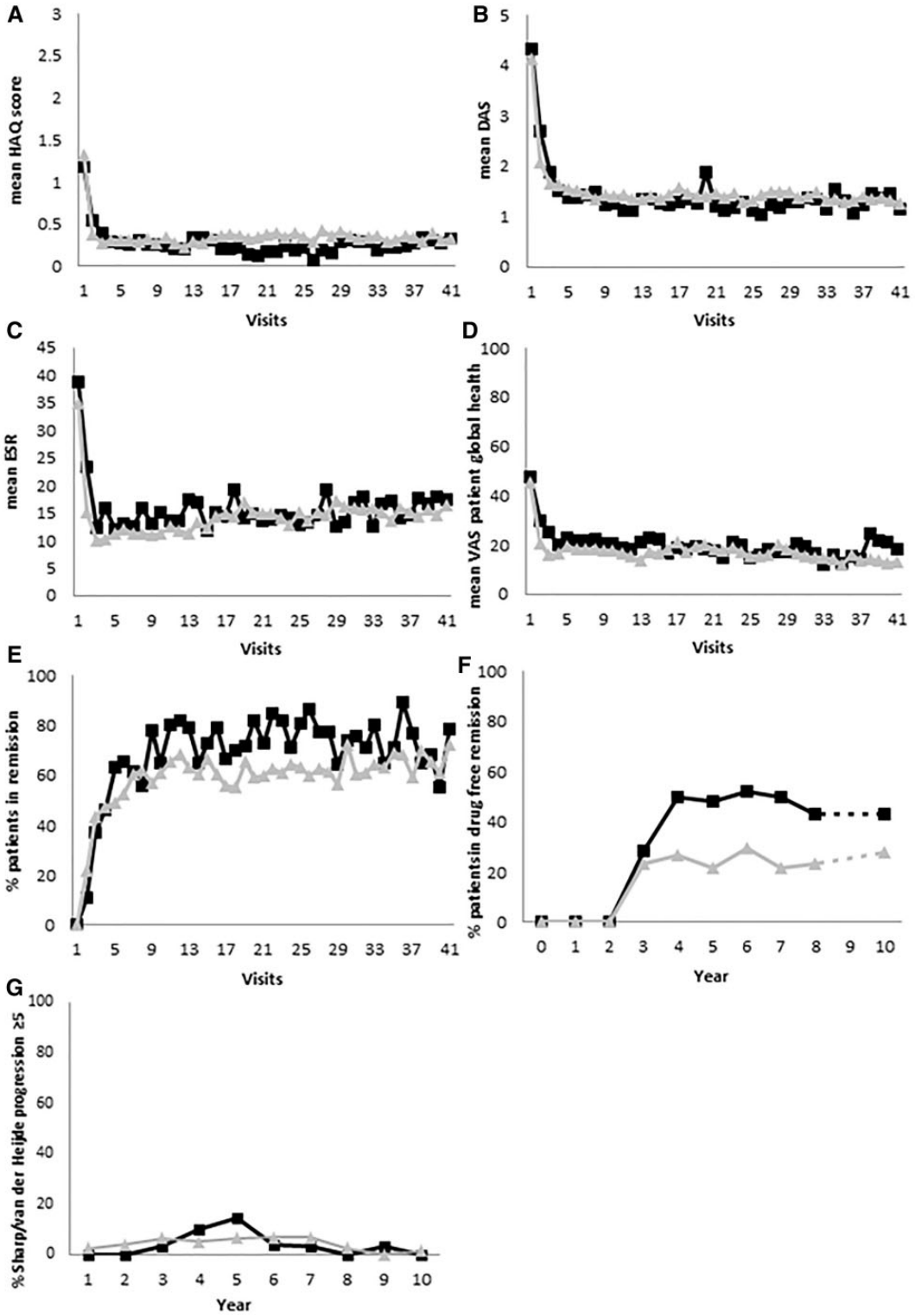
In this study, we investigated whether for RA patients who achieve continuous low disease activity during 10 years on their first DMARD, there are differences in clinical or radiological outcomes that can be attributed to whether that first DMARD was MTX monotherapy or MTX initially combined with SSZ and prednisone or with infliximab. We hypothesized that earlier improvement on initial combination therapy, or a disconnect between disease activity and radiologic damage progression associated with prednisone and infliximab, might result in better outcomes in

Table 1 Baseline characteristics of patients who are MTX monotherapy continuous responders compared with those who are combination therapy continuous responders

Characteristic	MTX monotherapy continuous responders, $n = 28$	Combination therapy continuous responders, $n = 68$	*P*-value for between-group differences[a]
Age, mean (S.D.), years	54.8 (11.7)	54.2 (10.4)	0.797
Gender, % female	57.1	63.2	0.577
RF positive, %	60.7	60.3	0.969
ACPA positive, %	46.4	54.4	0.477
BMI, mean (S.D.)	25.7 (2.6)	25.1 (3.2)	0.382
Alcohol users (current), %	60.7	61.2	0.965
Smoking status (ever), %	28.6	22.1	0.497
Symptom duration, median (range), weeks	14.0 (1.14–191)	28.3 (3.9–263.1)	0.004
DAS, mean (S.D.)	4.3 (1.0)	4.1 (0.84)	0.300
ESR, mean (S.D.), mm/h	38.8 (31.9)	34.8 (22.2)	0.554
CRP, median (range), mg/l	38.7 (45.5)	24.5 (29.4)	0.429
Ritchie articular index, median (range)	9.5 (4–47)	11 (2–29)	0.830
Swollen joint count, median (range)	13 (6–36)	13.5 (4–31)	0.269
VAS patient global health, mean (S.D.), mm	47.6 (17.8)	45.2 (20.8)	0.584
VAS physician global health, mean (S.D.), mm	54.5 (18.6)	50.9 (18.7)	0.391
HAQ, mean (S.D.)	1.2 (0.7)	1.3 (0.7)	0.452
Sharp/van der Heijde score, median (range)[b]	0 (0–16)	2.5 (0–25.5)	0.014

[a]Tested using *t* test for continuous, normally distributed variables, tested using Mann–Whitney U tests for continuous, non-normally distributed variables, tested using Chi-square tests for categorical/dichotomous variables. [b]$n = 27$ in MTX monotherapy responders, $n = 66$ in combination therapy responders.

FIG. 2 Clinical and radiological outcomes over 10 years of follow-up in MTX monotherapy and combination therapy responders



Clinical and radiological outcomes over time in MTX monotherapy responders (black lines) and combination therapy responders (grey lines) during 10 years of follow-up. Results for drug-free remission at year 9 are not shown, due to a large amount of missing data at this time point.

Table 2 Differences over time between MTX monotherapy responders ($n = 28$) and combination therapy responders ($n = 68$)

Linear mixed model analyses	**β (95% CI)**
HAQ	
Treatment group[a]	0.08 (−0.07, 0.22)
Time in years	−0.01 (−0.02, −0.01)
Constant	0.27 (0.02, 0.53)
DAS	
Treatment group[a]	−0.03 (−0.24, 0.19)
Time in years	−0.12 (−0.15, −0.08)
Treatment group × Time	0.01 (0.00, 0.04)
Constant	1.91 (1.53, 2.28)
ESR	
Treatment group[a]	−3.20 (−7.41, 1.02)
Time in years	−0.76 (−1.23, −0.29)
Treatment group × Time	0.43 (0.16, 0.70)
Constant	20.23 (12.78, 27.68)
VAS patient global health	
Treatment group[a]	−3.98 (−9.39, 1.43)
Time in years	−1.70 (−2.30, −1.09)
Treatment group × Time	0.36 (0.02, 0.70)
Constant	30.17 (20.60, 39.74)
Generalized linear mixed model analyses	**OR (95% CI)**
SvdH score progression ⩾5	
Treatment group[a]	0.83 (0.17, 4.01)
Time in years	0.94 (0.83, 1.07)
Constant	0.00 (0.00, 0.16)
Remission	
Treatment group[a]	0.58 (0.32, 1.08)
Time in years	1.18 (1.15, 1.21)
Constant	1.68 (0.56, 5.04)
Drug-free remission	
Treatment group[a]	0.14 (0.03, 0.61)
Time in years	1.06 (1.03, 1.08)
Constant	0.38 (0.03, 4.77)

[a]Difference between treatment groups; MTX monotherapy responders as reference group. VAS: visual analogue scale; SvdH: Sharp/van der Heijde; OR: odds ratio.

the initial combination therapy group. In contrast, we found that all long-term continuous good responders had similar clinical and radiological outcomes, but that initial MTX monotherapy responders achieved drug-free DAS-remission more often.

In recent years it has become clear that early initiation of anti-rheumatoid therapy is important for ensuring rapid clinical improvement, restoring functional ability, preventing productivity loss and avoiding radiologic damage. Many studies have shown that more patients have rapid clinical improvement on initial treatment with a combination of MTX and a CS or a biologic DMARD than on initial MTX monotherapy [4, 5, 7, 18]. This suggests that, perhaps through multipathway targeting, more types of RA (ACPA positive or negative, with signs of high or low systemic inflammation, erosive or likely to rapidly show damage or not, etc.) and/or more types of patients (male or female, young or old, high or low BMI, or other hidden characteristics) respond to combination therapy, while only a certain (as yet undefined, maybe milder) subgroup will respond to MTX monotherapy. There is also the (perhaps instinctive) expectation that early treatment with multipathway combination therapy in some way can stop or even reverse disease processes that go unchecked with only MTX monotherapy, resulting in lower disease activity, more remission, better functioning and the possibility of tapering and stopping medication, resulting in drug-free remission without radiologic progression and possibly cure of RA.

If that was the case, patients who responded well on initial combination therapy would fare better than patients who responded well on initial MTX monotherapy. We did not find this. We did see that more patients who started on initial combination therapy achieved a continuous good response (DAS $\leqslant 2.4$) compared with patients who started on initial MTX monotherapy. Thirty-five percent of patients who started on initial MTX monotherapy achieved a DAS of $\leqslant 2.4$ after 6 months, and of those, only 33% maintained a DAS of $\leqslant 2.4$ on MTX monotherapy for the next 9.5 years. This compared with 59% of patients who achieved a DAS of $\leqslant 2.4$ at 6 months on initial combination therapy, of whom 44% maintained a DAS of $\leqslant 2.4$, having tapered to SSZ or MTX monotherapy. But all patients who had continuous DAS $\leqslant 2.4$ had mostly similar disease outcomes over time, regardless of initial treatment. We even observed that more MTX monotherapy responders than combination therapy responders achieved drug-free DAS remission. It is left to speculation whether the differences in drug-free DAS remission could be due to discontinuation of prednisone or infliximab or indicates slight differences in efficacy between MTX monotherapy and SSZ monotherapy (after discontinuation of prednisone and MTX in one of the initial combination therapy arms). Functional ability and radiologic damage progression were similar between groups, with a trend towards a slight increase in the combination therapy group compared with in the MTX monotherapy group over time. An interaction between treatment group and time was found for most outcome measures except for the HAQ and the percentages of patients in remission and drug-free remission. However, the interaction effects are small and seem to be clinically negligible.

If fewer patients respond to MTX monotherapy than to combination therapy, patients who respond well to initial MTX monotherapy might be a more tightly defined subgroup based on baseline criteria. We only saw a slightly higher percentage of ACPA-negative patients in the MTX monotherapy group. Previously, it has been suggested that ACPA-negative patients may achieve drug-free remission more often than ACPA-positive patients, possibly irrespective of effort of treatment [19]. In the PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study, ACPA-negative patients with undifferentiated arthritis did not benefit from MTX compared with placebo, but ACPA-positive patients did [20]. On the other hand, more ACPA-negative patients achieved drug-free remission. In the current analysis, a

slightly higher percentage of ACPA-negative patients in the MTX monotherapy responders was accompanied by a higher percentage of drug-free remission over time. MTX monotherapy responders also had slightly shorter symptom duration and slightly lower SHS at baseline than combination therapy responders. Patient numbers were, however, too small to go beyond these observations.

The ideal of personalized medicine should avoid delays in response as well as unnecessary costs and potential side effects based on baseline predictors. Previous research has focused on predictors of initial, rather than early continuous good response. Male gender, lower age, lower BMI, low baseline disease activity, absence of IgM RF, not smoking, and several genetic factors were found to be associated with response to MTX monotherapy within 6–12 months [21–23]. In our early and continuous MTX responders, the baseline characteristics do not suggest that continuous response after initial response is associated with these predictors, although we are not informed about the genetic factors. There may be other additional factors required for continuous good response during prolonged follow-up that remain as yet unidentified.

As long as personalized medicine is not yet possible, it appears that although MTX monotherapy may be similarly effective, the main benefit from starting with combination therapy in all patients is that more patients achieve and maintain (after tapering to MTX monotherapy) low disease activity. More recent studies have suggested that the initial prednisone dose can be lower [24–26] and that SSZ may be omitted [26], making a case for low-dose CS bridging therapy combined with MTX as optimal initial treatment.

A strength of this study is that all patients were treated based on randomization across the treatment arms. Although we analysed a selection of the originally randomized patients, additional adjustment for baseline symptom duration, which differed between the groups at baseline, did not change the results. A limitation of this study was the low number of patients in the MTX monotherapy responders group, which might have reduced the power to detect differences between the groups. However, the lower number of patients in the MTX monotherapy group is in line with previous research showing higher effectiveness of combination therapy [7–10]. A second limitation was the high number of drop-outs among responders. An earlier analysis of the BeSt study has shown that having achieved drug-free remission (independent of initial treatment) and having limited joint damage are risk factors for early termination in the BeSt study [27]. Therefore, specifically the patients selected for this study, those who respond well to therapy early in the study, had a high risk of dropping out. Indeed, on average, patients in both groups were in low disease activity at the last available visit before they dropped out.

We conclude that regardless of initial induction therapy, those who remain in low disease activity have similar long-term outcomes, with only the proportion of patients in drug-free remission being higher in the MTX monotherapy group. However, more patients achieve early and continuous low disease activity on prednisone or infliximab combination therapy tapered to SSZ or MTX monotherapy than when initially on MTX monotherapy, although there appear to be no additional benefits.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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