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Feasibility of tailored treatment based on risk stratification in patients with early rheumatoid arthritis

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ABSTRACT

Objective

Personalized medicine is the holy grail of medicine. The EULAR recommendations for the management of rheumatoid arthritis (RA) support differential treatment between patients with baseline characteristics suggestive of a non-poor prognosis (non-PP) or poor prognosis (PP) (presence of autoantibodies, a high inflammatory activity and damage on radiographs). We aimed to determine which prognostic risk groups benefit more from initial monotherapy or initial combination therapy.

Methods

508 patients were randomized to initial monotherapy or initial combination therapy. Disease outcomes of initial monotherapy and initial combination therapy were compared within non-PP or PP groups as determined on baseline characteristics.

Results

PP patients treated with initial combination therapy after three months more often achieved ACR20 (70% vs 38%, p<0.001), ACR50 (48% vs 13%, p<0.001) and ACR70 response (24% vs 4%, p<0.001) than those treated with initial monotherapy, and had more improvement in HAQ (median decrease 0.75 vs 0.38, p<0.001). After 1 year, differences in ACR20 response and DAS-remission remained; PP patients treated with initial combination therapy (vs initial monotherapy) had less radiographic progression (median 0.0 vs 1.5, p=0.001).

Non-PP patients treated with initial combination therapy after three months more often achieved an ACR response (ACR20: 71% versus 44%, p<0.001; ACR50: 49% vs 13%, p<0.001; ACR70: 17% vs 3%, p=0.001) than with initial monotherapy, and functional ability showed greater improvement (median decrease in HAQ 0.63 vs 0.38, p<0.001). After 1 year, differences in ACR20 and ACR50 response remained; radiographic progression was comparable between the groups.

Non-PP and PP patients responded equally well to initial combination therapy in terms of improvement of functional ability, with similar toxicity.

Conclusions

Since PP and non-PP patients benefit equally from initial combination therapy through earlier clinical response and functional improvement than with initial monotherapy, we conclude that personalized medicine as suggested in the guidelines is not yet feasible. The choice of treatment strategy should depend more on rapid relief of symptoms than on prognostic factors.

INTRODUCTION

Clinical trials have shown that on a group level, patients with early rheumatoid arthritis (RA) treated with initial combination therapy achieve earlier decrease in disease activity, improvement in functional ability and less radiographic joint damage progression than patients treated with initial monotherapy.[1–7] However, for individual patients there is a need for individualized treatment. The 2010 European League Against Rheumatism (EULAR) recommendations stated that 'patients with a favourable prognosis very often respond similarly to low-intensity monotherapy or intensive medication strategies', suggesting that for patients with a poor prognosis this might be different.[8] It was also formulated that 'occasional patients with a particular need for rapid, highly effective intervention, may benefit from starting a biological agent plus methotrexate as a viable and useful option', which was built on the idea that 'patients with poor prognostic factors have more to gain'.[8] This opinion was abandoned in the updated 2013 recommendations, but these also state that 'risk stratification is an important aspect of the therapeutic approach to RA',[9] detailing that after failure to achieve low disease activity on methotrexate monotherapy, 'in patients with a low risk of poor RA outcome, another conventional synthetic disease-modifying antirheumatic drug (DMARD) strategy would be preferred, while in patients with a high risk, the addition of a biologic DMARD would be preferred'.[9] Hence, the recommendations encourage rheumatologists to use risk stratification in daily practice and to implement a personalized approach in the treatment of patients with RA.

In this post hoc analysis of the BeSt study, we investigated whether patients with poor or non-poor prognostic factors (based on previously developed prediction models)[10–13] respond differently to initial monotherapy, and whether patients with a poor or non-poor prognosis respond differently to initial combination therapy, as suggested by the EULAR recommendations. Furthermore, we studied the efficacy of a second conventional synthetic DMARD in patients with a low risk of poor RA outcome who failed on the first.

PATIENTS AND METHODS

Study design

In the BeSt (Dutch acronym for treatment strategies) study, 508 patients with early RA fulfilling the 1987 criteria[14] were included and randomized to one of four treatment strategies: (1) sequential monotherapy, (2) step-up combination therapy, (3) initial combination with methotrexate (MTX), sulfasalazine (SSA) and a tapered high dose of prednisone, (4) initial combination with MTX and infliximab. For this analysis, groups 1 and 2 (both starting with MTX monotherapy) were combined, because they had very similar disease outcomes during the first year of follow-up,[5] as also group 3 and 4 (both starting with combination therapy as shown in Figure 1). Three-monthly clinical assessments included the disease activity score (DAS) and the health assessment questionnaire (HAQ) to measure functional ability.

Radiographs of hands and feet were collected yearly and assessed by two independent readers, in random order and blinded to patient identity, using the Sharp/ van der Heijde score (SHS).[15]

In all groups, the treat-to-target strategy required treatment adjustments when DAS was >2.4 (treatment steps are depicted in Figure 1). Dose tapering occurred if DAS was ≤2.4 for ≥6 months and the last antirheumatic drug was discontinued if DAS was <1.6 for ≥6 months (for details see previous publications).[5,7] The ethics committees of all participating centers approved the study protocol and patients gave written informed consent.

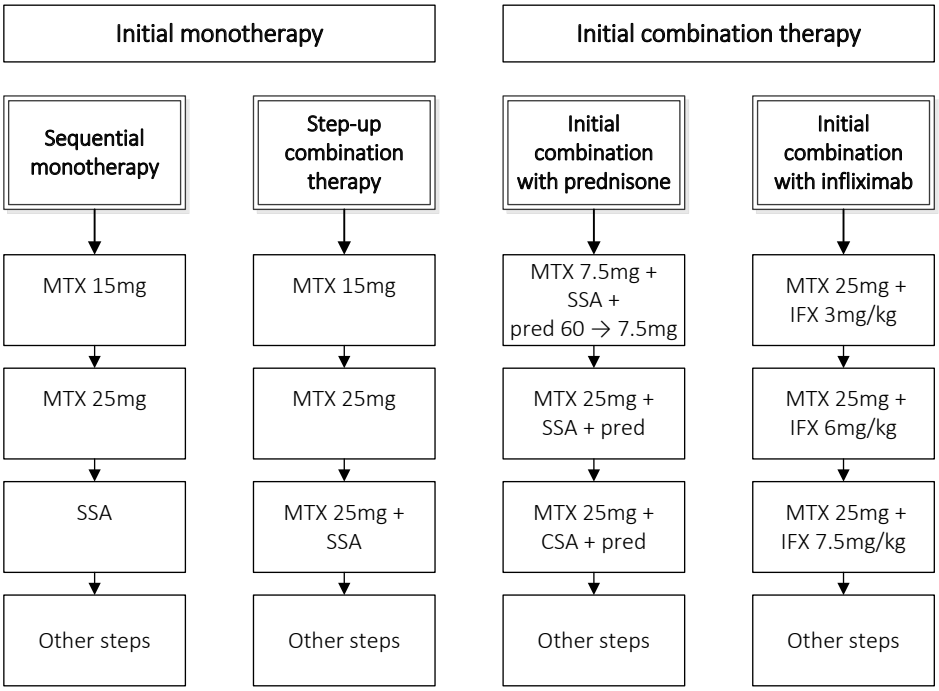

Figure 1. Treatment steps per strategy.
CSA, ciclosporine A 2.5 mg/kg/day; MTX, methotrexate; IFX, infliximab; pred, prednisone 7.5 mg/day unless indicated otherwise; SSA, sulphasalazine 2000 mg/day.

Stratification for prognosis

Because there is no unambiguous method to determine which patients are 'poor prognosis patients' (PP patients), we used two different methods and tested both. The first method defined poor prognosis as presence of at least three out of four baseline disease characteristics, based on determinants used in prediction models: DAS ≥3.7, swollen joint count (SJC) ≥10, erosions ≥4 and both rheumatoid factor (RF)-positive and anti-citrullinated protein autoantibodies (ACPA)-positive.[10–13] Consequently, non-poor prognosis patients (non-PP patients) were defined as having ≤2 features of poor prognosis. The latter category represents a heterogeneous group, including patients in a range from an evident favourable

prognosis to patients with a moderate prognosis. The results of this stratification method are discussed in Results.

The second method was to classify all patients according to the matrix risk model for rapid radiographic progression (RRP, defined as an increase of ≥5 points in SHS during the first year) designed in the BeSt study.[11] This model estimates the risk of RRP with three baseline characteristics: the number of erosions, C-reactive protein and RF and ACPA status. Using the matrix for initial monotherapy, a cutoff of 50% risk for RRP was used to distinguish PP and non-PP patients. The results of this stratification method are shown in Supplementary files 1, 2, 3 and 4, and are not discussed in Results.

Study endpoints

Percentages of PP and non-PP patients treated with initial combination therapy who could discontinue prednisone or infliximab during the first year, because of a good response, were compared. Percentages of PP and non-PP patients receiving initial monotherapy who failed to achieve DAS ≤2.4 on MTX monotherapy after six months were compared, as well as percentages of DAS ≤2.4 three months after the introduction of a second conventional synthetic DMARD. To assess the outcomes of initial treatment options in non-PP and PP patients, we compared the clinical response (percentage of patients achieving DAS-remission, defined as DAS <1.6;[16] American College of Rheumatology (ACR)20, ACR50 and ACR70 response;[17] median decrease in HAQ) after three months and after one year. To define which patients benefit the most from initial combination therapy, the steepness of the slope of decrease in HAQ was compared between PP and non-PP patients. This was also tested for PP and non-PP patients receiving initial monotherapy. Radiographic progression (increase in SHS) at year one and the percentage of patients with RRP were compared between the groups. Adverse events (AE) and serious adverse events (SAE) were compared between PP and non-PP patients treated with initial combination therapy.

Statistical analysis

The independent t-test, Mann-Whitney U-test, Fischer's exact test, chi square ($\chi 2$) test, logistic regression analysis and linear regression analysis were used, depending on dichotomy or continuity and distributions of determinants and outcomes. For radiographic progression as the outcome, Poisson regression was used to take into account the non-normal distribution of radiographic progression, with an excess of zeros. To compare the decrease in HAQ between PP and non-PP patients, the mean difference was calculated and tested with the independent t-test. A p value <0.05 was considered statistically significant.

RESULTS

Here, the results of defining PP patients by the presence of ≥3 of 4 poor prognostic factors (and consequently the non-PP patients by the presence of ≤2 of these factors) are discussed. The results of prognosis stratification according to the RRP matrix model of Visser et al.[11] are shown in Supplementary files 1, 2, 3 and 4.

Of 508 patients, 417 (82%) were classified as having a poor or a non-poor prognosis based on the available data. Of the 192/417 patients (46%) with PP, 100 (52%) had been randomized to initial monotherapy and 92 (48%) to initial combination therapy. Of 225/417 patients (54%) with a non-PP, 100 (44%) were treated with initial monotherapy and 125 (56%) with initial combination therapy.

Baseline characteristics per treatment strategy and prognosis category are shown in Table 1. Characteristics were similar among the randomization arms, but principally as a consequence of the stratification for prognosis, there were differences between prognosis categories. Although age was not a determinant to classify prognosis, patients with a poor prognosis were found to be older than patients with a non-poor prognosis.

Treatment response

Of 92 PP patients who received initial combination therapy, 47 (51%) could discontinue prednisone or infliximab after achieving low disease activity during at least six consecutive months. Similarly, of 125 non-PP patients treated with initial combination therapy, 70 (56%) could discontinue prednisone or infliximab (p=0.674). After six months, 55/100 PP patients (55%) and 33/100 non-PP patients (33%) who had been allocated to initial monotherapy had not achieved a DAS ≤2.4 on MTX monotherapy despite a dose increase at three months from 15 mg/week to 25 mg/week (p=0.007). Three months later, 39/55 (72%) PP patients and 25/33 non-PP patients (76%) had also failed to achieve DAS ≤2.4 after switching to or adding SSA (p=0.364) and one non-PP patient (3%) was treated outside of protocol.

Clinical outcomes after three months follow-up

Significantly more PP patients who were treated with initial combination therapy fulfilled the ACR20 response criteria after three months than those treated with initial monotherapy (70% versus 38%, p<0.001). This was the same for ACR50 response (48% versus 13%, p<0.001), ACR70 response (24% versus 4%, p<0.001) and for DAS-remission (17% versus 5%, p=0.016). Patients treated with combination therapy had a significantly greater improvement in functional ability (median decrease in HAQ 0.75 versus 0.38, p<0.001). This resulted in a mean HAQ score at 3 months of 0.60 in patients treated with initial combination therapy compared to a mean HAQ score of 1.08 in patients treated with initial monotherapy (see also Figure 2).

Table 1. Baseline characteristics of 417 patients classified as having a 'poor prognosis' or a 'non-poor prognosis'.

	Poor prognosis patients		Non-poor prognosis patients		
	Initial monotherapy	Initial combination therapy	Initial monotherapy	Initial combination therapy	p value
	n=100	n=92	n=100	n=125	
Age, mean (SD)	56 (13)	58 (15)	53 (13)	51 (13)	0.002
Gender, n (%) female	68 (68)	60 (65)	72 (72)	78 (62)	0.481
Treatment strategy, n (%)					<0.001
1. Sequential monotherapy (MTX)	51 (51)	0	54 (54)	0	
2. Step-up combination therapy (MTX)	49 (49)	0	46 (46)	0	
3. Initial combination therapy with MTX, SSA and prednisone	0	43 (47)	0	61 (49)	
4. Initial combination therapy with MTX and infliximab	0	49 (53)	0	64 (51)	
DAS, mean (SD)	4.8 (0.7)	4.5 (0.6)	4.3 (0.9)	4.1 (0.9)	<0.001
Swollen Joint Count, median (IQR)	17 (11 – 22)	15 (12 – 18)	11 (8 – 16)	11 (8 – 17)	<0.001
Tender Joint Count, median (IQR)	14 (11 – 19)	13 (10- 19)	13 (8 – 16)	12 (8 – 17)	<0.001
ESR, mean (SD)	51 (30)	44 (29)	37 (25)	35 (24)	<0.001
VAS gh, mean (SD)	61 (21)	57 (22)	60 (23)	60 (21)	0.754
HAQ, mean (SD)	1.4 (0.7)	1.4 (0.7)	1.3 (0.7)	1.3 (0.7)	0.633
RF positive, n (%)	85 (85)	79 (86)	49 (49)	54 (43)	<0.001
ACPA positive, n (%)	87 (89)	76 (84)	40 (41)	49 (40)	<0.001
Erosive disease, n (%)	79 (81)	78 (85)	62 (63)	74 (60)	<0.001

ACPA, anti-citrullinates protein antibodies; Erosive disease, defined as the presence of >0.5 erosion on radiographs of hands and feet; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire (range 0 – 3); Initial combination therapy, with either prednisone or infliximab; Initial monotherapy, with methotrexate; MTX, methotrexate; Non-poor prognosis patients (presence of ≤2 of 4 poor prognostic factors); Poor prognosis patients (presence of ≥3 of 4 poor prognostic factors); RF, IgM rheumatoid factor; SSA, sulphasalazine; VAS gh, visual analogue scale (0 to 100 millimeter scale) of general health.

Non-PP patients treated with initial combination therapy more often met the ACR response criteria at three months compared to those treated with initial monotherapy; ACR20 (71% versus 44%, p<0.001), ACR50 (49% versus 13%, p<0.001) and ACR70 (17% versus 3%, p=0.001). They also showed more DAS-remission (18% versus 7%, p=0.017) and a larger increase in functional ability (median decrease in HAQ score 0.63 versus 0.38, p<0.001). After three months, mean HAQ score was 0.59 in non-PP patients treated with initial combination therapy and 0.92 in those treated with initial monotherapy (see also Figure 2). In Table 2 the main results are summarized. With regression analyses similar results were obtained (data not shown).

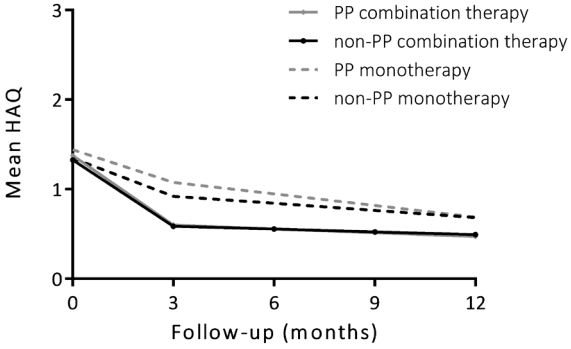

Figure 2. Mean difference in health assessment questionnaire (HAQ) score in patients treated with initial combination therapy or initial monotherapy when prognosis was defined by prognostic factors.
HAQ, health assessment questionnaire (range 0 – 3); non-PP, non-poor prognosis; PP, poor prognosis.

Clinical and radiographic outcomes after one year follow-up

Following initial combination therapy, after one year, PP patients more often achieved ACR20 response (93% versus 80%, p=0.026) and DAS-remission (36% versus 21%, p=0.034) than following initial monotherapy. Other clinical outcomes were not significantly different after one year between PP patients treated with initial combination therapy or with initial monotherapy. Radiographic damage progression after one year was lower in PP patients treated with initial combination therapy than those treated with initial monotherapy (median [IQR] increase in SHS 0.0 [0.0 – 2.0] versus 1.5 [0.0 – 5.0], p=0.001) and there were significantly fewer patients with RRP (10% versus 26%, p=0.006).

After one year, more non-PP patients treated with initial combination therapy also fulfilled the ACR20 response criteria (85% versus 72%, p=0.024) and the ACR50 response criteria (68% versus 52%, p=0.027) than non-PP patients treated with initial monotherapy. Median (IQR) increase in SHS was 0.0 (0.0 – 0.5) in non-PP patients treated with initial combination therapy and 0.0 (0.0 – 1.0) in those treated with initial monotherapy (p=0.451). RRP occurred

in 11% of non-PP patients treated with initial monotherapy compared to 4% in those treated with initial combination therapy (p=0.054). Table 2 shows a summary of these results. With regression analyses similar results were obtained (data not shown).
During the first year of follow-up, the improvement in HAQ score after initial combination therapy was similar in PP and non-PP patients (p=0.795 after three months; p=0.687 after one year) (Figure 2). There was less improvement in HAQ score after initial monotherapy, again similarly in PP and non-PP patients (p=0.108 after three months; p=0.967 after one year).

Toxicity

To evaluate possible toxicity of overtreatment with initial combination therapy, the numbers of PP and non-PP patients treated with initial combination therapy who reported an AE and/or SAE were compared. Of 92 PP patients randomized to initial combination therapy, 31 (34%) reported at least one AE or SAE, compared to 58/125 patients (46%) with a non-PP. Twenty-eight of 92 PP patients (30%) and 54/125 non-PP patients (43%) reported one or more AE (p=0.066). Four PP patients (4%) and six non-PP patients (5%) reported one or more SAE (p=1.000).

DISCUSSION

The results of this post hoc analysis in the BeSt study show that patients with recent-onset RA with a non-poor prognosis and patients with a poor prognosis respond similarly to the treatment strategy options. Both groups benefit more from initial combination therapy than from initial monotherapy and the success of a second conventional DMARD after failing on the first is limited in both groups.
Previous studies have shown that initial combination therapy results in better clinical and radiographic outcomes than initial monotherapy in patients with early RA on a group level.[1–6] It was suggested in the 2010 recommendations for the management of RA that patients with favourable prognostic factors at baseline do not need initial combination therapy because they will respond equally well to initial monotherapy and that patients with a poor prognosis would benefit more from initial combination therapy.[8] This was revoked in the 2013 update: it is now recommended that all patients should receive a similar initial treatment.[9] Still, the updated recommendations state that risk evaluation is an important aspect in the therapeutic approach of RA, and that patients with a favourable prognosis would require a different type of follow-up treatment than patients with a poor prognosis after failure on initial MTX monotherapy.[9]
To test these recommendations, we classified patients as having a poor prognosis (PP) or a non-poor prognosis (non-PP), as a representative of the heterogeneous group of patients 'with a low risk of poor RA outcome' mentioned in the updated 2013 recommendations, based on well-known and frequently used risk factors.[10–13] We tested whether these risk groups, over three-monthly evaluations in the first year of the BeSt study, responded differently to these treatments.

Table 2. Main clinical and radiographic outcomes of poor and non-poor prognosis patients receiving initial monotherapy or initial combination therapy after 3 months and after 1 year.

	Non-poor prognosis patients		
	Initial monotherapy	**Initial combination therapy**	**p value**
DAS-remission			
after 3 months	7 (7)	23 (18)	0.017
after 1 year	35 (36)	43 (36)	1.000
ACR20 response			
after 3 months	38 (44)	79 (71)	<0.001
after 1 year	63 (72)	96 (85)	0.024
ACR50 response			
after 3 months	12 (13)	56 (49)	<0.001
after 1 year	44 (52)	77 (68)	0.027
ACR70 response			
after 3 months	3 (3)	20 (17)	0.001
after 1 year	29 (33)	45 (39)	0.380
Decrease in HAQ, median (IQR)			
after 3 months	-0.38 (-0.75 – 0)	-0.63 (-1.13 – -0.25)	<0.001
after 1 year	-0.63 (-1.13 – -0.13)	-0.88 (-1.25 – -0.31)	0.040
SHS progression			
After 1 year, median (IQR)	0 (0 – 1.5)	0 (0 – 1.0)	0.451
RRP	10 (11)	4 (4)	0.054
	Poor prognosis patients		
	Initial monotherapy	**Initial combination**	**p value**
DAS-remission			
after 3 months	5 (5)	15 (17)	0.016
after 1 year	21 (21)	31 (36)	0.034
ACR20 response			
after 3 months	35 (38)	57 (70)	<0.001
after 1 year	73 (80)	75 (93)	0.026
ACR50 response			
after 3 months	12 (13)	40 (48)	<0.001
after 1 year	52 (57)	59 (71)	0.060
ACR70 response			
after 3 months	4 (4)	20 (24)	<0.001
after 1 year	28 (30)	35 (44)	0.081
Decrease in HAQ, median (IQR)			
after 3 months	-0.38 (-0.63 – 0.06)	-0.75 (-1.13 – -0.25)	<0.001
after 1 year	-0.75 (-1.13 – -0.38)	-0.88 (-1.38 – -0.38)	0.110
SHS progression			
After 1 year, median (IQR)	1.5 (0 – 5.0)	0 (0 – 2.0)	0.001
RRP	24 (26)	8 (10)	0.006

Numbers indicate number of patients (percentage) unless indicated otherwise.
ACR response: according to the American College of Rheumatology criteria;[17] DAS-remission, disease activity score <1.6;[16] Initial combination therapy, with either prednisone or infliximab; Initial monotherapy, with methotrexate; non-poor prognosis (presence of ≤2 of 4 poor prognostic factors); HAQ, health assessment questionnaire (range 0 – 3); poor prognosis (presence of ≥3 of 4 poor prognostic factors); SHS, Sharp/ van der Heijde score; RRP, rapid radiographic progression, defined as increase in Sharp/ van der Heijde score ≥5 points during the first year.

We found that in both PP and non-PP patients, initial combination therapy is more effective, compared to monotherapy, in inducing an early (that is, after three months) decrease in disease activity and early improvement in functional ability, this notwithstanding the fact that after six months on MTX monotherapy significantly more non-PP patients than PP patients achieved a low DAS (64% versus 43%). The improvement in functional capacity in patients treated with initial combination therapy was equal in PP and non-PP patients, both after three months and after one year. This indicates an early equal gain in functional capacity in both prognosis categories. These differences in clinical outcomes are explicit after three months, and remain, following treat-to-target adjustments in therapy, only marginal after one year.

There was no difference among PP and non-PP patients in response to SSA as the second conventional synthetic DMARD after failure to achieve a low DAS on initial MTX monotherapy: similarly low percentages of patients achieved a DAS ≤2.4 (21% of non-PP patients and 28% of PP patients). This appears to be at odds with recommendation 8 of the updated 2013 EULAR recommendations for the management of RA.[9]

Overall, as a consequence of the definition of poor or non-poor prognosis, patients with a non-PP showed less radiographic joint damage progression than patients with a poor prognosis. After one year of targeted treatment, significantly less radiographic joint damage progression occurred after initial combination therapy in PP patients than after initial monotherapy. Thus it appears that for radiographic damage progression indeed, as originally formulated in the 2010 EULAR recommendations for the management of RA, PP patients 'have more to gain' from the initial treatment choice.[8]

Our definition of poor or non-poor prognosis was based on factors that are associated with (rapid) radiographic progression and are also used in prediction models.[10–13] However, early treatment initiation and targeted therapy, including the option of biologic DMARDs, have contributed to prevent this disease outcome in most BeSt patients to date. As RRP nowadays can also be better prevented with early effective treatment, models designed to predict RRP perform moderately in clinical practice. In addition, they do not provide information on clinical outcomes. Of the patients defined as PP according to the presence of ≥3 risk factors, only 26% actually developed RRP when treated with initial monotherapy and 10% developed RRP when treated with initial combination therapy. When PP is defined according to the matrix model of Visser et al.,[11] 46% and 12% developed RRP when treated with initial monotherapy or combination therapy, respectively (Supplementary file 2). Thus, despite familiarity with prognostic factors, it is still difficult to predict the prognosis.

Consequently, it is proper to evaluate the efficacy of the initial treatment choice in terms of rapid relief of symptoms and functional improvement due to suppression of inflammation. Our data show that initial combination therapy is more successful in achieving these outcomes than initial MTX monotherapy, both for PP patients and for non-PP patients. In fact, clinical responses were very similar (and satisfactory) in all patients if they received initial combination treatment. In addition, although maybe not clinically relevant, PP patients

showed less radiographic damage progression after initial combination therapy than after initial monotherapy. Also, more than half of the patients receiving initial combination therapy could discontinue prednisone or infliximab due to low disease activity, as soon as the protocol allowed drug discontinuation.

There was no significant difference in the number of AEs and SAEs reported by PP or non-PP patients on initial combination therapy. Similar toxicity among the four treatment arms has already been reported.[5,7] Hence, it appears that extra caution for the use of combination therapy in either group is not warranted.

The definition of non-poor or poor prognosis shows a moderate performance in predicting radiographic progression, despite the use of two different methods and based on risk factors in validated prediction models. Overall, patients in the BeSt study benefitted from initial combination therapy with better clinical outcomes and more functional improvement at three months than after initial monotherapy, regardless of prognosis category. Response to a second conventional synthetic DMARD after failure on methotrexate monotherapy was similar in patients with a poor or a non-poor prognostic profile, and generally disappointing. These results suggest that prognostic factors associated with future radiographic damage progression contribute little to predict early clinical response to initial treatment, and therefore, in our opinion tailored treatment based on prognosis as suggested by the EULAR guidelines is currently not feasible. The choice of treatment strategy may depend less on these prognostic factors and more on the estimated need for rapid relief of symptoms and limitations due to active disease in our patients.

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SUPPLEMENTARY MATERIAL

Supplementary File 1. Additional results

Poor prognosis (PP) or non-poor prognosis (non-PP) patients were defined by the matrix risk model for rapid radiographic progression, using a cut off of 50%. Using this method, 398 of 508 patients (78%) could be classified, of which 92 patients (23%) were defined as having PP. Of these, 44 received initial monotherapy and 48 initial combination therapy. Of 306/398 (77%) classified as having a non-PP, 144 were treated with initial monotherapy and 162 with initial combination therapy. In Supplementary Table 1 and Supplementary Table 2, clinical responses after three months and after one year are shown.

During the first year, mean difference in HAQ was similar in PP and non-PP patients (p=0.506 for comparison after three months; p=0.551 for comparison after one year), as also shown in the Supplementary Figure.

In patients treated with initial combination therapy, results with regard to (severe) adverse events and discontinuation of prednisone or infliximab were similar (data not shown). Success rates of the introduction of sulphasalazine in patients who failed on methotrexate monotherapy were similar too (data not shown).

Supplementary Table 1. Stratification by matrix model: t tests and Fischer's Exact tests to determine differences clinical and radiological responses between initial monotherapy and initial combination therapy. Separate analyses were performed for poor prognosis (PP) and non-poor prognosis (non-PP) patients.

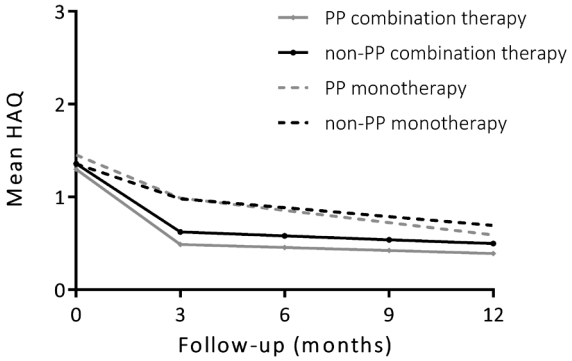
	PP patients			Non-PP patients		
	Initial monotherapy N=44	Initial combination N=48	p value	Initial monotherapy N=144	Initial combination N=162	p value
DAS-remission						
at 3 months	3 (7)	10 (21)	0.075	9 (6)	26 (16)	0.011
at 1 year	9 (21)	18 (41)	0.063	43 (30)	54 (34)	0.538
ACR20 response						
at 3 months	15 (38)	36 (86)	< 0.001	54 (42)	96 (66)	< 0.001
at 1 year	36 (88)	36 (84)	0.757	93 (73)	131 (90)	< 0.001
ACR50 response						
at 3 months	5 (12)	25 (57)	< 0.001	18 (13)	68 (45)	< 0.001
at 1 year	26 (63)	30 (71)	0.488	65 (52)	102 (69)	0.005
ACR70 response						
at 3 months	2 (5)	14 (32)	0.002	5 (4)	24 (16)	0.001
at 1 year	13 (31)	19 (45)	0.261	43 (33)	60 (40)	0.216
Decrease in HAQ, median (IQR)						
at 3 months	-0.50 (-0.75 – -0.09)	-0.75 (-1.25 – -0.38)	0.007	-0.31 (-0.63 – 0)	-0.63 (-1.13 – -0.25)	< 0.001
at 1 year	-0.75 (-1.13 – -0.38)	-0.88 (-1.50 – -0.25)	0.561	-0.63 (-1.13 – -0.12)	-0.88 (-1.13 – -0.38)	0.013
SHS progression						
at 1 year, median (IQR)	4.0 (1.0 – 10.0)	0.5 (0 – 2.5)	0.001	0 (0 – 1.8)	0 (0 – 1.0)	0.074
RRP	18 (46)	5 (12)	0.001	15 (11)	7 (5)	0.073

Numbers indicate number of patient (percentage), unless indicates otherwise.
ACR response, according to the American College of Rheumatology criteria;[17] DAS-remission defined as Disease Activity Score <1.6;[16] non-PP, non-poor prognosis; HAQ, health assessment questionnaire (range 0 – 3); IQR, interquartile range; Mo, months; PP, poor prognosis; SHS, Sharp van der Heijde Score; RRP, rapid radiographic progression, defined as increase in Sharp van der Heijde Score ≥5 points during the first year; Yr, year.

Supplementary Table 2. Stratification by matrix model: regression analyses to determine differences between initial monotherapy and initial combination therapy. Initial monotherapy was set as reference. Separate analyses for non-PP and PP patients were performed.

	Poor prognosis		Non-poor prognosis	
Logistic regression	**OR**	**95% CI**	**OR**	**95% CI**
DAS-remission				
at 3 months	3.51	0.90 – 13.73	2.83	1.28 – 6.26
at 1 year	2.62	1.01 – 6.76	1.18	0.73 – 1.92
ACR20 response				
at 3 months	10.00	3.41 – 29.32	2.72	1.67 – 4.45
at 1 year	0.71	0.21 – 2.46	3.29	1.70 – 6.36
ACR50 response				
at 3 months	9.74	3.22 – 29.49	5.39	2.98 – 9.74
at 1 year	1.44	0.57 – 3.63	2.04	1.25 – 3.33
ACR70 response				
at 3 months	9.33	1.97 – 44.21	4.99	1.85 – 13.46
at 1 year	1.84	0.76 – 4.50	1.38	0.85 – 2.25
Poisson regression	**RR**	**95% CI**	**RR**	**95% CI**
RRP	0.25	0.13 – 0.51	0.59	0.34 – 1.03
Linear regression	**Beta**	**95% CI**	**Beta**	**95% CI**
Decrease in HAQ				
at 3 months	-0.37	-0.62 –-0.12	-0.38	-0.53 –-0.22
at 1 year	-0.10	-0.37 – 0.18	-0.21	-0.377 –-0.05

95% CI, 95% confidence interval; ACR response, according to the American College of Rheumatology criteria;[17] DAS-remission defined as Disease Activity Score <1.6;[16] non-PP, non-poor prognosis; HAQ, health assessment questionnaire (range 0 – 3); OR, odds ratio; PP, poor prognosis; SHS, Sharp/ van der Heijde score; RR, relative risk; RRP, rapid radiographic progression; defined as increase in Sharp/ van der Heijde Score ≥5 points during the first year.



Supplementary Figure 1. Mean difference in HAQ in patients treated with initial combination therapy or with initial monotherapy, when prognosis defined by the matrix model of Visser et al.
HAQ, health assessment questionnaire (range 0 – 3).