Worldwide treatment opportunities of rheumatoid arthritis

Bergstra, S.A.

CHAPTER 6

Rheumatoid Arthritis Patients with Continued Low Disease Activity have Similar Outcomes over 10 Years, Regardless of Initial Therapy

S.A. Bergstra, R.B.M. Landewé, T.W.J. Huizinga, C.F. Allaart

Rheumatology (Oxford) 2017; 56(10):1721-28

ABSTRACT

Objective: To compare 10 years disease outcomes of rheumatoid arthritis (RA) patients with continuous low disease activity on methotrexate (MTX) with or without initial combination therapy with infliximab or prednisone and sulfasalazine.
Methods: recent onset RA patients with 10 years follow-up from the BeSt study were analyzed. Treatment was tightly controlled, targeted at DAS≤2.4. Selected patients had low disease activity from 6 months until 10 years and therefore did not intensify treatment. Patients were grouped in MTX monotherapy or initial combination therapy. Between-group differences over time were compared using (generalized) linear mixed model analyses, for the outcomes DAS, HAQ, ESR, VAS patient global health, % patients in (drug free) remission and % patients with Sharp/van der Heijde score progression ≥5.
Results: At 10 years 28/247 (11%) patients on MTX monotherapy (some tapered to drug free) had continued DAS≤2.4 compared to 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 VAS patient's global health, but 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 appear 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.

INTRODUCTION

Earlier initiation of treatment, targeted treatment and the use of disease modifying anti-rheumatic drugs (DMARDs) have led to great improvements in the treatment of rheumatoid arthritis (RA).[1, 2] Current guidelines recommend the use of methotrexate (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 corticosteroids 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 corticosteroids 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 with initial prednisone or infliximab combination therapy may prevent chronicity of inflammation, resulting in long term remission and drug free remission more readily than MTX monotherapy with slightly delayed clinical response.

Therefore we hypothesized that compared to 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 follow-up.

METHODS

Data from the BeSt (Dutch acronym for Treatment Strategies) study were used. The BeSt study is a multicenter randomized trial (Dutch trial registry, NTR262 and NTR265) with 10 years follow-up, in which 508 recent onset RA patients (1987 American College of Rheumatology criteria[14]) were included. Patients were included 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 three-monthly calculations of the Disease Activity Score in 44/53 joint (DAS).[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≤2.4 for at least 6 consecutive months, MTX was tapered to 10 mg/week. Patients in the initial combination therapy with prednisone group initiated 7.5 mg/week MTX + 2,000 mg/day sulfasalazine + 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 case DAS≥2.4. If DAS remained ≤2.4 from week 28, prednisone was tapered and stopped and from week 40 the MTX dose was tapered and stopped, until sulfasalazine monotherapy remained. From year 3, if patients who had tapered to MTX 10 mg/week monotherapy or sulfasalazine 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≤2.4 from month 6). Tapering to 3 mg/kg/8 weeks occurred if DAS≤2.4 for at least 6 months, and ultimately with persistent DAS≤2.4, infliximab was stopped. Then, if DAS remained ≤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 at each following year, radiographs of the hand and feet were made and assessed according to the Sharp/van der Heijde score[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.[17]
For the present study, patients ('responders') from all 4 randomization arms were selected with continuous DAS≤2.4 from 6 months until the final visit at 10 years. This includes patients who at three 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 group 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.[18]
Between-group differences at baseline were compared using *t*-tests, Mann-Whitney *U* tests or χ^2-tests, as appropriate. Between-group differences over time were compared for the outcomes 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 the percentage of patients with Sharp / van der Heijde score progression ≥5. For continuous, normally distributed outcomes linear mixed model (LMM) analyses with 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 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-value <0.05 was considered statistically significant.

RESULTS

In figure 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≤2.4 on MTX monotherapy at 6 months (43 had increased the MTX dose to 25 mg/week at month 3). Of these 86 patients, 36 dropped out, 22 changed therapy because of DAS>2.4 and 28 (11.3% of initial 247, 32.9% of initial responders) kept responding to MTX monotherapy with DAS≤2.4 until year 10. Of the 261 patients who initiated combination therapy, 155 (59.4%) patients had a DAS≤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 DAS>2.4 and 68 (26.1% of 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.

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 slightly lower SHS score (median 0 vs. 2.5, p=0.014) than combination therapy responders.

In figure 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 Sharp/van der Heijde score progression ≥5 are displayed for MTX monotherapy continuous responders and initial combination therapy continuous responders over 10 years follow-up. Both groups show similar results over time for HAQ, DAS, ESR, VAS patient global health and similar Sharp/van der Heijde score progression (fig 2A, 2B, 2C, 2D, 2G). There seem to be higher remission and drug free remission rates in MTX monotherapy responders than combination therapy responders (fig 2E, 2F). 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 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 to the MTX monotherapy responders, but the effects seem to be very small. For the outcomes HAQ, percentage Sharp/van der Heijde progression ≥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 for 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 between both groups differed (table 1) and was thought to be a potential confounder. However, this did not lead to a relevant change in results (online supplementary file 1, table 1). Also additional adjustment for baseline Sharp/van der Heijde score did not change the results (online supplementary file 1, table 2).

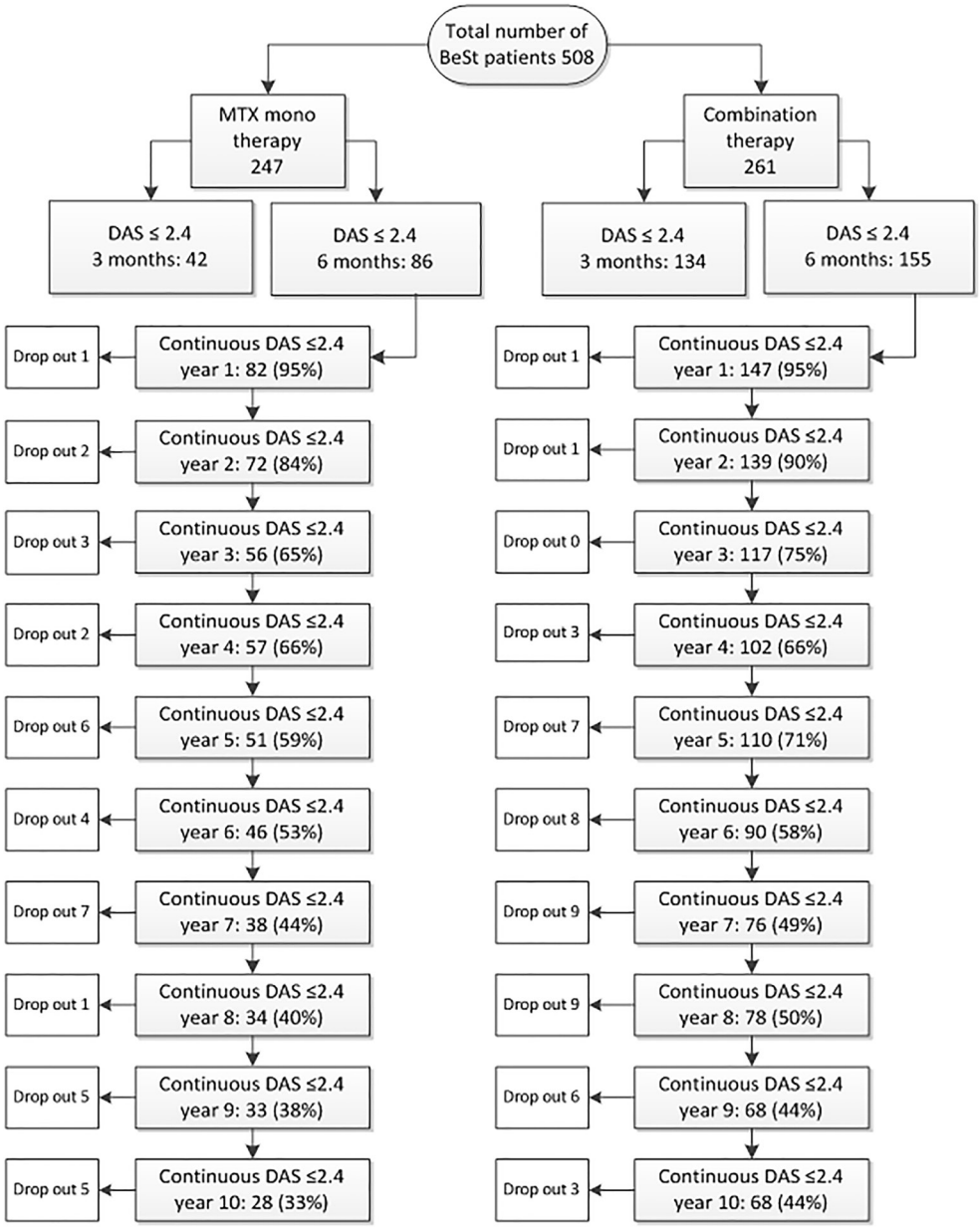

Figure 1: Flowchart of patients with continuous DAS≤2.4 from 6 months until the end of follow-up.

Table 1: baseline characteristics MTX monotherapy continuous responders and combination therapy continuous responders

	MTX monotherapy continuous responders, n=28	Combination therapy continuous responders, n=68	p-value for between-group differences*
Age (years) *mean (SD)*	54.8 (11.7)	54.2 (10.4)	0.797
Gender (% female)	57.1	63.2	0.577
Rheumatoid factor positive (%)	60.7	60.3	0.969
ACPA positive (%)	46.4	54.4	0.477
Body Mass Index *mean (SD)*	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 (weeks) *median (range)*	14.0 (1.14 – 191)	28.3 (3.9 – 263.1)	0.004
Disease Activity Score *mean (SD)*	4.3 (1.0)	4.1 (0.84)	0.300
Erythrocyte Sedimentation Rate (mm/hr) *mean (SD)*	38.8 (31.9)	34.8 (22.2)	0.554
C-reactive protein (mg/l) *median (range)*	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 (mm) *mean (SD)*	47.6 (17.8)	45.2 (20.8)	0.584
VAS physician global health (mm) *mean (SD)*	54.5 (18.6)	50.9 (18.7)	0.391
Health Assessment Questionnaire *mean (SD)*	1.2 (0.7)	1.3 (0.7)	0.452
Sharp / van der Heijde score *median (range)***	0 (0 – 16)	2.5 (0 – 25.5)	0.014

*Tested using *t*-test for continuous, normally distributed variables, tested using Mann-Whitney *U* tests for continuous, non-normally distributed variables, tested using χ^2-tests for categorical/ dichotomous variables.

**n=27 in MTX monotherapy responders, n=66 in combination therapy responders.

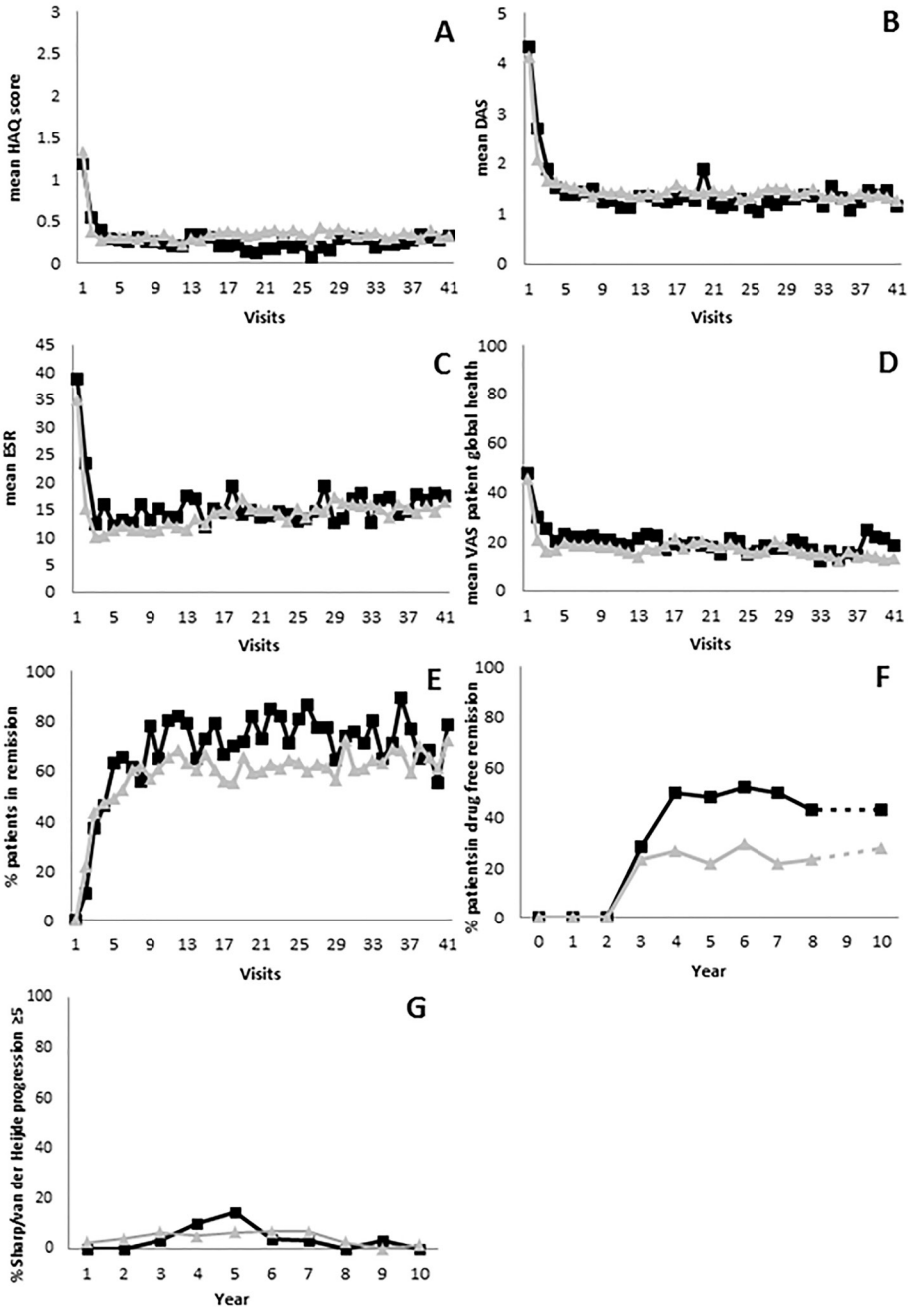

Figure 2: Clinical and radiological outcomes over time in methotrexate monotherapy responders (black lines) and combination therapy responders (grey lines) during 10 years follow-up. Results for drug free remission at year 9 are not shown, due to a high amount of missing data at this time point.

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 HAQ = Health Assessment Questionnaire, DAS = disease activity score, ESR = erythrocyte sedimentation rate, VAS = visual analogue scale, SvdH = Sharp/van der Heijde, SE = standard error, OR = odds ratio, 95% CI = 95% confidence interval

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 sulfasalazine 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 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 to ensure rapid clinical improvement, restore functional ability, prevent productivity loss and avoid radiologic damage. Many studies showed that more patients have rapid clinical improvement on initial treatment with a combination of MTX and a corticosteroid or a biologic DMARD than on initial MTX monotherapy.[4, 5, 7, 19] This suggests, that perhaps through multi-pathway targeting, more 'types' of rheumatoid arthritis (ACPA positive or negative, with signs of high or low systemic inflammation, erosive or likely to rapidly show damage or not, etcetera) and/or more 'types' of patients (male or female, young or old, high or low body mass index, 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 multi-pathway 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 and better functioning and the possibility to taper and stop medication, resulting in drug free remission without radiologic progression and possibly 'cure' of RA.

If that would be the case, patients who respond well on initial combination therapy would fare better than patients who respond well on initial MTX monotherapy. We did not find this. We *did* see that more patients who started on initial combination therapy achieved continuous good response (DAS≤2.4) compared to patients who started on initial MTX monotherapy. Thirty-five percent of patients who started on initial MTX monotherapy achieved DAS≤2.4 after 6 months, and of those, only 33% maintained DAS≤2.4 on MTX monotherapy for the next 9.5 years. This compared to 59% of patients who achieved DAS≤2.4 at 6 months on initial combination therapy, of whom 44% maintained DAS≤2.4, having tapered to sulfasalazine or MTX monotherapy. But all patients who had continuous DAS≤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 indicate slight differences in efficacy between MTX monotherapy and sulfasalazine 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 for a slight increase in the combination therapy group compared to 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 clinically negligible.

If fewer patients respond to MTX monotherapy than to combination therapy, patients who respond well to initial MTX monotherapy might be a tighter 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.[20] In the PROMPT study ACPA negative patients with undifferentiated arthritis did not benefit from MTX compared to placebo, but ACPA positive patients did.[21] 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 Sharp/van der Heijde progression scores at baseline than combination therapy responders. Patient numbers are 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 rheumatoid factor, not-smoking and several genetic factors were found to be associated with response to MTX monotherapy within 6 to 12 months.[22-24] 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[25-27] and that sulfasalazine may be omitted[27], making a

case for low dose corticosteroid 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.[28] Therefore specifically the patients selected for this study, 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 sulfasalazine or MTX monotherapy than on MTX monotherapy, although there appear no additional benefits.

REFERENCES

1. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS . Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004; 43:906-14.
2. Smolen JS, Breedveld FC, Burmester GR et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016; 75:3-15.
3. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73:492-509.
4. Kavanaugh A, Fleischmann RM, Emery P et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013; 72:64-71.
5. Breedveld FC, Weisman MH, Kavanaugh AF et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54:26-37.
6. Klareskog L, van der Heijde D, de Jager JP *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; 363:675-81.
7. Goekoop-Ruiterman YP, 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.
8. Hetland ML, Stengaard-Pedersen K, Junker P et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. *Arthritis Rheum* 2006; 54:1401-9.
9. Detert J, Bastian H, Listing J et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013; 72:844-50.
10. Bakker MF, Jacobs JW, Welsing PM et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012; 156:329-39.
11. Smolen JS, Han C, Bala M et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005; 52:1020-30.
12. Boers M, van Tuyl L, van den Broek M, Kostense PJ, Allaart CF . Meta-analysis suggests that intensive non-biological combination therapy with step-down prednisolone (COBRA strategy) may also 'disconnect' disease activity and damage in rheumatoid arthritis. *Ann Rheum Dis* 2013; 72:406-9.
13. Landewe R, van der Heijde D, Klareskog L, van VR, Fatenejad S . Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum* 2006; 54:3119-25.
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. Siegert CE, Vleming LJ, Vandenbroucke JP, Cats A . Measurement of disability in Dutch rheumatoid arthritis patients. *Clin Rheumatol* 1984; 3:305-9.
16. van der Heijde D . How to read radiographs according to the Sharp/van der Heijde

method. *J Rheumatol* 1999;26: 743-5.
17. Goekoop-Ruiterman YP, 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.
18. Markusse I, Akdemir G, Dirven L al. Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: a randomized trial. *Ann Int Med* 2016; 164:523-31.
19. Emery P, Breedveld FC, Hall S et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 372:375-82.
20. van der Woude D, Visser K, Klarenbeek NB et al. Sustained drug-free remission in rheumatoid arthritis after DAS-driven or non-DAS-driven therapy: a comparison of two cohort studies. *Rheumatology (Oxford)* 2012; 51:1120-8.
21. 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.
22. Wessels JA, 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.
23. Hoekstra M, van Ede AE, Haagsma CJ et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62:423-6.
24. Saevarsdottir S, Wallin H, Seddighzadeh M et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. *Ann Rheum Dis* 2011; 70:469-75.
25. 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.
26. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van ZD, van der Lubbe PA *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.
27. Verschueren P, De CD, Corluy L, Joos R, Langenaken C, Taelman V *et al.* Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. *Arthritis Res Ther* 2015; 17:97.
28. Markusse IM, Dirven L, Han KH, Ronday HK, Kerstens PJ, Lems WF *et al.* Continued participation in a ten-year tight control treat-to-target study in rheumatoid arthritis: why keep patients doing their best? *Arthritis Care Res (Hoboken)* 2015; 67:739-45.