# Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study

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**Key words:** Early onset RA, treatment strategies, DAS-guided treatment, remission.

**ABSTRACT**

**Aim:** *To evaluate the efficacy and safety of four different treatment strategies for patients with early rheumatoid arthritis (RA).*

**Methods:** *In the BeSt study, 508 patients with newly diagnosed (< 2 years) active RA were randomised to be treated according to four treatment strategies: 1. sequential monotherapy, 2. step up to combination therapy (both starting with methotrexate), 3. initial combination therapy with methotrexate, sulphasalazine, and a tapered high dose of prednisone, and 4. initial combination therapy with methotrexate and infliximab. Three-monthly therapy adjustments were dictated by calculation of the Disease Activity Score (DAS), with the goal to achieve and maintain a DAS ≤ 2.4. Functional ability was measured every 3 months with the Health Assessment Questionnaire. Radiographs of hands and feet were assessed yearly, blinded for patient identity and treatment, and in random order, to measure joint damage progression (Sharp/van der Heijde score).*

**Results:** *After 2 years of treatment, 80% of all patients achieved the goal of DAS ≤ 2.4, and 42% reached clinical remission (DAS < 1.6). Initial combination therapy, either with prednisone (group 3) or with infliximab (group 4), resulted in earlier improvement in functional ability, more continuous clinical remission (DAS < 1.6), and less joint damage progression than initial monotherapy (groups 1 and 2). Patients in groups 1 and 2 needed more therapy adjustments, including introduction of combination therapy with prednisone or infliximab, to achieve a DAS ≤ 2.4, whereas many patients in groups 3 and 4 were able to taper their medication to sulphasalazine or methotrexate, respectively, monotherapy. The adverse events profile was comparable in all groups. The presence or absence of rheumatoid factor, HLA DR4, or anti-CCP was not associated with radiologic damage progression.*

**Conclusion:** *In patients with early, active RA, remarkable clinical improvement and suppression of joint damage progression can be achieved with frequent, objectively steered treatment adjustments. The best chance for an early clinical and radiologic response lies with initial combination therapy with either methotrexate, sulphasalazine and prednisone or with methotrexate and infliximab, which can be tapered to DMARD monotherapy once low disease activity is achieved.*

Over the last two decades, the treatment of patients with rheumatoid arthritis (RA) has seen dramatic changes. The focus of treatment has shifted from symptom relief to prevention of structural damage and functional declines (1). Combinations of DMARDs as well as TNF-inhibitors have shown superiority to DMARD monotherapy in patients with early (2-11) and longstanding RA (12-15). Intensive monitoring of disease activity and adjustment of treatment also improves disease outcomes (16).

The BeSt study (Dutch acronym for Behandel-Strategieën, ''treatment strategies'') combines early introduction of treatment with aggressive therapy adjustments based on intensive disease monitoring (using a disease activity score [DAS], based on a 44-joint score ≤ 2.4). Rather than individual drugs, the BeSt study compares treatment strategies: sequential monotherapy (group 1) and step-up combination therapy (group 2), both starting with

methotrexate (MTX), with initial combination therapy consisting of a tapered high-dose prednisone, MTX, and sulphasalazine (SSA) (group 3) with initial combination therapy consisting of MTX and infliximab (IFX) (group 4). Primary outcomes were functional ability as measured by health assessment questionnaire (HAQ) and radiographic joint damage (Sharp/van der Heijde score, SHS). Secondary analyses were directed to the number of patients achieving clinical remission defined as DAS < 1.6, the number of treatment adjustments, and the number of patients able to taper and stop medication because of continued good response per group. Laboratory tests were performed to attempt identification of patients who benefitted most from different treatment strategies.

**Table I.** Baseline demographic and disease characteristics.

| | Sequential monotherapy (N = 126) | Step-up combination therapy (N = 121) | Initial combination with prednisone (N = 133) | Initial combination with infliximab (N = 128) |
|---|---|---|---|---|
| Age, years* | 54 (13) | 54 (13) | 55 (14) | 54 (14) |
| Female sex† | 86 (68) | 86 (71) | 86 (65) | 85 (66) |
| Time diagnosis-inclusion, weeks‡ | 2 (1-5) | 2 (1-4) | 2 (1-4) | 3 (1-5) |
| Symptom duration, weeks‡ | 23 (14-54) | 26 (14-56) | 23 (15-53) | 23 (13-46) |
| Previous antimalarial therapy† | 9 (7) | 13 (11) | 10 (8) | 11 (9) |
| IgM rheumatoid factor positive† | 84 (67) | 77 (64) | 86 (65) | 82 (64) |
| DAS44* | 4.5 (0.9) | 4.5 (0.8) | 4.4 (0.9) | 4.3 (0.9) |
| HAQ* | 1.4 (0.7) | 1.4 (0.6) | 1.4 (0.7) | 1.4 (0.7) |
| Total Sharp-van der Heijde | 3.5 (1.5-9.5) | 5.0 (1.5-8.1) | 3.5 (1.5-8.5) | 4.0 (1.5-8.5) |
| Score‡* | 7.3 (9.5) | 6.3 (6.9) | 5.9 (6.5) | 7.0 (10.0) |
| Erosion score‡* | 2.0 (0.5-4.5)<br>4.1 (6.2) | 2.0 (0.5-4.5)<br>3.5 (4.3) | 2.0 (0.5-4.5)<br>3.3 (4.3) | 2.0 (0.5-5.0)<br>3.9 (5.8) |
| Narrowing score‡* | 1.0 (0.0-4.0)<br>3.2 (4.9) | 2.0 (0.0-4.5)<br>2.8 (3.2) | 1.5 (0.0-4.0)<br>2.6 (3.2) | 1.5 (0.0-3.5)<br>3.1 (5.2) |
| Erosions on hand/foot radiograph† | 89 (72) | 82 (70) | 93 (71) | 93 (73) |

DAS44:Disease Activity Score; HAQ: Health Assessment Questionnaire.
*Mean (standard deviation); †Number (percentage); ‡Median (interquartile range).

## Patients and methods

All patients with rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) 1987 revised classification criteria with a disease duration of < 2 years, at least 6 of 66 swollen joints, and at least 6 of 68 tender joints, and either an ESR ≥ 28 mm/h or a Visual Analogue Scale (VAS) global health ≥ 20 mm (on a scale of 0 to 100 mm, 0 = best, 100 = worst) were eligible for inclusion. Exclusion criteria included previous treatment with DMARDs other than antimalarials, concomitant treatment with an experimental drug, a malignancy within the last 5 years, bone marrow hypoplasia, a serum ASAT/ALAT > 3 times the upper limit of normal, a serum creatinine > 150 mmol/L or an estimated creatinine clearance < 75 mL/min, diabetes mellitus, alcohol or drug abuse, concurrent pregnancy, wish to conceive during the study period, or inadequate contraception. Baseline characteristics of the 508 patients who entered the study are given in Table I.

Every 3 months, before they are seen by the rheumatologist, the patients are seen by a trained nurse who remains blind to the treatment arm, and who performs a full joint assessment with calculation of the Disease Activity Score (DAS). With the DAS result written down on a piece of paper, the patient then sees the rheumatologist, who adjusts the therapy according to the pharmacoprotocol: if the DAS is > 2.4, the treatment is increased or (after tapering and discontinuation) restarted, or the next (combination of) drug(s) is prescribed; if the DAS is ≤ 2.4 for at least 6 months, the medication may be tapered to monotherapy in maintenance dose. A synopsis of the pharmacoprotocol per arm is shown in Figure 1.

## Primary outcomes

After 3 months, functional ability had improved significantly more (from 1.4 to 0.6) in group 3 (initial MTX+SSA +tapered high dose of prednisone) and group 4 (initial MTX and IFX), than in groups 1 and 2 (initial MTX monotherapy) (from 1.4 to 1.0). After 6 and 9 months the HAQ further improved in all groups, remaining significantly lower in groups 3 and 4 than in groups 1 and 2 (after 12 months lower in groups 3 and 4 than in group 1). In the next 12 months, no significant further improvement was seen in functional ability, and no significant differences were seen between the treatment groups (Table II).

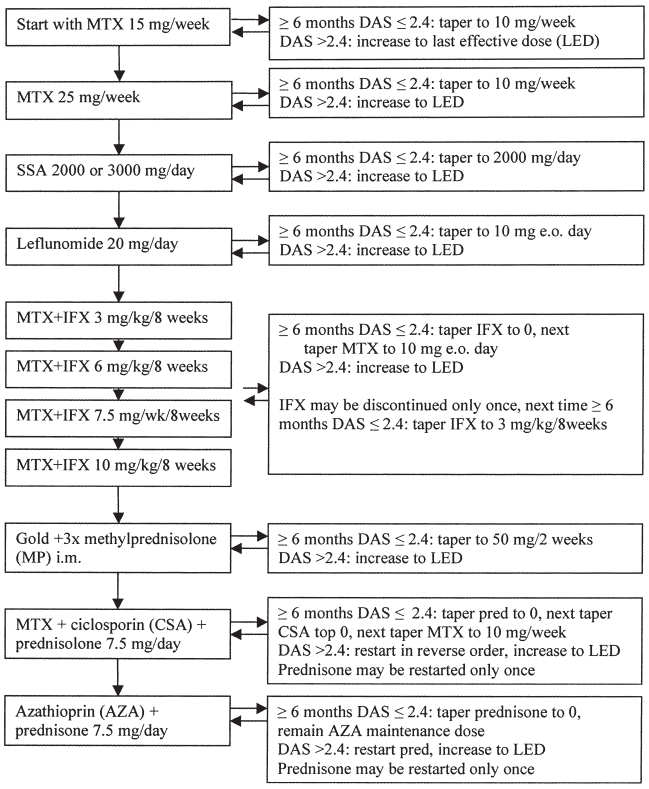
After 1 year, there was significantly less radiologic progression in groups 3 and 4 compared to groups 1 and 2. The median increase in the total SHS was 2.0 in group 1, 2.5 in group 2, 1.0 in group 3, and 0.5 in group 4 ($p = 0.003$ for group 1 vs group 3; $p < 0.001$ for group 1 vs group 4 and for group 2 vs group 4, $p = 0.007$ for group 2 vs group 3). After 2 years of treatment, median SHS remained the same in the 4 groups. Forty percent of patients in group 1, 34% in group 2, 20% in group 3, and 18% in group 4 had SHS progression greater than the smallest detectable difference, SDC (4.64).

There were no significant differences in the number of adverse events or serious adverse events between the four treatment arms during the first 2 years of treatment.

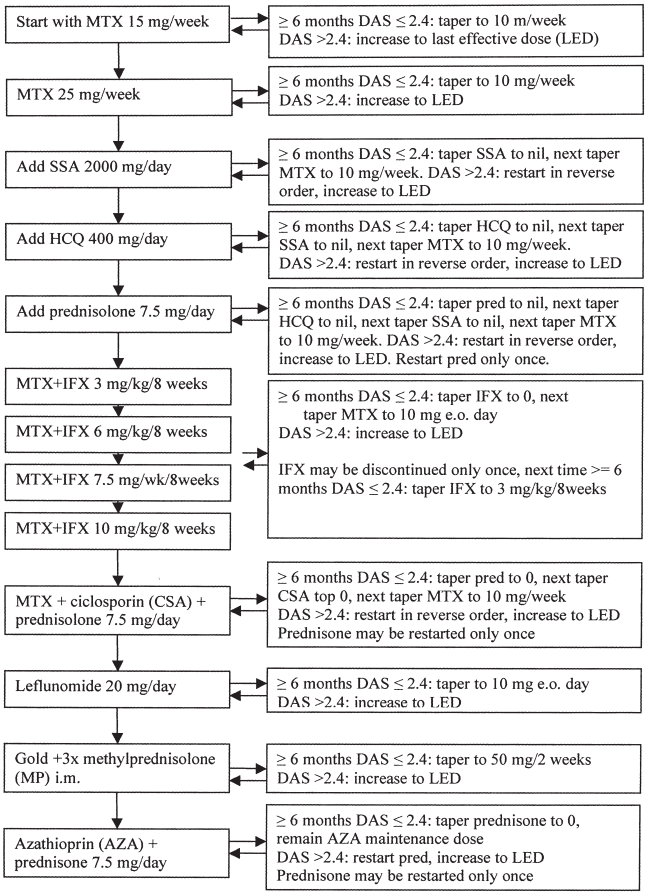
## Outcomes of disease activity

After 2 years of treatment, the goal of a DAS44 2.4 was reached by 75% of patients in group 1, 81% in group 2, 78% in group 3, and 82% in group 4 (p = NS.). To achieve this, more patients in groups 1 and 2 than in groups 3 and 4 had changed from the

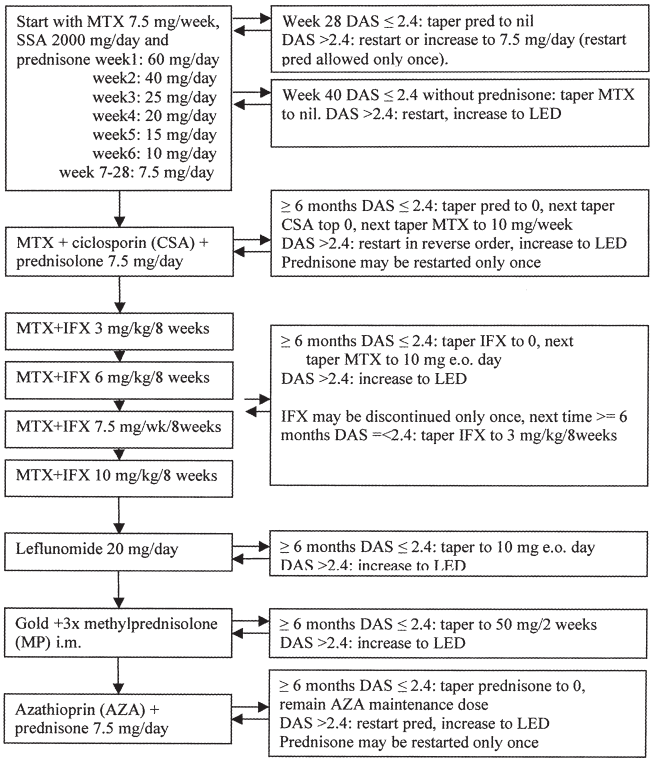
Group 1. Sequential monotherapy. Three monthly DAS evaluations.



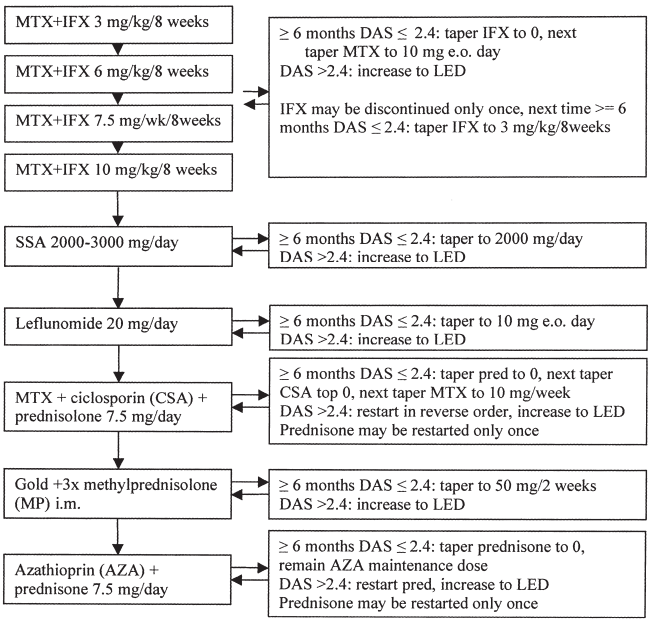

Group 2. Step-up combination therapy.




Group 3. Initial combination therapy including prednisone.




Group 4. Initial combination therapy with infliximab.




DAS: disease activity scale; IFX: infliximab; MTX: methotrexate; SSA: sulphasalazine.

**Fig. 1**. Overview of pharmaprotocol.

**Table II.** Primary patient outcomes during 2 years of follow-up.

| HAQ- improvement compared to baseline | Sequential monotherapy | Step-up combination therapy | Initial combination with prednisone | Initial combination with infliximab | p value |
|---|---|---|---|---|---|
| 3 months | 0.4 ± 0.6 | 0.3 ± 0.6 | 0.8 ± 0.7 | 0.7 ± 0.6 | <0.001† |
| 6 months | 0.5 ± 0.7 | 0.5 ± 0.7 | 0.9 ± 0.7 | 0.8 ± 0.6 | <0.001† |
| 9 months | 0.6 ± 0.7 | 0.6 ± 0.7 | 0.8 ± 0.7 | 0.8±0.6 | 0.01† |
| 12 months | 0.7 ± 0.7 | 0.7 ± 0.7 | 0.9 ± 0.7 | 0.9 ± 0.7 | 0.03‡ |
| 15 months | 0.7 ± 0.7 | 0.8 ± 0.7 | 0.7 ± 0.8 | 0.9 ± 0.7 | 0.30 |
| 18 months | 0.7 ± 0.7 | 0.8 ± 0.7 | 0.8 ± 0.8 | 0.9 ± 0.7 | 0.26 |
| 21 months | 0.7 ± 0.7 | 0.8 ± 0.7 | 0.8 ± 0.7 | 0.9 ± 0.7 | 0.22 |
| 24 months | 0.7 ± 0.7 | 0.8 ± 0.7 | 0.9 ± 0.7 | 0.9 ± 0.7 | 0.26 |
| Progression of SHS compared to baseline | | | | | |
| Total SHS | 9.0 ±17.9 | 5.2 ± 8.1 | 2.6 ± 4.5 | 2.5 ± 4.6 | <0.001† |
| Median | 2.0 | 2.0 | 1.0 | 1.0 | |
| Interquartile range | 0.0-8.6 | 0.3-7.0 | 0.0-2.5 | 0.0-3.0 | |
| Erosion-score | 4.7 ± 9.0 | 3.1 ± 5.0 | 1.1 ± 2.2 | 1.3 ± 2.7 | <0.001† |
| Median | 1.5 | 1.0 | 0.5 | 0.5 | |
| Interquartile range | 0.0-5.6 | 0.0-5.3 | 0.0-2.0 | 0.0-2.0 | |
| Narrowing-score | 4.3 ± 9.8 | 2.1 ± 3.8 | 1.5 ± 3.2 | 1.2 ± 2.9 | 0.07 |
| Median | 0.0 | 0.5 | 0.0 | 0.0 | |
| Interquartile range | 0.0-3.5 | 0.0-3.0 | 0.0-1.5 | 0.0-1.5 | |
| Relative risk for SHS-progression§ | 1.0 | 0.91 (0.73-1.12) | 0.74 (0.61-0.89) | 0.73 (0.61-0.88) | |

*HAQ: Health Assessment Questionnaire; SHS: Sharp/van der Heijde score. Plus-minus values are means ± standard deviation; Numbers in parentheses are 95% confidence intervals.
†$p < 0.050$ for all comparisons between groups 1 and 2 versus groups 3 and 4.
‡$p < 0.050$ for group 1 versus groups 3 and 4.
§Relative risk for progression of radiographic joint.

initial treatment step to subsequent therapy adjustments, whereas more patients in groups 3 and 4 had been able to taper and discontinue drugs of the initial combination therapy because of continuous low disease activity. As a result, at the end of the second year of treatment, 33% of patients in group 1 and 31% in group 2 were still treated with monotherapy (MTX) as initially started), compared to 36% of patients in group 3 and even 54% in group 4 who had tapered their treatment to monotherapy (SSA in group 3, MTX in group 4). At t = 2 years, following failure on MTX, next SSA and finally leflunomide, 27% of patients in group 1 had started IFX+MTX, compared to 7% of patients in group 2 (after failing on MTX, MTX+SSA, next MTX +SSA+hydroxychloroquine [HCQ], and finally MTX+ SSA+HCQ+prednisone) and compared to 13% of patients in group 3 (after failure on MTX+SSA+ prednisone and on MTX+ciclosporine +prednisone), whereas in group 4, 18% were still using IFX (Fig. 2).

Of the 77 (67%) patients in group 4 who were able to discontinue initial IFX because of a DAS ≤ 2.4 for ≥ 6 months, 30 (39%) first needed a dose increase of IFX before a DAS ≤ 2.4 was achieved (maximum dose of IFX 6 mg/kg/8weeks in 22 patients, 7.5 mg/kg/8weeks in 5 patients and 10 mg/kg/8weeks in 3 patients). Ten of the 77 patients experienced a flare after discontinuation (after median of 2 months) and restarted IFX, all again with good response. The 67 patients with continuous DAS ≤ 2.4 after discontinuation of IFX were also able to taper MTX to maintenance dose (mean dose at t = 2 years 12 mg/week). Thirteen (11%) patients remained on variable dosages IFX throughout the 2 years follow up, because they did not achieve DAS ≤ 2.4 for ≥6 months. Twenty-two (18%) patients did not achieve a DAS ≤ 2.4 on IFX+MTX, despite IFX dose increases, and 8 others discontinued IFX because of (non-serious) infusion reactions.

The number of patients achieving a DAS < 1.6 was initially higher in groups 3 and 4, but after 2 years, no statistically significant differences were seen in percentages of patients in clinical remission: 46% in group 1, 38% in group 2, 41% in group 3, and 42% in group 4 (Fig. 3).

**Risk profiles**

We compared the joint damage progression in patients who had continuous good response (DAS ≤ 2.4) on MTX monotherapy and in patients who had failed on MTX monotherapy, regardless of their response on subsequent treatment steps in the sequential monotherapy group and the step-up combination therapy group. We found that 32% of patients were initial MTX responders. In those patients after 2 years, SHS progression was significantly lower (mean 3.3, median 1.0) than patients who had failed or responded incompletely to initial MTX (mean 9.3, median 2.5, p = 0.008).

Next, we compared patients who had continuous clinical remission to the initial therapy (DAS < 1.6 from 6 months to 2 years follow-up [1x > 1.6 but ≤ 2.4 allowed]), with patients who had shown continuous insufficient response (DAS > 2.4 from 6 months to 2 years follow-up [1x ≤ but > 1.6 allowed]). Continuous remission occurred twice as often in patients who started with initial combination therapy with either prednisone or infliximab (15%) than in patients who started with initial monotherapy (8%, p = 0.034). Of patients who achieved continuous remission after initial monotherapy, 25% still had joint damage progression (Sharp/van der Heijde progression > smallest detectable change = 4.64), compared to 3% of patients who achieved continuous remission after initial combination therapy. No statistically significant differences were seen in percentage of patients with continuous failure, but patients with continuous failure in groups 3 and 4 (initial combination therapy) had significantly more improvement in functional ability (HAQ area under the curve 1.1) than patients with continuous failure in

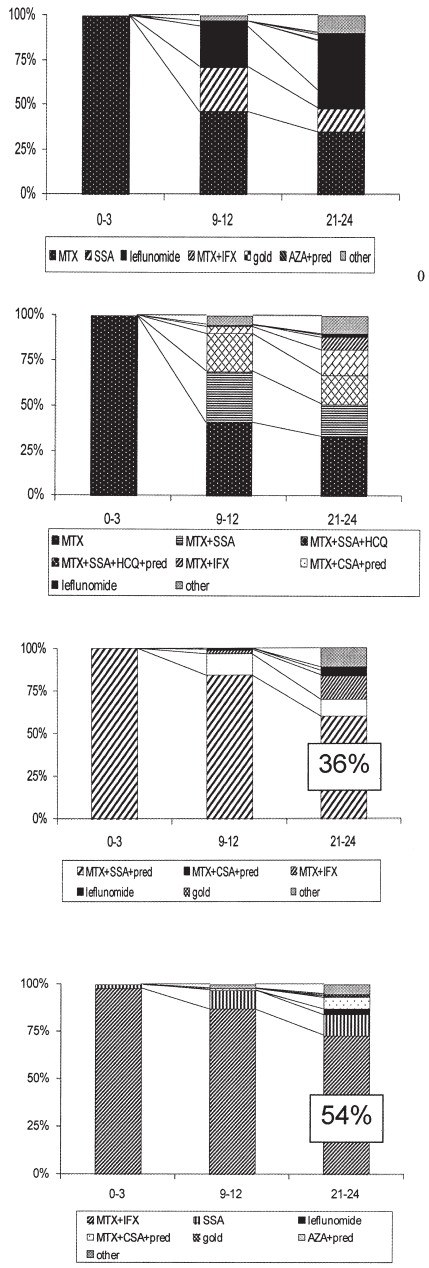
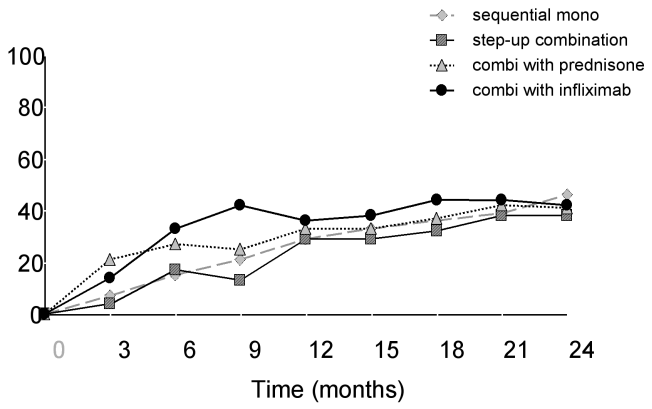



**Fig. 2.** Treatment changes: progression over time following the treatment protocol per study arm. Boxed numbers in groups 3 and 4 (initial combination therapies) represent percentages of patients still in the first treatment step who could taper to monotherapy.

**Fig. 3.** Percentage of patients in remission (DAS <1.6) over time per group.




DAS: Disease activity scale

groups 1 and 2 (sequential monotherapy and step-up therapy) (HAQ AUC 1.5, p = 0.037).

To investigate whether we could (in retrospect) identify patients who have sufficient response on MTX monotherapy and might not need initial combination therapy, we investigated whether in the four treatment groups, the presence or absence of rheumatoid factor (RF), HLA DR4, and anti-CCP antibodies was associated with progression of radiologic joint damage over 2 years. Univariate and multiple linear regression analyses were performed, correcting for baseline characteristics including symptom duration, ESR at baseline and presence or absence of erosions at baseline.

For all groups the SHS progression did not differ significantly between DR4 + and DR4 - patients. In group 1, but not in the other groups, a positive RF and a positive aCCP werte significantly associated with SHS progression.

We conclude that treatment is the main determinant of disease outcome, and that all patients are likely to benefit more from initial combination therapy than from initial monotherapy with MTX.

## Conclusions

In patients with early, active rheumatoid arthritis, remarkable improvement can be achieved with currently available antirheumatic drugs. With intensive monitoring of disease activity and therapy adjustments, after 2 years 80% of patients achieve the targeted DAS ≤ 2.4, and 42% achieve clinical remission (DAS < 1.6). Patients treated with initial combination therapy, either with a tapered high dose of prednisone or with infliximab, achieve low disease activity earlier than patients treated with initial MTX monotherapy, have earlier improvement of functional ability, and are more likely to achieve continuous remission. More than half of them can stop prednisone or infliximab because of a continued good response. Initial combination therapy results in less joint damage progression than initial monotherapy. The effect of these therapies is such that previously identified risk factors are not associated with joint damage progression in this patient cohort. There was no extra toxicity from initial combination therapy compared to sequential monotherapy and step-up therapy. We conclude that initial combination therapy with MTX+SSA +prednisone or with MTX+IFX is superior to initial monotherapy with MTX in patients with recent onset RA. We have not found statistically significant differences in the clinical and radiologic outcomes after 2 years that indicate that one initial combination therapy would be superior over the other.

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