Concise Report

Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add?

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Objectives. MTX, either alone or in combination with SSZ, is effective in the treatment of RA. Trials have shown that, after SSZ failure, the addition of MTX to SSZ is more effective than a switch to MTX. Whether this is also the case in daily practice has not been analysed yet. In this study, we compared the efficacy of a switch to MTX monotherapy with that of the addition of MTX to SSZ in the daily clinical practice of RA patients who had failed SSZ monotherapy in the Nijmegen RA Inception Cohort.

Methods. For this study, 230 patients who failed to SSZ monotherapy were followed for up to 52 weeks. A total of 124 underwent a switch to MTX alone, whereas 106 patients received the combination of MTX and SSZ. The primary outcome measure was the mean change in the disease activity score (DAS28) after 24 weeks.

Results. Both treatment groups showed a significant decrease in DAS28 after 24 weeks, which was similar in both groups. Drug survival analysis showed that the chance to stop with a DMARD within 52 weeks was higher in the MTX–SSZ group ($P<0.01$).

Conclusions. In RA patients who failed to SSZ the clinical efficacy of a switch to MTX monotherapy was similar to that of the addition of MTX, suggesting that in daily clinical practice a switch to MTX is a good option for patients with an inadequate response to SSZ.

Key words: Rheumatoid arthritis, Combination drug therapy, Methotrexate, Sulphasalazine, Therapeutic use.

Introduction

MTX and SSZ, either alone or in combination, are DMARDs of first choice in clinical practice [1–3]. Both agents are relatively inexpensive, have proven their efficacy in clinical trials and daily practice, and have a low toxicity profile [3–12].

MTX monotherapy, SSZ monotherapy and MTX–SSZ combination have comparable efficacy in randomized controlled trials (RCTs) in patients naive to those agents [13–15]. Add-on trials have shown that the addition of MTX is better than a switch to MTX monotherapy after SSZ failure [16, 17]. For daily clinical practice, the combination of MTX and SSZ might be adequate after a suboptimal response to SSZ. Though the BehandelStrategieën voor Reumatoide Artritis (BeSt) trial suggests that this might not be the case after an inadequate response to MTX [18, 19], in that study, the addition of SSZ in case of MTX failure was not superior to a switch to SSZ monotherapy. This, however, may cast some doubt on the benefit of the combination of SSZ and MTX if one of the drugs previously failed. Daily practice data may be of complementary value to data from RCTs. We therefore analysed the data from a large Dutch observational cohort to study whether the addition of MTX in SSZ failures is beneficial compared with a switch to MTX monotherapy in daily clinical practice.

Methods

Design

Non-randomized observational comparison was performed among RA patients who failed to treatment with SSZ, who switched to MTX monotherapy and those who received MTX in addition to SSZ, in a large, well-defined, early RA inception cohort [20]. The propensity score method and confounder correction was used in order to correct for confounding by indication at baseline.

Data collection

The Nijmegen RA Inception Cohort encompasses patients visiting the outpatient clinic of the rheumatology departments of the Radboud University Nijmegen and the Sint Maartenskliniek in Nijmegen. Patients are included when they have RA according to the 1987 revised ACR criteria for RA [21], are $\geq$18 years of age, have a disease duration of $<1$ year and had no prior use of DMARDs. Enrolment started in July 1986 and all patients are regularly assessed in 3-month visits, but treatment decisions can be made at any time. The patients are treated according to the discretion of the treating physician. Data on patient characteristics, medication use and clinical and laboratory measures are prospectively stored in an electronic database. The local medical ethics committee [Commissie Mensgebonden Onderzoek (CMO), Region Arnhem—Nijmegen, The Netherlands] approved the study.

Patients

For this study, we screened the data from 903 patients from the Nijmegen Inception Cohort who were included between July 1986 and September 2007. We focused on patients who started treatment with SSZ as first or second DMARD followed by either (i) a switch to MTX or (ii) the addition of MTX to SSZ. Analogous to a clinical trial, the moment of switch to MTX or addition of MTX to SSZ was regarded as baseline in our study. Patients who used concomitant DMARD therapy other than MTX or SSZ at baseline were excluded. Assessments of disease activity scores (DAS28) within 2 weeks from baseline and a minimal follow-up of 3 weeks were required. Selection details are summarized in Fig. 1.

Treatment strategy

Included patients were analysed according to two treatment strategies: switching to MTX monotherapy or the addition of
MTX to their ongoing SSZ therapy. Prior to ‘switching’ or ‘adding’, patients had been treated with SSZ in doses of 750–3000 mg/day. Oral MTX was started at a weekly dose of 7.5 mg, which could be increased to a maximum of 30 mg. The daily dose of SSZ at study entry ranged from 750 to 3000 mg. Dose adjustments of MTX and SSZ, concomitant NSAIDs in usual doses and/or glucocorticoids were used in both treatment strategies based on the opinion of the individual rheumatologist. Patients received folic or folinic acid during treatment with MTX. Before 2004, the folic or folinic acid dose used was 1 mg/day and after 2004, this was 5 mg/week with an increase to 10 mg/week in case of an MTX dose of ≥15 mg/week.

Clinical assessments

The following baseline patient characteristics were retrieved from the database: age, sex, duration of RA, RF positivity, DAS28 and concomitant glucocorticoids. From previous DMARD therapies, in particular SSZ, information concerning dosage, dosing schedule and treatment duration were collected. Clinical efficacy and response to therapy were assessed using the 3 monthly DAS28 [22] and the European League Against Rheumatism (EULAR) response criteria [23] at 6 and 12 months, respectively. Specially trained research nurses assessed the variables needed for the DAS28. The DAS28 includes the 28-joint counts for swelling and tenderness, general health (on a visual analogue scale of 100 mm) and the value for ESR measured by the Westergren method [22–24]. Changes in DMARD therapy and co-medication and the reason for change, including occurrence of adverse events, were recorded during follow-up.

The primary outcome measure of this study was the mean change in the DAS28 from baseline to 6 months. Secondary outcome measures included the mean change in the DAS28 from baseline to 12 months, the EULAR response criteria at 6 and 12 months, the course over time of the DAS28, and cumulative drug survival at 12 months of MTX monotherapy or MTX–SSZ combination therapy.

Sample size determination

It was assumed that the ‘addition’ group would show more efficacy than the ‘switch’ group. For this study, each treatment group consisted of at least 100 patients. Then, with an α of 0.05 and a power of 0.80 and a total sample size of 200 patients, a difference between the groups of 0.4 DAS28 points could be detected. This difference is smaller than the difference that was detected in both clinical trials [16, 17].

Statistical analyses

Mean changes in the DAS28 were compared between the two treatment strategies using linear regression including treatment, baseline DAS28 and other confounders as covariates. To test whether there was a difference in EULAR response rates the chi-square test was assessed. The course over time of the DAS28 was analysed using longitudinal linear regression (mixed models), correcting for repeated measurements using an autoregressive covariance structure.

Differences in continuation were determined using a Kaplan–Meier curve with a log rank test. A Cox proportional hazards model was used to calculate the hazard for discontinuation within 1 year. Discontinuation was defined as stopping with either MTX or SSZ within 1-year treatment, including starting with other concomitant DMARD therapy or anti-TNF-α treatment.

A propensity score was added to the regression models in order to account for confounding by indication, and additional confounders were added using 10% change in main effect as selection criterion. The propensity score was defined as the conditional probability of receiving MTX or MTX plus SSZ given the individual’s covariates [25]. Logistic regression with a backward selection procedure (P < 0.20 as selection criterion) was used to
determine as to which baseline variables were imbalanced between
the two groups and were included in the propensity score. Patients
were stratified based on quintiles of the propensity score. After
stratification, balance of each baseline variable between the two
treatment strategies was assessed by using two-way analyses of
variance (parametric) or van Elteren’s test (non-parametric) for
continuous variables and logistic regression for dichotomous
variables. Furthermore, the fit of the propensity score model was
assessed by the Hosmer–Lemeshow test.

In the clinical efficacy analyses, each patient remained in the
treatment group to which they had been assigned, regardless of
whether they completed or received that treatment (intention-to-
treat). In case of treatment discontinuation (i.e. the use
of concomitant therapy other than MTX or SSZ), the last available
data were carried forward. In a sensitivity analysis, these results
were compared with the results from the analysis in which only
patients who actually received the intended treatment
(‘completers’) were used.

For the clinical efficacy analyses, the level of significance was
set at P < 0.05. The analyses were carried out using SPSS 14.0
statistical software package.

Results

Patients

As shown in Fig. 1, we analysed 230 patients who had failed to
SSZ. Out of those, 124 (54%) switched to MTX monotherapy
and 106 (46%) patients received MTX in combination with SSZ.
Reasons for SSZ discontinuation in patients who switched to
MTX monotherapy were adverse events (n = 53, 43%) and lack
of efficacy (n = 57, 46%). Lack of effect of SSZ (n = 88, 83%) was
the most common reason for adding MTX to the ongoing SSZ
therapy, besides toxicity (n = 11, 10%). During follow-up, 81.5%
of the MTX group and 69.8% of the MTX–SSZ combination
group had a drug survival of at least 6 months. The 1-year drug
survival was 66.1% and 50.0% of the MTX monotherapy group and
the MTX–SSZ combination group, respectively (Fig. 1).

The main demographic and disease characteristics of the
patients at baseline are summarized in Table 1. Patients had
active disease at baseline as was demonstrated by a mean
DAS28 of ~5.0. For 86% of the patients, SSZ was their first
DMARD after onset of RA. The duration of previous SSZ use
was significantly longer in the combination group than in the
MTX group (median of 47 vs 14 weeks). Prior to SSZ treatment,
there was no significant difference in disease duration. The use of
previous DMARDs, other than SSZ, was almost similar between
the two treatment groups (15 vs 13%).

Since the inclusion time frame was >15 years and changes in
treatment strategies during that time are expected, we investigated
whether year of treatment start did differ between both strategies.
Both treatment groups (‘switch’ or ‘add’) were equally employed
during the cohort time frame and there was no significant
difference in the starting year of SSZ between both groups.
and 2004–07) were defined within the total cohort based on the
date of starting with SSZ. Patient profiles within each sub-cohort
were investigated as well and no differences were found between
both treatment groups in age, disease duration, RF positivity and
disease activity prior to starting SSZ (data not shown).

Propensity score

Table 1 shows the balance of baseline variables between both
treatment strategies, before and after stratification based on the
propensity score quintiles. Before stratification, four variables
(RF positivity, length of previous SSZ use, DAS28 at baseline
and hospital) were found significantly different between the
two groups and were included in the propensity score. After
adjustment for propensity score quintile, all variables were
balanced between the two treatment groups. However, the
P-values for age and DAS28 moved in an opposite direction.
Therefore, these variables were regarded as potential confounders.
The Hosmer–Lemeshow test was 3.9 (df = 8, P = 0.87), which
indicated good fit of the propensity score model.

Clinical efficacy

Mean change in DAS28. After 6 months of treatment, there
was a statistically significant decline in the mean DAS28 over time
in both the therapy groups (P < 0.0001). The mean changes (s.d.)
in DAS28 over 6 months were −0.9 (1.3) in the MTX group and
−0.8 (1.3) in the combination group and this was not statistically
significant after adjustment for baseline DAS28 and propensity
score (P = 0.737; Table 2).

After 1 year, a significant (P < 0.0001) decrease in DAS28
was observed in both groups [mean (s.d.) of −1.1 (1.3) and −0.9 (1.2)
for the MTX group and combination group, respectively]. This
was not significantly different between both therapy groups
(P = 0.756), after analysis of covariance adjusted for DAS28 at
baseline, the propensity score and age (Table 2).

Since there were several reasons to start either MTX mono-
therapy or MTX–SSZ combination therapy after using SSZ
monotherapy (inefficacy of SSZ, adverse events by SSZ or reasons
unknown), aforementioned analyses were adjusted for these
reasons as well. Applying this adjustment did not alter the main
effect of the two treatment groups and no difference in clinical
efficacy was observed between the two groups: a difference of
0.036 in DAS28 decrease between both groups (P = 0.849).
Moreover, reasons to ‘switch’ or to ‘add’ were not effect
modifiers: the difference between both treatment groups was
equal in all the subgroups formed by stratification for reason.
Additionally, when the reason was ‘lack of efficacy’, a decrease in
DAS28 of −1.1 and −0.9 in the ‘switch’ and ‘addition’ group,

<table>
<thead>
<tr>
<th>Table 1. Demographic and baseline disease characteristics of patients</th>
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<tbody>
<tr>
<td><strong>MTX</strong></td>
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<tr>
<td><strong>n = 124</strong></td>
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<tr>
<td><strong>Age, mean ± s.d., years</strong></td>
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<tr>
<td><strong>Women, n (%)</strong></td>
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<td><strong>RF positive, n (%)</strong></td>
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<tr>
<td><strong>DAS28, mean ± s.d.</strong></td>
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<tr>
<td><strong>Disease duration, median (IQR), weeks</strong></td>
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<tr>
<td><strong>SSZ dose prior to two treatments, mean ± s.d., mg/day</strong></td>
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<tr>
<td><strong>Concomitant glucocorticoid use, n (%)</strong></td>
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<td><strong>Previous DMARDs, n (%)</strong></td>
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<td><strong>Hospital treatment, n (%)</strong></td>
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</table>

*At baseline, includes duration of SSZ treatment as well. **Other than SSZ. *Comparison of variables between the two groups after adjusting for propensity score quintile. Two-way analyses of variance (parametric) or van Elteren’s test (non-parametric) was performed for continuous variables and logistic regression for dichotomous variables. **Significant in propensity score model based on logistic regression with a backward selection procedure with P < 0.2 as selection criterion. IQR: interquartile range.
respectively, was shown. These responses were not found to be significantly different \( (P = 0.217) \). Since ‘adverse events’ were actually only a reason to ‘switch’, the change of DAS28 in this group was \(-1.0\) and was comparable with the overall response rate in the ‘addition’ group \( (P = 0.693) \).

**Course over time of the DAS28.** Although patients in the MTX group started from a somewhat higher level \((5.1 \text{ vs } 4.9)\), the changes in DAS28 were very similar with both groups. Patients from both treatment strategies reached a mean DAS28 of \(4.0\) after 1-year treatment (Fig. 2). The mean difference between the two groups in the change of DAS28 at 6 and 12 months was not significantly different, after mixed models analyses adjusted for the propensity score and DAS28 at baseline \( (P = 0.153) \).

**EULAR response.** The EULAR response for the two treatment groups is shown in Fig. 3. Most patients achieved a moderate EULAR response. In both treatment strategies, most patients had a moderate level of disease activity after 6 and 12 months of treatment. After 12 months, 53% in the MTX group and 51% in the MTX–SSZ combination group achieved good/moderate response. None of the differences in EULAR responses between the two groups was found to be significant.

**DMARD and concomitant therapy**

As is shown in Table 3, patients in both treatment strategies received similar doses of MTX during follow-up. In both strategies, the starting dose of MTX was \(7.5 \text{ mg/week} \) and the median number of MTX dose changes was two \((\text{range } 1–3)\) and did not differ between both treatments \( (P = 0.70) \). Despite the fact that MTX dose was relatively low in both the groups \((\approx 13 \text{ mg/week})\), a large proportion of patients \((41\%)\) received \(\geq 15 \text{ mg/week} \). In the group of patients who were treated with MTX monotherapy, 79% received concomitant folic acid and in the group of patients with combination therapy this proportion was 86% \( (P = 0.18) \).

During intervention, a comparable number of patients used oral glucocorticoids in the MTX group \((12\%)\) and in the MTX–SSZ group \((8\%)\). Also, the median time-averaged doses of concomitant glucocorticoids did not differ between the two groups \( (P = 0.83; \text{Table 3}) \). With regard to the use of intramuscular methylprednisolone, significantly more patients in the MTX monotherapy received one or more intramuscular injections with methylprednisolone than the combination group \((28 \text{ vs } 17\%)\), respectively. The frequency of the intramuscular injections during treatment was in both groups similar \( (\text{Table 3}) \). Most patients received their injection at the beginning of the follow-up; within 4 months. Since the effect of intramuscular corticosteroids may influence the results in case of performing injections \(\leq 4 \text{ weeks} \) before evaluation of disease activity, the time points of the injections were assessed as well. However, there were only a few patients (three ‘switchers’ and two ‘adders’) who received intramuscular corticosteroids 4 weeks before evaluation of disease activity.

**FIG. 2.** Mean change of DAS28 for both treatment strategies (patients using MTX or a combination of MTX with SSZ). Mixed models were used with time-averaged DAS28 as dependent variable, treatment group as factor, the propensity score and baseline DAS28 as covariates. Error bars indicate 95% CI.

**FIG. 3.** (A) EULAR response after 6 and 12 months. Good: good response \((\text{DAS28 of } <3.2 \text{ and an improvement from } >1.2)\); moderate: moderate response \((\text{DAS28 of } <5.1 \text{ and an improvement of } 0.6–1.2)\); none: no response \((\text{DAS28 improvement of } \leq 0.6)\). EULAR responses were compared by using chi-square test. (B) Disease activity at 6 and 12 months. High: high disease activity \((\text{DAS28 of } >5.1)\); moderate: moderate disease activity \((\text{DAS28 of } >3.2 \text{ and } \leq 5.1)\); low: low disease activity \((\text{DAS28 of } <3.2)\); remission \((\text{DAS28 } <2.6)\).
prior to the evaluation of 6 months and four patients (two ‘switchers’ and two ‘adders’) prior to 12 months. Excluding this group of patients from efficacy analyses did not alter the main treatment effect between the ‘switch’ group and the ‘add’ group (data not shown).

Furthermore, the patients included were concurrently treated with NSAIDs. No difference in the number of prescribed NSAIDs was detected between the two groups: 96% in the MTX monotherapy group and 95% in the combination group ($P = 0.80$).

### Sensitivity analyses

A sensitivity analysis was performed based on data from only patients who completed their 6 months of treatment and showed us that the mean decrease in DAS28 (s.d.) was 1.1 (1.3) in the ‘switch’ group and 0.9 (1.2) in the ‘add’ group. There was no significant difference between both the groups ($P = 0.866$). Moreover, these results were comparable with those obtained from the main effect measured from data from all patients regardless of their treatment continuation. Furthermore, we performed a sub-analysis within the ‘addition’ group of those who discontinued SSZ early and those who completed their 1-year treatment of SSZ. The mean change of DAS28 after 1 year was 1.0 and 0.7 in the ‘completers’ and SSZ discontinuation group, respectively. The difference was not found statistically significant ($P = 0.158$).

### Drug survival analyses

Cox proportional hazards models showed that the relative hazard to stop a DMARD within 1 year was 1.7 in the MTX–SSZ combination group, compared with the MTX monotherapy group (95% CI 1.11, 2.46; $P < 0.01$ by log rank test). Accordingly, the 1-year cumulative drug survival was lower in patients who received MTX in combination with SSZ (0.49 ± 0.04) than in those who switched to MTX monotherapy (0.64 ± 0.04; $P < 0.05$; Fig. 4A). Drug survival of the combination was limited by the survival of SSZ. Drug survival of MTX was lower in the ‘switch’ group than in the ‘addition’ group (0.64 vs 0.77; $P < 0.05$; Fig. 4B).

### Reasons for discontinuation

The rate of discontinuation was significantly lower in the MTX group compared with the combination group after 12 months of treatment (42 vs 53 patients; $P = 0.013$). This difference was mainly determined in the first 6 months (Table 4).

The most frequent reason to discontinue MTX therapy was toxicity (78 vs 64% after 6 months and 26 vs 25% after 12 months, respectively; Table 4). In the MTX group, MTX was

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**Table 3. Doses of DMARD used and concomitant glucocorticoid use**

<table>
<thead>
<tr>
<th>Intervention DMARD use</th>
<th>MTX, $n = 124$</th>
<th>MTX + SSZ, $n = 106$</th>
<th>$P$-value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTX dose, mean ± s.d., time-averaged, mg/week</strong></td>
<td>13.4 (5.4)</td>
<td>13.3 (4.9)</td>
<td>0.825</td>
</tr>
<tr>
<td><strong>SSZ dose, mean ± s.d., time-averaged, mg/day</strong></td>
<td>–</td>
<td>2000 (476)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Concomitant glucocorticoid use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral glucocorticoid use, n (%)</strong></td>
<td>15 (12)</td>
<td>9 (8)</td>
<td>0.373</td>
</tr>
<tr>
<td><strong>Glucocorticoid dose, median (IQR), time-averaged, mg/day</strong></td>
<td>9.8 (7.9, 10.0)</td>
<td>9.6 (8.1, 16.4)</td>
<td>0.834</td>
</tr>
<tr>
<td><strong>Intramuscular methylprednisolone, n (%)</strong></td>
<td>35 (28)</td>
<td>18 (17)</td>
<td>0.044$^{**}$</td>
</tr>
<tr>
<td><strong>Frequency methylprednisolone, median (IQR)</strong></td>
<td>1 (1, 2)</td>
<td>1 (1, 1)</td>
<td>0.310</td>
</tr>
</tbody>
</table>

$^*$Comparison of variables between the two groups using independent t-test (parametric) or Mann–Whitney U-test (non-parametric) for continuous variables and chi-square test for dichotomous variables. $^{**}$Significant after comparing the MTX group with the MTX + SSZ group by chi-square test. Time-averaged: mean dose within period of medication use; IQR: interquartile range.
Discussion

There are only a few clinical trials available that investigated the clinical efficacy of MTX–SSZ combination therapy after failure to one of these agents. The results of the latter are not consistent and seem to differ depending on the fact whether the initial failure was to SSZ or to MTX. Herein, we chose to compare the clinical outcome of a ‘switch’ to MTX monotherapy with the ‘addition’ of MTX to SSZ, in a cohort [20] of RA patients who failed to previous SSZ monotherapy and were treated according to ‘usual’ care.

Our results show that switching to MTX monotherapy and combination of MTX and SSZ resulted in a significant, and similar, decline in the mean DAS28 and EULAR responses after 1 year. Switching to MTX monotherapy yielded a better 1-year drug survival than the addition of MTX to SSZ. Adverse events of MTX occurred more frequently in the ‘switch’ group. Since a great proportion of this group started MTX after experiencing toxicity of SSZ and both DMARDs share common pathways, this may be a reason for toxicity of MTX as well. In patients who received MTX–SSZ combination therapy, the SSZ survival was lower than the survival of MTX. Lack of efficacy was mostly the reason to stop SSZ, when combined with MTX. From these results, therefore, we may conclude that MTX monotherapy has similar efficacy compared with MTX–SSZ combination therapy after SSZ failure in daily clinical practice.

In this observational study, the magnitude of the treatment effects was of the same magnitude than those found in earlier clinical trials [16, 17]. The finding of no difference in effect is, however, in contrast with the results from two add-on trials, which demonstrated that the addition of MTX is more effective than a switch to MTX alone in patients with an inadequate response to SSZ [16, 17]. On the other hand, the results from this study are comparable with the findings in patients who had an inadequate response to MTX, as was investigated in the BeSt study. This strategic study demonstrated that in MTX failures, the addition of SSZ was not more effective than a switch to SSZ [18].

A cause for the discrepancy between trial results and results from daily clinical practice might have been differences in the included patients and their disease characteristics. Especially, the DAS at baseline and the use of previous DMARDs are characteristics that may differ between patient groups in RCTs and cohort studies. After comparison of these characteristics between the clinical trials and clinical practice, however, we observed no difference in DAS at baseline or previous use of DMARDs. Furthermore, the patients included had comparable age, disease duration, duration of SSZ use prior to the switch or addition of MTX, there were similar percentages of women and RF-positive patients and no time trend towards ‘switch’ or ‘addition’ has been observed. Besides, in both study designs, outcomes were evaluated as an intention-to-treat analysis and a continuous outcome measure (DAS in trials and DAS28 in this study) had been used.

Concomitant medication and treatment intervention itself may also be another cause for the inconsistency between the clinical trials and clinical practice. With regard to DMARD intervention, MTX and SSZ dosage schedules were comparable with those applied in the RCTs. In the MTX group, more patients received concomitant intramuscular injections with methylprednisolone; mostly within 4 weeks after starting with MTX. Only a few patients received their injections 4 weeks prior to evaluation of 6 or 12 months and excluding these patients from analyses did not alter the main treatment effect. However, the fact that the MTX monotherapy group received more intramuscular corticosteroids may be indirectly related to a delay of action of MTX or the occurrence of more disease flares in comparison with the MTX–SSZ combination group.

Overall, the different results from clinical trials and clinical practice cannot be explained by either differences in the included patients, treatment dosage schedules, disease characteristics at baseline or the number of patients who discontinued their treatment. In the study of intended effects, randomized controlled studies are conceptually superior to observational studies. The most important difference between RCT and observational study design, the lack of control over treatment allocation, may lead to biased estimates of treatment effects. In order to reduce this confounding by indication bias, the propensity score was used to balance the baseline characteristics between the two treatment groups. It was evaluated whether the propensity score model did fit the data by comparing the baseline variables before and after adjustment for the propensity score and by performing the Hosmer–Lemeshow test. Balance was achieved between the two treatment groups and the propensity score model fitted the data well. Although it is assumed that use of the propensity score contributed to estimate the true treatment effects, bias in patient selection could not definitely be ruled out by means of the propensity score because of unmeasured confounders. Therefore, the difference found in results between the present study and the clinical trials might still be due to confounding by indication bias.

Loss to follow-up and missing data (e.g. information bias) could also be an important potential cause of bias in cohort data. To overcome this bias, the clinical efficacy was evaluated according to an intention to treat analysis using last observation carried forward. The change in DAS at 3 and 6 months did not differ between those patients who stopped combination therapy and continued with monotherapy (MTX or SSZ) and those who continued their MTX–SSZ combination. Moreover, a sensitivity analysis based on data from only patients who completed their 1-year treatment was performed and did not change the results that were obtained from data from all patients regardless of their
treatment continuation. Therefore, it is not likely that this type of bias influenced the results.

Although MTX and SSZ are currently regarded as the DMARDs of first choice in clinical practice, available evidence to support the use of MTX–SSZ combination is limited and only based on the results from a few clinical trials. A switch to MTX after inadequate SSZ response may be the preferred treatment choice in clinical practice. After MTX monotherapy, the addition of SSZ to MTX seems to be less effective [18]. Starting with MTX–SSZ combination therapy is not more effective than monotherapy and may, therefore, not be the first choice in early, DMARD-naïve RA patients [13, 14].

In conclusion, the results of this observational study suggest that there is no difference in clinical efficacy between MTX and SSZ combination therapy and MTX monotherapy in patients who failed to SSZ monotherapy, which is in contradiction to results of clinical trials. Both addition of MTX and switch to MTX lead to >50% responders, suggesting that in daily clinical practice an immediate switch to MTX monotherapy and addition of MTX are equivalent therapeutic options for patients with an inadequate response to SSZ.

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**References**