EXTENDED REPORT

Step-up combination versus switching of non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study

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Background: In rheumatoid arthritis (RA), treatment with disease-modifying antirheumatic drugs (DMARDs) frequently needs to be changed because of insufficient effectiveness.

Aim: To compare the clinical outcomes of two potential strategies for patients experiencing DMARD discontinuations related to ineffectiveness: switching to another DMARD or step-up combination therapy of the present DMARD with a new one.

Methods: In a large observational database of 4585 DMARD courses in 1214 patients with RA, all patients who had experienced a change in treatment regimen were identified, and retention, effectiveness and safety of these subsequent treatment courses between the two strategies (switching vs step-up combination). All analyses were stratified according to the type of the new DMARD into methotrexate (MTX), sulphasalazine (SSZ) or leflunomide (LEF); all other DMARDs were excluded.

Results: Kaplan–Meier analysis for MTX courses showed no significant difference in overall retention rates between the strategies of adding MTX and switching to MTX ($p=0.49$ by log rank test). Likewise, switching or adding did not result in significantly different retention rates for SSZ and LEF ($p=0.61$ and 0.74 , respectively). This similarity between strategies remained after adjusting for several confounding variables. The frequencies of treatment terminations related to ineffectiveness or toxicity were likewise similar between the two strategies for the MTX, SSZ and LEF groups. This was also confirmed by the similarity of erythrocyte sedimentation rates that were reached at the end of the two therapeutic strategies for all three drugs, in adjusted analysis.

Conclusion: Given all limitations of observational studies, the present data indicate that in situations of ineffective DMARD treatments, step-up combination therapy using traditional DMARDs, such as MTX, SSZ or LEF, bears no clear clinical advantage over switching to the new DMARD. Our results do not implicate any predication about step-up design including biologicals, where the benefit of combination therapy has been suggested convincingly.

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Rheumatoid arthritis (RA) is a chronic disabling disease. The mainstay of treatment for RA is the use of disease-modifying antirheumatic drugs (DMARDs), which are characterised by their ability to improve signs and symptoms, to reduce progression of structural damage in RA^{1–4} and, consequently, improve functional disability, a major adverse outcome of the disease.^{5–7} Several DMARDs are available for treating patients with RA, including methotrexate (MTX), the most commonly used agent.^{8–9} Treatment strategies in recent years have propagated to shorten delays in DMARD initiation^{10–12} and to rapidly change DMARD regimens that do not lead to sufficient reduction of RA activity.^{13–14} Insufficient effectiveness of DMARDs, however, is frequently seen in patients treated in practice,¹⁵ and drug retention rates are generally low, with even MTX allowing for an average treatment duration of only <3 years.^{16–17}

As a consequence of DMARD ineffectiveness, DMARD regimens are frequently changed.¹⁵ There are generally two therapeutic strategies in this respect—namely, to switch the insufficiently effective DMARD to another DMARD monotherapy or to continue the insufficiently effective DMARD and combine it with an additional DMARD (“step-up” combination therapy or “add-on” strategy). Various randomised controlled trials have evaluated the benefit of the step-up strategy. However, the effects of the added DMARD were usually compared with the addition of placebo to the insufficiently effective DMARD,^{17–20} but not with monotherapy of the new DMARD used in the combination arm. Not surprisingly, results

of these studies mostly reveal a better efficacy of step-up combination therapy compared with continuing the ineffective DMARD with addition of placebo. This trial design, however, does not directly relate to the approach in clinical practice, where the question is more whether an insufficiently effective DMARD should be switched to another DMARD or whether a new DMARD should be added to the continued previous regimen.²¹ The advantage of step-up combination therapy has clearly been shown for biological agents,^{22–26} but the value of add-on non-biological DMARDs in contrast with switching these DMARDs is not completely resolved in the literature, and more evidence is needed.²¹

We designed a study to address this question based on a large prospective observational cohort of patients with RA. We compared the strategies of DMARD switching with step-up DMARD combination therapy using retention rates, reasons for discontinuation, and effectiveness as outcomes of DMARD treatment.

METHODS

Patient database

The basis of this study is a cohort of patients with RA, for whom data obtained at each outpatient visit were documented in a

Abbreviations: DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; SSZ, sulphasalazine

prospective dataset. The observational data have been collected until September 2005 in two rheumatology clinics in Vienna, the Hietzing Hospital and the General Hospital. The dataset included patient demographics, disease characteristics (rheumatoid factor status, duration of RA), information on treatment (DMARDs used, maximum stable dose, duration of treatment, reason for discontinuation of DMARD, if applicable) and acute-phase reactants, such as C reactive protein and erythrocyte sedimentation rate (ESR). At the time of data extraction, the dataset comprised 1214 patients and 4585 treatment courses. All patients fulfilled the American College of Rheumatology criteria for RA. At some point during follow-up, all patients had given their permission to document and anonymously analyse these data. A more detailed general description of the database and the methods of data collection can be found in previous publications.^{15 27–29} None of the rheumatologists or patients were aware of the purpose of the current study at the time of patient assessment, since this registry was not specifically designed for the purpose of this investigation.

Identification of eligible treatment courses

We identified all patients in whom a DMARD course turned out to be ineffective, and who had therefore been subjected to a new DMARD regimen. We assessed the clinical outcomes of these subsequent DMARD regimens, comparing courses where treatment had been switched to a new DMARD monotherapy (switch or monotherapy) with those using a step-up combination therapy with that same new DMARD added to the insufficiently effective previous one. We focused our analyses on three commonly used DMARDs, methotrexate (MTX), sulphasalazine (SSZ) and leflunomide (LEF).

Outcomes and statistical analyses

Time-to-event analyses

We first assessed the retention of DMARD treatment using Kaplan–Meier analysis, which allows accounting for the fact that retention of some of the treatment courses is not known because they were still ongoing at the time of data evaluation (“censored” courses). Patients whose treatment was stopped because of remission, loss to follow-up or noncompliance were categorised as not having reached the end point (ie, they were also censored). We compared overall cumulative drug retention rates between the switch and the add-on strategies, separately for MTX, SSZ and LEF, using the log rank statistics. To adjust for confounding by indication, we used Cox proportional hazard models, in which we adjusted retention rates for baseline ESR, maximum stable dose of DMARD, total number of previous DMARDs and type of the ineffective previous DMARD (using binary dummy variables for MTX, SSZ, LEF and antimalarials), and for mean steroid dose.

Reasons for treatment termination

We next investigated the reasons for treatment termination as adjudicated by the treating doctor. Separately for MTX, SSZ and LEF courses, we compared the rates of terminations because of ineffectiveness and adverse events between switched and step-up combination therapies. These two reasons account for the majority of DMARD discontinuations in RA.³⁰ As described previously,³¹ we categorised all reasons for treatment discontinuation as “terminated for ineffectiveness” or “not terminated for ineffectiveness”, and as “terminated for adverse events” or “not terminated for adverse events”. Remission, loss to follow-up, noncompliance and ongoing treatments were categorised as both “not terminated for ineffectiveness” and “not terminated for adverse events”. Patients whose treatment was terminated to enrol them in a clinical trial were categorised as “terminated for ineffectiveness” and “not terminated for adverse events”.

Patients in whom comorbidities were the reason for cessation of treatment were categorised as “not terminated for ineffectiveness”; however, if comorbidities were related to treatment by adjudication of the evaluator, the respective treatments were categorised as “terminated for adverse events”. We used χ^2 statistics to compare the frequencies of termination for both ineffectiveness and adverse events, between the switch and the step-up groups.

Reduction of acute-phase response

Finally, we compared the effectiveness of switch and step-up treatments by using ESR as a surrogate for overall disease activity. We used a generalised linear model to analyse whether there was a difference based on strategy (switch vs step-up) with respect to ESR at end point, adjusting for baseline ESR, maximum stable dose of DMARD used, total number of previous DMARDs, type of the ineffective previous DMARD (using binary dummy variables for MTX, SSZ, LEF and antimalarials), reason for treatment discontinuation (using the two dummy variables indicating ineffectiveness or adverse events, as described above) and mean steroid dose. On the basis of that model, we estimated the final ESR for each of the two strategies. We also performed an identical analysis in the subgroup of patients in whom treatment was terminated for reasons other than ineffectiveness to avoid the related bias in the end point (instead of adjusting for it as above).

In all statistical analyses, we regarded a two-sided *p* value of 0.05 as significant. All analyses were performed using SPSS V.13.0.

RESULTS

Eligible treatment courses

We identified 374 patients who had not received MTX in a DMARD course terminated for insufficient effectiveness, but in whom MTX was part of the subsequent therapeutic regimen. Among these patients, 262 experienced switching to MTX, and 112 patients received MTX as a step-up combination therapy (table 1). We also identified 139 patients who had not received SSZ in the insufficiently effective course, but did so in the subsequent one: 87 patients were switched to SSZ and 52 patients received it as an add-on. For LEF (*n* = 139), these numbers were 119 and 20, respectively. Table 1 shows the characteristics of the patients studied by drug and by strategy. Patients who were switched to a new DMARD tended to be older than those who received add-on therapy, and to receive higher doses of the respective DMARD, especially in the case of MTX. Patients who switched to MTX had fewer previous DMARDs than those who received add-on MTX, and the insufficient previous DMARD was more frequently SSZ and less frequently LEF.

Temporal trends in the use of the two strategies

Figure 1 depicts the frequency distribution of the two strategies for MTX, SSZ and LEF over time. It can be seen that for MTX and SSZ, the add-on strategy appeared later in the therapeutic armament. However, in recent years, step-up combination therapy using these two DMARDs has been used with similar frequency as switching to one of these DMARDs. For LEF, combination step-up therapy has been used at relatively low rates compared with the switch strategy.

Similar retention of monotherapy and step-up combination therapy

To describe retention rates (drug survival) of DMARD treatments, we used time-to-event analyses. In the MTX groups, the median overall drug retention was 27 months for the switch cases, and 22 months for the step-up treatments (*p* = 0.49 by

Table 1 Patients' characteristics

	MTX (n = 374)				SSZ (n = 139)				LEF (n = 139)			
	All DMARDs	Switch-to	Add-on	p Value*	Switch-to	Add-on	p Value*	Switch-to	Add-on	p Value*	Switch-to	Add-on
n (% within DMARD)	652	262 (70.1)	112 (29.9)	—	87 (62.6)	52 (37.4)	—	119 (85.6)	20 (14.4)	—	119 (85.6)	20 (14.4)
Mean (SD) age (years)	59.0 (13.5)	60.6 (13.3)	57.0 (13.7)	0.02	61.3 (14.2)	58.7 (13.1)	0.30	56.6 (13.1)	54.9 (13.0)	0.60	56.6 (13.1)	54.9 (13.0)
Sex, female (%)	83.4	81.3	83.9	0.56	80.5	84.6	0.31	83.2	85.0	0.90	83.2	85.0
RF positive (%)	50.7	53.1	53.6	0.87	48.3	46.2	0.91	34.5	35.0	0.86	34.5	35.0
Mean (SD) duration of RA	10.4 (13.0)	9.8 (12.8)	10.8 (13.0)	0.55	8.7 (9.0)	10.1 (8.3)	0.42	12.7 (17.2)	11.3 (7.9)	0.80	12.7 (17.2)	11.3 (7.9)
Mean (SD) previous DMARDs	2.7 (1.7)	2.6 (1.7)	3.3 (1.7)	<0.01	2.7 (1.3)	3.2 (2.3)	0.13	2.3 (1.3)	2.2 (1.6)	0.81	2.3 (1.3)	2.2 (1.6)
Dose†	—	14.7 (6.1)	12.5 (5.0)	<0.01	2.2 (0.7)	2.0 (0.6)	0.20	20.6 (3.3)	18.0 (4.1)	0.01	20.6 (3.3)	18.0 (4.1)
Baseline ESR	34.1 (24.2)	33.7 (24.3)	36.1 (24.5)	0.43	40.7 (26.5)	31.9 (20.8)	0.06	31.1 (23.6)	28.3 (21.2)	0.63	31.1 (23.6)	28.3 (21.2)
Glucocorticoid therapy (%)	64.0	63.8	65.7	0.73	63.2	53.3	0.29	66.7	70.6	0.75	66.7	70.6
Mean (SD) steroid dose (mg/d)	6.1 (4.1)	5.8 (3.0)	6.3 (3.4)	0.29	6.2 (6.1)	6.6 (3.3)	0.78	6.0 (4.8)	6.6 (6.3)	0.70	6.0 (4.8)	6.6 (6.3)
Type of insufficient previous DMARD (%)	MTX: 24.7 SSZ: 23.6 AM: 15.6	SSZ: 42.0 AM: 20.2 LEF: 8.0	LEF: 38.4 SSZ: 20.5 AM: 17.0	<0.01	MTX: 35.6 AM: 25.3 LEF: 10.3	MTX: 59.6 AM: 13.5 LEF: 11.5	0.04	MTX: 71.4 SSZ: 14.3 AM: 0.8	MTX: 70.0 SSZ: 20.0 AM: 0.0	0.84	MTX: 71.4 SSZ: 14.3 AM: 0.8	MTX: 70.0 SSZ: 20.0 AM: 0.0

AM, antimalarials; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulphasalazine; —, not applicable.
*Statistics used to compare the switch and the add-on groups were adjusted for age, for sex, previous DMARDs (type and number), dose of DMARD, mean steroid dose and ESR at the beginning of treatment.
†Doses are given in mg/week for MTX, in g/day for SSZ and in mg/day for LEF.

log rank statistics; table 2). The top panel of fig 2A shows the Kaplan–Meier curve for the crude analysis. The respective Cox model adjusting for baseline ESR, maximum stable dose of DMARD, total number of previous DMARDs, type of the ineffective previous DMARD and mean steroid dose showed a tendency towards smaller hazard of termination for add-on courses. This would suggest a potentially mild advantage of the combination; however, this trend was not statistically significant (hazard ratio (HR) of 0.4 for adding compared with switching; 95% CI 0.2 to 1.1; $p = 0.07$; table 2). The bottom panel of fig 2A depicts the adjusted survival curve for the MTX group. Likewise, switching or adding did not result in significantly different median drug retention rates for SSZ (switch: 13 months, add: 14 months, $p = 0.61$; table 2; fig 2B, top panel), indicating that there is no increased hazard of treatment comparing switching with adding (HR = 0.5; 95% CI 0.2 to 1.4; $p = 0.18$; fig 2B, bottom panel; adjustments performed as above). We found similar results when performing the analyses for the LEF cases: the median drug

retention time for the switching and adding groups was 21 and 29 months, respectively ($p = 0.74$; table 2; fig 2C, top panel). This similarity did not change after adjustment for several potential confounding factors, giving a HR of 1.2 (95% CI 0.4 to 4.2; $p = 0.73$; table 2; fig 2C, bottom panel). There was a variable degree of censoring across the different drug groups, with a tendency towards higher rates of censoring in the step-up combination groups (table 2), indicating more current treatments in these groups at the time of data evaluation. This is mainly related to temporal trends, and is supported by the fact that no difference in censoring rates was seen for LEF, which was used in both strategies already at the time of its introduction (fig 1).

Reasons for treatment discontinuation are similar between monotherapy and step-up combination therapy

Table 3 shows the frequencies of the various reasons leading to treatment discontinuation. For better comparability between

Figure 1 Temporal trends in the use of the two therapeutic strategies. Panels display the annual numbers of newly initiated treatment courses over time that used the switching strategy (solid bars) or the step-up combination approach (hatched bars), for (A) methotrexate, (B) sulfasalazine and (C) leflunomide.

Figure 2 Retention of treatment: cumulative survival of switched and added disease-modifying antirheumatic drugs (DMARDs). The top panels show the Kaplan–Meier estimates for drug retention over the course of 4 years (with cases marked when censoring occurred), whereas the bottom panels represent the retention curves based on a Cox proportional hazards regression model adjusting for several confounders (see text). p Values relate to the comparison of the switching strategy (black lines) with the step-up combination therapy (grey lines). Separate panels are shown for (A) methotrexate, (B) sulfasalazine and (C) leflunomide. The line at 50% indicates the median time of drug retention.

the groups, each treatment course was recoded as “terminated for ineffectiveness” or not, and as “terminated for adverse events” or not, as described in the Methods section. Overall, 29.8% of courses were classifiable as ineffective, and 11.7% as not sufficiently safe. Table 3 shows the proportions of courses terminated for ineffectiveness or for adverse events for the switching and the step-up combination strategy groups. The crude analysis of reasons for discontinuation showed significantly higher rates for both ineffectiveness and toxicity, in the MTX monotherapy group compared with step-up combination therapy ($p=0.02$ for both). However, this crude analysis included ongoing treatments that we classified as “not terminated for ineffectiveness” and “not terminated for

toxicity”. Since the frequency of ongoing treatments varied between the strategies, we excluded these treatments in an additional analysis. In this analysis, rates became similar for the two MTX treatment strategies ($p=0.36$ and 0.17 , respectively). The rates of termination related to ineffectiveness and toxicity in the SSZ groups and the LEF groups were also similar (table 3).

Improvement of acute-phase response

We finally compared the strategies of switching and adding for their ability to reach a low ESR as a laboratory surrogate of the inflammatory activity. Overall mean (SD) baseline ESR was 34.1 (24.2) mm/h, and was similar across treatment regimens

Table 2 Average disease-modifying antirheumatic drug retention times and hazard of treatment termination associated with the add-on strategy

	Kaplan–Meier analysis drug survival (months), median (quartiles; percentage censored)			Cox regression model* (add-on vs switch)	
	Switch	Add-on	p Value (log rank)	HR (95% CI)	p Value
Methotrexate 12.0 (5–27)	27.0 (10–63; 44.6%)	22.0 (9–57; 63.9%)	0.49	0.4(0.2–1.1)	0.07
Sulfasalazine 8.5 (4–20)	13.0 (4–27; 23.5%)	14.0(6–40; 35.3%)	0.61	0.5(0.2–1.4)	0.18
Leflunomide 11.0 (5–21.3)	21.0 (9–38; 49.6%)	29.0(15–46; 50.0%)	0.74	1.2(0.4–4.2)	0.73

*Cox model adjusting for type of the insufficient disease-modifying antirheumatic drug (DMARD), number of previous DMARDs, maximum stable dose of DMARD used in the new strategy, mean steroid dose at baseline and baseline erythrocyte sedimentation rate.

Table 3 Reasons for treatment discontinuation

	MTX			SSZ			LEF		
	Switch-to	Add-on	p Value*	Switch-to	Add-on	p Value*	Switch-to	Add-on	p Value*
Reasons for treatment discontinuation, all categories (rates, %)									
Ineffectiveness	30.4	19.2	0.001	53.5	36.6	0.04	37.3	38.9	0.26
Adverse events	16.5	7.1		16.9	9.8		6.4	5.6	
Remission	0.4	3.0		0	2.4		0	0	
Lost to follow-up	7.0	3.0		5.6	4.9		0	0	
Incompliance	2.6	8.1		5.6	0		0	5.6	
Other disease	1.3	1.0		0	4.9		0.9	0	
Current treatment	40.4	57.6		16.9	36.6		54.5	50.0	
Enrolment in trial	1.3	0		0	2.4		0	0	
Other reasons	0	1.0		1.4	2.4		0.9	0	
Reasons for treatment discontinuation, recoded† (rates, %)									
Ineffectiveness	31.7	19.2	0.02	53.5	39.0	0.14	37.3	38.9	0.90
Adverse events	17.8	8.1	0.02	16.9	14.6	0.75	7.3	5.6	0.79
Reasons for treatment discontinuation, recoded, current treatments excluded‡ (rates, %)									
Ineffectiveness	53.3	45.2	0.36	64.4	61.5	0.80	82.0	77.8	0.77
Adverse events	29.9	19.0	0.17	20.3	23.1	0.78	16.0	11.1	0.71

LEF, leflunomide; MTX, methotrexate; SSZ, sulphasalazine.

* χ^2 test.

†Reasons for treatment discontinuation were recoded according to the following algorithm: "remission", "loss to follow up" and "incompliance" were categorised as ongoing treatments—that is, "not terminated for ineffectiveness" and "not terminated for adverse events"; enrolment in clinical trials was classified as "terminated for ineffectiveness" and "not terminated for adverse events"; and comorbidities were categorised as "not terminated for ineffectiveness" and as "terminated for adverse events" or "not terminated for adverse events" depending on the attribution by the assessor (see text).

‡Excluded current treatments (overall percentages): 35.0% in the switch group, 50.9% in the step-up group.

($p = 0.93$). Generally, the effects on ESR (based on the last observation during treatment) were small across all drugs. The final levels of ESR that had been reached during treatment, were similar between the switch and the step-up groups (table 4, crude analysis). We used a generalised linear model to estimate final ESR levels that would be seen if the level of potentially confounding variables at baseline had been similar in the switch and in the step-up groups. The final ESR levels estimated from these models were similar for the MTX, SSZ and LEF comparisons (table 4, adjusted analysis). In a subgroup analysis looking at courses that had been terminated for any reason except for ineffectiveness, the LEF comparisons showed a difference in the estimated final ESR in favour of the switch group (table 4, adjusted analysis). However, because the LEF group had the smallest sample size and since this was a subgroup analysis, the data cannot be interpreted as reliably representing a true difference for the two LEF groups.

DISCUSSION

The results of this study indicate that step-up combination therapy with MTX, SSZ or LEF may not be superior to switching to the respective DMARD as a monotherapy, when retention rates of DMARD courses, an integrative outcome in terms of clinical utility of DMARDs in RA,^{3 27 32 33} is used as the main end point. These data, obtained from long-term observations in outpatient clinics, suggest that continuation of an ineffective DMARD may not provide a therapeutic advantage in the course of a subsequent DMARD regimen.

The superiority of DMARD combination therapy has been claimed for many years on the basis of several randomised controlled clinical trials. However, as pointed out in various reviews,^{21 30 31 34} this inference may be confounded by a variety of factors: many studies showing a benefit of combination therapy used a step-up approach where the addition of a DMARD was compared with the addition of placebo in patients with insufficient effectiveness of the previous DMARD; studies showing a benefit of combination therapy versus monotherapy in a parallel design fashion frequently comprised a clearly

superior drug or higher glucocorticoid doses in the combination arm.²¹ In contrast with these study designs, the decision that practising rheumatologists frequently face in patients with an insufficient response to a DMARD is to either use a step-up approach or switch treatment to the new drug. It is interesting that especially for MTX this question has not yet been adequately answered in randomised controlled clinical trials. Therefore, we addressed this issue using prospectively collected data of an observational dataset.

The present study is based on a large dataset from two specialised clinics, which allowed us to analyse more treatment courses than investigator-driven randomised controlled studies usually can realise. We compared a total of 652 treatment courses focusing on 3 of the most commonly used traditional DMARDs. We obtained similar results from the analysis of each of these DMARDs, further bolstering the notion on the similarity of monotherapy and step-up combination therapy. Our study did not evaluate the effects of tumour necrosis factor inhibitors. However, in contrast with traditional DMARDs, tumour necrosis factor inhibitors have repeatedly and unequivocally been shown to exhibit superior efficacy in combination with DMARDs compared with monotherapies of the biologicals and/or MTX^{35–37} and, therefore, are only rarely used as monotherapy in clinical practice.

Since patients had not been randomised to the switch or step-up groups, and different rheumatologists were involved in making the treatment decisions, one issue in our observational study is bias by indication—that is, the possibility that patients whose treatment was switched were systematically different from those who received combination therapy. In fact, this was the case, as can be seen from the slopes of the adjusted versus the unadjusted retention curves in fig 2: after adjusting for several factors that are probably associated with more severe or refractory disease, such as baseline ESR, total number of previous DMARDs or type of the ineffective previous DMARD, the trend favouring switching of DMARDs inverted, although the difference remained insignificant. Although we observed higher MTX doses in the monotherapy group than in the

Table 4 Final erythrocyte sedimentation rate (mm/h) at the end of treatment based on a generalised linear model

	All courses			Only courses not terminated for ineffectiveness		
	Switch-to	Add-on	p Value	Switch-to	Add-on	p Value
Methotrexate						
Crude analysis, mean (SD)	28.7 (20.2)	28.6 (21.0)	0.97	28.7 (21.0)	26.3 (18.1)	0.43
Adjusted analysis*	28.8	24.3	0.91	28.1	24.9	0.89
Sulphasalazine						
Crude analysis, mean (SD)	36.5 (27.6)	28.9 (23.4)	0.12	36.0 (27.6)	27.8 (22.5)	0.27
Adjusted analysis*	40.1	30.7	0.93	40.9	28.6	0.15
Leflunomide						
Crude analysis, mean (SD)	27.7 (21.0)	27.9 (19.4)	0.97	26.6 (22.1)	31.6 (21.3)	0.48
Adjusted analysis*	27.5	36.3	0.34	28.7	47.6	0.03

*Estimated marginal means for final erythrocyte sedimentation rate (ESR); models adjusted for baseline ESR, maximum stable dose of disease-modifying antirheumatic drug (DMARD) used, total number of previous DMARDs, type of the ineffective previous DMARD (using binary dummy variables for methotrexate, sulphasalazine, leflunomide and antimalarials), reason for discontinuation of treatment (using the two dummy variables indicating ineffectiveness or adverse events) and mean steroid dose.

combination therapy group, which could be interpreted as an indication that higher MTX doses were needed in the absence of another DMARD to reach similar effectiveness, the MTX dose was part of the above adjustment process. Likewise, this adjustment for MTX dose takes into consideration the increasing dosing scheme of MTX. In addition, we included glucocorticoid use in the adjustment process, although there was no significant difference between the two groups. Despite the rigorous adjustment for major confounders, residual bias by indication is still possible, but it is unlikely that it would significantly affect the results. The overall retention times of MTX observed here are slightly shorter than those reported in other studies^{15 38 39}; however, the current study comprised only a subgroup of the overall patient population receiving MTX—namely, those patients who failed a previous treatment, which reduces the average duration.¹⁵

Although this is a retrospective observational study, the interpretability of its results is probably not biased, since at the time of obtaining data neither the treating rheumatologists nor the patients were aware of the planned analyses. Moreover, at least with respect to SSZ, the results of this observational study are in line with a recent randomised controlled clinical trial by Dougados *et al.*,⁴¹ in which a step-up combination strategy of adding SSZ to insufficiently effective LEF did not reveal a significant difference compared with switching from LEF to SSZ monotherapy.³⁴ One reason for the lack of superiority of the combination of SSZ and MTX in our study might be an inhibition of cellular uptake of MTX by SSZ, as demonstrated *in vitro*.⁴⁰ Whether this is also pertinent *in vivo* is currently unknown, and in the recently published BeSt Trial, patients taking MTX who received step-up combination therapy with SSZ experienced a beneficial effect, although it was not significantly different from switching to SSZ.⁴² These two trials, like our observational study, are along the lines of new trends in study designs to address clinically important questions that help guide treatment decisions rather than to assess the statistical significance for the benefit of a regimen compared with placebo.⁴³ This pragmatic approach to clinical trial design has rarely been used to address the question of benefits of combination therapies—mostly because there is no major support by industry—and the trials needed are more likely to be of equivalence design, requiring large sample sizes. However, one additional problem in the translation of evidence of clinical

trials of therapeutic strategies to clinical practice is a limited generalisability, especially since trials usually comprise younger age groups, and patients with lower levels of comorbidities (according to the trials' exclusion criteria) compared with patients followed in clinical practice. Observational studies, such as the present one, can therefore be of particular help in providing evidence for clinicians.⁴⁴

In conclusion, this observational study suggests that a step-up strategy involving MTX as the add-on DMARD is not superior to mere switching to MTX. The data reveal that in clinical practice, MTX, and also SSZ and LEF, do not confer an advantage as part of a step-up combination DMARD therapy compared with monotherapy replacing the previous DMARD. The results presented have several implications: first, given that patients with RA in clinical practice frequently experience comorbidities and need to take drugs other than antirheumatic agents, the data indicate that it is possible to reduce the burden of medicinal intake without the risk of losing effectiveness. A collateral effect of reduced requirement of medication is a possible increase in adherence to treatment; second, combination therapy does not seem to constitute an important step, let alone prerequisite, before prescription of biological agents; and third, on the basis of the accumulating evidence, including evidence provided in this study, the use of combination therapy, especially as a step-up strategy, should not necessarily be regarded as a "more intensive" treatment strategy than DMARD monotherapy.

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