Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components

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Abstract

***Objectives*—To investigate the potential clinical benefit of a combination therapy.**

***Methods*—205 patients fulfilling the ACR criteria for rheumatoid arthritis (RA), not treated with disease modifying anti-rheumatoid drugs previously, with an early (≤1 year duration), active (Disease Activity Score (DAS) > 3.0), rheumatoid factor and/or HLA DR 1/4 positive disease were randomised between sulphasalazine (SASP) 2000 (maximum 3000) mg daily (n = 68), or methotrexate (MTX) 7.5 (maximum 15) mg weekly (n = 69) or the combination (SASP + MTX) of both (n = 68).**

***Results*—The mean changes in the DAS during the one year follow up of the study was −1.15, −0.87, −1.26 in the SASP, MTX, and SASP + MTX group respectively (p = 0.019). However, there was no statistically significant difference in terms of either EULAR good responders 34%, 38%, 38% or ACR criteria responders 59%, 59%, 65% in the SASP, MTX, and SASP + MTX group respectively. Radiological progression evaluated by the modified Sharp score was very modest in the three groups: mean changes in erosion score: +2.4, +2.4, +1.9, in narrowing score: +2.3, +2.1, +1.6 and in total damage score: +4.6, +4.5, +3.5, in the SASP, MTX, and SASP + MTX groups respectively. Adverse events occurred more frequently in the SASP + MTX group 91% versus 75% in the SASP and MTX group (p = 0.025). Nausea was the most frequent side effect: 32%, 23%, 49% in the SASP, MTX, and SASP + MTX groups respectively (p = 0.007).**

***Conclusion*—This study suggests that an early initiation therapy of disease modifying drug seems to be of benefit. However, this study was unable to demonstrate a clinically relevant superiority of the combination therapy although several outcomes were in favour of this observation. The tolerability of the three treatment modalities seems acceptable.**

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The state of current drug therapy of rheumatoid arthritis (RA) is not satisfactory and proposals have been brought forward to improve this situation. One of these proposals is to start disease modifying anti-rheumatoid drugs at an early phase of the disease,[1] another one is to combine disease modifying drugs.[2–12]

The criticism of using disease modifying anti-rheumatoid drugs at an early phase of the disease is that the natural history of the disease might result in a long term spontaneous remission and that a systematic disease modifying anti-rheumatoid drug therapy might result in unacceptable adverse events. To overcome this, it has been proposed to focus this treatment in patients at an early phase fulfilling criteria picked up in previous epidemiological studies as predictive of poor long term outcome. For example, some studies have henceforth suspected that a persistent polysynovitis and/or a persistent increase in biological signs of inflammation and/or the presence of HLA DR 1/4 might be predictive of a poor long term outcome.[13–18]

The results of current treatment even in early RA are not satisfactory. By analogy to anticancer treatment, combination therapy has been proposed although some questions still remain to be answered: which drug to use? How many drugs to combine? When to start?

These preliminary remarks prompted us to conduct a study evaluating the symptomatic and also the structural effects of the combination of methotrexate (MTX) and sulphasalazine (SASP) and to compare these effects with those observed with MTX or SASP alone in patients with an early, active disease fulfilling some criteria of potential poor long term outcome.

Methods

PATIENT POPULATION

Outpatients fulfilling the criteria of the American College of Rheumatology (ACR) for the diagnosis of RA were recruited for the study.[19] Other criteria for entry were the presence of active disease, as defined by a Disease Activity Score (DAS) ⩾ 3.0[20] and the presence of rheumatoid factor and/or HLA DR1/4 positive disease. The DAS calculation was based on the Ritchie articular index, the 44 swollen joint count, and the erythrocyte sedimentation rate. The disease duration (interval of time between the screening visit and the date the patient ful-

filled the ACR criteria) had to be less than one year (we also collected the information related to the date the patient complained from a clinical symptom probably related to RA). Previous drug treatment for RA other than analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) was not allowed—that is, all the patients were corticosteroid and disease modifying drug naive. Patients with contraindications to the use of SASP or MTX were excluded.

STUDY DESIGN

This double blind, double dummy controlled, multicentre trial of 52 week duration was conducted in three European countries (Finland, France, Germany) and was approved by the ethical review board of each participating centre.

DRUG ADMINISTRATION

After confirming that the patient fulfilled the entry criteria defined above and after written informed consent was obtained, patients were randomly assigned to receive SASP, MTX or both drugs. Those in the SASP group received SASP 500 mg enteric coated tablets (an initial dose of 1 g daily for four days rising to 1.5 g the next four days, reaching the maintenance dose of 2 g daily from day 9) and MTX placebo tablets (three tablets per week at one dose occasion), those in the MTX group received MTX 2.5 mg tablets and SASP placebo tablets with the same regimen as in the SASP group; those in the SASP + MTX group received MTX 2.5 mg tablets and SASP tablets with the same regimen as in the other groups. This dose remained constant from day 9 to week 16. After week 16, if efficacy was inadequate, patients could be optionally treated with 3 g daily SASP (or placebo) and 15 mg weekly MTX (or placebo).

EFFICACY SYMPTOMATIC ASSESSMENT

Each patient was evaluated by the same observer every two weeks for the first four weeks and every four weeks thereafter until week 52. The following evaluations were included:

(a) global assessment by the patient and the doctor using a Likert scale from 1 = asymptomatic to 5 = very severe;

(b) severity of pain, as evaluated using a 100 mm visual analogue scale and by the Ritchie articular index[21];

(c) degree of inflammation assessed according to the latent period before resolution of early morning stiffness, the number of synovitis (44 joints), and the degree of biological inflammation (erythrocyte sedimentation rate (mm/1st h) and C reactive protein (mg/l));

(d) functional impairment, as estimated by the Health Assessment Questionnaire.[22–24]

The primary evaluation criterion was the mean change in the DAS over time for each individual patient. In this study, the DAS consisted of the Ritchie articular index, the number of swollen joints, and the erythrocyte sedimentation rate.

Moreover, in analysing the trial, patients were grouped as responders and non-responders according to both the EULAR[25] and the ACR criteria.[26]

EFFICACY STRUCTURAL ASSESSMENT

Structural severity of the disease was evaluated by the radiological damage according to the Sharp method modified by van der Heijde.[27–30] For this purpose, hand and feet radiographs were taken at baseline, week 24 and 52. One single observer evaluated the films of all the patients. All the films of a single patient were analysed during the same session. The observer was aware of the chronology of the films, but unaware of the allocated study drug. For each

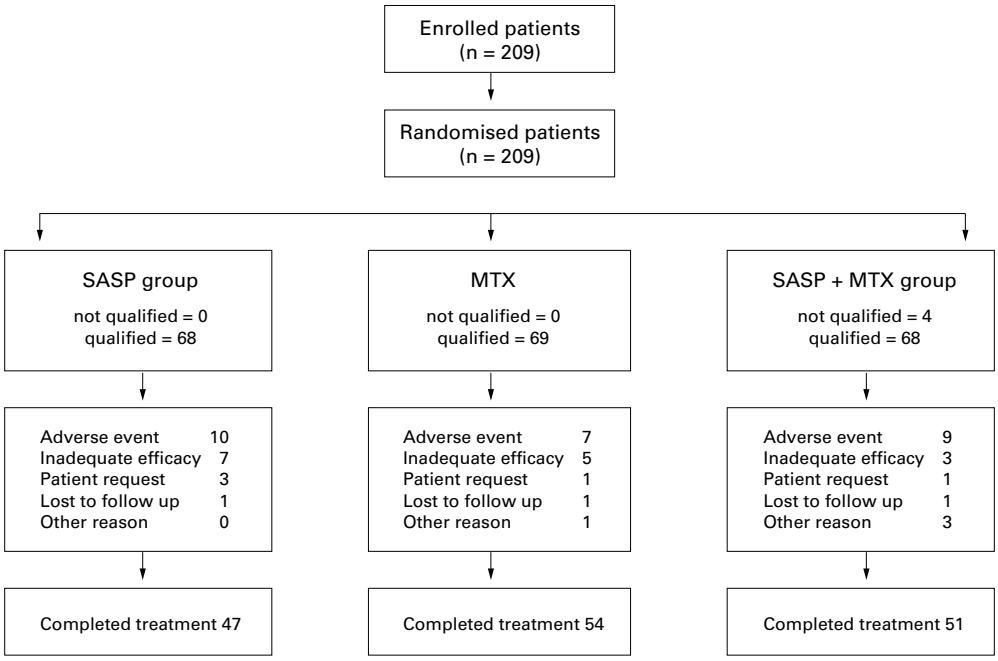

Figure 1 Course of the 52 week randomised controlled trial in RA patients.

*Table 1 Baseline characteristics of the rheumatoid arthritis patients studied by treatment groups**

Characteristic	Treatment group		
	SASP n=68	*MTX n=69*	*SASP+MTX n=68*
Age (y)	52 (2)	50 (2)	52 (2)
Time since diagnosis (months)	2.9 (0.3)	2.3 (0.3)	3.4 (0.3)
Time since onset (months)	10.8 (1.2)	18.4 (5.2)	10.6 (1.0)
Sex (% female)	71	74	77
HLA DR1 positive (%)	28	36	31
HLA DR4 positive (%)	53	54	57
Rheumatoid factor positive (%)	75	62	71

*Values are either the mean (SEM) or the percentage of patients.

patient, an erosion score, a narrowing score and a total damage score were noticed. Before the definite evaluation, the intraobserver intraclass coefficient of correlation was calculated and was very high: 0.93, 0.96, and 0.98 for the erosion score, narrowing score, and total damage score respectively.

Moreover, to determine a cut off value of changes in joint space width that allowed definition of radiological progression of RA not related to measurement method errors, we used the method proposed by Bland and Altman.[31] This method entails calculating the mean of the differences between two analyses. For this purpose, we selected 20 pairs of radiographs representative of the spectrum of the disease in terms of severity. The evaluated score in each analysis was the progression score observed in each individual patient. The two analyses of the progression score by the same observer were performed on the films taken at entry and at the end of the study. The mean (SD) of the differences between the two analyses were 0.56 (1.74), 0.16 (0.96), and 0.74 (2.42) for the erosion score, narrowing score, and total damage score respectively. For this study, radiological progression was therefore defined by a change in radiological score greater than the 95% confidence intervals of these differences—that is, a change of at least 3.98, 2.04, and 5.48 in the erosion score, narrowing score, and total damage score respectively.

SAMPLE SIZE CALCULATION

The sample size calculation was based on the intention to treat analysis of the patient's global assessment of disease activity. The within group standard deviation was assumed to be 1.0 and a clinically relevant mean difference between the combination and the single component groups was estimated at 0.5. Using a two sided test, at the 5% significant level and a power of 80%, it was calculated that 63 patients in each treatment group would be required.

STATISTICAL ANALYSIS

Continuous variables were compared by using analysis of variance and dichotomous variables by using the χ^2 test. Moreover, to estimate both the onset of action and the time the plateau of efficacy is achieved of the different study drugs, an analysis of variance on repeated measurement was also performed. Outcome clinical and biological measures were evaluated on all patients entering the study (intention to treat analysis: ITT). In order to perform the ITT analysis, the LOCF (Last Observation Carried Forward) technique was used. Outcome structural variables, for example, radiological were evaluated on the patients completing the study.

Results

PATIENTS AND STUDY COURSE

A total of 209 patients were enrolled in the study (fig 1 summarises the study course). Three patients never received the study drug and one had no data after baseline. Consequently, these four patients were classified as unqualified and thus 205 patients were included in the ITT analysis (68 in the SASP group, 69 in the MTX group, and 68 in the SASP + MTX group). One hundred fifty two patients (73% of those randomised) completed the 52 week treatment period. The main reasons for withdrawals were adverse event or inadequate efficacy.

Table 1 summarises the characteristics of the patients at the start of the trial. There were no statistically significant differences among treatment groups. Concerning the HLA-DR typing, 21% of the patients tested negative for both HLA DR1 and HLA DR4 while 9% tested positive for both. After week 16, because of inadequate efficacy, 81 patients increased the dose of the study drug: 26 (38%), 33 (48%), and 22 (32%) in the SASP, MTX, and SASP + MTX groups respectively.

*Table 2 Baseline values and changes in the outcome variables during the one year of the study by treatment group**

Efficacy variable	Baseline				Change during the study			
	SASP n=68	*MTX n=69*	*SASP+ MTX n=68*	*p value*	*SASP n=68*	*MTX n=69*	*SASP+ MTX n=69*	*p value*
Symptomatic efficacy variable								
Patient's global assessment	2.5	2.5	2.4	NS	−0.9	−0.9	−0.8	NS
Physician's global assessment	2.4	2.4	2.4	NS	−0.7	−0.7	−0.6	NS
Ritchie articular index	17.6	16.5	18.9	NS	−7.1	−4.2	−9.4	0.001
Swollen joints	10.5	9.4	9.4	NS	−4.5	−3.9	−4.5	NS
HAQ	1.38	1.25	1.32	NS	−0.74	−0.73	−0.70	NS
Morning stiffness (min)	78	92	95	NS	−46	−53	−55	NS
ESR (mm 1st h)	42	46	38	NS	−30	−24	−25	NS
CRP (mg/l)	30	37	29	NS	−8	−16	−17	NS
DAS	4.23	4.13	4.24	NS	−1.15	−0.87	−1.26	0.019
Structural efficacy variable†								
Erosion score	2.77	3.78	4.28	NS	+2.38	+2.38	+1.85	NS
Narrowing score	3.34	4.52	4.63	NS	+2.26	+2.12	+1.61	NS
Total damage score	6.11	8.30	8.91	NS	+4.64	+4.50	+3.46	NS

*Values given are mean and p value is referred to the statistical significance using the inter-group comparison (analysis of variance), in the intention to treat analysis.
†This analysis was performed in the completers with available radiographs (46, 49, and 49 patients in the SASP, MTX, and SASP + MTX groups, respectively).

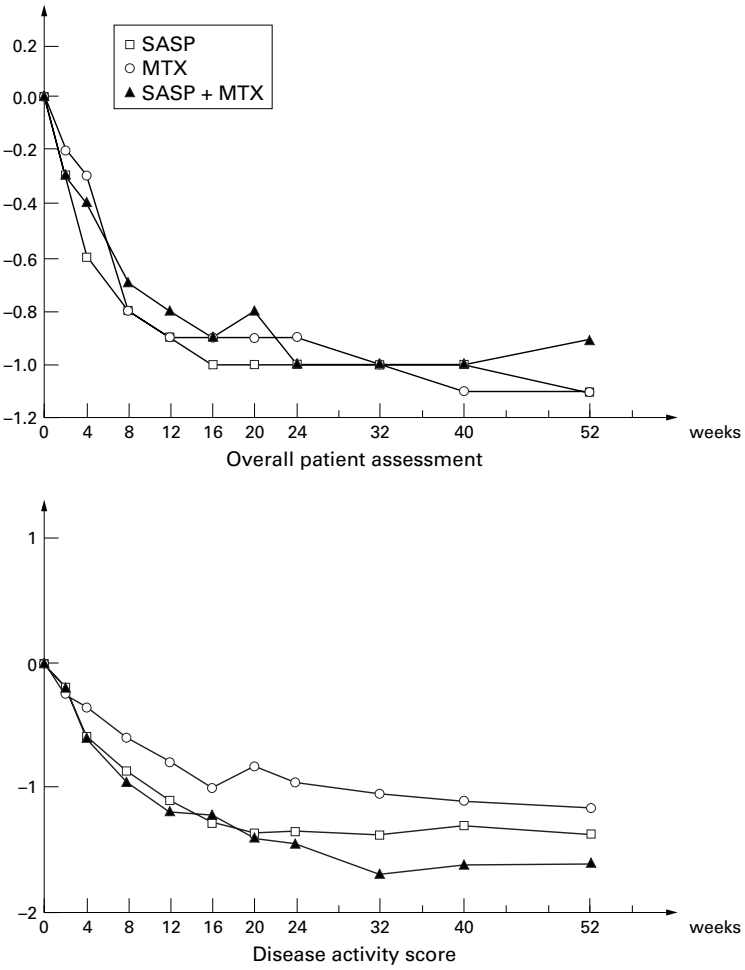

Figure 2 Mean changes in selected variables during the study in patients given SASP, MTX or SASP + MTX.

Table 3 Most commonly observed adverse events during the 52 weeks of the study treatment groups

	Treatment group		
Adverse event	*SASP n=68*	*MTX n=69*	*SASP+ MTX n=68*
Central nervous system			
Headache	6 (9)	3 (4)	8 (12)
Vertigo	4 (6)	1 (1)	2 (3)
Gastrointestinal disorders			
Nausea	22 (32)	16 (23)	33 (49)
Epigastralgia	6 (9)	4 (6)	9 (13)
Liver enzymes			
AST	0 (0)	0 (0)	22 (3)
ALT	0 (0)	1 (1)	6 (9)
Haematological disorders			
Leucopenia	7 (10)	1 (1)	6 (9)

Data shown in parentheses are percentages.

SYMPTOMATIC EFFICACY OF TREATMENTS

Table 2 summarises both the baseline values and the changes during the one year of the trial in all the efficacy variables. There was a statistically significant difference only for the variable Ritchie articular index with a better improvement in the SASP + MTX group (−9.4) than in the SASP or MTX group (−7.1 and −4.2 respectively). There was a statistically significant difference between the SASP + MTX group and the MTX group in favour of the combination therapy ($p < 0.001$), however, there was only a trend in favour of the combination therapy when compared with SASP ($p = 0.09$). This inter-group differences in the Ritchie articular index resulted also in a statistically significant difference in the changes in the DAS (−1.26 in the SASP + MTX group versus −1.15 and −0.87 in the SASP and MTX group respectively) because the Ritchie articular index is an important fraction of the DAS.

The ACR and EULAR response rates were high in both treatment groups without any statistically significant difference among treatment groups, although the SASP + MTX treatment group tended to have a higher number of responders. The ACR responder rates were 59%, 59%, and 65% in the SASP, MTX, and SASP + MTX groups, respectively. The EULAR responder rates were 34%, 38%, and 38% for the definition of good responders and 34%, 25%, 34% for the definition of moderate responders in the SASP, MTX, and SASP + MTX groups, respectively.

The latent period before the onset of the study drugs activity was estimated by detailed analysis of the changes in the DAS and the patient's overall assessment over time (fig 2). The analyses showed that the patients in the MTX group improved later than those in the SASP or SASP + MTX groups. The statistical analysis performed on the mean time to first good response showed a trend ($p = 0.077$) in favour of the combination therapy over the single therapy groups.

STRUCTURAL EFFICACY PARAMETERS

Table 2 summarises the baseline values and the observed changes in the three main radiological outcome variables (that is, erosion score, damage score, and total joint score). As expected, the obtained values were very low at baseline, there was a slight deterioration during the study without any statistically significant difference among the three treated groups. However, as observed also on the symptomatic parameters, there was a trend in favour of a lower progression in the combination group when compared with the two monotherapy groups. The percentage of patients showing a detectable radiological progression was 13%, 10%, 7% in the SASP, MTX, and SASP + MTX groups respectively for the erosion score, was 15%, 14%, and 12% for the narrowing score, and was 14%, 16% and 9% for the total damage score.

TOLERABILITY

During the study, 165 patients reported a total of 861 adverse events. Most of these events were mild to moderate in intensity. The number of patients experiencing any adverse event reached the statistical significant difference among treatment groups ($p = 0.025$) with adverse events in the SASP + MTX group occurring at a higher rate (91%) than in either the SASP (75%) or the MTX (75%) groups. Table 3 summarises the most commonly observed adverse events. The only statistically significant differences among treatment groups were for erythema, nausea, and increased serum aspartate aminotransferase (AST). Erythema was only observed in the SASP group

(4.4%) and never in the other two groups (p = 0.047). Nausea was more frequently observed in the SASP + MTX group (49%) than in the other groups (32% and 23% in the SASP and MTX groups respectively). Increased AST was only observed in MTX group (4.3%) and never in the other two groups (p = 0.05).

During the study, a total of 26 patients withdrew from the study because of medical events. Patients drop outs were equally distributed among treatment groups (10, 7, and 9 in the SASP, MTX, and SASP + MTX groups respectively). The main reasons for withdrawal in the SASP group were skin reactions (five patients), gastrointestinal disturbances (three patients), leucopenia (one patient) and symptoms associating coughing, dyspnea, and fever in the last patient. In the MTX group, two patients withdrew because of an increase in hepatic enzymes, two because of myocardial infarction, one because of skin eruption, one because of hair loss and nausea, and one because of vaginal haemorrhage without haematological disturbances. In the SASP + MTX group, two patients withdrew because of nausea, one because of reversible pancytopenia, one because of fatigue, two because of pneumopathy, one because of myocardial infarction, one because of amenorrhea, one because of gingivitis.

Discussion

This 52 week controlled study confirms both the efficacy and the acceptable safety profile of both the SASP and MTX when administered as monotherapy. Intergroup comparisons suggest a later onset of action of MTX when compared with SASP. Moreover, this study showed a trend in favour of a more potent effect of the combination but also a trend suggesting a more toxic profile of this combination.

The observed difference in the onset of action between SASP and MTX can probably be explained by the study design. In this study, a 2 g SASP daily dose regimen (which is usually considered as an efficient one) was achieved as soon as day 9. At variance, a 7.5 mg MTX weekly dose (stable in this study from entry to week 16) can be considered as a too low dose for most of the RA patients. This stable low dose can probably explain the relatively slower onset of action in the MTX group when compared with the two other groups. The safety profile of both study drugs (MTX and SASP) observed in this study is the one that was expected when these drugs were administered as monotherapy. When this study was planned, the utility of a systematic folic acid supplementation to patients receiving MTX was not demonstrated. Despite the lack of a systematic folic acid supplementation, the frequency and/or the severity of the observed adverse events during this study was similar to those previously reported in the literature. The statistical significant difference in the a priori chosen primary outcome variable—that is, changes in DAS—could argue in favour of a "positive trial". However, we consider that we failed to clearly demonstrate a clinically relevant difference in the combination therapy group when compared with the monotherapy groups although some variables, in particular the number of tender joints, showed a statistically significant difference among the three studied groups during the 52 weeks of the study. These results are similar to those obtained in an analogue recently reported study conducted in a single centre on a smaller sample size of patients.[7] This lack of difference between the combination group and the monotherapy groups applies also for the safety profile of the studied treatments. However, the detailed analysis of the different efficacy variables showed a trend in favour of the combination therapy group. Several arguments could probably be proposed to explain this absence of clinically and/or statistically significant difference:

(1) The first one is related to the study drug dose. The doses of MTX were quite low (from 7.5 to 15 mg weekly). Moreover, the possibility of dose escalation at week 16 might bias against finding an improved efficacy in the combination group. One could argue that it is not surprising that some patients taking 15 mg of MTX would have done as well as patients taking half that much MTX with the addition of SASP.

(2) The second one is the duration of the study. It is usually admitted that a six month duration study is sufficient to demonstrate statistically significant effect of an active drug over placebo. However, the demonstration of a statistically significant difference between two active procedures is much more difficult and requires probably studies of longer duration.

(3) The third argument is the studied population. This study was focused on patients with an early disease. This characteristic is probably appropriate to achieve a better outcome in patients suffering from RA. However, it is also well known that the progression of the disease is much more variable during the first two years of the disease than at a later stage.[32 33] This interpatient variability can also be an argument explaining the lack of demonstration of statistically significant difference between the three groups.

Finally, we can also admit that both the strategy of the combination therapy and the studied group were not the appropriate one to reach such objective.

In this study, we used the strategy that has been called the "step down bridge" approach—that is, to start combination from the beginning.[34] The other strategy called "adding on" or "step up" strategy consists in the addition of a second anti-rheumatic drug once the first one is not successful.[6 11] Such a strategy has been applied in patients with an established disease and who have a partial response with SASP.[6] In this open study, MTX was started whereas SASP was either continued or discontinued. The combination therapy group showed better improvement than MTX group alone.

Finally, one could also argue that the studied drugs, MTX and SASP, were not the appropriate ones. Another recently reported study suggests that a triple therapy combining SASP, MTX and also hydroxychloroquine is of better

benefit than the combination SASP + hydroxychloroquine or than the MTX alone.[9]

Besides the efficacy evaluation, it has to be noticed that the safety profile of the SASP + MTX combination seems acceptable in our study without any adverse synergistic effect. However, the detailed analysis of the different observed adverse events suggest a potential additive effect. For example, headache (a well known SASP side effect[35]) occurs in 9% and 12% in the SASP and SASP = MTX groups respectively and only in 4% in the MTX group.

Finally, further studies using different strategies, different durations and/or different studied drugs are necessary to permit an an objective evaluation of the potential benefit of a combination therapy in RA.

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