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Concise Report

Short-term efficacy of combination methotrexate and infliximab in patients with ankylosing spondylitis: a clinical and magnetic resonance imaging correlation

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Objective. To examine the short-term efficacy and safety of MTX in combination with infliximab compared with infliximab and placebo in the treatment of AS using MRI to monitor its effect.

Method. Thirty-eight subjects with active AS were randomized to receive MTX (MTX group) or placebo (placebo group) for 22 weeks. Both groups received infliximab for three infusions of 5 mg/kg at week 16, 18 and 22 and were followed up until week 30. MRI changes in the spine were assessed before and after infusion.

Results. The Assessments in Ankylosing Spondylitis (ASAS) 20 response at week 16 was 5.4% in the MTX group *vs* 15.8% in the placebo group ($P = 0.17$). In the MTX group, 5.4, 31.6, 52.6 and 63.2% of patients *vs* 15.8, 21.1, 57.9 and 68.4% patients in the placebo group achieved ASAS20 at week 16, 18, 22, 30, respectively. There were no significant differences between the two groups at any time points. Likewise, the secondary outcome showed no significant differences between the two groups. MRI changes in 31 subjects showed an overall improvement of 36.4% but the changes were not significant between the two groups.

Conclusions. Combination MTX with infliximab is as safe and as effective as infliximab monotherapy in the treatment of AS with a significant improvement in ASAS20 and in the different core sets in assessment. MRI improvements were also seen. However, there was no additional clinical or MRI improvement with the addition of MTX to infliximab in AS.

Key words: Ankylosing spondylitis, Magnetic resonance imaging, Infliximab, Methotrexate, Clinical efficacy.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with a prevalence of 0.5–1.9%. Spinal inflammation is the hallmark of AS, causing pain and stiffness leading to progressive spinal deformity and fusion [1]. The disease affects both sexes, though especially men aged between 20 and 30 yrs and often remains under diagnosed [2]. Approximately one-third leave the workforce within 20 yrs of diagnosis [3]. Patients also have a higher mortality than the general population [4]. Poor socio-economic background, long disease duration and high disease activity level have recently been shown to be associated with functional impairment [5].

Until recently, therapies for AS have been limited, comprising mainly NSAIDs. DMARDs, such as SSZ and MTX, that have shown efficacy in RA, a peripheral joint disease, do not appear to have any effect on spinal inflammation in AS [6–8]. In the treatment of AS with MTX, there are four randomized controlled trials which give conflicting results. MTX was not shown to be superior to placebo in two studies for spinal inflammation in which low-dose oral preparations were used [9, 10], and no benefit was seen in axial inflammation with subcutaneous injection in another [11]. Only in one study was a better response seen in some composite index, and a higher percentage of patients with peripheral arthritis was included [12]. It has been argued that the lack of efficacy seen with MTX in the treatment of AS might be due to inadequate dosing with the oral preparation.

Recent clinical trials targeting inhibition of the pro-inflammatory cytokine TNF-α have shown high efficacy in patients with AS. Active AS patients receiving the anti-TNF-α antibody infliximab have significant improvement in signs and symptoms [13]. This response was maintained for initially 1 yr [14], then 2 yrs [15] and now 3 yrs [16] in an open-label extension phase of the study. In all of these studies, infliximab was used as monotherapy. In one randomized, controlled study in which a combination of MTX and infliximab was used, the addition of MTX did not sustain the response of infliximab (see subsequently) [17].

In contrast to patients with RA, improved efficacy was seen when infliximab was used in combination with MTX compared to either drug being used alone [18]. A related study on the treatment of patients with Crohn's disease with infliximab suggested that concomitant treatment with AZA, MTX or glucocorticoids can prevent the production of anti-infliximab antibodies [19]. Recent studies suggest that the efficay of infliximab is related to the trough in serum infliximab levels due to the formation of anti-infliximab antibodies [20, 21]. One study suggests that there was an increase in efficacy [22] while two studies showed no improvement [17, 23]. It is therefore not clear if the enhanced clinical benefit that is seen in RA and Crohn's disease would be seen in subjects with AS with the addition of MTX.

The first part of our study aims at addressing the question of safety and efficacy in patients on combination treatment of infliximab and MTX in AS utilizing clinical parameters and MRI as an indicator of response. MRI is a sensitive imaging investigation that allows assessment of soft tissue and bone inflammation and disease activity [24]. The second part of our study aims to investigate the therapeutic effects of oral MTX (15 mg weekly) in patients with active AS.

In the study by Marzo-Ortega *et al.* [17] in which two groups of patients with AS were randomized to receiving either MTX and infliximab combination or MTX and placebo combination, their MTX and infliximab group failed to show extension of the dosing interval of infliximab; however, all patients in our study took MTX or placebo for 16 weeks before they received infliximab to ensure that a steady state of MTX had been reached. The dosage of MTX in our study was much higher at 15 mg/week (except the

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comparator arm did not have MTX), and both groups received infliximab. We compared the proportion of patients in each group achieving clinical response and not the prolongation of infliximab dosing interval. Because both arms in our study received infliximab, MRI imaging analysis between groups was possible.

Patients and methods

Study design and randomization

This study was designed as a 30-week, single-centre, randomized, double-blind placebo controlled trial examining (i) efficacy of a combination of MTX with infliximab to treat AS, and (ii) the efficacy of oral MTX. This study had the approval of the local research ethics committee. All subjects gave written informed consent. Randomization was performed by a computer generated number and kept by the School of Pharmacy, The Chinese University of Hong Kong and the nature of the coded study medications were not revealed to the patients or the assessors. Half of the subjects were in the MTX–infliximab group and the other half in the placebo group. Outcome criteria used were criteria established by an international consortium of experts, the Assessments in Ankylosing Spondylitis (ASAS) Working Group [25] and MRI assessment pre- and post-treatment.

Study drugs

Oral MTX tablets (2.5 mg each) and placebo were supplied by School of Pharmacy, The Chinese University of Hong Kong; the placebo tablets were designed to match the colour, appearance and taste of the MTX tablets. All subjects were provided with oral MTX or placebo with folic acid 5 mg daily coverage at week 0 to week 22. MTX was started at a dose of 7.5 mg weekly with an incremental dose of 2.5 mg every 2 weeks up to a total dosage of 15 mg by week 6. Infusion of infliximab (5 mg/kg in 250 ml 0.9% NaCl) was prepared by the researchers under aseptic conditions. The infusion regime was administered at weeks 16, 18 and 22.

Subjects

Participants eligible for the study were recruited from the rheumatology clinic at Prince of Wales Hospital, Hong Kong and were required to fulfil the modified New York criteria for AS [26], be older than age 18, be able to give consent and have active disease. Disease activity was measured using a set of visual analogue scales (VAS) on which patients rated severity of their symptoms from 0 (none) to 100 (most severe) in four symptom domains: (i) spinal inflammation; (ii) back pain; (iii) patient global assessment of disease activity; and (iv) physical function, which are the core set of the domains recommended by the ASAS Working Group [25, 26]. Active disease was defined as an average score $\geq$30 for spinal inflammation and a score $\geq$30 on at least two of the other three domains.

Patients were excluded if they were pregnant, had previously used biologic agents, DMARDs other thanHCQ, SSZ, MTX or prednisolone >7.5 mg or the equivalent daily; or had changed dose of NSAIDs within 4 weeks of baseline. All DMARDs were discontinued for 4 weeks before patients were randomized. In addition, subjects with known chronic infection, hepatitis, pneumonitis, alcohol or drug abuse, serious infection within past 3 months, a history of malignancy; haemoglobin level <8.5 gm/dl, white blood cell count $<3.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l, serum creatinine >150 μmol/l, serum alanine transaminase (ALT) 1.25 times the upper limit of normal or alkaline phosphatase >2 times the upper limit of normal were also excluded. Prior to the beginning of the study, chest X-ray and 5-TU purified protein derivative (PPD) skin test were performed. Those with a PPD skin test of >5 mm were started on tuberculosis prophylaxis with isonizide 300 mg and piridoxine daily for 9 months.

MRI

MRI examination of the spine was performed at baseline and 30 weeks. MRI examinations were performed on a 1.5 T imaging unit (Siemens Sonata, Siemens Limited, Germany), using a synergy spine coil and the patient in a supine position. Coverage extended from the base of skull to below the sacrum in two sections, namely base of skull to T10 followed by T8 to sacrum. Sagittal pre-contrast T1-weighted turbo spin-echo (TE 19 ms, TR 500 ms, 3 mm thickness, field-of-view 380 mm, matrix 512×512), T2-weighted short-tau inversion recovery (STIR) fat-suppressed (TE 77 ms, TR 3240 ms, 3 mm thickness, field-of-view 380 mm, matrix 256×256) and post-contrast sagittal T1-weighted spectral pre-saturation with inversion recovery (SPIR) fat-suppressed sequences (TE 9.6 ms, TR 570 ms, 3 mm thickness, field-of-view 380 mm, matrix 256×512) were performed. For contrast enhancement a bolus of gadoteric acid (Dotarem; Guerbet, Aulnay, France) at a concentration of 0.15 mmol/kg body weight was injected intravenously through a forearm or hand vein. No dynamic imaging was performed.

Assessment of efficacy and outcome

Subjects were seen for clinical evaluation at baseline at week 0, weeks 8, 16, 18, 22 and 30. The clinical response to inflximab was evaluated chiefly on the basis of response criteria recommended by the ASAS Working Group [25], which covered the four domains used in this study to assess disease activity at enrolment, namely spinal inflammation, back pain, patient global assessment and physical function. Spinal inflammation was scored as the average of two VAS questions regarding the duration and intensity of morning stiffness, as for the previously validated six-item Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [27]. Pain was scored as the average of two VAS questions about total back pain and nocturnal back pain. Patient global assessment was measured by VAS. Functional impairment was assessed by the 10-item Bath Ankylosing Spondylitis Functional Index (BASFI), a validated VAS-based composite of functional ability in patients with AS [28].

The primary efficacy end-point was the percentage of ASAS20 responders after 30 weeks of treatment. ASAS20 responders were patients who reported improvements of at least 20% and absolute improvement of at least 10 U in at least three of the four symptom domains, with no worsening in the remaining domain. Secondary end-points consisted of symptom improvement in individual ASAS domains and improvements in BASFI, BASDAI, CRP and Schober test at week 30, ASAS40 responders and lastly, the efficacy including partial remission [25] of MTX at week 16.

Safety analyses

Safety was monitored until the end of week 30 of the trial, whether or not the patient was continuing with trial medication. Adverse events observed by assessors at a study centre, reported by the patient at or between visits, or elicited from the patient by questioning and blood or urine tests performed at each visit were recorded. Serious side-effects including hepatotoxicity (ALT values >2 times upper limit of normal for at least 2 weeks) or thrombocytopenia (platelet count $<100\,000/mm^3$), leucopenia (white blood cell count $<3000/mm^3$), severe infections requiring hospitalization or renal toxicity (serum creatinine >150 μmol/l) resulted in premature termination of the trial.

MR image analysis

MR images were scored independently at the end of the study by two readers blinded to the patient name and date of examination. Pre- and post-treatment examinations were mixed to ensure that readers were not aware of whether the examination being evaluated was obtained pre- or post-treatment. MR images were

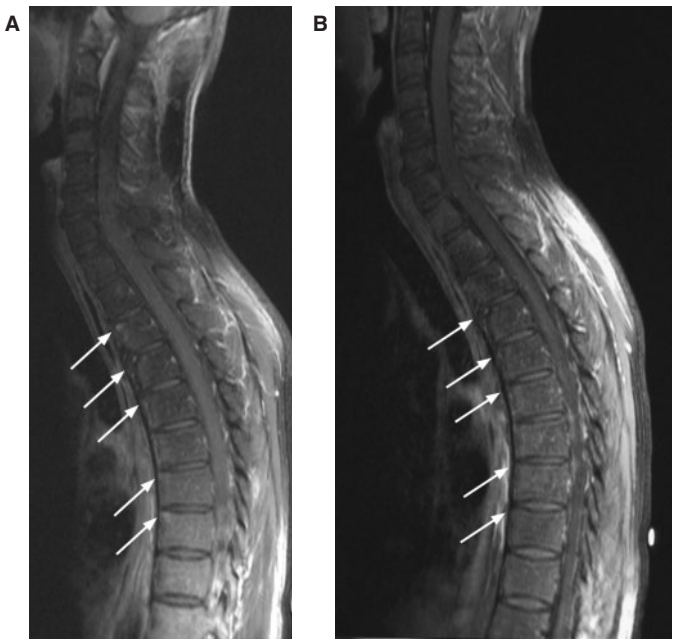

FIG. 1. Sagittal T1-weighted fat-suppressed post-contrast MR images of cervicothoracic spine.

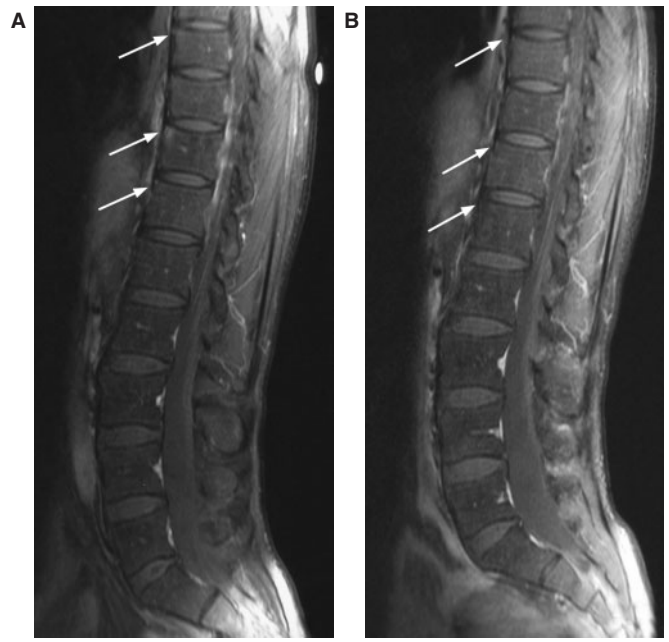

FIG. 2. Sagittal T1-weighted fat-suppressed post-contrast MR images of lumbar spine.

analysed using an MR-based scoring system specifically designed for AS spondyloarthopathy [29]. This scoring system separately grades active disease changes (erosions, oedema and inflammation) and chronic disease changes (sclerosis, squaring, syndesmophytes, spondylodiscitis, erosions, vertebral bridging and fusion) at each vertebral unit in turn [29]. A vertebral unit is defined as the area between two virtual horizontal lines through the middle of two adjacent vertebrae [29]. With 23 vertebral units being assessed, the total MRI Activity Score for the spine from C2 to S1 (23 vertebral units) ranged from 0 to 138. The mean of both readers' scores was used in the analysis. Summation of the individual vertebral units yielded a global activity score and a global chronic score for each patient's spine examination (Figs 1 and 2).

Statistical analysis

Primary efficacy measurement was the number of patients exhibiting an ASAS20 response to treatment at week 30. In a previous study, 53% of patients who received MTX achieved a composite 20% response compared with 17% of placebo-treated patients. Group sample sizes of 19 and 19 achieve 80% power to detect a difference of 0.468 between the null hypothesis that both group proportions are 0.638 and an alternative hypothesis that the proportion in Group 2 is 0.17 using a two-sided chi-square test with continuity correction and with a significance level of 0.05.

Analysis was by intention-to-treat. For the purposes of this analysis, patients who were unable to complete the 30 weeks of the trial for any reason (e.g. discontinuation of medication at their own or their physician's request or as a result of an adverse event) were considered non-responders from the day of withdrawal from the study. To include the participants who did not complete, when comparing the means at week 30, the last observation carried forward method was applied.

The proportions of patients responding to treatment according to ASAS criteria, as well as categorical demographic and safety variables, were compared among treatment groups using chi-square test or Fisher's exact test where appropriate. Paired *t*-test was used for changes in individual ASAS items. Student's *t*-test or Mann–Whitney U-tests were used for continuous variables where appropriate. Mantel–Haenszel chi-square test was used to assess for percentage improvement in MR activity score between the two treatment cohorts. All computations were performed using SPSS software (SAS Institute, Cary, NC, USA). All *P*-values are two-sided, and a *P*-value <0.05 will be considered statistically significant.

Results

All 38 subjects were randomized, 19 to receive MTX and 19 to receive placebo for 22 weeks. The baseline characteristics of patients in both groups are shown in Table 1. There were three dropouts: one at week 0 for protocol violation, and one each at weeks 8 and 16 who were lost to follow-up. A total of 35 subjects completed the study at week 30 (Fig. 3).

In the intention-to-treat-analysis (Table 2), at week 18, 22, 30, ASAS20 responses in the MTX group were 31.6, 52.6 and 63.2% *vs* 21.1, 57.9 and 68.4%, respectively in the placebo group without any significant differences between the two groups at any time points. Beyond week 30, ASAS20 response at week 38 in MTX group was 31.6% *vs* 36.8% in placebo group; $P=0.736$).

At weeks 18, 22, 30, ASAS40 responses in MTX group were 10.5, 5.3 and 26.3% *vs* 15.8, 26.3 and 26.3%, respectively in the placebo group without any significance differences between the two groups at any time points.

The partial remission at weeks 18, 22, 30 in MTX group was 55.6, 63.2 and 78.9% *vs* 27.8, 63.8 and 78.9%, respectively in the placebo group without any significance differences between the two groups at any time points.

There were significant improvements in pain, inflammation, patient global assessment, BASFI, BASDAI, CRP and Schober test at week 30 in both MTX and placebo groups ($P=0.03$, 0.05, 0.002, 0.036 and 0.03, 0.00, 0.06, 0.02, 0.01, respectively) but the differences between the two groups were not statistically significant.

The ASAS20 response at week 16 was 5.4% in the MTX group and 15.8% in the placebo group with no significant difference between the two groups ($P=0.29$). The partial remission at week 16 in MTX group and the placebo group was 15.8 and 15.8%, respectively with no significant difference between the two groups.

TABLE 1. Demographic and baseline characteristics of all patients

	Placebo	MTX
Age (yrs), mean (S.D.)	36.4 (9.9)	37 (10.9)
Men, *n* (%)	15 (79)	17 (89)
Duration of disease in yrs, mean (S.D.)	11.1 (6.7)	12.1 (10.4)
Weight (kg), mean (S.D.)	58.9 (11.4)	58.1 (10.4)
BASFI score, mean (S.D.)	4.7 (2.4)	4.2 (2.0)
BASDAI score, median (IQR)	6.3 (4.9–7.6)	6.6 (4.9–7.3)
Patients with BASDAI > 40, *n* (%)	17 (89.5)	16 (84.2)
VAS patient global assessment, median (IQR)	60 (50–70)	50 (40–60)
VAS inflammation, median (IQR)	61.1 (42.5–77.5)	60 (47.5–70)
VAS back pain, median (IQR)	70 (60–80)	70 (50–80)
CRP level (mg/l), median (IQR)	18.9 (4.1–42.9)	15.3 (8.7–21.7)
ESR (mm/h), median (IQR)	29.0 (19–49)	27.0 (13.5–39)
Patients with elevated CRP, *n* (%)	19 (100)	18 (94.7)
Patients with elevated ESR, *n* (%)	12 (63.2)	12 (66.7)
Modified Schober's test, median (IQR)	1.3 (0.5–3.5)	1.2 (0.75–2.0).
Chest expansion (cm), median (IQR)	2.7 (2.0–6)	3.5 (2.5–6)
Lateral lumbar flexion (cm), median (IQR)	9.7 (5.9–11.8)	8.0 (4.5–11.6)
Occipital-to-wall measurement (cm), median (IQR)	1.8 (0–10.1)	2.0 (0–9.0)
Tragus-to-wall measurement (cm), median (IQR)	8.3 (5.9–11.8)	7 (4.5–11.8)
Patients with hip involvement, *n* (%)	8 (44.4)	5 (55.6)
Concomitant use of oral NSAID, *n* (%)	18 (95)	19 (100)

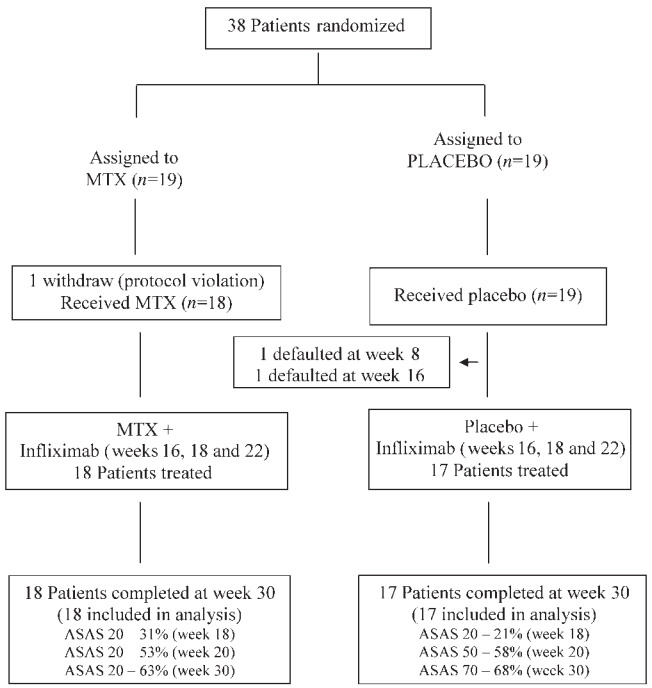

FIG. 3. Disposition of patients from enrolment to week 30.

Thirty-one (82%) of the 38 patients completed the MRI study. Overall chronicity score at baseline was 16.2 ± 8.3 while overall activity score at baseline was 10.1 ± 7.02. Following treatment, the overall activity score improved to 6.5 ± 5.5 yielding an overall improvement in activity score of 36.4% between baseline and post-treatment assessments. The MRI activity score (based on erosions, oedema and inflammation) in the MTX and infliximab combination improved more than the infliximab alone group but was statistically not significant ($P = 0.062$; Fig. 4).

Safety results

Combination of MTX and infliximab was generally well tolerated. Most adverse events were mild. There were 13 adverse events in the placebo group and 15 in MTX group and most of them were mild. Three patients developed infusion reaction which was transient in nature manifested as shortness of breath. Epigastric discomfort, insomnia, eye pain and palpitation occurred in MTX group. The others were cough, headache, diarrhoea, tiredness fungal skin infection and mild derangement in liver function, occurring in placebo group only. There were no cases of tuberculosis. One patient developed cough with bloody sputum at week 22, which was subsequently found to be due to mycetoma with *Scedosporium apiospermum*. He was initially treated medically but eventually underwent open left upper lobectomy and died 3 months after surgery from respiratory failure.

Discussion

The role of MTX in AS is not well defined although it is used successfully in RA. For this reason, our study was initiated based on the evidence from current studies that (i) MTX may be effective in AS [12] and (ii) efficacy of infliximab may be enhanced by the addition of MTX [21]. Despite using a higher dosage of oral MTX, 15 mg weekly, our double-blind, randomized, placebo controlled study failed to demonstrate that MTX is effective in treating patients with AS. There was no statistically significant improvement in ASAS20 response, partial remission, disease activity, function indices after 16 weeks of MTX therapy. Our finding therefore is in agreement with a systemic review of previous studies in the management AS in which MTX was used [9–11, 30].

Although the safety of MTX and infliximab combination over a 6-month period has been demonstrated in a recent study [17], the efficacy of this combination has not been compared against infliximab monotherapy in AS. Our study is therefore the only double-blind, randomized controlled trial to assess if improved efficacy occurs if MTX is combined with infliximab *vs* placebo with infliximab. Our findings demonstrate that there were no statistical differences between the two groups with respect to ASAS20 and ASAS40 response, composite indices, inflammation, pain, activity and functional measures. However, our results suggest that infliximab is efficacious especially from 6 to 14 weeks from the time of administration with infliximab, thus confirming the immediate improvement known to occur with this drug. The addition of MTX to infliximab did not provide any sustained effect beyond week 30 indicating disease reactivation in both groups upon stopping infliximab infusion and would support the new guidelines of a 6 weekly infusion interval schedule [31].

There are two similar studies using combination of infliximab and MTX [22, 23]. In one study in abstract form, with 123 subjects, combination group patients received MTX 12.5 mg weekly for 4 weeks before three infusions of infliximab. Superior efficacy was not demonstrated in MTX and infliximab combinations as compared with infliximab alone [23]. However, another recent study showed that infliximab in combination with MTX increases the efficacy in AS patients at 30 weeks [22]. The methodology in this study is different as it is an open-label study and assessment of outcome using BASDAI 50, ASAS20 and ASAS50 response. It is not clear how long the subjects had to stop other disease-modifying agents before being recruited as two subjects on combination infliximab–MTX were also taking SSZ. Furthermore, the population of subjects may not all have idiopathic AS as some have underlying subclinical IBD. Nonetheless, the findings are significant and would require further validation in a larger double-blind randomized controlled trial.

The adverse effects of combination MTX and infliximab were reported to be well tolerated previously [17] and our findings again support this observation at an even higher dosage of MTX for

TABLE 2. Intention-to-treat analysis of clinical outcome at all end-points

Variable	MTX + infliximab						Placebo + infliximab						*P*-value
	Week 0	Week 8	Week 16	Week 18	Week 22	Week 30	Week 0	Week 8	Week 16	Week 18	Week 22	Week 30	
BASFI	4.0 (2.9–6.8)	51.4 (30–76)	4.89 (2.9–6.9)	4.3 (2.0–6.0)	3.86 (2.0–5.1)	3.82 (2.0–5.9)	4.4 (0.32–6.5)	40 (26–59)	3.9 (2.8–5.8)	3.9 (1.6–6.0)	3.1 (2.2–5.5)	2.9 (2.3–4.9)	NS
Inflammation	55 (47.5–60)	55 (47.5–72.5)	52.5 (52.5–72.5)	35.2 (37.5–72.5)	35 (27.5–45)	27.5 (22.5–37.5)	60 (45–60)	57.5 (48.8–67.5)	57.5 (42.5–72.5)	42.5 (22.5–62.5)	35 (15–52.5)	31.6 (8.8–42.5)	NS
Pain	70 (60–80)	70 (60–80)	70 (60–80)	50 (40–60)	40 (30–60)	30 (30–50)	70 (60–80)	50 (40–60)	70 (50–80)	40 (20–70)	40 (20–60)	30 (10–60)	NS
Patient global assessment	60 (50–70)	70 (50–70)	70 (50–70)	53.9 (40–70)	51.5 (40–60)	45.8 (30–50)	50 (40–60)	50 (40–60)	50 (40–60)	50 (30–70)	50 (30–50)	50 (30–50)	NS
BASDAI	62 (49–69)	60.5 (60–72.5)	63 (47.5–72.5)	51.5 (28.3–51.5)	45 (39–50)	37.5 (27.5–52.5)	60 (50.5–69.5)	59 (51.5–67)	61 (44.5–69)	47.3 (30.3–61)	42.5 (28.3–53)	30.5 (23–52.5)	NS
CRP(mg/l)	16.6 (7.1–28.1)	19 (19–28)	20.5 (10.9–35)	1 (1.0–1.3)	1 (1.0–2.4)	1.1 (1.0–4.9)	15.2 (4.4–25.9)	9.1 (3.9–19.1)	9.5 (5–18.6)	1 (1.0–2.8)	1 (1.0–1.3)	1 (1.0–1.3)	NS

Values are median (range); NS, not significant.

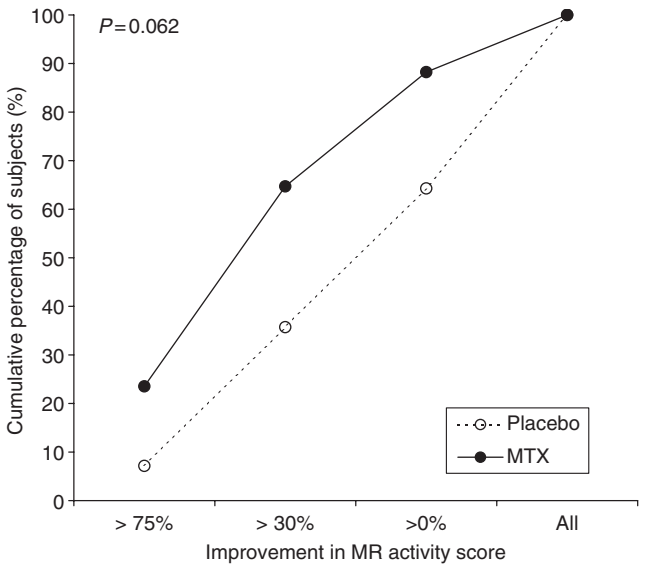

FIG. 4. MRI activity score (based on erosions, oedema and inflammation) in the MTX and infliximab combination improved more than the infliximab alone group but was statistically not significant.

treating AS than that used in other trials [32–34]. However, one patient in the placebo group with previous lung disease did succumb to severe pulmonary fungal infection. This serious adverse event once more highlights the need for vigilant surveillance of indolent or occult infections.

A limitation in our study needs to be considered in relation to the study design. The MTX/placebo was stopped at week 22 after the last infusion of infliximab instead of continuing until the end of the study at week 30. Whether a lengthened duration with MTX would have led to an extended interval in the MTX group before a disease flare is unknown though this is considered unlikely.

In conclusion, this study provides further evidence that MTX has no role in the treatment of the spinal manifestations of AS. It is also the first double-blind, randomized, placebo controlled trial showing no additional clinical or MRI improvement with the addition of MTX to infliximab in AS. Therefore, the combination of MTX and infliximab should be avoided, since association of MTX which has no efficacy and may have possible side-effects in the long term. One may postulate that this combination will not reduce the development of anti-infliximab antibodies. When this is established, the role of combination infliximab and MTX in AS will be even clearer.

Rheumatology key messages

- Combination MTX and infliximab is not more effective than infliximab monotherapy in the treatment of AS.
- MTX has no effect in the treatment of AS.

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References

1 Braun J, Bollow M, Remlinger G *et al.* Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41:58–67.
2 Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. Ann Rheum Dis 2001;60:199–206.
3 Boonen A, Chorus A, Miedema H *et al.* Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. Ann Rheum Dis 2001;60:353–8.
4 Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 1993;52:174–6.
5 Tam LS, Chan KY, Li EK. The influence of illness and variables associated with functional limitations in Chinese patients with ankylosing spondylitis. J Rheumatol 2007;34:1032–9.
6 Braun J, Sieper J. Therapy of ankylosing spondylitis and other spondyloarthritides: established medical treatment, anti-TNF-alpha therapy and other novel approaches. Arthritis Res 2002;4:307–21.
7 van der Horst-Bruinsma IE, Clegg DO, Dijkmans BA. Treatment of ankylosing spondylitis with disease modifying antirheumatic drugs. Clin Exp Rheumatol 2002;20(6 Suppl 28):S67–70.
8 Dougados M, Van der Linden S, Leirisalo-Repo M. Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. Arthritis Rheum 1995;38:618–27.
9 Altan L, Bingol U, Karakoc Y, Aydiner S, Yurtkuran M, Yurtkuran M. Clinical investigation of methotrexate in the treatment of ankylosing spondylitis. Scand J Rheumatol 2001;30:255–9.
10 Roychowdhury B, Bintley-Bagot S, Bulgen DY, Thompson RN, Tunn EJ, Moots RJ. Is methotrexate effective in ankylosing spondylitis? Rheumatology 2002;41:1330–2.
11 Haibel H, Brandt HC, Song IH *et al.* No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis 2007;66:419–21.
12 Gonzalez-Lopez L, Garcia-Gonzalez A, Vazquez-Del-Mercado M, Munoz-Valle JF, Gamez-Nava JI. Efficacy of methotrexate in ankylosing spondylitis: a randomized, double blind, placebo controlled trial. J Rheumatol 2004;31:1568–74.
13 Braun J, Brandt J, Listing J *et al.* Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187–93.
14 Braun J, Brandt J, Listing J *et al.* Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. Arthritis Rheum 2003; 48:2224–33.

15 Braun J, Brandt J, Listing J *et al.* Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis 2005;64:229–34.
16 Braun J, Baraliakos X, Brandt J *et al.* Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology 2005;44:670–6.
17 Marzo-Ortega H, McGonagle D, Jarrett S *et al.* Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64:1568–75.
18 Maini RN, Breedveld FC, Kalden JR *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552–63.
19 Baert F, Noman M, Vermeire S *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601–8.
20 de Vries MK, Wolbink GJ, Stapel SO *et al.* Inefficacy of infliximab in ankylosing spondylitis is correlated with antibody formation. Ann Rheum Dis 2007;66:133–4.
21 de Vries MK, Wolbink GJ, Stapel S *et al.* Decreased clinical response to infliximab in ankylosing spondylitis (AS) is correlated with anti-infliximab formation. Ann Rheum Dis 2007;66:1252–4.
22 Perez-Guijo VC, Cravo AR, Castro MD, Font P, Munoz-Gomariz E, Collantes-Estevez E. Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. Joint Bone Spine 2007;1:1.
23 Breban M, Ravaud P, Claudepierre P. No superiority of infliximab (INF) + methotrexate (MTX) over INF alone in the treatment of ankylosing spondylitis (AS): results of a one-year randomized prospective study. Arthritis Rheum 2005;52(Suppl. 9):S214.
24 Bollow M. [Magnetic resonance imaging in ankylosing spondylitis (Marie-Struempell-Bechterew disease)]. Rofo 2002;174:1489–99.
25 Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876–86.
26 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
27 Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
28 Calin A, Garrett S, Whitelock H *et al.* A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
29 Braun J, Baraliakos X, Golder W *et al.* Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 2003;48:1126–36.
30 Chen J, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database Syst Rev 2006(4):CD004524.
31 Braun J, Pham T, Sieper J *et al.* International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis [see comment]. Ann Rheum Dis 2003;62:817–24.
32 Sampaio-Barros PD, Costallat LT, Bertolo MB, Neto JF, Samara AM. Methotrexate in the treatment of ankylosing spondylitis. Scand J Rheumatol 2000;29:160–2.
33 Creemers MC, Franssen MJ, van de Putte LB, Gribnau FW, van Riel PL. Methotrexate in severe ankylosing spondylitis: an open study. J Rheumatol 1995;22:1104–7.
34 Biasi D, Carletto A, Caramaschi P, Pacor ML, Maleknia T, Bambara LM. Efficacy of methotrexate in the treatment of ankylosing spondylitis: a three-year open study. Clin Rheumatol 2000;19:114–7.