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ORIGINAL ARTICLE

Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial

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Abstract The superiority of the combination therapy of methotrexate (MTX) and anti-tumor necrosis factor (TNF) biological agents over anti-TNF monotherapy in MTX-naïve patients with rheumatoid arthritis (RA) has been demonstrated. We investigated the efficacy and safety of continuation versus discontinuation of MTX at the commencement of etanercept (ETN) in patients with active RA despite MTX therapy. In total, 151 patients with active RA despite treatment with MTX were randomized to either ETN 25 mg twice a week and MTX 6–8 mg/week (the E + M group) or ETN alone (the E group). Co-primary endpoints included the European League Against Rheumatism (EULAR) good response rate and the American College of Rheumatology (ACR) 50 response rate at week 24. Demographic and clinical features between groups at baseline were similar. The EULAR good response rates were significantly higher in the E + M group (52%) than in the E group (33%) at week 24 ($p = 0.0001$). Although the ACR50 response rate, one of the co-primary endpoints, and the ACR70 response rate at week 24 were not significantly greater in the E + M group (64 and 38%, respectively) than in the E group (48 and 26%, respectively), the ACR20 response rate was significantly greater in the E + M group (90%) than in the E group (64%; $p = 0.0002$). Safety profiles were similar for the groups. Thus, MTX should be continued at the commencement of ETN therapy, even in RA patients who show an inappropriate response to MTX.

Keywords ACR response · Anti-TNF · Biological agent · Combination therapy · EULAR response

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovitis affecting multiple joints of the hands, feet and many other mobile joints. Unless their disease activity is adequately controlled, patients with RA are likely to become disabled and short-lived due to joint destruction, extra-articular manifestations and accelerated atherosclerosis [1, 2]. Recent achievements in the management of RA have improved the activities of daily living (ADL) and the prognosis of RA patients. For the last decade, the mainstay of the management of RA has been early diagnosis and the introduction of methotrexate (MTX) therapy. In those refractory to MTX, the highest efficacy has been obtained by blockade of tumor necrosis factor (TNF) α activity with biological agents [2].

Etanercept (ETN) is a genetically engineered protein consisting of two molecules of the extracellular domain of TNF receptor II (p75) and the Fc portion of IgG1 [3]. ETN has been demonstrated to effectively reduce clinical signs and symptoms and the progression of joint damage, either as a monotherapy [3, 4] or a combination therapy with MTX [5]. Although the ETN plus MTX combination therapy produced a considerably better response than ETN monotherapy in RA patients refractory to disease-modifying anti-rheumatic drugs (DMARDs) other than MTX [6], the ETN + MTX combination therapy has not been shown to have superior efficacy compared to ETN monotherapy in patients with active RA despite MTX treatment [7].

Therefore, we are conducting the Japanese Etanercept Study on Methotrexate Resistance (JESMR), a prospective, randomized study aimed at examining whether the addition of ETN is a better option for RA patients whose disease activity has not been controlled with MTX than switching to ETN. Here, we report the 24-week results from this study. These results provide the first evidence of the beneficial effect of the combination of MTX with ETN over ETN alone, even in patients with active RA despite MTX therapy.

Methods

Patients

This prospective, randomized, 2-year, open-label study was conducted at 45 institutions in Japan between June 2005 and January 2007. The study protocol (ClinicalTrials.gov identifier: NCT00688103) was approved by an institutional review board or ethics committee. All patients provided written, informed consent according to the Declaration of Helsinki. Patients had to be at least 18 years of age, fulfill the 1987 revised classification criteria for RA from the American College of Rheumatology (ACR), meet the guideline for the proper use of ETN in Japan; have at least six tender joints and six swollen joints, and have either a serum C-reactive protein (CRP) level of more than 2 mg/dl or an erythrocyte sedimentation rate (ESR) of no less than 28 mm at 1 h, along with adequate safety profiles [8]. Patients also had to be ACR functional class I–III, receiving not less than 6 mg/week of MTX for a minimum of 3 months, and be dose stable for at least 4 weeks at the time of study enrollment. Patients who required concurrent use of prednisolone (PSL) >10 mg/day or its equivalent were excluded from the study. Other exclusion criteria not described in the above guideline include starting or increaseing the dose of PSL equivalents within 3 months of enrollment, undergoing anti-rheumatic therapy other than MTX and PSL equivalents, and previously receiving ETN or other biological treatments.

Procedures

Patients who had agreed to receive ETN for active RA were randomly assigned to continue MTX (6–8 mg/week, an approved dose in Japan), in other words MTX + ETN combination therapy, or discontinue MTX (switching to ETN monotherapy). Enrollment and randomization were performed on the University Hospital Medical Information Network (UMIN; Tokyo, Japan) on the website on the day on which the informed consent was received. Randomization was stratified by baseline age (<55 years or not), disease duration (<10 years or not), disease activity (DAS28 < 5.1 or not), and institution (difference of <3 in the number of enrolled patients between groups at each institute). Between June 2005 and January 2007, a total of 151 patients were enrolled in the JESMR study from 34 institutes in Japan. All of the patients enrolled were treated with ETN 25 mg as a subcutaneous injection twice weekly. Dose reductions of ETN were not permitted during the study. A temporary ETN dose interruption for up to 2 weeks was permitted if a mild or moderate toxicity event occurred that was not alleviated by therapeutic intervention. An MTX dose interruption of up to 2 weeks was permitted after an adverse event thought to be related to MTX.

The co-primary endpoints of the JESMR study were a good response according to the European League Against Rheumatism (EULAR) criteria, as based on the disease activity score with 28 joints (DAS28), and the ACR50 response rate at week 24 (using the last observation carried forward method), as well as radiographic progression as assessed by van der Heijde–modified Sharp score at week 52. Secondary endpoints included the proportion of patients in each treatment group achieving response rates of ACR20 and ACR70, and the DAS28 remission rate at week 24.

Safety assessments included vital signs and other physical examinations, and blood and urine analysis at screening, baseline and weeks 4, 8, 12 and 24. Adverse events and concomitant drugs were recorded throughout the study.

Statistical analysis

The primary analysis was conducted on an intention-to-treat population. Efficacy analyses included all patients who took the study drugs and had a valid baseline and at least one on-therapy value for each end point. Last observation carried forward values were used for missing data points. All of the analysis was performed by CMIC Co., Ltd. Data Center (Osaka, Japan). The proportions of participants who met the given criteria were compared with Fisher's exact test, while the mean values between groups were compared with the Mann–Whitney *U* test.

Results

Baseline characteristics

A total of 151 patients were enrolled in the JESMR study, of whom 74 were allocated to the ETN group (the E group) and 77 to the ETN + MTX group (the E + M group). Four patients were withdrawn from the study before the start of treatment, leaving 147 patients for the safety analysis (Fig. 1). Efficacy analysis was performed for 142 patients for whom sufficient clinical data were available. Sixteen patients (twelve in the E group and four in another) were withdrawn from the study by week 24 for the reasons given in Fig. 1. Demographic and baseline disease characteristics were generally comparable between treatment groups (Table 1). More than 80% of the patients were female. Average ages were approximately 57 years, disease durations were around 9 years, and arthritic signs and symptoms were similarly severe. Rheumatoid factor was positive in 91.5 and 86.7% of patients in the E group and the E + M group, respectively. Mean doses of MTX and PSL at enrollment were similar between groups: 7.0 mg/week and 2.3 mg/day, respectively, in the E group, and 7.4 mg/week and 3.3 mg/day, respectively, in the E + M group. Most of the patients had been receiving MTX for more than 6 months, except for eight and three patients in the E group and the E + M group, respectively. Notably, only 37.7 and 52.1% of the patients had been receiving supplementary folic acid in the E group and the E + M group, respectively.

Efficacy analysis

At week 24, the EULAR good response rate was 52.1% in the E + M group, which was significantly greater than its value (33.3%) in the E group (Table 2). In addition, the ACR50 response rates were 64.4% in the E + M group and 47.8% in the E group, respectively ($p = 0.06$; Table 3). Thus, one of the two co-primary endpoints at week 24 was met. According to a nonresponder imputation analysis, ACR50 response rates at 24 weeks were 60.3% in the E + M group and 44.9% in the E + M group, respectively ($p = 0.09$).

As shown in Table 2, the EULAR response rate was significantly better in the E + M group than the E group as early as week 4 (good responses in 31.5 and 17.4%, respectively, $p = 0.04$) and thereafter. Moreover, laboratory tests such as ESR and CRP showed significantly better results in the E + M group than the E group at week 24

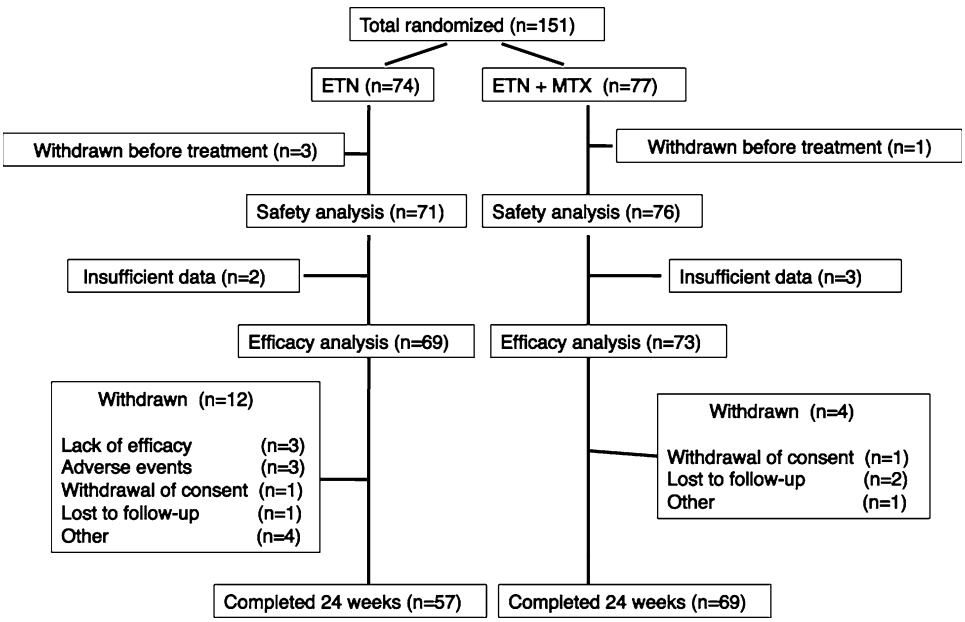

Fig. 1 Patient disposition data through week 24. A total of 151 patients were enrolled, 74 in the E group and 77 in the E + M group, and 126 patients completed 24 weeks per protocol

Table 1 Patient characteristics

	ETN ($n = 71$)	MTX + ETN ($n = 75$)	p value
Age (years)			
<55	24 (33.8)	27 (36.0)	0.863
≥55	47 (66.2)	48 (64.0)	
	58.1 ± 12.6	56.5 ± 11.1	0.213
Gender			
Male	9 (12.7)	15 (20.0)	0.269
Female	62 (87.3)	60 (80.0)	
Body weight (kg)	51.0 ± 8.4	54.6 ± 11.3	0.057
Disease duration (years)			
<10	45 (63.4)	52 (69.3)	0.486
≥10	26 (36.6)	23 (30.7)	
	10.6 ± 10.5	8.1 ± 7.7	0.234
Morning stiffness (min)	181.6 ± 325.0	196.1 ± 332.5	0.834
Tender joint count (68 assessed)	15.0 ± 9.4	14.9 ± 8.0	0.624
Swollen joint count (66 assessed)	12.5 ± 6.1	12.6 ± 6.5	0.870
Physician global assessment (scale of 0–100)	58.2 ± 21.5	58.2 ± 19.3	0.983
Patient global assessment (scale of 0–100)	62.9 ± 20.4	53.2 ± 23.6	0.014
Patient assessment of pain (scale of 0–100)	58.7 ± 22.4	53.0 ± 23.7	0.160
HAQ-DI	1.3 ± 0.8	1.2 ± 0.7	0.497
ESR (mm/1 h)	59.7 ± 28.4	59.5 ± 26.5	0.820
CRP (mg/dl)	2.5 ± 2.5	3.0 ± 3.2	0.347
Positive rheumatoid factor	65 (91.5)	65 (86.7)	0.431
MTX (mg/week)	7.0 ± 1.4	7.4 ± 1.1	0.099
Concomitant folic acid	26 (37.7)	38 (52.1)	0.094
Concomitant corticosteroids	32 (46.4)	44 (60.3)	0.130
(mg/day)	2.3 ± 3.0	3.3 ± 3.1	0.051

Except where indicated otherwise, values are the mean ± SD at study enrollment

There were no significant differences between groups except in patient global assessment values, for which the p value was 0.026

VAS visual analogue scale, *HAQ-DI* health assessment questionnaire–disability index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

Table 2 EULAR response and remission rates

	ETN ($n = 69$)			ETN + MTX ($n = 73$)			p value
	Good	Moderate	No	Good	Moderate	No	
2 weeks	7.2	58.0	34.8	15.1	61.6	23.3	0.16
4 weeks	17.4	56.5	26.1	31.5	56.2	12.3	0.04
8 weeks	17.4	63.8	18.8	37.0	56.2	6.8	0.01
12 weeks	21.7	50.7	27.5	42.5	50.7	6.8	0.001
24 weeks	33.3	37.7	29.0	52.1	43.8	4.1	0.0001

Values are %, except for p values for the proportion of good, moderate and no response rates between groups

(Table 3). However, various clinical variables such as tender/swollen joint count, patient global assessment, and HAQ-DI score were not sensitive enough to distinguish between treatment groups for a period of 24 weeks. In terms of comprehensive assessments, the ACR20 response rate was as high as 90.4% in the E + M group versus 63.8% in the E group ($p = 0.0002$ between groups) at week 24. Notably, the ACR20 response rate was 65.8% in the E + M group, which was significantly greater than that in the E group (47.8%; $p = 0.04$) as early as week 2 (data not shown). Similarly, the DAS28 score decreased from 6.0 (95% CI 5.8–6.2) at baseline to 3.9 (95% CI 3.6–4.1) at week 4, and to 3.3 (95% CI 3.0–3.5) at week 24 in the E + M group, while it decreased from 6.1 (95% CI 5.9–6.4) at baseline to 4.4 (95% CI 4.1–4.7) at week 4 and to 4.1 (95% CI 3.8–4.5) at week 24 (Fig. 2a). Thus, the DAS28 score was significantly lower in the E + M group than the E group at weeks 4 ($p = 0.02$), 8 ($p = 0.009$), 12 ($p = 0.001$) and 24 ($p = 0.0003$) with the Mann–Whitney U test. The improvement in the disease activity was also evaluated by the handy RA activity score with 38 joints (HRAS38), in which the cut-off values for low disease activity and high disease activity are 50 and 100, respectively [9]. The HRAS38 score is the cumulative sum of a global assessment of disease activity by the patient (0–100), a swollen joint score graded from 0 to 3 based on a 38-joint assessment by a physician (0–114), and the serum CRP level (mg/l). The HRAS38 score decreased from 103.6 (95% CI 92.1–115.2) at baseline to 51.8 (95% CI 43.9–59.7) at week 2, 43.9 (95% CI 35.9–51.9) at week 4, and 30.8 (95% CI 25.2–36.5) at week 24 in the E + M group, while it decreased from 107.6 (95% CI 97.4–117.7)

Table 3 Comparison of clinical efficacy between treatment groups

	ETN ($n = 69$)			MTX + ETN ($n = 73$)			p value at 24 weeks between groups
	0 week	24 weeks	p value	0 week	24 weeks	p value	
Tender joint count (68 assessed)	15.0 ± 9.4	4.5 ± 8.0	<0.0001	15.1 ± 8.1	2.4 ± 3.9	<0.0001	0.119
Swollen joint count (66 assessed)	12.4 ± 6.1	4.3 ± 5.2	<0.0001	12.5 ± 6.5	3.0 ± 3.8	<0.0001	0.109
Patient global assessment	62.5 ± 20.5	31.5 ± 28.4	<0.0001	53.7 ± 23.7[a]	21.6 ± 18.8	<0.0001	0.138
HAQ-DI	1.3 ± 0.8	0.9 ± 0.8	<0.0001	1.2 ± 0.7	0.7 ± 0.6	<0.0001	0.208
ESR (mm/1 h)	59.7 ± 28.4	41.6 ± 25.4	<0.0001	59.5 ± 26.5	29.9 ± 23.3	<0.0001	0.001
CRP (mg/dl)	2.5 ± 2.5	1.2 ± 1.7	0.0002	3.0 ± 3.2	0.6 ± 1.0	<0.0001	0.002
DAS28 < 3.2 (%)	0	33.7	–	0	52.1	–	0.028
DAS28 < 2.6 (%)	0	10.1	–	0	27.4	–	0.010
ACR20 responder (%)	–	63.8	–	–	90.4	–	0.0002
ACR50 responder (%)	–	47.8	–	–	64.4	–	0.063
ACR70 responder (%)	–	26.1	–	–	38.4	–	0.152

Except where indicated otherwise, values are the mean ± SD

[a] A significant difference between groups was observed at week 0 (~4 weeks after the enrollment shown in Table 1) for patient global assessment value, for which the p value was 0.025

at baseline to 66.1 (95% CI 57.3–75.0) at week 2, 58.8 (95% CI 49.6–68.0) at week 4 and 54.2 (95% CI 43.7–64.6) at week 24 (Fig. 2b). Thus, the HRAS38 score was significantly lower in the E + M group than the E group as early as week 2 ($p = 0.014$). Furthermore, the low disease activity rate (DAS28 < 3.2) and the remission rate (DAS28 < 2.6) at week 24 were significantly higher in the E + M group than in the E group (52.1 vs. 33.7%, $p = 0.028$; and 27.4 vs. 10.1%, $p = 0.010$, respectively; Table 3). These findings clearly show that ETN + MTX combination therapy has a greater efficacy than ETN monotherapy in RA patients who show an inadequate response to a similar or greater dose of MTX.

Safety analysis

Safety profiles between the two treatment groups were comparable. Most of the adverse events reported were minor, such as upper airway tract infection and injection site reaction (Table 4). Serious adverse events were reported for two patients in the E + M group (one case each of cellulitis and bone fracture) and for one in the E group (bone fracture). No development of tuberculosis or malignancies was observed. Thus, continuation of MTX after the commencement of ETN did not result in the development of more frequent or severe adverse events.

Discussion

Although only one of two co-primary endpoints at week 24 was met, many of the variables shown in Table 3 support the continuation of MTX as a better choice than its discontinuation at the initiation of ETN treatment in patients with active RA despite MTX therapy. As shown in the JESMR study, the ACR20 response rate is more discriminative between two treatment groups ($p = 0.0002$). We chose ACR50 as a primary endpoint because of its clinical importance, and the EULAR good response rate because of its concordance with patient satisfaction (reflecting both a significant response to the therapy and a currently acceptable disease state) in daily clinical practice. Taken together with the results from the TEMPO study [6], combination therapy with ETN + MTX provides active RA patients with a better outcome than ETN monotherapy, regardless of their prior use of MTX or their response to MTX.

The question of whether a DMARD which has failed to control disease activity should be continued or discontinued when another therapeutic agent is initiated has long been a controversial issue [10]. The BeSt study did not prove the superiority of step-up combination therapy to sequential monotherapy [11]. Theoretically, an existing DMARD that has shown sufficient tolerability may be continued when either a partial response to the DMARD has been observed or a positive rather than a negative additive/synergistic effect with the new agent can be expected. One randomized controlled trial comparing the addition of ETN with switching to ETN in inadequate responders to sulfasalazine failed to demonstrate the overall superiority of the combination therapy [12]. On the contrary, the TEMPO study clearly demonstrated the superior efficacy and comparable safety of ETN + MTX combination therapy compared with either MTX or ETN monotherapy in basically MTX-naïve patients with RA

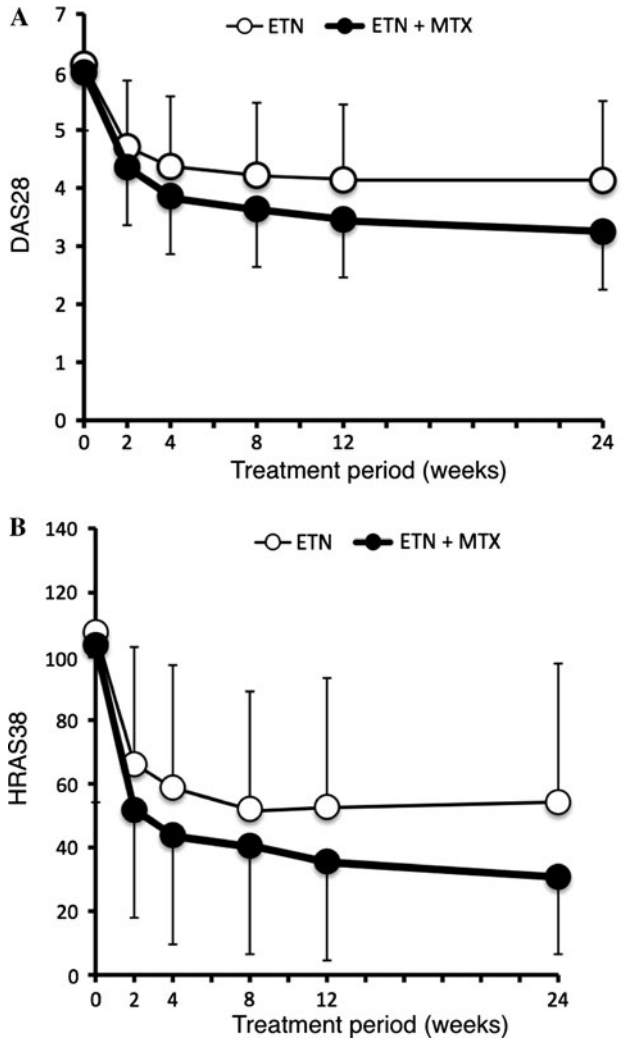

Fig. 2 Mean improvements in DAS28 (**a**) and HRAS38 (**b**). **a** The DAS28 score was significantly lower in the E + M group ($n = 73$; *solid circles*) than the E group ($n = 69$; *open circles*) at weeks 4 ($p = 0.02$), 8 ($p = 0.009$), 12 ($p = 0.001$) and 24 ($p = 0.0003$) with the Mann–Whitney *U* test. *Vertical error bars* indicate SD. **b** The HRAS38 score was significantly lower in the E + M group ($n = 73$; *solid circles*) than the E group ($n = 69$; *open circles*) at weeks 2 ($p = 0.014$), 4 ($p = 0.015$), 12 ($p = 0.012$) and 24 ($p = 0.003$) with the Mann–Whitney *U* test. *Vertical error bars* indicate SD

[6, 13]. In the present study, we demonstrated, for the first time, that the addition of ETN to MTX is a better choice than switching to ETN in active RA patients despite MTX therapy.

The ADORE study, reported in 2006, was the first clinical trial to examine the efficacy and safety of ETN + MTX versus ETN alone in active RA patients with an inadequate response to MTX [7]. As in the present study, the incidence of severe infections in the two treatment groups was comparable. In contrast, however, the ADORE study failed to demonstrate the superior efficacy of ETN + MTX combination above ETN monotherapy.

Table 4 Adverse events

System organ class	ETN ($n = 71$)	ETN + MTX ($n = 76$)
Blood and lymphatic system disorders	2	0
Gastrointestinal disorders	3	4
General disorders and administration site conditions	13	7
Hepatobiliary disorders	1	2
Infections and infestations	22	23
Injury, poisoning and procedural complications	1	2
Metabolism and nutrition disorders	0	1
Musculoskeletal and connective tissue disorders	1	0
Nervous system disorders	2	2
Reproductive system and breast disorders	0	1
Respiratory, thoracic and mediastinal disorders	2	2
Skin and subcutaneous tissue disorders	8	3
Total adverse events	55	47
Total serious adverse events	1	2

Values are numbers of events

Possible reasons may be the relatively short observation period (16 weeks) and the gradual dose reduction of MTX over a month. On this basis, a carryover effect of MTX is likely to affect the results. Indeed, significant differences in some of the present efficacy assessments, such as DAS28 remission, were observed at week 24 but not at week 12, regardless of the abrupt discontinuation of MTX at the initiation of ETN in the E group. Furthermore, two of three patients in the E group who had discontinued this study due to lack of efficacy (Fig. 1) were successfully treated with ETN + MTX combination thereafter (data not shown).

Our study has a few limitations. First, the study is not a double-blind one. Therefore, one may assume that awareness of the treatment affects the evaluations by physicians and by patients. However, the changes in acute phase reactants stand against that possibility (Table 3). For example, the mean serum level of CRP decreased from 2.5 at baseline to 1.0 at week 8 and to 1.2 at week 24 in the E group, while it decreased from 3.0 at baseline to 0.8 at week 8 ($p = 0.02$ vs. the E group) and 0.6 at week 24 ($p = 0.002$ vs. the E group) in the E + M group. Similarly, the mean ESR decreased from 59.7 at baseline to 41.5 at week 8 and to 41.6 at week 24 in the E group, while it decreased from 59.5 at baseline to 29.1 at week 8 ($p = 0.0004$ vs. the E group) and 29.9 at week 24 ($p = 0.001$ vs. the E group) in the E + M group. Second, the dose of MTX approved by the Japanese Ministry of Health, Labour and Welfare is only 6–8 mg/week [14], although, concordantly, the use of supplementary folic acid

is also limited to approximately half of the patients receiving MTX. However, the overall efficacy at this dose in Japanese RA patients is acceptable, as previously described: remission in 11% and non-remission improvement (at least 50% improvement in arthritis and serum CRP level) in 41% [14]. Moreover, the clinical and radiographic efficacy of infliximab added to MTX 7–9 mg/week in Japan [9, 15–17] was comparable to that seen in ATTRACT [18, 19] and ASPIRE studies [20]. Because of the lack of available data concerning MTX doses in Japanese RA patients living abroad, it has not yet been determined whether a similar dose of MTX to that used in many other countries (10–25 mg/week) is also appropriate for Japanese RA patients.

With regard to observational registries, ETN + MTX combination therapy resulted in a better response than ETN monotherapy in the Stockholm TNFα Follow-Up Registry (STURE) [21] and the British Society for Rheumatology Biologics Register [22]. Given that the PREMIER study clearly demonstrated the superiority of adalimumab + MTX combination therapy to adalimumab or MTX monotherapy, the additive or synergistic effects of MTX and an anti-TNFα biological agent are not restricted to ETN [23]. In addition, ETN with continuous MTX was very recently reported to be more efficacious than ETN with MTX tapered and discontinued in patients with MTX-refractory active psoriasis (not less than 3 months; not less than 7.5 mg/week, 13–14 mg/week for 83–90 kg of body weight on average) [24].

In conclusion, these 24-week data from the JESMR study demonstrate the superior clinical efficacy and comparable safety of the continuation of MTX compared to the discontinuation of MTX at the initiation of ETN treatment in RA patients with an inadequate response to MTX. The addition of ETN is therefore preferable to switching to ETN for RA patients whose condition is not controlled with a tolerable dose of MTX.

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References

1. Keystone EC. Strategies to control disease in rheumatoid arthritis with tumor necrosis factor antagonists—an opportunity to improve outcomes. Nat Clin Pract Rheumatol. 2006;2:594–601.
2. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370:1861–74.
3. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997;337:141–7.
4. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343:1586–93.
5. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253–9.
6. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial. Lancet. 2004;363:675–81.
7. van Riel PLCM, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis. 2006;65:1478–83.
8. Miyasaka N, Takeuchi T, Eguchi K. Guidelines for the proper use of etanercept in Japan. Mod Rheumatol. 2006;16:63–7.
9. Kameda H, Sekiguchi N, Nagasawa H, Amano K, Takei H, Suzuki K, et al. Development and validation of handy rheumatoid activity score with 38 joints (HRAS38) in rheumatoid arthritis patients receiving infliximab. Mod Rheumatol. 2006;16:381–8.
10. Choy EH. Two is better than one? Combination therapy in rheumatoid arthritis. Rheumatology. 2004;43:1205–7.
11. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different strategies in patients with early rheumatoid arthritis (the BeSt Study). Arthritis Rheum. 2005;52:3381–90.

12. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65:1357–62.
13. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis. Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54:1063–74.
14. Kameda H, Amano K, Sekiguchi N, Takei H, Ogawa H, Nagasawa H, et al. Factors predicting the response to low-dose methotrexate therapy in patients with rheumatoid arthritis: a better response in male patients. Mod Rheumatol. 2004;14:442–6.
15. Yamanaka H, Tanaka Y, Sekiguchi N, Inoue E, Saito K, Kameda H, et al. Retrospective study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM). Mod Rheumatol. 2007;17:28–32.
16. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcome (RECONFIRM-2). Mod Rheumatol. 2008;18:146–52.
17. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18:447–52.
18. Maini E, St clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. Lancet. 1999;354:1932–9.
19. Lipsky PE, van der Heijde DMFM, St. Claire EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med. 2000;343:1594–602.
20. St. Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis. A randomized, controlled trial. Arthritis Rheum. 2004;50:3432–43.
21. van Vollenhoven RF, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. Arthritis Res Ther. 2003;5:R347–51.
22. Hyrich KL, Symmons DPM, Watson KD, Silman AJ, on behalf of the British Society for Rheumatology Biologics Register. Comparison of the response to infliximab or etanercept monotherapy with response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis. Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54:1786–94.
23. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26–37.
24. Zachariae C, Mørk NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88:495–501.