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ORIGINAL ARTICLE

The usefulness of a new triple combination treatment utilizing methotrexate, salazosulfapyridine, and bucillamine in rheumatoid arthritis

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Abstract

Objectives. Combination treatment with methotrexate, salazosulfapyridine and bucillamine as an alternative to treatment with TNF-inhibiting biologics in rheumatoid arthritis was investigated.
Methods. Twenty-six facilities allied with the Japan Association of Rheumatologists in Private Practice participated in this study. One hundred and twelve patients enrolled in this study, all of whom were within 3 years of diagnosis with rheumatoid arthritis for whom treatment with one DMARD or a combination of two DMARDs had failed (DAS28 > 3.2). Patients chose their own treatment. The triple DMARDs combination group was comprised of 72 patients; the TNF-inhibiting biologics treatment group was comprised of 40 patients.
Results. DAS28 scores for the triple DMARDs combination group and the TNF-inhibiting biologics treatment groups were 4.84 ± 0.96 and 5.23 ± 1.26, and there was no significant difference between the two groups. From the 6th month, average disease activities of both groups were reduced, and there was no difference between the two groups at 12 months (DAS28, 3.39 ± 1.43 and 3.05 ± 1.43, $p = 0.39$). Furthermore, there was no significant difference in the degree of bone destruction between the two groups at 12 months.
Conclusions. The triple DMARD combination therapy provided a new treatment option for those patients for whom treatment with biologics is difficult.

Keywords

Antirheumatic agents, Bucillamine, Methotrexate, Rheumatoid arthritis, Sulfasalazine

History

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Introduction

Since the introduction of anti-TNF and other biologic treatments into rheumatoid arthritis (RA) treatment, the improvement of long-term prognosis in RA is possible [1]. However, issues such as the high cost of treatment, and the risk of side effects associated with the use of biologics have not been resolved. In recent years, triple combination therapy with oral DMARDs has received attention as an alternative therapy to therapy with biologics, and in the 2012 ACR treatment recommendations [2], the 2014 EULAR treatment recommendations [3], and NICE (British National Institute for Health Care Excellence) Guidance [4], combinational treatment with oral DMARDs is recommended before use of biologics. In particular combination therapy with salazosulfapyridine (SASP), methotrexate (MTX) and hydroxychloroquine (HCQ) has been highlighted in recent years as evidence accumulates regarding not only the economic aspects, but also regarding effects on disease activity, indicating this as an effective treatment option [5–8]. In addition, it has been shown that combination treatment with three DMARDs before treatment with biologics has a large effect on the total health insurance budget [9].

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On the other hand, due to ocular toxicity HCQ has not been approved for use in RA in Japan, and so the three-drug regimen used in Europe and the United States cannot be used in practice. Therefore, the Japan Rheumatism Association in Private Practice (JRAP) conducted the clinical study to research the effects of utilizing bucillamine (BUC) [10,11], a frequently used DMARD for which there is evidence of a synergistic effect with MTX, as the third DMARD in a triple DMARD combination as an alternative to treatment with biologics (JaSTAR Study). The objective of our study was to investigate the efficacy and safety of the combination treatment with MTX, SASP, and BUC (TriD) compared with the treatment with TNF-inhibiting biologics in RA patient in whom previous treatment with conventional DMARD had failed.

Patients and methods

Study design

Japanese Strategic Treatment of Aggressive RA Study (JaSTAR Study): UMIN Clinical Registry ID #UMIN000003807 https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function = brows&action = brows&type = summary&recptno = R000004587&language = J. The study was conducted by 36 rheumatologists from 26 facilities affiliated with JARP. It was carried out as an open-label comparative study, in accordance with the Declaration of Helsinki.

Participating patients

One hundred and twelve RA patients diagnosed with the 1987 ACR Criteria [12] from the participating facilities, who were within 3 years of diagnosis who had inadequate response to monotherapy with MTX, SASP or BUC or two-drug combination therapy from these three DMARDs (DAS28 > 3.2), and who had never used biologics were recruited. Consent for participation was obtained after a verbal explanation of the study by rheumatologist. Each patient then decided for themselves whether they would undergo TriD treatment or treatment with anti-TNF biologics and the patients were assigned to their groups. Oral steroid dosage was allowed up to 10 mg/day. Patients who received intra-articular injections, plasma exchange therapy, or leukocyte removal therapy within 4 weeks of the start of the study, and patients who had undergone surgery which had possible effects on the results of the study at the discretion of the attending physicians were excluded.

Drug treatment

Adjustment of drug dosages was allowed within upper limits of 16 mg/week for MTX, 1,000 mg/day for SASP, and 300 mg/day for BUC at the discretion of the physician. The TNF inhibitor to be utilized for each patient was one of four, such as infliximab, etanercept, adalimumab, and golimumab, chosen after consultation with the attending physician. Information on usage and dosage is attached.

Evaluation method

The first endpoint was average DAS28 scores at 6 months and 12 months from the start of the study. The second endpoint was average CDAI scores, DAS28 remission rates, CDAI remission rates, the modified total Sharp score (mTSS), erosion scores (ES), and joint space narrowing scores (JSN) from the beginning of the study to 12 months. All photographs were read by 2 trained assessors who were blinded with regard to patient identity and patient characteristics and treatment, but the time order was known, to improve sensitivity to change.

Statistical method

Continuous comparison of the two groups was achieved in the case of parametric data by Student's *t*-test and in the case of non-parametric data, Aspen–Welch *t*-test was employed. Comparison of retention rate of both groups was performed by log-rank comparison. These were represented as *p* values, $p < 0.05$ being statistically significant.

Results

For the present study 112 patients were enrolled, their consent was obtained, and subsequently the patients themselves chose to participate in either the TriD treatment or the anti-TNF treatment. Of the 112, 72 chose TriD treatment and 40 chose anti-TNF treatment. By the 6-month point 11 patients in the TriD Group had ceased treatment (adverse effects-2, no effect/insufficient effects-5, and change of hospital/failure to appear for treatment-4); in the TNF group 5 patients ceased treatment (no effect/insufficient effects-4 and disease remission-1). Between 6 and 12 months post initiation in the TriD group 7 patients ceased treatment (no effect/insufficient effects-4, change of hospital/failure to appear for treatment-1, the desire to bear a child-1, and entry into a clinical trial-1). In the same time period, in the TNF group 5 patients ceased treatment (adverse effects-1, no effect/insufficient effects-3, and change of hospitals/failure to appear for treatment-1). The number of patients who completed the treatment for the 12-month period was 54 in the TriD group and 30 for the TNF group (Figure 1).

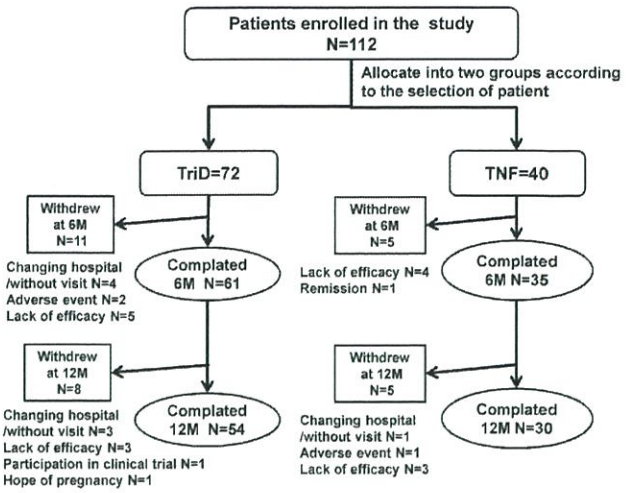


Figure 1. Schematic diagram showing the number of study participants in each group who withdrew and number who completed month 6 and 12 of JaSTAR study. *TriD* triple DMARD combination therapy, *TNF* combination therapy of TNF inhibitor and methotrexate.

Concerning adverse events related to the discontinuation of the study, one stomach discomfort, one itching, and one liver dysfunction were developed in the TriD group (including two were developed in the same case), while one liver dysfunction was developed in the TNF group. All cases recovered by the discontinuation of treatment.

The background data for both groups at the start of the study is shown in Table 1. The patients were not assigned randomly to each group, but chose which group to participate. A statistically significant difference was observed in the mean values between the two groups in several categories. As for age, there were few patients of advanced age who chose the TNF group, no one was aged 80 years or more. Background factors that support the inflammatory activity such as MMP-3, CRP, and ESR were significantly higher in the TNF group. However, there was no significant difference between the two groups in the average value of the DAS28, CDAI, and the mTSS. There was no statistically significant difference between the two groups in the background of other factors, including RF-positive rate and the ACPA-positive rate.

Table 1. Baseline characteristics of the patients.

	TriD $n = 72$	TNF $n = 40$	*P* value
Age (years)	57.0 ± 11.9	53.3 ± 12.8	N.S.
Female (%)	79.1	80	N.S.
Disease duration (months)	29.8 ± 40.1	29.2 ± 37.3	N.S.
ESR (mm/1 h)	30.76 ± 21.68	46.95 ± 32.74	<0.01
CRP (mg/dL)	1.05 ± 1.45	2.26 ± 2.72	<0.01
MMP-3 (ng/mL)	115.4 ± 113.9	179.0 ± 164.3	<0.05
ACPA positive (%)	71.1	90.5	N.S.
RF positive (%)	72.3	83.8	N.S.
DAS28	4.87 ± 1.00	5.20 ± 1.26	N.S.
CDAI	24.0 ± 10.3	25.7 ± 11.8	N.S.
mTSS	36.5 ± 50.6	44.3 ± 47.7	N.S.

TriD triple DMARD combination therapy, *TNF* combination therapy of TNF inhibitor and methotrexate, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MMP-3* Matrix Metalloproteinase-3, *mTSS* modified total Sharp score.

Data are shown by number of patients (%) for categorical data and the means for continuous data. Statistical difference was assessed by Student's *t*-test for parametric data and Aspin–Welch *t*-test for non-parametric data. Statistical difference for categorical data was assessed by chi-square test. *P* values are shown as <0.01, <005, N.S. (not significantly).

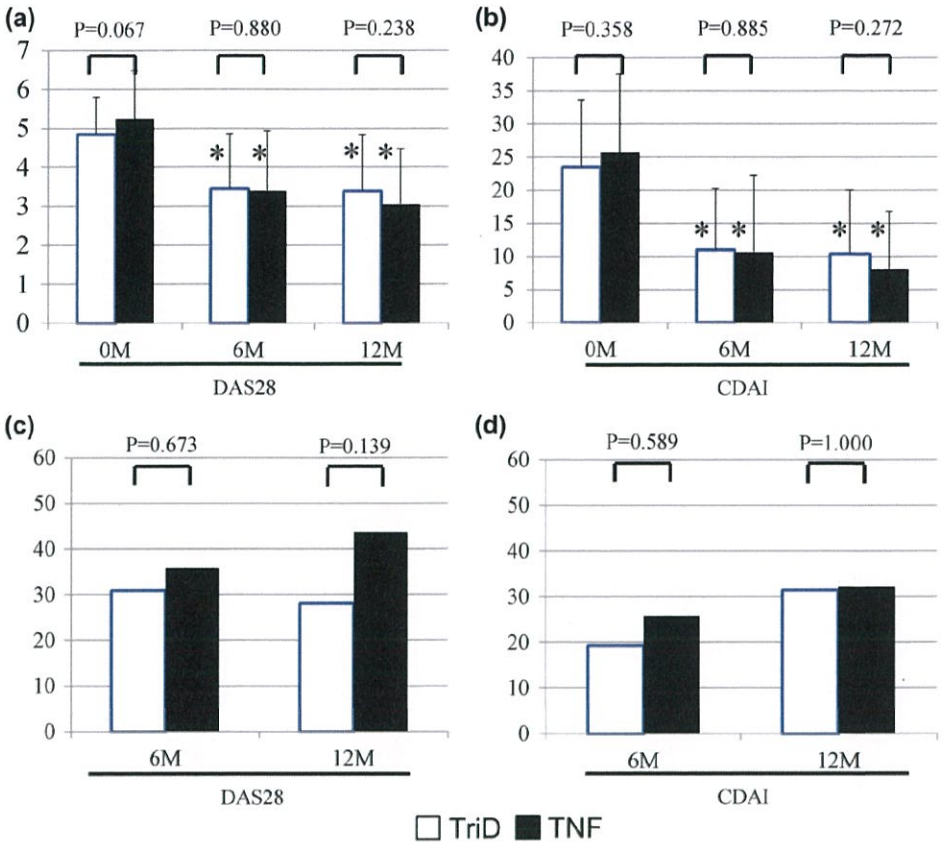


Figure 2. Averages of DAS28 score (a) and CDAI score (b) in each treatment group and proportion of patients achieving remission according to DAS28 (<2.6) (c) and CDAI (<2.8) (d) at 6 months and 12 months. Averages of DAS28 score and CDAI at 6 and 12 M significantly reduced from those at 0M in each treatment group (*; $p<0.01$, Student's t-test). There is no statistically significant difference between two groups at 0, 6, and 12 M. There is no statistically significant difference in DAS28 and CDAI remission rates between the two groups at 6 and 12 M (Chi-square test). White square represents data of triple conventional DMARDs combination therapy (TriD) and black square represents data of TNF inhibitor therapy (TNF).

Indicators of disease activity, DAS28 and CDAI, are shown in Figure 2a and b. Statistically significant inhibition of disease activity was observed and maintained in both groups for the 12-month duration of the study. At 6 months and 12 months after initiation of the study, no significant difference in effects of treatment on disease was seen between the two groups, as determined by DAS28 and CDAI scores. DAS28 and CDAI remission rates for both treatment groups are shown in Figure 2c and d. There was also no statistically significant difference in rates of remission achieved in both groups.

Indicators of inflammation levels, CRP, ESR, and MMP-3 are shown in Table 2. In both groups, at 12 months all indicators of inflammation were significantly reduced and there was no significant difference between the two groups. The other DAS28 components (SJC, TJC, and patient's VAS) were no different before and after treatment between two groups.

Figure 3 shows retention rate of both TriD and anti-TNF treatment methods in a graph as determined by the Kaplan–Meier estimator. There was no difference in the retention rates of the two groups, at 75% for both groups (log-rank test $p = 0.84$).

Table 2. Changes in ESR, CRP, and MMP-3 during a treatment period of 12 months.

		0 M	12 M	P value (0 M vs 12 M)
ESR	TriD	29.8 ± 20.3	19.4 ± 18.7	<0.01
	TNF	47.0 ± 32.7	22.1 ± 20.5	<0.01
	P value (TriD vs TNF)	<0.01	N.S.	
CRP	TriD	1.05 ± 1.45	0.60 ± 1.46	<0.05
	TNF	2.26 ± 2.72	0.77 ± 2.05	<0.01
	P value (TriD vs TNF)	<0.01	N.S.	
MMP-3	TriD	115.0 ± 114.8	99.4 ± 134.8	N.S.
	TNF	179.2 ± 169.2	90.1 ± 70.6	<0.01
	P value (TriD vs TNF)	<0.05	N.S.	

TriD triple DMARD combination therapy, *TNF* combination therapy of TNF inhibitor and methotrexate.

There were significant differences for ESR, CRP, and MMP-3 at baseline between two therapeutic groups. During a treatment period of 12 months, those three factors were reduced significantly in both therapeutic groups and there was no significant difference for those values at 12 months between the two treatment groups. P values are shown as <0.01, <0.05, N.S. (not significantly).

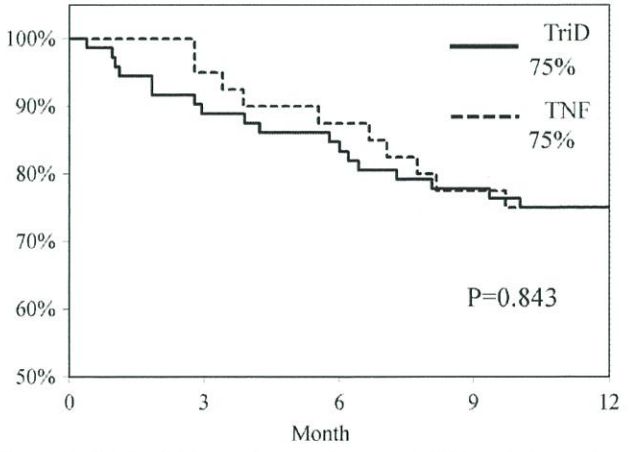


Figure 3. Kaplan–Meier estimate of the probability of the patients remaining on triple conventional DMARDs combination therapy (TriD) or TNF inhibitor therapy (TNF). Statistical difference in survival between the two groups was assessed by log-rank test.

Figure 4 shows the changes during the study period for mTSS, ES, and JSN values. At the time of the start of the study there was no significant difference between the groups in average mTSS. For the TriD group, the average was 36.5 ± 50.6, and for the TNF group the average was 44.3 ± 47.7 in the TNF group ($p = 0.55$). At 12 months the mTSS average in the TriD group was 41.0 ± 51.9 and in the TNF group 47.7 ± 50.4, again no significant difference was seen ($p = 0.62$). In the case of ES and JSN as well, no statistically significant difference was seen either at the start of the study, or at the 12-month mark (Figure 4). The change in mTSS seen in the 12 months of the study in the TriD group was 4.14 ± 6.63, and in the TNF group 3.82 ± 8.37, with no statistically significant difference ($p = 0.87$). ES and JSN values also showed no significant difference in the 12-month study period.

In this study a range of dosage was set, not a single dosage, so adjustments for patient condition were possible. Therefore, regulation of the dose was possible. The dose calculations for this study (the final optimal dose) showed median doses for each DMARD as 6 mg/week for MTX, 100 mg/day for BUC, and 500 mg/day for SASP. For 25.4% of patients, the highest allowable dose for SASP in Japan (1000 mg/day) was necessary, and there were no patients who reached the allowable maximums for MTX and BUC (16 mg/week, 300 mg/week). In contrast, in the TNF group the median dose of MTX was 8 mg/week, and for 2.3% of patients the maximum allowable dose (16 mg/week) was necessary.

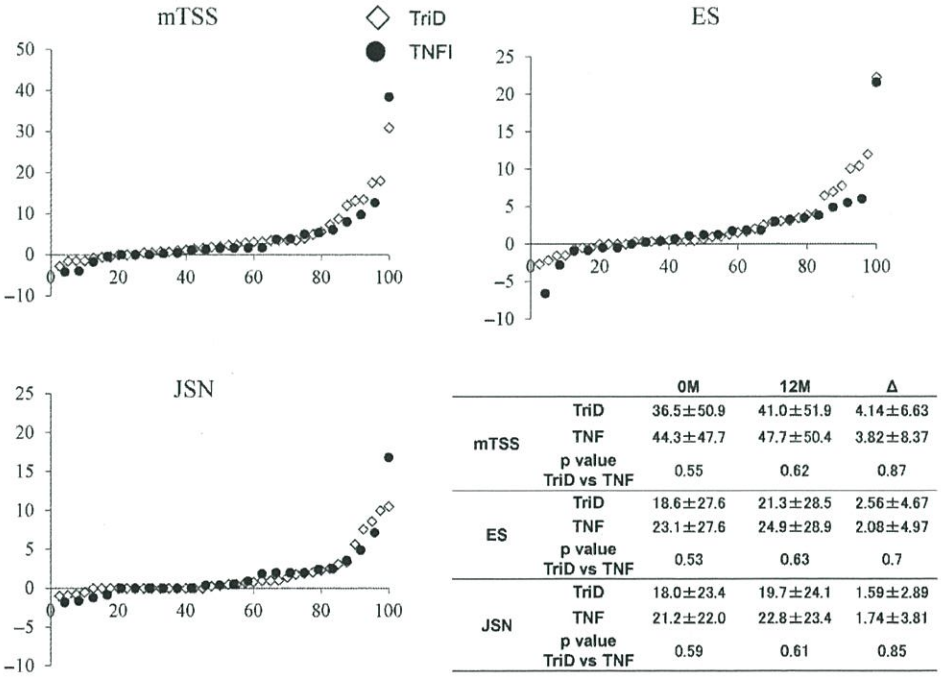
Discussion

In this study, it was shown that TriD treatment and anti-TNF treatment are effective for patients in the early stages of RA, less than 3 years from diagnosis, for whom drug treatment had previously failed. Needless to say, these results were caused by some limitations, one is small sample size and another is non-randomized study design. Therefore, there was a difference in basal inflammation degree (CRP and ESR) between the two groups. However, the difference is eliminated between the groups which are close to the normal value at the time of the last observation. The larger volume of change in DAS28 during observational period in TNF group than TriD group was affected by the difference in basal ESR between two groups. These results show that treatment with TriD is a viable option to treatment with biologics, which is often fraught with the risk of side effects and infections. The groups were not assigned randomly, but were determined by choice of treatment at patient discretion, and this accounted for statistical differences in the patient background between groups. However, DAS28 and CDAI values, as well as RF- and ACPA-positive results, and bone erosion results showed no significant difference, and thus the two groups are comparable.

We believe that the validity of the substitution of BUC in place of HCQ in the usual triple combination pattern of MTX + SASP+ HCQ is demonstrated by the wide range of suppression of cytokines achieved. In RA, it is been reported that MTX suppresses IL-6 while it does not suppress TNF and IL-1 [13,14]. SASP suppresses TNF and IL-1 while having no effect on IL-6 [15]. HCQ in SLE decreased serum levels of IFN and correlation with reduced disease activity would seem to indicate an IFN suppression function of HCQ [16]. In other words, we believe that the effect of MTX + SASP + HCQ treatment, comparable to that of biologics, is due the suppression of a wide range of cytokines such as TNF, IL-6, IL-1, and IFN. It is conceivable that the substitution of BUC for HCQ would produce the same cytokine suppression (INF) [17] as the original triple DMARD combination.

Concerning safety, in this study, 2 participants out of 72 ceased treatments due to adverse effects in the TriD group, and 1 out of 43 in the TNF group, the difference was not statistically significant (2.8% vs. 2.3%). There is a general impression that DMARDs therapy carries a higher risk of adverse effects. This can be thought to be due to the fact that before biologics were marketed, it was common to add another DMARD to treatment of those patients for whom the maximum dose of a single DMARD was ineffective, thereby increasing the risk of adverse effects [18].

In this study, the final optimal doses were less than half the maximum allowed dosage for each, which can be thought to account for the preservation of the safety of the treatment while increasing the efficacy. In Western comparative testing of anti-TNF and triple DMARD combination treatment (TEAR [5], SWEFOT [6], and RACAT [7]) the drug combination is MTX, SASP, and HCQ, but each drug is used at its maximum dosage. The Japanese combination preserves safety and efficacy while keeping the doses lower, which would seem to indicate it as a good treatment option.



		0M	12M	Δ
mTSS	TriD	36.5±50.9	41.0±51.9	4.14±6.63
	TNF	44.3±47.7	47.7±50.4	3.82±8.37
	p value TriD vs TNF	0.55	0.62	0.87
ES	TriD	18.6±27.6	21.3±28.5	2.56±4.67
	TNF	23.1±27.6	24.9±28.9	2.08±4.97
	p value TriD vs TNF	0.53	0.63	0.7
JSN	TriD	18.0±23.4	19.7±24.1	1.59±2.89
	TNF	21.2±22.0	22.8±23.4	1.74±3.81
	p value TriD vs TNF	0.59	0.61	0.85

Figure 4. Cumulative probability plot of radiological progression data (intention-to-treat population). Each points on the plot represents the radiographic progression in an individual patient (score after one year minus score at baseline), for the treatment groups separately. *mTSS* modified total Sharp score, *ES* erosion score, *JSN* joint space narrowing score.

In addition, because in Japanese patient out-of-pocket payment is required which is 30% of total medical cost by public health insurance, the amount of the out-of-pocket of the patient who is treated with TNF inhibitor is from $ 200/month to $ 325/month. The amount of out-of-pocket payment of patients who received triple DMARDs combination treatment introduced in this study is significantly lower than that of patients treated with TNF inhibitors ($ 27/month).

The cases in this study were all patients with RA of about 2 years' duration, many with a poor prognosis for whom initial DMARD treatment was not successful, and for whom progression of bone destruction was expected to be rapid [19]. The results of this study, ⊿ mTSS during the treatment period of 12 months to TriD group and the TNF group, were roughly 4 which was lower than 5 as indicated by RRP [20], showing the inhibitory effect on bone destruction. Aletaha et al. reported [21] that at least 6 months for control of disease activity is necessary in order to suppress bone destruction processes. However, several cases in TriD exceed the 10 in the graph of cumulative probability curve of ΔmTSS, while there were only two cases in the TNF group. This difference is likely to reflect the difference of Δerosion score between two groups. However, there was no statistically significant difference in ΔTSS between the two groups. To clarify this difference, it was considered to be necessary perform further long-term observation.

The authors have demonstrated that the effects of TriD treatment equal those of anti-TNF treatment. Retention rate of anti-TNF therapy past the initial 6 months of this study led to an increase in participants ceasing treatment due to lack of effectiveness/insufficient effects. A calculation of these statistics by DANBIO [22] showed that loss of effect in the first year led to an increase in the number of participants that dropped out of treatment, we propose formation of anti-drug antibodies to be a likely cause [23,24].

New conclusions can be drawn from this study

1. The Japanese drug combination of MTX + SASP+BUC triple DMARDs combination in place of the Western MTX + SASP+HCQ combination by comparison allows effectiveness equal to that of anti-TNF + MTX, at half the maximum dosage.
2. Anti-TNF treatment and TriD treatment, compared after treatment of 1 year, yielded equal results. The anti-TNF treatment group, after 6 months' treatment experienced more dropouts from treatment due to lack of efficacy.
3. We noticed a tendency of elderly patients to refrain from anti-TNF treatment, at the same time we noticed a likelihood of patients with elevated indicators of inflammation (CRP, ESR, and MMP-3) to choose anti-TNF treatment.

Until now there was little evidence to supply a new treatment method for those RA patients with high disease activity levels who are reluctant to undergo DMARD treatment, the results of this study will provide a new treatment option—triple DMARDs treatment—for those patients for whom treatment with biologics is difficult.

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Conflict of interest

The Japan Association of Rheumatologists in Private Practice was founded by Santen pharmaceutical Co. Ltd.

None.

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