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ORIGINAL ARTICLE

Prevention of joint destruction by tacrolimus in patients with early rheumatoid arthritis: a post hoc analysis of a double-blind, randomized, placebo-controlled study

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Abstract
Objectives A multicenter, randomized, double-blind, placebo-controlled study of the oral calcineurin inhibitor tacrolimus was performed in patients with early rheumatoid arthritis who had responded poorly to disease-modifying antirheumatic drugs (DMARDs), and factors related to suppression of joint destruction were investigated.
Methods The change in the total Sharp score (ΔTSS) was assessed by univariate analysis in patients with X-ray films to identify the main determinant of a ΔTSS of <0.5 in week 52. Patients with this factor were then investigated further.
Results Univariate analysis showed that a baseline C-reactive protein (CRP) level of <1.5 mg/dL was the major determinant of ΔTSS <0.5 at week 52 in the tacrolimus group. Detailed analysis of patients with a baseline CRP of <1.5 mg/dL revealed no significant differences in background factors between the two groups. In week 52, ΔTSS was significantly smaller in the tacrolimus group than in the placebo group (2.67 ± 5.40 vs. 8.05 ± 10.32, respectively, $p = 0.017$). Both groups had a similar incidence of adverse reactions.
Conclusions Adding tacrolimus to DMARDs significantly suppressed disease activity and joint destruction in patients with early rheumatoid arthritis, a disease duration ≤3 years, a CRP <1.5 mg/dL, and a poor response to oral DMARDs.

Keywords DMARD · Rheumatoid arthritis · Tacrolimus

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Introduction

Tacrolimus is a macrolide antibiotic that was first identified as a metabolic product of the actinomycete *Streptomyces tsukubaensis*. It is a calcineurin inhibitor that shows strong immunosuppressive activity by selectively blocking T-cell activation [1, 2]. Tacrolimus was initially used clinically in Japan in organ transplantation, after which its efficacy for myasthenia gravis, rheumatoid arthritis (RA), lupus nephritis, and ulcerative colitis was also demonstrated.

In Japan, oral tacrolimus was approved for the treatment of RA in April 2005 (it is indicated for patients in whom conventional therapy is inadequate), after its efficacy and safety had been confirmed in clinical studies of RA patients who showed a poor response to disease-modifying antirheumatic drugs (DMARDs) [3, 4]. Recently, tacrolimus has often been used concomitantly with DMARDs, including methotrexate (MTX), and the improvement of symptoms through the use of this concomitant therapy has been reported [5, 6]. However, its effect on joint destruction is yet to be clarified.

Previously, we performed a double-blind placebo-controlled study [7] to investigate the efficacy and safety of tacrolimus, as well as its capacity to prevent joint destruction, in 123 patients with early RA <3 years in duration, who had a diagnosis of RA based on the 1987 criteria of the American College of Rheumatology (ACR). According to the ACR criteria [9], the ACR20 improvement rate was significantly higher ($p = 0.005$) in the tacrolimus group than the placebo group. Also, according to the European League Against Rheumatism (EULAR) criteria [10, 11], a significantly higher ($p < 0.001$) percentage of the tacrolimus group showed a moderate or good response compared with the placebo group. Furthermore, the percentage of patients with a final disease activity score in 28 joints (DAS28) [12] of <2.6 was significantly higher ($p = 0.005$) in the tacrolimus group than in the placebo group. There was no significant difference between the two groups with regard to the incidence of adverse events or discontinuation due to adverse events.

However, evaluation of joint destruction in week 52 by the modified Sharp method [13] revealed the following results for the tacrolimus group and the placebo group, respectively: the total Sharp score (TSS) was 6.16 ± 10.84 (mean ± SD) versus 7.73 ± 12.23 and the bone erosion score was 2.50 ± 4.56 versus 4.27 ± 7.53 ($p = 0.090$). There were no significant differences in the change in TSS (ΔTSS) between the two groups, but the bone erosion score was lower in the tacrolimus group, suggesting that tacrolimus has the potential to reduce the progression of bone erosion. In the present study, therefore, we performed subanalyses to determine factors related to the prevention of joint destruction by tacrolimus therapy, and we found that tacrolimus suppressed disease activity and joint destruction in patients with early rheumatoid arthritis and lower levels of serum CRP (<1.5 mg/dL).

Materials and methods

Patients and study protocol

The enrollment criteria for this study were as follows: (1) males or females aged 20–65 years with a diagnosis of RA according to the ACR criteria [8]; (2) duration of disease ≥6 to ≤3 years; (3) at least 6 tender joints out of 68 joints surveyed; (4) at least 3 swollen joints out of 66 joints surveyed; (5) a C-reactive protein (CRP) level ≥1.0 mg/dL or erythrocyte sedimentation rate (ESR) ≥30 mm/h; (6) radiographic bone erosion at more than one site in the hands or lower limbs; and (7) current treatment with MTX (6–8 mg/week), salazosulfapyridine (1 g/day), or bucillamine (100–300 mg/day), and a compliance rate of ≥75 % during the minimum administration period (8 weeks before baseline, 8 weeks, or 12 weeks).

The exclusion criteria were (1) previous treatment with tacrolimus; (2) class 4 of Steinbrocker's functional classification; (3) treatment with biological products (infliximab or etanercept) or leflunomide within 12 weeks before the study for suppression of joint destruction; (4) steroid therapy at >7.5 mg/day (as prednisolone equivalent) within 4 weeks before the study, (5) administration of >2 tablets/suppositories of nonsteroidal anti-inflammatory drugs (NSAIDs) daily; and (6) diseases such as renal dysfunction, pancreatitis/impaired glucose tolerance, hyperkalemia, advanced hepatic dysfunction, cardiac disease (ischemic heart disease, arrhythmia requiring treatment, cardiac failure, etc.), severe respiratory disease, severe infection, drug hypersensitivity, or malignancy.

Subjects who fitted the above criteria, and who gave written informed consent, were randomized to a tacrolimus (3 mg/day) or a placebo group. Study drugs were administered once a day after the evening meal for a period of 52 weeks. The dosages of concomitant MTX, salazosulfapyridine, bucillamine, and NSAIDs were not changed, while dose reduction was allowed for steroids, but an increase above the baseline dose was not permitted. Initiation of new antirheumatic drugs or steroids was also not permitted.

At enrollment, in week 28, and in week 52 (or at discontinuation), plain X-ray films of both hands and both lower limbs were taken. Two blinded evaluators employed the modified Sharp method to determine the bone erosion score (ES) and the joint space narrowing (JSN) score from the X-ray films, and the sum of the ES and JSN scores was calculated as the TSS [9, 10]. The change in TSS from baseline (ΔTSS) was used to assess the progression of joint destruction. All participating institutions received the approval of their governing institutional board or equivalent, and the trial was implemented in accordance with the ethical principles of the Declaration of Helsinki and good clinical practice (GCP) guidelines, as well as relevant laws or regulations promulgated by the Institutional Review Boards for clinical trials. This study is registered at ClinicalTrials.gov (NCT00319917).

Statistical analysis

Factors with an influence on the suppression of joint destruction by tacrolimus were extracted by univariate analysis, employing gender (male, female), age (<49, ≥49 years), disease duration (<1.3, ≥1.3 years), stage (stages I/II, stages III/IV), functional class (class 1, classes 2–4), CRP (<1.5, ≥1.5 mg/dL), ESR (<41.5, ≥41.5 mm/h), DAS28-CRP (≤5.1, >5.1), DAS28-ESR (≤5.1, >5.1), TSS (<11.0, ≥11.0), ES (<5.0, ≥5.0), JSN score (<3.5, ≥3.5), yearly progression (<9.2, ≥9.2), rheumatoid factor

(<63.5, ≥63.5 IU/mL), matrix metalloproteinase-3 (MMP-3) (<187.5, ≥187.5 ng/mL), concomitant MTX therapy (yes, no), and the dose of MTX (<8, ≥8 mg/week) at the start of tacrolimus administration. CRP = 1.5, which was the median value of the population, was used in the analysis to keep the number of cases in the two groups uniform. Age, disease duration, CRP, ESR, TSS, ES, JSN, yearly progression, rheumatoid factor, MMP-3, and baseline dose of MTX were analyzed after being dichotomized at the median value (<median, ≥median).

For each factor extracted by univariate analysis, the effect on ΔTSS was compared between the tacrolimus group and the placebo group, and the factors that showed a significant difference between the two groups were selected. Next, the patients in whom a significant difference in these factors was observed were selected and used to perform a comparison between the tacrolimus and placebo groups with respect to each patient background factor, use of DMARDs, dose of DMARDs, changes in the Sharp score in week 52, improvement according to the EULAR criteria, and adverse events.

Changes in Sharp scores were examined by an analysis of variance in relation to the baseline score and the use of MTX as a covariate. The improvement rate according to the EULAR criteria was examined by logistic regression analysis. Background factors and adverse events were compared between the tacrolimus group and the placebo group by Fisher's exact test, the *t* test, or the Wilcoxon rank-sum test. Statistical significance was accepted at $p < 0.05$ (two-sided). Results are reported as the mean ± SD.

Missing radiographic data were compensated for using the linear extrapolation method, while other missing values were compensated for using the last-observation-carried-forward method.

Adverse events were classified by system organ class and preferred terms were taken from the ICH Medical Dictionary for Regulatory Activities (MedDRA Ver.11.1).

Results

Among the 123 randomized patients (61 in the tacrolimus group and 62 in the placebo group) registered in this study, 116 patients (58 in each group) had TSS data (Fig. 1). There were no differences between the background factors of the 116 patients and those of the 123 patients (data not shown). Also, there were no differences in background factors between both groups (tacrolimus and placebo) within this set of 116 patients, and the results were similar to the profile observed for all 123 patients.

Factors that influenced the achievement of ΔTSS <0.5 in week 52 were investigated in the tacrolimus group ($n = 58$) by univariate analysis, and this revealed significant influences of CRP, ESR, and DAS28-CRP (Table 1). When stratified analysis was carried out using these factors, a significant difference in ΔTSS in week 52 between the tacrolimus and placebo groups was (only) observed in the subgroup of patients with a baseline CRP of <1.5 mg/dL.

Among the 116 patients for whom the TSS was calculated, 29 patients from the tacrolimus group and 31 patients

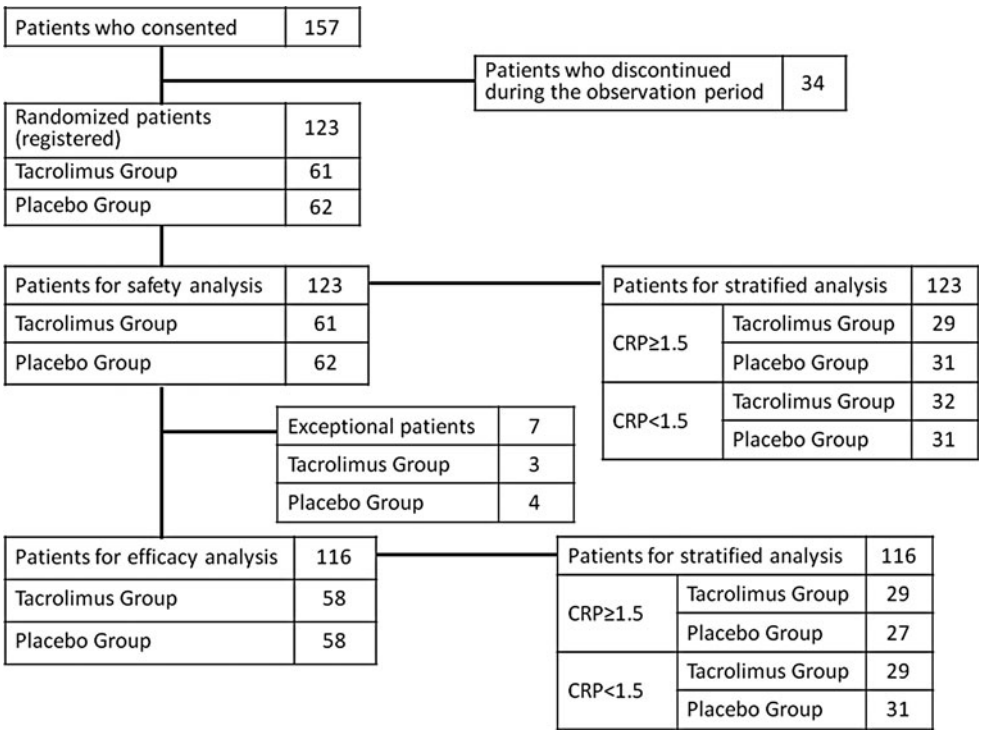

Fig. 1 Patient disposition. One hundred twenty-three RA patients were registered in this study. A total of 123 patients were randomized to either the tacrolimus group (61 patients) or the placebo group (62 patients) for safety analysis. The patients were then stratified according to CRP (<1.5, ≥1.5). Also, a total of 115 patients were randomized to either the tacrolimus group (58 patients) or the placebo group (58 patients) for efficacy analysis. Again, these patients were stratified according to CRP (<1.5, ≥1.5)

Table 1 Univariate analysis of the influence of background factors on the achievement of ΔTSS <0.5 in the tacrolimus group ($n = 58$)

		p value
Gender	Male (0/6) vs. female (14/52)	0.972
Age	<49 (8/29) vs. ≥49 (6/29)	0.541
Disease duration (years)	<1.3 (10/29) vs. ≥1.3 (4/29)	0.073
Stage classification	I, II (10/42) vs. III, IV (4/16)	0.925
Functional classification	1 (3/12) vs. 2–4 (11/46)	0.938
CRP (mg/mL)	<1.5 (11/29) vs. ≥1.5 (3/29)	0.021
ESR (mm/h)	<41.5 (11/29) vs. ≥41.5 (3/29)	0.021
DAS28-CRP	≤5.1 (13/32) vs. >5.1 (1/26)	0.009
DAS28-ESR	≤5.1 (6/15) vs. >5.1 (8/43)	0.103
Total score (modified Sharp method)	<11.0 (8/29) vs. ≥11.0 (6/29)	0.541
Bone erosion score (modified Sharp method)	<5.0 (6/27) vs. ≥5.0 (8/31)	0.751
Joint space narrowing score (modified Sharp method)	<3.5 (9/29) vs. ≥3.5 (5/29)	0.225
Yearly progression	<9.2 (7/29) vs. ≥9.2 (7/29)	1.000
Rheumatoid factor (IU/mL)	<63.5 (8/29) vs. ≥63.5 (6/29)	0.541
MMP-3 (ng/mL)	<187.5 (8/29) vs. ≥187.5 (6/29)	0.541
Concomitant MTX at the start of administration	with (8/39) vs. without (6/19)	0.358
MTX dose at the start of administration (mg/week)	<8 (9/33) vs. ≥8 (5/25)	0.523

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score 28, *MMP-3* matrix metalloproteinase-3, *MTX* methotrexate

from the placebo group had a baseline CRP of <1.5 mg/dL. Among all 123 patients, 32 patients in the tacrolimus group and 31 in the placebo group were subjected to safety analysis. With regard to background factors and concomitant medications, no significant differences were observed between both groups (Table 2).

Analysis of the clinical response of patients with a CRP level of <1.5 mg/dL at baseline was performed. In week 52, the tacrolimus group ($n = 32$) included 18 patients with a good response (56.3 %), 7 patients with a moderate response (21.9 %), and 7 patients with no response (21.9 %). Accordingly, 78.1 % of patients showed a moderate or good response. In the placebo group ($n = 31$), there were 10 patients with a good response (32.3 %), 6 patients with a moderate response (19.4 %), and 15 patients with no response (48.4 %), so 51.6 % of the patients had a moderate response or better. Again, there was a significant difference between the two groups ($p = 0.030$) (Fig. 2).

Evaluation of joint destruction showed the following yearly progression of TSS by week 52 in the tacrolimus group and the placebo group, respectively: ΔTSS was 2.67 ± 5.40 versus 8.05 ± 10.32 ($p = 0.017$), the change in the ES was 1.16 ± 3.10 versus 4.12 ± 6.28 ($p = 0.034$), and the change in the JSN score was 1.52 ± 3.19 versus 3.94 ± 5.14 ($p = 0.050$). ΔTSS and the change in ES were significantly smaller in the tacrolimus group than in the placebo group, and the change in the JSN score was also smaller in the tacrolimus group (Fig. 3a).

When the cumulative probability of ΔTSS up to week 52 was plotted, the cumulative probability of ΔTSS ≤0 was 37.9 % (11/29 patients) in the tacrolimus group and 16.1 % (5/31 patients) in the placebo group (Fig. 3b). This was approximately 1.57 times higher than the cumulative probability of ΔTSS ≤0 of 24.1 % for the tacrolimus group in the overall study (and 1.15 times higher for the placebo group), but this difference between groups was not significant ($p = 0.056$).

Regarding safety, the occurrence of adverse events among patients with a CRP of <1.5 mg/dL was noted in 81.3 % of those from the tacrolimus group (26/32 patients, 102 events) versus 90.3 % of such patients from the placebo group (28/31 patients, 85 events) (Table 3). Assessment according to system organ class showed no significant differences in event incidence between the two groups, and the event incidence revealed by this analysis was similar to that obtained in the overall study. Severe adverse events were observed in one patient from the tacrolimus group (3.1 %) versus seven patients from the placebo group (22.6 %), while discontinuation of administration due to adverse events occurred in two patients (6.3 %) and five patients (16.1 %), respectively.

Discussion

Since joint destruction progresses from the early stage of RA and eventually causes irreversible functional impairment, appropriate diagnosis and early treatment are needed. The 2012 ACR Recommendations [14] state that treatment with DMARDs should be initiated before joint destruction is evident. Moreover, to minimize the progression of joint destruction in patients with a disease duration of six-months or longer, administration of DMARDs alone or concomitantly is recommended, with re-evaluation every

Table 2 Comparison of the patients included in the safety analysis with CRP <1.5 mg/dL

		Tacrolimus group ($n = 32$)	Placebo group ($n = 31$)	p value
Female sex	Patients (%)	28 (96.6)	28 (90.3)	0.613[a]
Age (years)	Mean ± SD	48.6 ± 9.8	51.5 ± 11.6	0.291[b]
Height (cm)	Mean ± SD	156.9 ± 6.1	157.2 ± 8.1	0.866[b]
Weight (kg)	Mean ± SD	52.7 ± 6.0	53.0 ± 10.2	0.881[b]
Disease duration (years)	Mean ± SD	1.5 ± 0.7	1.6 ± 0.7	0.590[b]
Stage classification (stage)				
I (early stage)	Patients (%)	0	1 (3.2)	0.632[c]
II (middle stage)	Patients (%)	21 (72.4)	23 (74.2)	
III (advanced stage)	Patients (%)	8 (27.6)	5 (16.1)	
IV (terminal stage)	Patients (%)	0	2 (6.5)	
Functional classification (class)				
1	Patients (%)	7 (24.1)	7 (22.6)	0.888[c]
2	Patients (%)	22 (75.9)	24 (77.4)	
3	Patients (%)	0	0	
4	Patients (%)	0	0	
Number of painful joints	Mean ± SD	12.1 ± 7.8	11.5 ± 5.2	0.746[b]
Number of swollen joints	Mean ± SD	10.0 ± 5.1	8.5 ± 5.2	0.283[b]
Physical function evaluation by patients	Mean ± SD	0.4 ± 0.4	0.5 ± 0.3	0.214[b]
CRP (mg/dL)	Mean ± SD	0.5 ± 0.4	0.7 ± 0.4	0.257[b]
ESR (mm/h)	Mean ± SD	36.1 ± 18.1	42.4 ± 20.3	0.214[b]
Rheumatoid factor (IU/mL)	Mean ± SD	98.3 ± 126.5	115.9 ± 118.8	0.581[b]
DAS28-CRP				
≤3.2	Patients (%)	2 (6.9)	1 (3.2)	–
>3.2, ≤5.1	Patients (%)	21 (72.4)	25 (80.6)	
>5.1	Patients (%)	6 (20.7)	5 (16.1)	
	Mean ± SD	4.4 ± 0.8	4.3 ± 0.7	0.927[b]
DAS28-ESR				
≤3.2	Patients (%)	0	0	–
>3.2, ≤5.1	Patients (%)	11 (37.9)	11 (35.5)	
>5.1	Patients (%)	18 (62.1)	20 (64.5)	
	Mean ± SD	5.3 ± 0.8	5.2 ± 0.8	0.934[b]
Total score (modified Sharp method)	Mean ± SD (min–max)	15.9 ± 17.0 (2.0–75.0)	16.7 ± 17.1 (0.0–65.5)	0.858[b]
Bone erosion score (modified Sharp method)	Mean ± SD (Min–Max)	9.0 ± 8.3 (2.0–33.0)	7.7 ± 8.2 (0.0–40.5)	0.531[b]
Joint space narrowing score (modified Sharp method)	Mean ± SD (min–max)	6.9 ± 10.6 (0.0–42.0)	9.0 ± 12.1 (0.0–41.0)	0.471[b]
Yearly progression	Mean ± SD (min–max)	10.4 ± 8.7 (1.3–32.1)	10.7 ± 10.9 (0.0–46.0)	0.891[b]
Concomitant agents				
Methotrexate				
Dose (mg/week)	Patients (%)	16 (55.2)	18 (58.1)	1.000[a]
	Mean ± SD	7.0 ± 1.0	7.3 ± 1.0	0.339[b]
Salazosulfapyridine				
Dose (g/day)	Patients (%)	10 (34.5)	6 (19.4)	0.247[a]
	Mean ± SD	1.0 ± 0.0	1.0 ± 0.0	–
Bucillamine				
Dose(mg/day)	Patients (%)	3 (10.3)	7 (22.6)	0.302[a]
	Mean ± SD	166.7 ± 57.7	142.9 ± 53.5	0.545[b]

Table 2 continued

		Tacrolimus group ($n = 32$)	Placebo group ($n = 31$)	p value
Steroids				
Dose (mg/day)	Patients (%)	15 (51.7)	11 (35.5)	0.297[a]
	Mean ± SD	5.0 ± 2.2	4.8 ± 1.7	0.802[b]

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score 28

[a] Fisher's exact test

[b] *t* test

[c] Wilcoxon rank sum test

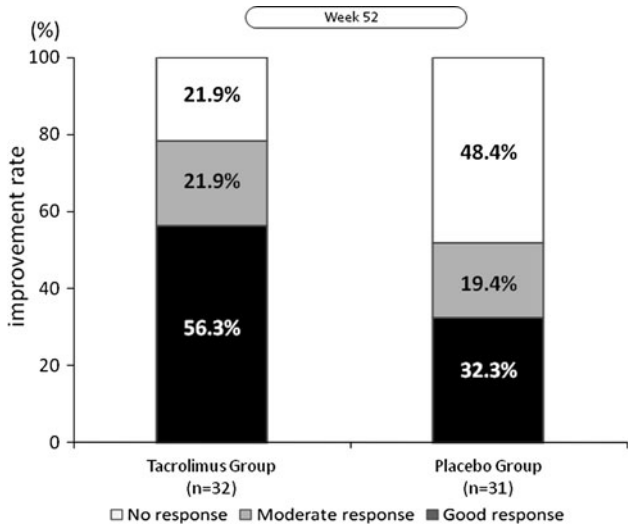

Fig. 2 Improvement rates [according to the EULAR (DAS28-CRP) criteria] in the tacrolimus group and the placebo group. *$p < 0.05$ by the Wald test for estimated parameter values

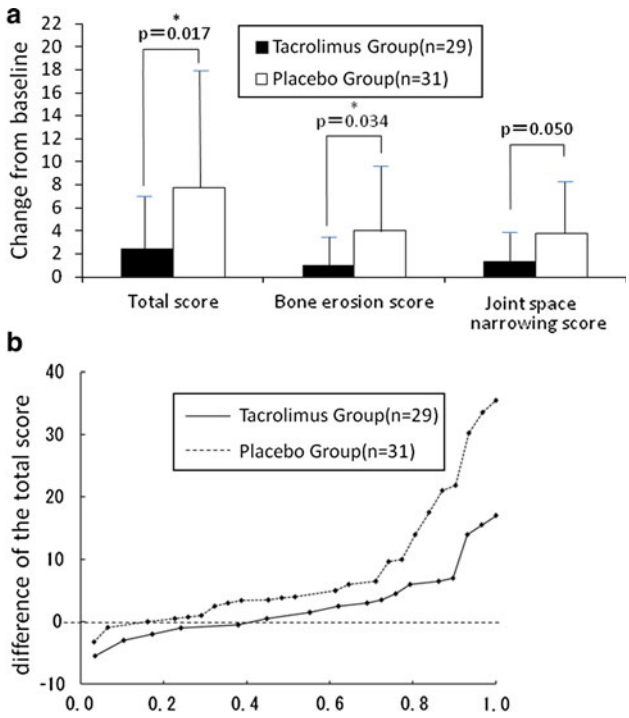

Fig. 3 **a** Evaluation of joint destruction. Joint destruction was evaluated by monitoring ΔTSS, the change in the ES, and the change in the JSN score by week 52 in the tacrolimus group and the placebo group, respectively. *TSS* total Sharp score, *ES* erosion score, *JSN* joint space narrowing; *$p < 0.05$ by analysis of covariance versus before administration in patients with or without MTX. **b** Cumulative probability of ΔTSS ≤0 up to week 52 in the tacrolimus group and the placebo group

three months until remission or low disease activity is achieved. However, there is insufficient evidence regarding the prevention of joint destruction by DMARDs apart from MTX. Tacrolimus is approved for the treatment of RA in Japan and shows good efficacy, suggesting that it could be useful for controlling joint destruction.

We previously investigated patients with a disease duration of RA of less than three years who showed an inadequate response to DMARDs. A double-blinded, placebo-controlled study of tacrolimus treatment was carried out for 12 months, with suppression of joint destruction as the primary outcome measure. Although baseline TSS showed no significant differences between the tacrolimus group and the placebo group, ΔTSS ≤0 was achieved in 24.1 % of the tacrolimus group versus 14.0 % of the placebo group [7]. Accordingly, the present subgroup analysis was performed, and CRP <1.5 mg/dL was identified as a factor that influenced the suppression of joint destruction by tacrolimus therapy according to univariate analysis. There were significantly smaller changes in TSS and ES in the patients with CRP <1.5 mg/dL from the tacrolimus group compared with those from the placebo group, as well as a smaller change of the JSN score, indicating that tacrolimus suppressed the progression of joint destruction in patients with early RA who had low disease activity and comparatively low CRP levels.

There have already been several reports about the prevention of joint destruction by biological agents [15–20],

Table 3 Adverse events (patients targeted for safety analysis and patients with CRP < 1.5 mg/dL)

	Tacrolimus group ($n = 32$)	Placebo group ($n = 31$)	Test[a]
Adverse event rate	81.3 % (26 patients, 102 events)	90.3 % (28 patients, 85 events)	$p = 0.474$
Severe adverse event rate	3.1 % (1 patient)	22.6 % (7 patients)	$p = 0.026$
Discontinuation rate due to adverse events	6.3 % (2 patients)	16.1 % (5 patients)	$p = 0.257$
Infections and infestations	40.6 % (13 patients, 25 events)	38.7 % (12 patients, 24 events)	$p = 1.000$
Benign, malignant and unspecified neoplasms (incl. cysts and polyps)	3.1 % (1 patient, 1 event)	3.2 % (1 patient, 1 event)	$p = 1.000$
Blood and lymphatic system disorders	6.3 % (2 patients, 2 events)	3.2 % (1 patient, 1 event)	$p = 1.000$
Psychiatric disorders		3.2 % (1 patient, 1 event)	$p = 0.492$
Nervous system disorders	9.4 % (3 patients, 4 events)	9.7 % (3 patients, 6 events)	$p = 1.000$
Eye disorders	9.4 % (3 patients, 3 events)	3.2 % (1 patient, 1 event)	$p = 0.613$
Vascular disorders	3.1 % (1 patient, 1 event)	6.5 % (2 patients, 2 events)	$p = 0.613$
Respiratory, thoracic, and mediastinal disorders	15.6 % (5 patients, 7 events)	16.1 % (5 patients, 6 events)	$p = 1.000$
Gastrointestinal disorders	31.3 % (10 patients, 15 events)	19.4 % (6 patients, 11 events)	$p = 0.387$
Skin and subcutaneous tissue disorders	21.9 % (7 patients, 7 events)	22.6 % (7 patients, 7 events)	$p = 1.000$
Musculoskeletal and connective tissue disorders	9.4 % (3 patients, 4 events)	9.7 % (3 patients, 3 events)	$p = 1.000$
Reproductive system and breast disorders	3.1 % (1 patient, 2 events)		$p = 1.000$
Congenital, familial and genetic disorders	3.1 % (1 patient, 1 event)		$p = 1.000$
General disorders and administration site conditions	6.3 % (2 patients, 3 events)	6.5 % (2 patients, 2 events)	$p = 1.000$
Investigations	40.6 % (13 patients, 26 events)	35.5 % (11 patients, 17 events)	$p = 0.797$
Injury, poisoning and procedural complications	3.1 % (1 patient, 1 event)	9.7 % (3 patients, 3 events)	$p = 0.355$

[a] Fisher's exact test

and the 2012 ACR Recommendations [14] suggest the use of biological agents combined with MTX for patients with early RA whose disease activity is high. However, it was reported that patients with early RA show no difference in their response to biological agents plus MTX versus DMARDs with regard to improvement of symptoms and suppression of bone erosion [21]. Thus, biological agents prevent further joint damage in patients with early RA who have higher disease activity and significant joint destruction, while the present study suggested that tacrolimus can suppress joint destruction in patients with early RA and CRP <1.5 mg/dL.

Tacrolimus has been reported to suppress the production of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6 [2, 22, 23], and it also delays the maturation of osteoclasts by inhibiting calcineurin and prevents the activation of T cells. In fact, animal studies have revealed the dose-dependent suppression of collagen-induced arthritis in rats by tacrolimus [24, 25], as well as the concentration-dependent induction of chondrocyte differentiation of progenitor cells in mouse [26]. In addition to an indirect action via the suppression of inflammatory cells, tacrolimus inhibits the maturation of osteoclasts by reducing the activation of NFATc1, a key regulator of osteoclast differentiation. Thus, tissue repair due to the promotion of bone/cartilage differentiation through direct action on osteoclasts helps tacrolimus to lessen joint destruction, and such a mechanism seems to support the results of the present subgroup analysis.

Our analysis revealed that joint destruction was prevented by adding treatment with tacrolimus at 3 mg daily in patients with early RA and CRP < 1.5 mg/dL who showed resistance to DMARDs. These results suggest that the combination of DMARDs and tacrolimus safely achieves clinical improvement in patients with early RA and CRP <1.5 mg/dL by preventing the progression of joint destruction. However, further studies will be required to confirm the suppression of joint destruction by tacrolimus in other patient populations.

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