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ORIGINAL ARTICLE

Concomitant iguratimod therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate: a randomized, double-blind, placebo-controlled trial

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Abstract
Objectives To investigate the efficacy and safety of iguratimod (T-614) in Japanese patients with active rheumatoid arthritis who had inadequate response to stable background methotrexate (MTX) alone.
Methods In this multicenter, double-blind, controlled trial, a total of 253 patients were randomized at 2:1 ratio to either the iguratimod group or the placebo group. Iguratimod was orally administered at dosages of 25 mg/day for the first 4 weeks (25 mg once daily) and 50 mg/day for the subsequent 20 weeks (25 mg twice daily). MTX at dosage of 6 or 8 mg/week was administered to patients in both groups.
Results The rate of 20 % improvement in American College of Rheumatology criteria (ACR20) at week 24 was 69.5 % in the iguratimod group compared with 30.7 % in the placebo group ($P < 0.001$). Significant improvements in the ACR50, ACR70, Health Assessment Questionnaire Disability Index, Disease Activity Score 28 <3.2, and rheumatoid factor were also observed. The most commonly reported adverse events (AEs) were blood iron decrease, nasopharyngitis, and lymphocyte decrease. These AEs were mild or moderate in severity. No deaths occurred.
Conclusion The study results suggest that iguratimod in combination with MTX was efficacious and had a manageable safety profile.

Keywords Disease-modifying antirheumatic drug · Iguratimod · Methotrexate · Rheumatoid arthritis · T-614

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory arthritis that can result in permanent joint damage, and is associated with high morbidity and mortality. Methotrexate (MTX), one of the disease-modifying antirheumatic drugs (DMARDs), has been most selected for initial RA treatment because of its efficacy, acceptable safety profile, and low cost. Recently, combination therapies of MTX with either biological agents such as infliximab [1] and adalimumab [2] or other small-molecule antirheumatic drugs such as salazosulfapyridine [3], leflunomide [4], and bucillamine [5] have been reported to have greater efficacy than MTX alone. The American College of Rheumatology (ACR) 2008 guideline recommends use of nonbiologic and biologic DMARDs based on RA disease duration, RA disease activity, prognostic factors for RA, and previous experience of DMARDs, including failure of prior MTX monotherapy [6]. Currently, treatment choices are dominated by patient and physician preferences, side-effects, and costs [7]. Because a patient's response to available medications shows variability in efficacy, toxicity, and unpredicted necessity of discontinuation, combination therapy of a new small-molecule antirheumatic drug with MTX is needed to provide more options, especially in terms of switching medications and lowering treatment costs compared with biological agents.

Iguratimod (T-614) is a small-molecule antirheumatic drug for which the rate of 20 % improvement in ACR criteria (ACR20) was not inferior to that of salazosulfapyridine in Japanese patients with active RA (63.1 % for iguratimod versus 57.7 % for salazosulfapyridine) [8]. Iguratimod suppressed tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 via inhibition of nuclear factor-kappa B activation in cultured human synovial cells and human acute monocytic leukemia cells [9–11]. Iguratimod also reduced immunoglobulin (Ig) production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation [12]. In a clinical trial, iguratimod significantly decreased rheumatoid factor and the production of IgG, IgM, and IgA compared with placebo in patients with active RA [8]. Thus, iguratimod has been suggested to be a clinically useful DMARD with unique mechanisms of action [8, 13, 14]. Recently, an increased release of extracellular adenosine and a decreased production of lymphotoxins such as ammonia and superoxide have been shown to be involved in the anti-inflammatory mechanisms of MTX [15–17]. Thus, the combination of MTX and iguratimod may have synergic efficacy for RA treatment, but the efficacy of the combination therapy of iguratimod with MTX in patients with RA has not been reported. This randomized, double-blind trial compared iguratimod + MTX treatment with placebo + MTX treatment in patients who had inadequate response to MTX and evaluated efficacy using the ACR20, ACR50, ACR70, Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score using 28 joint counts (DAS-28), and rheumatoid factor.

Patients and methods

Patients

Patients who gave written informed consent were enrolled in this study. Eligible patients had a diagnosis of active RA for less than 10 years based on ACR criteria [18]. They were aged 20 to <70 years and had active RA despite MTX therapy (≥6 mg/week) for more than 12 weeks, including stable low dosages of MTX (6–8 mg/week) for at least 8 weeks before study enrollment. Eligible patients also fulfilled the following criteria: at least 6 tender joints (excluding distal interphalangeal joints), at least 4 swollen joints (excluding distal interphalangeal joints), and an erythrocyte sedimentation rate (ESR) of at least 28 mm/h or a blood C-reactive protein (CRP) concentration of at least 1.0 mg/dL. A 4-week washout period before initiation of study treatment was established for previous DMARDs (except for MTX) or immunosuppressive drugs. A 3-month washout period was established for biological antirheumatic agents and a 6-month washout period for leflunomide and other RA clinical trial drugs. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids at prednisolone-equivalent doses of 7.5 mg or less was permitted throughout the study if patients had been taking these medications at stable doses for at least 4 weeks before study drug administration.

Exclusion criteria were as follows: impaired hepatic function as shown by abnormal results on liver function tests [i.e., elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels above the upper limit of normal], known hematopoietic disorder (absolute leukocyte count <4000/μL, platelet count <100,000/μL, hemoglobin level <9.0 g/dL), positive results on serologic tests for hepatitis B or C, pregnancy or breast feeding, history of drug or alcohol abuse, persistent or severe infection, active digestive diseases, previous treatment with iguratimod, body weight <40 kg, and RA with Steinbrocker's class IV.

Study design

The study was conducted in 99 medical institutions in Japan between August 2009 and February 2011. The study drugs were provided by the study sponsors (Toyama

Chemical and Eisai, Tokyo, Japan). An independent efficacy and safety evaluation committee was organized to discuss study protocol amendments and premature termination of the study. The study was conducted in compliance with the Declaration of Helsinki. The institutional review board at each institute approved the study protocol. This study was registered at http://clinicaltrials.gov (NCT00965757).

The study consisted of a 4-week observation period and a 24-week double-blind treatment period. Eligible patients were separated into either the iguratimod group (iguratimod + MTX) or the placebo group (placebo + MTX) in 2:1 randomization. Iguratimod was orally administered at dosages of 25 mg/day for the first 4 weeks (25 mg once daily) and 50 mg/day for the subsequent 20 weeks (25 mg twice daily). MTX at low dosages of 6 or 8 mg/week and folic acid at dosage of 5 mg/week were administered to patients in both groups for the treatment period.

Measurement of efficacy and safety

The primary efficacy endpoint was the rate at which patients (the full analysis set) achieved ACR20 at week 24 or last observation carried forward (LOCF) [19]. Clinical improvement was assessed by 20 % improvement in 68 tender joint counts and 66 swollen joint counts, and 20 % improvement in three of the following five criteria: patient's assessment of pain intensity on a visual analog scale (VAS, 0–100 mm), patient's global assessment of disease activity on a VAS (0–100 mm), physician's global assessment of disease activity on a VAS (0–100 mm), HAQ-DI [20], and CRP, or ESR. Secondary endpoints included the ACR50, ACR70, ACR components, DAS28-CRP [21, 22], and HAQ-DI. A decrease in HAQ-DI scores shows improvement, and a decrease greater than 0.22 represents the minimum clinically important difference [23]. The state of disease activity was evaluated based on DAS28 score as remission (<2.6), low disease activity (<3.2), moderate disease activity (≥3.2 and ≤5.1), or high disease activity (>5.1) [22, 24]. These evaluations were undertaken at 8-week intervals.

Safety was evaluated by adverse event reports, laboratory assays for changes in hematologic characteristics, blood chemistry, urinalysis, and liver function, and physical examinations. These evaluations were undertaken during the observation period and at each visit in the treatment period (0, 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after start of treatment).

Statistical analysis

Assuming ACR20 response rates of 50 % in the iguratimod group and 25 % in the placebo group, a sample size of 128 patients and 64 patients (randomization ratio of 2:1), respectively, was estimated to be necessary to demonstrate a 25 % difference in ACR20 response rates with 90 % power for Fisher's exact test and an alpha of 0.05. Taking potential dropouts into consideration, a total of 240 subjects (160 patients in the iguratimod group and 80 patients in the placebo group) was estimated to be necessary.

Demographic and baseline characteristics were compared between the groups using the *t* test for continuous variables and Fisher's exact test for categorical variables.

All efficacy analyses were primarily performed on the full analysis set, defined as all randomized patients who received at least one dose of study drug and from whom at least one assessment of efficacy under double-blind medication was available. The primary efficacy endpoint of ACR20 at week 24 (LOCF) was compared between the iguratimod group and the placebo group using the Fisher's exact test. For ACR20, results on the per protocol set were also presented. Changes from baseline in individual ACR core components, immunological test values, HAQ-DI, and DAS28 were presented as summary statistics for each group, and intragroup comparison was made using the paired *t* test and intergroup comparison was made using the *t* test.

All safety analyses were performed on the safety analysis set, defined as all randomized patients who received at least one dose of study drug and from whom at least one assessment of safety under double-blind medication was available. The incidence of adverse events was calculated, and the two groups were compared using Fisher's exact test.

Significance levels in the tests were as follows: two-sided 15 % for uniformity between groups and two-sided 5 % for intergroup and intragroup comparisons.

Results

Patient characteristics

A total of 389 patients were assessed for eligibility. Among these patients, 253 eligible patients were randomly assigned to the iguratimod group ($n = 165$) and the placebo group ($n = 88$) in 2:1 ratio (Fig. 1). One patient in the iguratimod group was excluded from the safety analysis set and full analysis set because data on efficacy and safety were not available. A total of 34 patients (20 patients in the iguratimod group and 14 patients in the placebo group) were excluded from the per protocol set due to protocol violation, eligibility violation, or/and early discontinuation of medication (less than 16 weeks or less than 8 weeks due to aggravation of symptoms) (Fig. 1).

The percentage of patients who did not complete the 24-week treatment was 10.3 % in the iguratimod group and

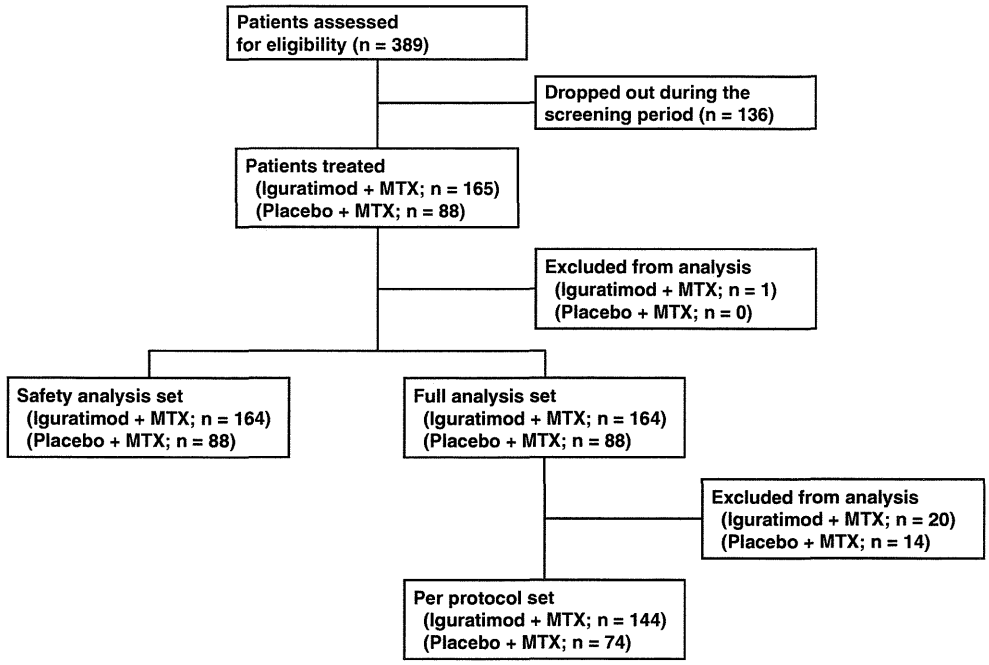

Fig. 1 Randomization protocol and patient disposition. Eligible patients were allocated to either the iguratimod group (iguratimod + MTX) or the placebo group (placebo + MTX) in 2:1 ratio. *MTX* methotrexate

Table 1 Demographics at baseline of patients with active rheumatoid arthritis (full analysis set)

	Iguratimod + MTX ($n = 164$)	Placebo + MTX ($n = 88$)
Female, *n* (%)	134 (81.7)	70 (79.5)
Age (SD), years	54.8 ± 9.9	53.5 ± 10.0
Age ≥65 years, *n* (%)	32 (19.5)	16 (18.2)
Duration of RA (SD), months	53.8 ± 35.0	50.3 ± 34.0
Positive for rheumatoid factor, *n* (%)	128 (78.0)	67 (76.1)
Positive for anti-CCP antibodies, *n* (%)	144 (87.8)	78 (88.6)
Previous therapy with DMARDs except for MTX, *n* (%)	61 (37.2)	28 (31.8)
Concomitant medication, *n* (%)		
NSAIDs	151 (92.1)	81 (92.0)
Corticosteroids	86 (52.4)	48 (54.5)
Folic acid	164 (100)	88 (100)
MTX at baseline, *n* (%)		
6 mg/week	51 (31.1)	27 (30.7)
8 mg/week	113 (68.9)	61 (69.3)

Values are number of patients (%) or mean ± SD

RA rheumatoid arthritis, *CCP* cyclic citrullinated peptides, *DMARDs* disease-modifying antirheumatic drugs, *NSAIDs* nonsteroidal anti-inflammatory drugs, *MTX* methotrexate

20.5 % in the placebo group; 4.2 % of patients in the iguratimod group and 12.5 % in the placebo group discontinued due to aggravation of symptoms, and 4.2 % in the iguratimod group and 3.4 % in the placebo group discontinued due to adverse events.

Table 1 presents baseline demographics, and Table 2 presents baseline clinical characteristics of patients in the safety analysis set and the full analysis set. There were no statistically significant differences between groups at baseline ($P < 0.15$). In each group, 92 % of patients were treated with NSAIDs. Only one patient in each group had been previously treated with biologic DMARDs. A total of 37.2 and 31.8 % of patients in the iguratimod and placebo groups, respectively, had history of treatment with nonbiologic DMARDs (except for MTX) and/or immunosuppressants.

ACR response rates

The ACR20 response rate, which was the primary efficacy endpoint in this study, was significantly improved by 24-week (LOCF) treatment with iguratimod compared with placebo: 69.5 % (iguratimod) versus 30.7 % (placebo) in the full analysis set ($P < 0.001$). Similarly, the secondary efficacy endpoints, ACR50 and ACR70, at week 24 in the iguratimod group were significantly greater than those of the placebo group: 38.4 versus 15.9 % for ACR50 ($P < 0.001$) and 17.1 versus 5.7 % for ACR70 ($P = 0.010$), respectively. Figure 2 shows the ACR20 response rate as a function of treatment period, indicating that a significant improvement in ACR20 was also achieved by 8- and 16-week treatments with iguratimod compared with placebo. The data in Fig. 2 were based on observed cases. When ACR20 was analyzed based on the per protocol set,

Table 2 Mean changes in secondary variables from baseline to week 24 (LOCF) (full analysis set)

	Iguratimod + MTX (n = 164)	Placebo + MTX (n = 88)	P value[a]
Tender joint count (n)			
Baseline	12.5 ± 6.5	13.3 ± 8.1	
Change from baseline	−7.4 ± 6.0	−4.6 ± 7.8	0.001
Swollen joint count (n)			
Baseline	11.5 ± 6.3	11.1 ± 5.7	
Change from baseline	−6.5 ± 5.9	−2.9 ± 6.7	<0.001
Patient's assessment of pain (mm)			
Baseline	47.5 ± 22.2	46.4 ± 23.1	
Change from baseline	−22.0 ± 23.8	−2.5 ± 27.0	<0.001
Patient's global assessment of disease activity (mm)			
Baseline	47.7 ± 24.3	50.1 ± 23.5	
Change from baseline	−21.2 ± 26.4	−5.0 ± 27.1	<0.001
Physician's global assessment of disease activity (mm)			
Baseline	52.6 ± 18.3	53.2 ± 19.0	
Change from baseline	−27.1 ± 19.3	−10.4 ± 26.6	<0.001
HAQ-DI			
Baseline	0.82 ± 0.55	0.73 ± 0.51	
Change from baseline	−0.35 ± 0.45	0.03 ± 0.55	<0.001
C-reactive protein level (mg/dL)			
Baseline	1.84 ± 1.94	1.71 ± 1.58	
Change from baseline	−0.53 ± 2.07	0.47 ± 2.03	<0.001
Erythrocyte sedimentation rate (mm/h)			
Baseline	45.6 ± 21.0[b]	41.8 ± 22.5	
Change from baseline	−9.3 ± 20.8[b]	2.6 ± 19.7	<0.001
Rheumatoid factor (U/mL)			
Baseline	117.1 ± 181.9	147.9 ± 279.1	
Change from baseline	−37.4 ± 63.0	31.7 ± 190.9	<0.001[c]
IgG (mg/dL)			
Baseline	1535 ± 377	1517 ± 350	
Change from baseline	−152 ± 190	15 ± 151	<0.001[c]
IgM (mg/dL)			
Baseline	129 ± 154	124 ± 63	
Change from baseline	−15 ± 25	5 ± 22	<0.001[c]
IgA (mg/dL)			
Baseline	311 ± 123	307 ± 109	
Change from baseline	−42 ± 41	−2.3 ± 38	<0.001[c]
DAS28-CRP			
Baseline	4.87 ± 0.89	4.97 ± 0.86	
Change from baseline	−1.51 ± 1.22	−0.66 ± 1.28	<0.001
HAQ-DI responders (>0.22), n (%)	104 (63.4)	32 (36.4)	<0.001

Values are the mean ± SD

[a] Intergroup comparisons between the changes were made by t test unless indicated

[b] n = 163

[c] These intergroup comparisons were made by Wilcoxon rank-sum test. *HAQ-DI* Health Assessment Questionnaire Disability Index, *DAS28* Disease Activity Score using 28 joint counts, *CRP* C-reactive protein level

ACR20 in the iguratimod group (71.5 %) was significantly greater than that in the placebo group (35.1 %) ($P < 0.001$).

The ACR20 response rate in the full analysis set at week 24 in the iguratimod group did not depend on the duration of RA disease; 71.1 % (32 of 45 patients) for <2 years, 64.0 % (32/50) for 2–5 years, and 72.5 % (50/69) for 5–10 years showed an ACR20 response. Corresponding values in the placebo group were 29.2 % (7/24), 34.5 % (10/29), and 28.6 % (10/35), respectively. Furthermore, ACR20 at week 24 in the iguratimod group was not significantly affected by the presence or absence of history of treatment with DMARDs (except for MTX) and/or immunosuppressants; 65.6 and 71.8 % showed an ACR20 response in the presence and absence of this previous history, respectively ($P = 0.483$). Corresponding values in the placebo group were 21.4 and 35.0 %, respectively.

Changes from baseline in individual ACR core components, immunological test values, HAQ-DI, and DAS28

Changes from baseline in secondary variables at week 24 (LOCF) are presented in Table 2. In the iguratimod group, tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, CRP level, and ESR rate at week 24 significantly improved compared with baseline (all values of $P \leq 0.001$; intragroup paired t test comparisons). In the placebo group, tender joint count, swollen joint count, and physician's global assessment of disease activity at week 24 significantly improved compared with baseline, but no significant

improvements were found in patient's assessment of pain, patient's global assessment of disease activity, and ESR rate. Furthermore, in the placebo group, a significant worsening in CRP level was found ($P = 0.032$; intragroup comparison).

Changes at week 24 from baseline in tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, CRP level, and ESR in the iguratimod group were significantly greater than those in the placebo group (all values of $P \leq 0.001$).

The rheumatoid factor at week 24 in the iguratimod group significantly improved compared with baseline ($P < 0.001$; intragroup comparison), but that in the placebo group worsened, although not significantly ($P = 0.652$; intragroup comparison). Total amounts of serum IgG, IgM, and IgA at week 24 in the iguratimod group significantly decreased compared with baseline (all values of $P < 0.001$; intragroup comparison), but those at week 24 in the placebo group did not significantly change compared with baseline. The change of rheumatoid factor at week 24 from baseline in the iguratimod group was significantly greater than that in the placebo group ($P < 0.001$) (Table 2). Similarly, changes in the total amounts of IgG, IgM, and IgA in the iguratimod group were also significantly greater than those in the placebo group, respectively (all values of $P < 0.001$) (Table 2).

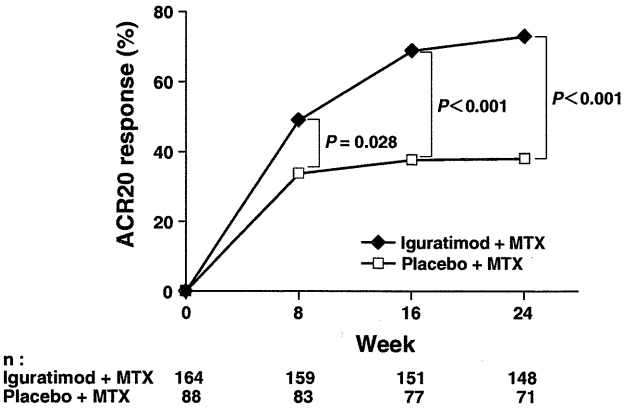

Fig. 2 Rate of response for patients who achieved 20 % improvement in American College of Rheumatology rheumatoid arthritis criteria (ACR20) as a function of treatment period in iguratimod and placebo groups. Data are based on observed cases

Physical function as measured by HAQ-DI at week 24 significantly improved compared with baseline in the iguratimod group ($P < 0.001$; intragroup comparison), but almost no change was found in the placebo group. The mean change in HAQ-DI of −0.35 in the iguratimod group at week 24 from baseline was significantly different from that of 0.03 in the placebo group ($P < 0.001$). Significantly more patients in the iguratimod group achieved a minimum clinically important difference (−0.22) in HAQ-DI at week 24 (LOCF) compared with patients in the placebo group (63.4 versus 36.4 %, respectively; $P < 0.001$).

Mean disease activity score (DAS28-CRP) in the iguratimod group in the full analysis set at week 24 was 3.37 ± 1.18, which was significantly lower than the score of 4.31 ± 1.31 in the placebo group ($P < 0.001$). Significantly more patients in the iguratimod group showed remission (DAS28-CRP <2.6) at week 24 (LOCF) compared with the placebo group (27.4 versus 9.1 %, respectively; $P < 0.001$). Significantly more patients in the iguratimod group showed low disease activity (DAS28-CRP <3.2) compared with patients in the placebo group (47.6 versus 20.5 %, respectively; $P < 0.001$) (Fig. 3).

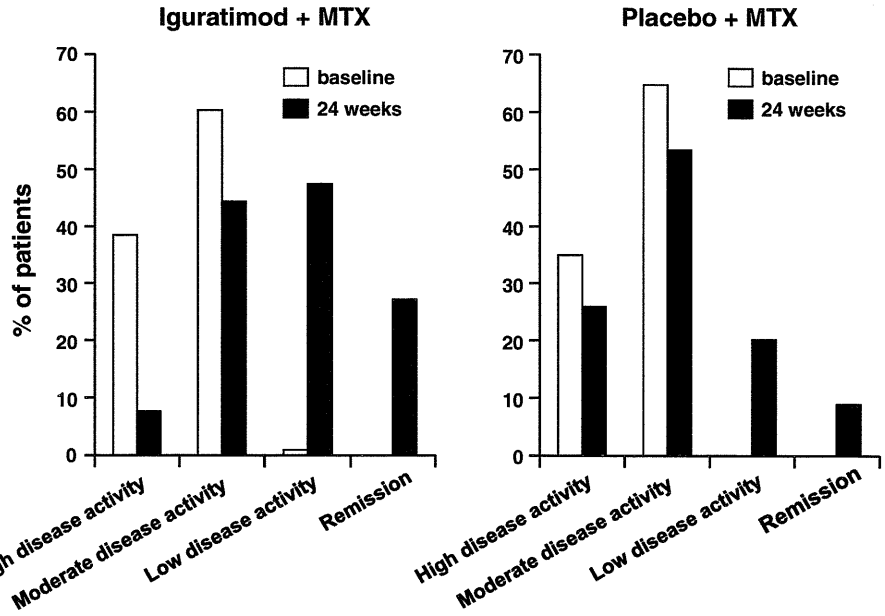

Fig. 3 Percentage of patients in remission with low, moderate, and high RA disease activities at baseline and at the end of 24-week treatment (LOCF) (full analysis set). The measure of the disease activity is DAS28-CRP; remission (DAS28 <2.6), low disease activity (<3.2), moderate disease activity (≥3.2 and ≤5.1), and high disease activity (>5.1). *DAS28* Disease Activity Score using 28 joint counts, *CRP* C-reactive protein

Safety

Adverse events (AEs) were reported in 80.5 % of patients in the iguratimod group and 75.0 % in the placebo group, with no significant differences between groups. AEs in older patients (≥65 years) occurred in 96.9 % of patients in the iguratimod group and 81.3 % of patients in the placebo group, and AEs in younger patients (<65 years) occurred in 76.5 and 73.6 % of patients, respectively. Table 3 presents the AEs occurring in ≥5 % of patients. No statistically significant difference was seen in incidence for any of the AEs listed in Table 3 between groups. The most commonly reported AEs coded by the Medical Dictionary for Regulatory Activities-preferred term were blood iron decreased, nasopharyngitis, and lymphocyte count decreased in both the iguratimod and placebo groups. These AEs were mild or moderate in severity. Seven patients in the iguratimod group discontinued due to AEs: cell marker (KL-6) increased, interstitial lung disease, stomatitis, white blood cell count decreased, back pain, diarrhea/flank pain, and anemia/white blood cell count decreased/red blood cell count decreased/hemoglobin decreased/hematocrit decreased. Three patients in the placebo group discontinued due to AEs: synovial rupture, cardiac failure, and joint sprain. Serious AEs were reported by 5 patients in the iguratimod group (gastroduodenal ulcer, tendon rupture, carbon monoxide poisoning, interstitial lung disease, and retinal hemorrhage) and 3 patients in the placebo group (synovial rupture, fallopian tube cancer, and cardiac failure). No deaths were reported.

Increases in ALT and AST levels were reported in both the iguratimod and placebo groups (Table 3). ALT or AST levels more than 100 U/L were observed in 3 patients in the iguratimod group (1.8 %) and in 2 patients in the placebo group (2.3 %). No patients discontinued study treatment due to increases in ALT and AST levels. One patient each in the iguratimod group showed a notable decrease in leukocyte (<2.0 × 10^3/μL) and erythrocyte (<2.5 × 10^6/μL) counts; these abnormal laboratory findings resolved after the patients stopped study treatment. No notable trends in blood pressure compared with baseline were observed in any group.

Table 3 Adverse events occurring in ≥5 % of patients

	Iguratimod + MTX (n = 164)	Placebo + MTX (n = 88)
Nasopharyngitis	28 (17.1)	14 (15.9)
Pharyngitis	7 (4.3)	6 (6.8)
Upper respiratory tract inflammation	9 (5.5)	2 (2.3)
Stomatitis	11 (6.7)	2 (2.3)
Lymphocyte count decreased	23 (14.0)	8 (9.1)
AST increased	16 (9.8)	5 (5.7)
ALT increased	9 (5.5)	7 (8.0)
β2-Microglobulin increased	13 (7.9)	2 (2.3)
β2-Microglobulin urine increased	11 (6.7)	1 (1.1)
Blood iron decreased	35 (21.3)	16 (18.2)

Values are the number of patients (%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Discussion

This study is the first to demonstrate that the combination of two small-molecule RA agents, iguratimod and MTX, is associated with statistically and clinically meaningful improvements in patients with active RA with inadequate response to MTX compared with the combination of placebo and MTX. The primary endpoint of ACR20 response rate at week 24 was 69.5 % in the iguratimod group compared with 30.7 % in the placebo group ($P < 0.001$). The ACR20 rate with iguratimod was significantly improved compared with placebo at week 8 and week 16 (Fig. 2). Treatment with iguratimod for 24 weeks was consistently superior to placebo for the ACR50, ACR70, HAQ-DI, and DAS28-CRP.

Recently, guidance for treatment to target was proposed to improve the management of RA in clinical practice [25], in which low disease activity was set as an acceptable therapeutic goal, particularly in patients with long-standing disease, considerable joint damage, and several prior treatment failures. In the present study, the mean duration of RA was more than 4 years in both groups and the numbers of tender joints and swollen joints were ≥6 and ≥4, respectively, at baseline. Thus, we consider that the therapeutic goal for patients enrolled in the present study is "low disease activity" (DAS28-CRP <3.2). After the 24-week treatment, this goal was achieved in 47.6 % of patients in the iguratimod group and 20.5 % in the placebo group. At baseline, patients with low disease activity were 1.2 % in the iguratimod group and 0 % in the placebo group. Furthermore, clinical remission (DAS28-CRP <2.6) was achieved in 27.4 % of patients in the iguratimod group and 9.1 % in the placebo group.

B cells can produce autoantibodies against antigens such as the Fc region of IgG, the target of rheumatoid factor. The sensitivity of rheumatoid factor in the diagnosis of RA is about 75 % in most cross-sectional studies, and about 25 % of patients with RA have no detectable serum rheumatoid factor [26]. Rheumatoid factor-positive RA patients had more severe disease, both functionally and radiographically, than rheumatoid factor-negative patients [27].

Recently, the presence of rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) antibodies and elevated IgG levels have been shown to be two simple biomarkers that can be used routinely before therapy to predict response to rituximab, a B cell-depleting monoclonal antibody, in patients with refractory RA [28]. In the present study, rheumatoid factor after 24-week treatment with iguratimod + MTX significantly decreased from baseline by 33 % ($P < 0.001$), whereas with placebo + MTX it increased from baseline by 14 % (not significant). Furthermore, IgG, IgM, and IgA levels at week 24 in the iguratimod group significantly decreased from baseline (all values of $P < 0.001$), whereas these levels in the placebo group did not significantly change (slight increases for IgG and IgM and a slight decrease for IgA) (Table 2). These results indicate that iguratimod and/or iguratimod-induced synergic effects have immunological actions, but MTX alone did not.

Previously, ALT and AST levels of more than 100 U/L were observed in 9.8 and 6.9 %, respectively, of RA patients who were treated with iguratimod (without MTX) for 52 weeks [13]. These ALT and AST increases were mostly evident between week 4 and week 8 and resolved spontaneously during treatment or upon discontinuation of treatment [13]. Thus, one of the safety concerns when combining MTX with iguratimod was potential hepatotoxicity. However, in the present study, ALT and AST levels of more than 100 U/L were found only in 1.2 and 0.6 %, respectively, of RA patients treated with iguratimod + MTX; similar increases were seen in 1.1 and 1.1 %, respectively, of patients treated with placebo + MTX. These results indicate that the combination of iguratimod with MTX did not increase the risk of hepatotoxicity. Because this study selected patients who had been treated with MTX for more than 12 weeks and had AST or ALT levels less than the upper limit of normal range, a possibility is considered that the hepatic function in the patients previously treated with MTX had a relatively good safety profile for use of iguratimod + MTX. One patient each in the iguratimod group showed a notable decrease in leukocyte ($<2.0 \times 10^3/\mu L$) and erythrocyte ($<2.5 \times 10^6/\mu L$) counts, and these abnormal laboratory findings resolved after patients stopped study treatment. These results suggest that the combination therapy of iguratimod with MTX can be used safely with hepatic enzyme and hematologic monitoring.

In this study, lower dosages of MTX (6 or 8 mg/week) were used, compared with dosages used in Europe and the USA, because the approved maximum dosage in Japan was 8 mg/week at the beginning of this study (higher dosages of MTX were approved in February 2011). A future study is necessary to confirm whether the greater efficacy of combination therapy with MTX and iguratimod is achieved when a higher dosage of MTX is used instead of the present low dosages.

Because the mode of action of iguratimod is different from that of MTX and the present efficacy of the combination therapy of MTX + iguratimod is greater than that of MTX + placebo, the present combination therapy is a good treatment option for patients who have inadequate response to MTX or for patients who cannot afford expensive biological agents.

In conclusion, the present new combination of iguratimod with MTX is efficacious and tolerated over 24 weeks in patients with active RA with inadequate response to MTX.

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ORIGINAL ARTICLE

Dislocation of the extensor carpi ulnaris tendon in rheumatoid wrists using three-dimensional computed tomographic imaging

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Abstract The purpose of this study was to evaluate dislocation of the extensor carpi ulnaris (ECU) tendon in patients with rheumatoid arthritis (RA) using three-dimensional computed tomography (3DCT). We then determined the value of 3DCT for predicting spontaneous extensor tendon rupture. 3DCT images of 102 wrists from 96 patients with RA were analyzed. Dislocation of the ECU tendon was evaluated from the 3DCT images with a soft tissue window. Dorsal subluxation of the ulnar head was evaluated as the dorsal subluxation ratio (DSR), and carpal supination was evaluated as the carpal supination angle (CSA) from the 3DCT images with a bone tissue window. Extensor tendon rupture was found in 43 of 102 wrists (42 %). Dislocation of the ECU tendon was found in 35 of 102 wrists (34 %). Dislocation of the ECU tendon was a strong risk factor for extensor tendon rupture in the multivariable logistic regression analysis, with an odds ratio of 26 (95 % confidence interval 7–99, $p<0.001$). The DSR ($p=0.029$) and CSA ($p=0.035$) were significantly larger in wrists with a dislocated ECU tendon. Dislocation of the ECU tendon was well depicted using 3DCT images. It was strongly associated with extensor tendon rupture in the rheumatoid wrist.

Keywords Extensor carpi ulnaris tendon · Extensor tendon · Rheumatoid arthritis · Rupture · Three-dimensional computed tomography

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Introduction

The extensor carpi ulnaris (ECU) tendon is situated in the wrist at the groove between the head and styloid process of the ulna. The ECU tendon resides within its own subsheath, which is separate from the overlying extensor retinaculum and stabilizes the tendon within its groove along the distal ulna. The ECU tendon therefore contributes to the stability of the distal radioulnar joint (DRUJ), and its relation to the anatomy of the extensor retinaculum allows unrestricted forearm rotation. In some rheumatoid arthritis (RA) patients, synovial thickening increases in the subsheath of the ECU tendon, resulting in destruction of the restraining subsheath. Under these conditions, the ECU tendon can dislocate. Having lost functional support of the ECU tendon, the DRUJ can dislocate by gradual stretching of the DRUJ and the disk. Primary rheumatoid involvement of the DRUJ is not needed for this situation to occur [1].

Tenosynovitis involving the extensor tendons of the wrist is observed in 50–64 % of patients with RA [2]. An important complication is spontaneous rupture, which has been explained by two mechanisms: mechanical attrition by the bone structure and invasion of the tendon by tenosynovial pannus [3]. During attrition of the bone structure, the sharp edge of the distal ulna related to DRUJ instability abrades and tears the extensor tendons. There is then direct synovial invasion and devascularization of the tendon, causing rupture.

As DRUJ instability is associated with extensor tendon rupture, we hypothesized that dislocation of the ECU tendon is also associated with extensor tendon rupture. We evaluated dislocation of the ECU tendon using three-dimensional computed tomography (3DCT) and investigated its clinical relevance. The purpose of this study was to examine the value of 3DCT for predicting spontaneous extensor tendon rupture in patients with RA.

Materials and methods

Patients

3DCT images of 102 wrists in 96 patients with RA were reviewed retrospectively. Inclusion criteria were RA diagnosed according to the 1987 criteria of the American College of Rheumatology and persistent wrist pain for more than 6 months despite ongoing medical treatment. Exclusion criteria included subluxated fourth and fifth carpometacarpal joints and severe ulnar head resorption (e.g., pencil-like tapering). The possibilities of dislocation of the extensor tendons at the metacarpophalangeal (MCP) joints, volar dislocation of the MCP joints, and posterior interosseous nerve palsy were excluded before a definitive diagnosis of extensor tendon rupture was established.

A series of 3DCT images of the wrists were routinely obtained in patients complaining of persistent wrist pain for more than 6 months from January 2007 to September 2008. We investigated the wrists with respect to each joint. If patients were having wrist pain and it was bilateral, both hands were included in the study. The images were obtained with the informed consent of the RA patients in accordance with the Declaration of Helsinki.

Image acquisition

Imaging was performed on a multi-slice CT scanner (Aquilion, Super Heart Edition; Toshiba, Japan). Imaging parameters included a slice thickness of 1 mm with an interval of 0.5 mm, a gantry rotation speed of 7.5 mm/rotation, 120 kV, and 100–200 mA. Each patient was placed in a prone position with the involved arm above the head. The image was taken with the forearm in maximum pronation, the wrist in neutral position, and the fingers in a resting position. The 3DCT images were reconstructed in the range between the cross-section of the middle point of the third metacarpal perpendicular to its long axis and the cross-section of the distal forearm 3 cm proximal to the radiocarpal joint in the sagittal plane (bone tissue window). The volume rendering system and Aquarius Net Station, version 1.5 (TeraRecon, San Mateo, CA, USA) allowed depiction of the extensor tendons and skeletal structures (soft tissue window). A window level value of approximately 60 and window width of approximately 60 were used.

Image analysis

Dorsal subluxation of the ulnar head was evaluated as the dorsal subluxation ratio (DSR), and carpal supination was evaluated as the carpal supination angle (CSA) from 3DCT images with a bone tissue window. The distance (DS) between the most protruded point of the ulnar head and the tangential line was measured. The width of the ulnar head (UW) was measured using an image from the ulnar side. The DSR was calculated as (DS/UW)×100(%) (Fig. 1). Next, a line was drawn that connected the center of the second and the fifth metacarpal cross-sections. The CSA was obtained by measuring the angle (θ) between the connection line of the metacarpals and the tangential line of the dorsal surface of the distal radius (Fig. 1). Ishikawa et al. [4] stated that the DSR and the CSA were useful parameters for quantifying wrist deformity and predicting the risk of extensor tendon rupture. The cutoff values for extensor tendon rupture were 32 % for the DSR and 14° for the CSA. There was excellent interobserver and intraobserver repeatability of the DSR and the CSA. The interrater interclass correlation coefficients (ICCs) for the DSR and the CSA were 0.82 and 0.79, respectively. The intrarater ICCs were 0.96 and 0.92, respectively.

We examined whether the ECU tendon was dislocated based on the 3DCT images with a soft tissue window. For example, Fig. 2a shows synovitis in the DRUJ and dorsal subluxation of the ulnar head where the ECU tendon was not dislocated and situated in the groove. By contrast, Fig. 2b shows dorsal subluxation of the ulnar head, and the ECU tendon was dislocated volarly. Three orthopedic surgeons

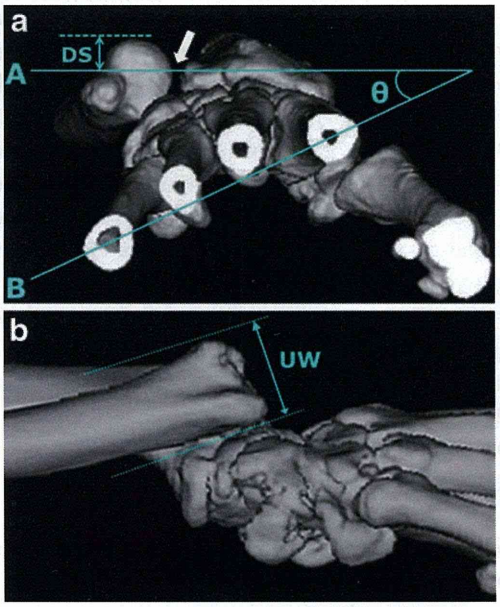

Fig. 1 **a** Image of the wrist viewing a cross section of the third metacarpal 10° from the distal dorsal side to the proximal palmar side. *Line A* is the tangential line of the plateau of the fourth dorsal compartment, passing the level of the contact point (*arrow*) between the radius and the ulna. *Line B* is the connecting line of the center of the second and the fifth metacarpal cross-sections. The carpal supination angle (CSA) is defined as the angle (θ) between *lines A* and *B*. The CSA is used as a quantitative indicator of carpal supination deformity in the rheumatoid wrists. DS is the distance between the most protruding point of the ulnar head and *line A*. **b** Image from the ulnar side. The UW was measured using an image from the ulnar side. The dorsal subluxation ratio (DSR) was calculated by DS/UW×100 (%). The DSR was used as a quantitative indicator of distal radioulnar joint (DRUJ) subluxation

evaluated the patients to determine if the ECU tendon was dislocated. In cases of disagreement, a consensus was reached.

Assessment of covariates

The following parameters were assessed in all patients: age, sex, and duration of disease. The examined side (right or left) and Larsen grade [5, 6] in the radiograph were assessed separately for each wrist. We studied the four factors (dislocation of the ECU tendon; CSA; DSR using 3DCT imaging; and the scallop sign [7] on the radiograph) that might predict extensor tendon rupture. The scallop sign is diagnosed when radiography reveals an erosive scalloped concavity on the radial side of the DRUJ.

We examined ruptures of the extensor digitorum minimi (EDM) tendon, the extensor digitorum communis (EDC) tendon from the index finger to the little finger, the extensor indicis proprius (EIP) tendon, and the extensor pollicis longus (EPL) tendon. Tendon rupture was diagnosed clinically by sudden loss of finger extension. The EDM test [8] was used to diagnose rupture of the EDM tendon.

Statistical analysis

The outcome variable was the occurrence of extensor tendon rupture. The univariate comparisons were conducted with the χ^2 test for categorical variables and Student's t test or the Mann–Whitney U test for continuous independent variables. Multivariable logistic regression analyses were used to estimate the association between the measured variables and extensor tendon rupture. The CSA and the DSR with or without dislocation of the ECU tendon were compared using Student's t test. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Altogether, 102 wrists from 96 RA patients were classified into two groups: wrists with extensor tendon rupture (rupture group) and wrists without extensor tendon rupture (nonrupture group). The rupture group comprised 43 wrists (42 %) in 43 patients, and the nonrupture group included 59 (58 %) wrists in 53 patients. EDM tendon rupture was found in 33 wrists, EDC V tendon in 21, EDC IV tendon in 18, EDC III tendon in 6, EDC II tendon in 1, EIP tendon in 2, and EPL tendon in 4.

The characteristics of wrists in the two groups are shown in Table 1. In an unadjusted comparison, the wrists with extensor tendon rupture had a significantly higher Larsen grade than those without rupture. Rupture occurred more frequently on the right side than on the left side. Among the expected risk factors (Table 2), dislocated ECU tendon, DSR >32 %, and CSA >14° were associated with extensor tendon rupture. The scallop sign was not a significant risk factor. Increased risk (odds ratio) of tendon rupture in the wrist with dislocation of the ECU tendon was 22.2 [95 % confidence interval (CI) 7.55–65.10] and was the highest ratio among the risk factors.

The results of the multivariable logistic regression analysis showed that Larsen grade, dislocation of the ECU tendon,

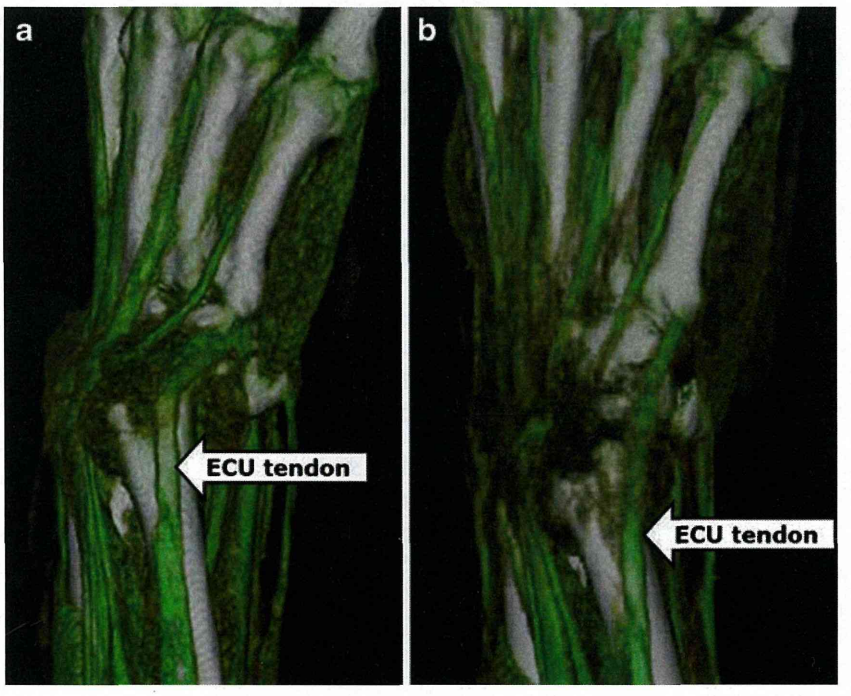

Fig. 2 **a** Synovitis in the DRUJ and the dorsal dislocation of ulna were seen in a patient with rheumatoid arthritis. The extensor carpi ulnaris (ECU) tendon was situated in the anatomical groove in the ulnar head. **b** Dorsal dislocation of the ulnar head and volarly dislocated extensor carpi ulnaris (ECU) tendon were seen

Table 1 Characteristics of 102 rheumatoid wrists

	Nonrupture group	Rupture group	OR	95 % CI	*P* value
No. of wrists	59 (58 %)	43 (42 %)			–
Age, mean±SD, years	60±14	61±13			0.643
Disease duration (years), mean±SD	10±9	13±7			0.106
Sex (male/female)	13:46	7:36	1.36	0.49–3.76	0.547
Side (right/left)	28:31	34:9	0.24	0.10–0.59	0.001
Larsen grade					
I	3	0			
II	8	1			
III	17	14			
IV	30	22			
V	1	6			0.022

Except where indicated otherwise, values are the number (%) of wrists

OR odds ratio, *95 % CI* 95 % confidence interval, *SD* standard deviation

DSR >32 %, and CAS >14° were significantly associated with extensor tendon rupture (Table 3). The odds ratio of tendon rupture in the wrist with dislocation of the ECU tendon was 26.2 (95 % CI 7.01–98.2), which was the highest ratio among the explanatory variables.

Correlation between the DSR and dislocation of the ECU tendon is shown in Fig. 3a. The DSR was larger in the wrists with dislocation of the ECU tendon than in those without ECU tendon dislocation. This difference was statistically significant (p=0.029). Correlation between the CSA and dislocation of the ECU tendon is shown in Fig. 3b. The CSA was larger in the wrists with dislocation of the ECU tendon than in those without ECU tendon dislocation. This difference was statistically significant (p=0.035).

Discussion

We used 3DCT imaging to analyze dislocation of the ECU tendon in RA patients. We found that dislocation of the ECU tendon was strongly associated with extensor tendon rupture. Specifically, dislocation of the ECU tendon was associated with the DSR (parameters of dorsal subluxation of the ulnar head) and the CSA (parameters of carpal supination). Using 3DCT imaging with a soft tissue window, extensor tendons in RA patients were well depicted, and tendon rupture was detected at the wrist level, as described by Abe et al. [9]. Using 3DCT imaging with a bone tissue window, Ishikawa et al. [4] demonstrated that the DSR and CSA were useful parameters for quantifying wrist deformity. Thus, three factors (dislocation of the ECU tendon, DSR and CSA, extensor tendon rupture) could be assessed simultaneously using 3DCT imaging.

To our knowledge, this study represents the largest patient series to address factors associated with extensor tendon rupture in rheumatoid wrists. Several factors associated with extensor tendon rupture in rheumatoid wrists were studied. Ryu et al. [10] stated that the risk factors for extensor tendon rupture were (1) dorsal dislocation of the distal ulna, (2) the scallop sign on radiography, and (3) tenosynovitis persisting at least 6 months. Egi et al. [11] stated that volar dislocation of the ECU tendon on magnetic resonance imaging (MRI)

Table 2 Risk factors of extensor tendon rupture in an unadjusted comparison

	Nonrupture group (n=59)	Rupture group (n=43)	OR	95 % CI	*P* value
Scallop sign	23 (39)	21 (49)	1.73	0.78–3.87	0.177
Dislocation of the ECU tendon	5 (8)	30 (70)	22.2	7.55–65.1	<0.001
DSR >32 %	29 (49)	34 (79)	3.91	1.59–65.1	<0.001
CSA >14°	23 (39)	31 (72)	4.04	1.73–9.43	<0.001

Except where indicated otherwise, values are the number (%) of wrists

OR odds ratio, *95 % CI* 95 % confidence interval, *DSR* dorsal subluxation ratio, *CSA* carpal supination angle

Table 3 Multivariable logistic regression analysis of factors associated with extensor tendon rupture

Variable	OR	95 % CI	*P* value
Right side (vs. left side)	2.43	0.63–9.28	0.194
Larsen grade (per degree)	2.33	1.02–5.32	0.043
Dislocation of the ECU tendon (yes vs. no)	26.2	7.01–98.2	≤0.001
DSR >32 % (yes vs. no)	4.30	1.16–16.1	0.030
CSA >14° (yes vs. no)	4.74	1.31–17.1	0.017

OR odds ratio, *95 % CI* 95 % confidence interval

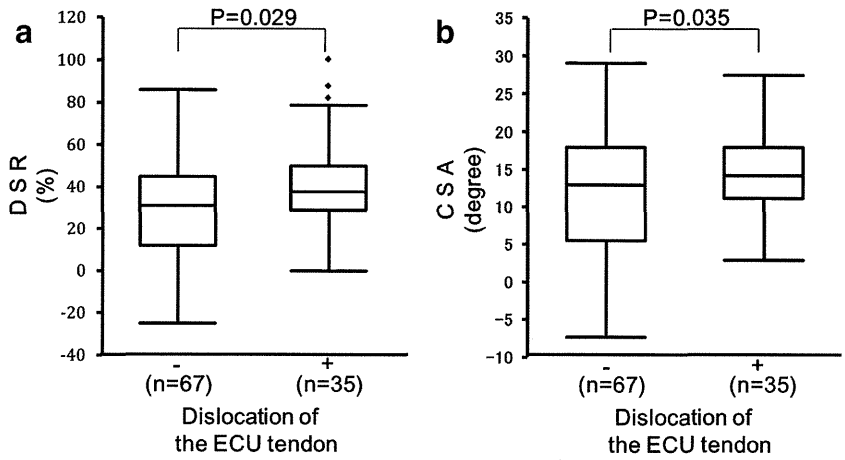

Fig. 3 **a** Correlation between the DSR and dislocation of the ECU tendon. The DSR was greater in wrists with a dislocated ECU tendon than in those without it. These differences were statistically significant, as assessed by Student's *t* test. **b** Correlation between the CSA and ECU tendon dislocation. The CSA was greater in wrists with a dislocated ECU tendon than in those without it. These differences were statistically significant, as assessed by Student's *t* test

was associated with extensor tendon rupture in rheumatoid wrists. Ishikawa et al. [4] stated that the DSR and CSA were related to the risk of extensor tendon rupture. They used a receiver operating characteristic curve to determine the cut off values of extensor tendon rupture, which were 32 % (sensitivity 70 %, specificity 75 %) for the DSR and 14° (71 %, 68 %, respectively) for the CSA. In the present study, we examined four factors (dislocation of the ECU tendon, CSA, and DSR using 3DCT imaging; scallop sign on radiography) that might predict extensor tendon rupture. We found that dislocation of the ECU tendon was strongly associated with extensor tendon rupture.

Not only did wrist deformity and the ECU tendon dislocation contribute to the risk of extensor tendon rupture, so did extensor tenosynovitis. However, it was difficult to identify and measure the severity of extensor tenosynovitis by 3DCT imaging. Two other imaging modalities—ultrasonography (US) and MRI—can confirm the clinical diagnosis of tenosynovitis. US and MRI are noninvasive and do not irradiate the patient. Also, US has the highest special resolution, and power Doppler can help detect synovial tissue. The accuracy of the diagnosis by US is dependent on the examiner's skill, and individual assessment of each tendon is necessary when multiple tendons are involved. With MRI, it was difficult to depict an individual tendon along its complete course or the severity of the extensor tenosynovitis within the short scanning time. There are no reports in the literature that discuss US and MRI of extensor tenosynovitis. Therefore, assessment of extensor tenosynovitis using US and MRI was not addressed in this study.

Tenosynovitis is commonly seen in patients with RA, and the ECU tendon is one of those most frequently involved [12, 13]. In a study in which patients were examined by US, several were reported to have complete rupture of the ECU tendon [12]. In our series, 3DCT found no ruptured ECU tendons. Weakness or rupture of the ECU tendon is expected to be well depicted by the development of this new imaging technique. Dislocation of the ECU tendon is associated with tenosynovitis. Although tenosynovitis was found in most of the ECU tendons in our series using 3DCT, it was difficult to quantify the severity of synovitis because of image blurring.

According to the latest study by Lillegraven et al. [14], US-assessed tenosynovitis of the ECU tendon predicted the development of erosive joint damage in a cohort of patients with early RA. Navalho et al. [15] noted that MRI-assessed tenosynovitis of the ECU tendon was significantly associated with progression to RA in patients who had had arthritis for less than 3 months. We presume that the tenosynovitis around the ECU tendon that arises during early RA is associated with wrist deformity and extensor tendon rupture. Thus, it can be a predictive indicator of disease progression.

Conclusions

We demonstrated that dislocation of the ECU tendon was well depicted using 3DCT images with a soft tissue window. Dislocation of the ECU tendon was strongly associated with extensor tendon rupture and wrist deformity. Thus, dislocation of the ECU tendon seen on 3DCT imaging can be a predictive indicator of extensor tendon rupture. Extensor tendon rupture causes immediate dysfunction of the hand and requires surgical reconstruction. If dislocation of the ECU tendon is found, surgical reconstruction of the wrist might be undertaken to avoid extensor tendon rupture. Analysis of bone and soft tissue imaging of the rheumatoid wrist using 3DCT enhances our pathomechanical consideration of extensor tendon rupture. We hope that US and/or MRI—each a noninvasive procedure that does not irradiate the patient—can similarly depict the pathology of a dislocated ECU tendon.