was 12.4 years, and estimated yearly progression was significantly high, with 20.8 (1.3) at baseline. Considering the results of the impact on radiographic and clinical response to infliximab therapy concomitant with methotrexate in patients with rheumatoid arthritis by trough serum level in a dose escalating (RISING) study, in which we reported a disease duration of ~8 years and mean estimated yearly progression of 8.1 (9.1) [23], the present study included patients with remarkably severe clinical features with long disease duration and progressive joint destruction. Irrespective of these severe conditions, the 95% inhibitory effect of tocilizumab indicates how powerful its inhibition of joint destruction is. Surprisingly, we found that tocilizumab inhibits the radiographic damage, not only in patients treated without TNF inhibitors, but also in those treated with TNF inhibitors. Although further research is needed, our findings suggest that the pathological condition of RA is dependent on TNF. The good results obtained with tocilizumab are consistent with those of both domestic and foreign studies.

On the other hand, functional remission was achieved in 26.4% of the patients at 52 weeks, which is lower than the clinical remission rate at 52 weeks (43.7%) and that of radiographic non-progression at 52 weeks (62.8%). The longer duration of disease and high HAQ-DI at baseline may be responsible for the lower functional remission rate observed in the present study. Although Nagasawa *et al.* [17] reported that the incidence of HAQ remission (HAQ $\leqslant$ 0.5) after 2 years of treatment with infliximab was 41.6%, it is difficult to compare this result with our own because the methods of statistical analysis used in these two studies differed markedly. Smolen *et al.* [24] analysed the damage-associated HAQ-DI score in the Best Life in RA (BELIRA) trial and seven pivotal clinical trials including anti-TNF biologics, MTX and LEF [24]. According to their report, damage-associated HAQ-DI corresponds to 0.01 per point of total vdH–Sharp score. The total vdH–Sharp score of 140.5 at baseline in this study appears to correspond to a damage-associated HAQ-DI of 1.41, and thus maximum improvement after tocilizumab treatment may be assumed to be an HAQ-DI of 1.56 at baseline minus 1.41, which is 0.15. The real change observed in this study (0.27) was better than that determined based on the above assumption. Considering factors such as the severe baseline HAQ in the present study, our findings suggest that administration of tocilizumab before worsening of HAQ, in the very early stage, might lead to attaining rates of high clinical, structural and functional remission. We should master use of tocilizumab towards achievement of a higher treatment goal in RA patients.

Although the duration of disease in the patients in this study was long and 60% of the patients had used anti-TNF agents previously, the incidences of SAEs and serious infections were comparable with those in the RISING study, in which the incidences of SAEs and serious infections were 11.6 and 5.2%, respectively [23]. These results indicate that attention must be paid to the onset of serious infections, including pneumonia, during tocilizumab treatment as well as with anti-TNF agents. Most of the laboratory test abnormalities in this study were transient and not associated with SAEs. These findings indicate that the safety profile of tocilizumab was acceptable in actual clinical practice.

In conclusion, the REACTION study showed that clinical remission could be achieved in ~40% of patients and radiographic non-progression could be achieved in ~60%. Tocilizumab was well tolerated over 52 weeks, and the most frequent adverse drug reaction was pneumonia. Although functional remission was obtained in 28% of the patients at Week 52, it was confirmed that higher remission rates may be attained with earlier administration of tocilizumab before worsening of HAQ. Additionally, the multivariate logistic regression model that we used provided insights into how the use of tocilizumab can be improved in clinical practice.

Rheumatology key messages

- The REACTION study showed the clinical, structural and functional response to tocilizumab in RA patients in real-world clinical practice.
- A multivariate logistic model provided insights into how the use of tocilizumab can be further improved.

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Original article

Sensitivity and specificity of 2010 rheumatoid arthritis classification criteria

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Abstract

Objective. To validate the sensitivity and specificity of the 2010 RA classification criteria.

Methods. A total of 313 undiagnosed subjects, who first visited Keio University Hospital with joint symptoms, including arthralgia, joint swelling and morning stiffness, without any previous treatment except for NSAIDs, were included in the present study. A clinical diagnosis of RA was made by rheumatologists, and the gold standard diagnosis of RA was defined as an indication for instituting DMARDs for RA.

Results. Seventy-six subjects were diagnosed as gold standard RA. Among these, 8 did not have any swollen joints, 50 were classified as definite RA under the 2010 criteria and the other 18 as not having RA. Eighty-two subjects were eligible for the 2010 criteria, and the sensitivity and specificity under the 2010 criteria were 73.5 and 71.4%, respectively, compared with 47.1 and 92.9% under the 1987 criteria. But the sensitivity of the 2010 criteria decreased to 15.8% when both RF and anti-CCP were negative. According to the result of a receiver-operated characteristic (ROC) curve of the scoring system, if swollen joints and differential diagnosis are not accurately detected, it would be better to use a score of 5 as the cut-off level to detect RA.

Conclusion. The 2010 classification criteria have a high sensitivity and have been verified to be useful for distinguishing RA at an early stage.

Key words: Rheumatoid arthritis, Classification criteria, Scoring system, Sensitivity, Specificity.

SCIENCE

Introduction

RA is a chronic inflammatory disease characterized by progressive destructive arthritis with pain and disability [1]. Recent progress in its treatment, such as MTX and biological DMARDs, has given remarkable benefits to RA patients [2–6]. To manage RA patients appropriately, a diagnosis and a treatment strategy are needed as early as possible [7]. However, at present, an RA diagnosis is usually made under the 1987 ACR classification criteria [8], which are considered to be unsuitable for an early diagnosis [9–10]. Since 2007, the European League against Rheumatism (EULAR) and the ACR have been cooperatively dealing with a revision of the classification criteria, which was finally published in August 2010 [11–13]. The new criteria consist of a classification scoring system, which noticeably puts a great deal of emphasis on small joint involvement and seropositivity of RF or ACPAs. In detail, classification as definite RA is based on the presence of synovitis in at least one joint, the absence of an alternative diagnosis better explaining the synovitis and a total score from individual scores in four domains (the number and site of involved joints, serological abnormality, elevated acute-phase response and symptom duration).

It has been described that the focus of the new classification criteria was not on developing diagnostic criteria or reference tools for primary care physicians, but on facilitating the study of persons with earlier stages of RA. However, since hereafter we are mainly going to use the 2010 classification criteria as an aid in the diagnosis of RA in the clinical field, we should be well acquainted with their strengths and limitations. The aim of this study is to validate the sensitivity and specificity of the 2010 criteria, and to find certain

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characteristics of patients with RA who are not classified as RA and vice versa.

Subjects and methods

This study was a retrospective single centre observational study. In order to optimize the quality and reproducibility of this validation study, the work was designed to comply with the criteria of the Standards for Reporting of Diagnostic Accuracy initiative [14].

Subjects

The subjects, all of whom first visited the out-patient clinic of the Division of Rheumatology, Department of Internal Medicine at the Keio University School of Medicine in January 2009 through March 2010, were reviewed retrospectively. Three hundred and fourteen undiagnosed subjects exhibited joint symptoms, including arthralgia, joint swelling and morning stiffness, without any previous treatment with the exception of NSAIDs. Among these, one patient was excluded from the study because of insufficient laboratory data to comply with the new criteria. Ultimately, 313 subjects were included in the present study. Medical ethics committee approval was waived because the study was a retrospective cohort study using anonymized information.

Diagnoses of RA and other diseases

Diagnoses of RA were made by at least one of six rheumatologists in our institution from a comprehensive standpoint, using clinical histories including when and how symptoms started, physical findings including the site and extent of involved joints and extra-articular lesions, blood tests including RF, ACPA, acute-phase reactants and MMP and X-rays. MRI of symptomatic joints was also used when diagnosis was not able to be settled, and synovitis with bone erosion or osteitis was considered as the presence of RA. Because the absolute gold standard diagnosis of RA does not exist, in the present study, the gold standard for a diagnosis of RA was defined as an indication for instituting DMARDs for RA, including salazosulphapyridine, bucilamine, tacrolimus, MTX, infliximab, etanercept, adalimumab and tocilizumab. The six above-mentioned rheumatologists are all specialists in rheumatology, each with >10 years of clinical experience. Diagnoses of other diseases were also made through a similar process. Subjects regarded as not being affected by particular diseases were termed no appreciable disease (NAD). Subjects observed having modest arthritis but where diagnosis of a particular disease was not sure enough for treatment despite repeated examinations, were termed undifferentiated peripheral inflammatory arthritis (UPIA).

Assessment of clinical manifestations and laboratory findings

Demographics and clinical manifestations, including sex, age, duration of symptoms, the number of tender joints and the number of swollen joints, were evaluated. Blood samples were examined in our hospital laboratory. The upper limits of CRP, measured by dry chemistry (Mitsubishi Chemical Medicine, Tokyo, Japan), the ESR, measured by the Westergren test, IgM-RF, measured by a latex-enhanced immunonephelometric assay (Eiken Chemical, Tochigi, Japan) and anti-CCP, measured by an ELISA (Medical & Biological Laboratories, Nagano, Japan) were 0.35 mg/dl, 10 mm/h for men and 15 mm/h for women, 20 IU/l and 4.5 U/ml, respectively.

Statistical analysis

Subject characteristics were summarized using medians and ranges, and the values of CRP and ESR, as well as the number of involved joints, were summarized using mean (S.D.). Comparisons of frequency between the two groups were performed using the Pearson chi-squared test. Comparisons of mean value were performed by Student's *t*-test. Sensitivity *vs* the false positive frequency (one-specificity) for the scoring system was analysed by a receiver-operated characteristic (ROC) curve. All reported *P*-values are two-sided. $P < 0.05$ was considered to be statistically significant. Data were analysed with SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics and diagnoses of 313 subjects

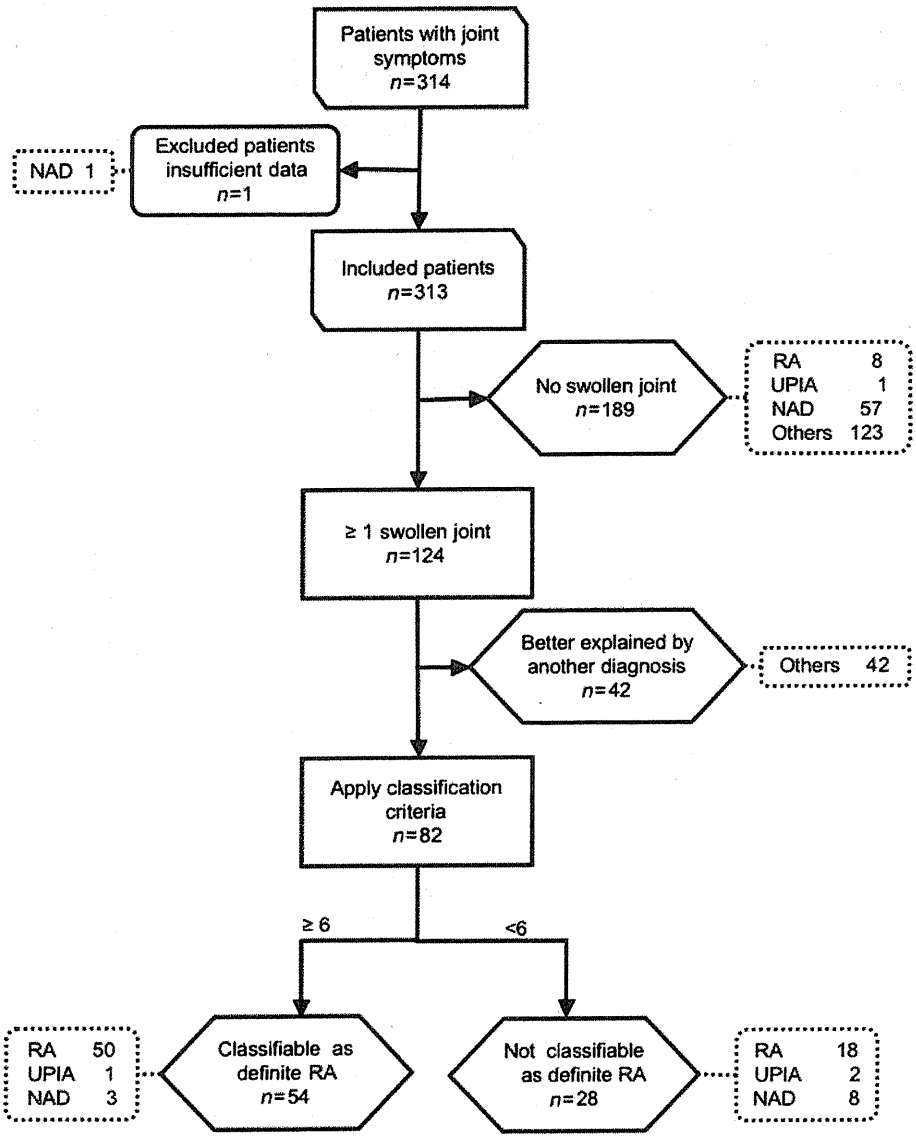
The subject characteristics were as follows: age, median (range) years, 54 (14–86); sex, *n* (%), female, 79; duration of symptoms, median (range) weeks, 18 (1–1040); interval between the first visit and the time of diagnosis, median (range) weeks, 2 (1–40). Diagnoses of subjects at the last visit were 76 with RA, 4 UPIA, 68 NAD and 165 other diseases. All subjects were observed until they were diagnosed or for >3 months if they could not be accurately diagnosed (i.e. UPIA).

At the point when the first laboratory and radiographic findings were available, mostly within 3 weeks from the first visit, the patients were assessed and subjected to the 2010 classification criteria. A flow diagram is shown in Fig. 1. Of 313 subjects, 124 had at least one swollen joint and, among these, 82 were eligible to be subjected to the classification scoring system. Fifty-four subjects achieved a total score of ⩾6, and their clinical diagnoses were 50 RA, 1 UPIA and 3 NAD. Twenty-eight subjects showed a score of <6, and their diagnoses were 18 RA, 2 UPIA and 8 NAD.

Among 76 RA patients, RF and anti-CCP were positive in 50 (66%) and 46 (61%) patients, respectively. Regarding the length of time between the first visit to our hospital and the time of diagnosis of RA, 71 (93%) subjects were diagnosed within 12 weeks, 3 (4%) within 24 weeks and 2 (3%) after >24 weeks.

Diagnoses of another 165 subjects included OA ($n = 74$), post-menopausal syndrome (PMS; $n = 14$), tendonitis ($n = 13$), SS ($n = 12$), SLE ($n = 6$), PM/DM ($n = 4$), PsA ($n = 4$), viral infection ($n = 4$), PMR ($n = 4$), palindromic rheumatism ($n = 3$), adult onset Still's disease ($n = 3$), post-injury (n = 3), AS ($n = 2$), shoulder periarthritis ($n = 2$),

FIG. 1 Flow chart of result. Of 314 subjects who visited our institute with joint symptoms without any treatment, 313 subjects were included in this study. One hundred and twenty-four subjects had at least one swollen joint, and among these, 42 were diagnosed with other diseases and 82 were submitted to the scoring system, resulting in 54 subjects with a total score of ⩾6. The clinical diagnoses of subjects at the last visit are shown in the dotted square.



pseudogout ($n=2$), steroid withdrawal syndrome ($n=2$), FM ($n=2$), SSc ($n=2$), remitting seronegative symmetrical synovitis with pitting oedema ($n=1$), humeral epicondylitis ($n=1$), diffuse fasciitis ($n=1$), sarcoidosis ($n=1$), infectious endocarditis ($n=1$), acute respiratory distress syndrome ($n=1$), amyloid arthropathy ($n=1$), SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome ($n=1$) and HScP ($n=1$).

Comparison of the 2010 and 1987 criteria

Table 1 presents a comparison of the 2010 and 1987 criteria. For 82 subjects who had at least one swollen joint not better explained by other diseases, the sensitivity of the 2010 criteria was much better than that of the 1987 criteria, but the specificity was worse (73.5 *vs* 47.1% and 71.4 *vs* 92.9%, respectively). The positive predictive values (PPVs) were comparable, and the negative predictive values (NPVs) and the positive likelihood ratios were better in the 1987 criteria (92.5 *vs* 97.0%, 35.7 *vs* 26.5% and 2.6 *vs* 6.6%, respectively).

Features of RA patients with or without classification as RA under the new criteria

Features of 68 RA patients with or without classification as RA are shown in Table 2. The positivity of RF and/or anti-CCP and the swollen/tender small joint counts were significantly higher in patients who were classifiable as definite RA under the 2010 criteria than in those who

TABLE 1 Comparison of sensitivity, specificity and accuracy between the 1987 and 2010 criteria

Outcome measure	1987 criteria ($n=82$)	2010 criteria: Subjects with swollen joints not better explained by other diseases ($n=82$)	Seropositive[a] ($n=54$)	Seronegative[b] ($n=28$)	2010 criteria: All subjects with swollen joints ($n=124$)	All subjects ($n=313$)
Sensitivity, %	47.1	73.5	95.9	15.8	73.5	72.4
Specificity, %	92.9	71.4	20.0	100	80.4	89.9
PPV, %	97.0	92.5	90.4	100	82.0	69.6
Negative prediction value, %	26.5	35.7	33.3	36.0	71.4	91.0
Positive likelihood ratio	6.6	2.6	1.2	NA	3.8	7.2

[a]RF and/or anti-CCP was positive. [b]Both RF and anti-CCP were negative. NA: not available.

TABLE 2 Comparison of RA patients who were classifiable as RA with those who were not

Characteristic	Classifiable ($n=50$)	Not classifiable ($n=18$)	*P*-value
RF positivity	43 (86)	1 (6)	*<0.001*
Low titre[a]	17	0	
High titre[a]	26	1	
Anti-CCP positivity	40 (80)	0 (0)	*<0.001*
Low titre[a]	3	0	
High titre[a]	37	0	
CRP positivity	32 (64)	14 (78)	0.38
CRP level, mean (S.D.), mg/dl	2.2 (3.1)	2.4 (3.4)	0.83
ESR positivity	45 (90)	15 (83)	0.43
ESR level, mean (S.D.), mm/h	55 (39)	54 (44)	0.44
Swollen small joint count[b], mean (S.D.)	5.1 (4.9)	2.5 (2.2)	*0.01*
Swollen large joint count[b], mean (S.D.)	1.6 (1.8)	0.6 (0.9)	0.09
Tender small joint count[b], mean (S.D.)	3.7 (3.3)	1.9 (1.9)	*0.006*
Tender large joint count[b], mean (S.D.)	1.6 (2.2)	0.8 (1.3)	0.76

Values are *n* (%) unless otherwise indicated. *P* values < 0.05, given in italics, were considered to be statistically significant. [a]High titre was defined as a value that was more than three times the upper limit in our own institute, following the new criteria. [b]Small/large joint was determined in accordance with the 2010 criteria.

were not. We divided 82 subjects into two groups according to the presence or absence of RF and/or anti-CCP, and the sensitivity and specificity were re-evaluated, as shown in Table 1. In the group of patients in whom RF and anti-CCP were both negative, sensitivity decreased remarkably to 15.8%. If we could include all subjects who had at least one swollen joint ($n=124$), or all subjects who were recruited in the present study ($n=313$), in the 2010 criteria, the specificity would increase (Table 1).

RA patients who were not classifiable as RA under the new criteria

Eighteen RA patients were not classifiable as RA under the new criteria at the point when the first laboratory and radiographic findings became available. Six patients exhibited small erosions on X-rays, but these were not significant and it was not obvious whether their histories were compatible with the 2010 criteria. Five patients were diagnosed with RA by reference to MRI findings. In addition, eight patients who had not had any swollen joints on the first visit and had not been subjected to the scoring system were later found to have swollen joints and were diagnosed with RA. Seven of a total of 26 patients had come to satisfy the 2010 criteria as definite RA during the period of 3–33 weeks from the first visit, whereas the others were treated with DMARDs before being able to fulfil the new criteria.

Cases of patients with other diagnoses who achieved a total score of $\geqslant 6$ under the 2010 criteria

If the 2010 criteria were applied to all subjects who were recruited in the present study, 11 subjects given other diagnoses achieved a total score of $\geqslant 6$. The features of these patients are shown in Table 3. Their diagnoses included three NAD, one UPIA, one PsA, two OA, one PMS, one SS, one SLE and one DM. Except for cases with an arthritis similar to RA, NAD and OA subjects with a minor count of swollen joints, high-titre RF positivity and

TABLE 3 Features of non-RA patients who achieved total score of ⩾6

Physical and experimental findings on the first visit										
Sex	Age	TJC	SJC	ESR	CRP	RF	Anti-CCP	Duration, weeks	Diagnosis	Treatment
F	31	1	3	28	0.9	41	0	21	UPIA	-
F	34	1	1	8	0.01	76	0	265	NAD	-
F	59	0	2	10	0.03	72	0	18	NAD	-
F	41	1	1	16	0.11	0	31	28	NAD	
M	46	3	2	58	10.22	153	100	12	PsA	MTX
M	43	10	11	26	0.06	0	0	9	DM	PSL
F	50	4	5	14	0.06	28	9.8	14	SLE	NSAIDs
F	55	2	1	18	0.02	64	0	104	PMS	-
F	53	1	1	18	0.1	79	0	52	OA	-
F	62	3	2	13	0.1	0	23	520	OA	-
F	57	14	6	4	0.01	0	0	11	SS	-

TJC: tender joint count (both small and large); SJC: swollen joint count (both small and large); PSL: prednisolone.

mildly elevated ESR were apt to be misclassified as having RA under the 2010 criteria.

Availability of scoring system and difficulties in detection of swollen joints and differential diagnoses

In the present study, 82 patients were subjected to the scoring system. A ROC curve depicted to decide the best cut-off score showed that the best was 6, as was the same with the definition of 2010 criteria (data not shown). However, it is not always easy to detect swollen joints and accurately make diagnoses of other diseases. Supposing a doctor had difficulty in assessing swollen joints and differential diagnoses, we tried to assign all 313 subjects to the scoring system. The results are shown in Fig. 2A. The median score was 7 in RA and 2 in non-RA subjects. A ROC curve in this setting was depicted (Fig. 2B) and the ROC plot that was the closest to the upper left corner was a score of 5 in this setting.

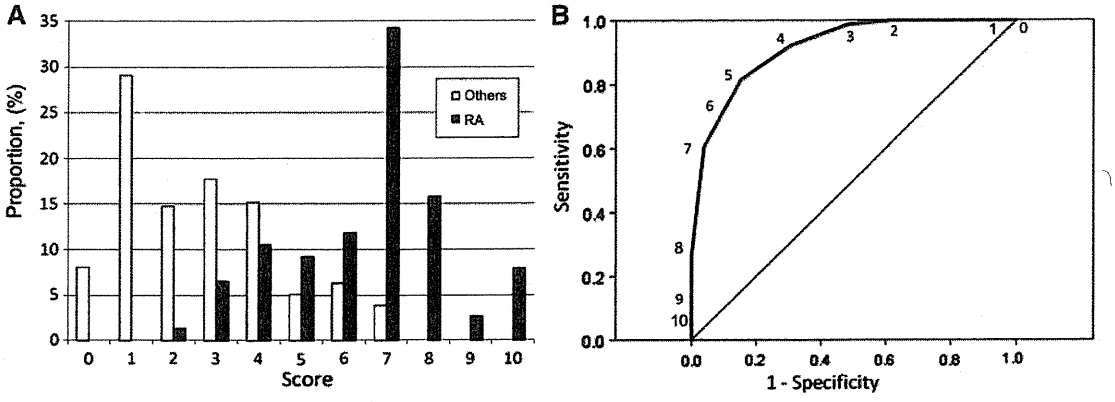
Discussion

Over the past decade, the clinical setting of RA has changed considerably. Destructive joint damage was shown to begin at an early stage [15, 16], and an early diagnosis with aggressive therapy may alter or modify the natural history of this destructive and dreadful disease [17]. The 1987 ACR classification criteria used widely to diagnose RA have been criticized for their low discriminative ability in recent onset arthritis [9, 10]. The main cause of this was that the 1987 criteria were created using data from established RA patients with a mean disease duration of 7.7 years [8]. Harrison *et al.* [9] reported that the Norfolk Arthritis Register data showed that only 38% of new cases of inflammatory polyarthritis could be classified as RA using the 1987 criteria when first seen. Moreover, only 50% of RA patients satisfied the 1987 criteria at 6 months and only 80% even at 2 years after enrolment [9]. Thus, the 2010 classification criteria were developed in order to distinguish RA earlier and start effective treatment as soon as possible to prevent or minimize joint destruction [7, 11–13].

At the time the 1987 criteria were declared, sensitivity and specificity were reported to be 91–94 and 89%, respectively [8]. In our study, sensitivity and specificity were 47.1 and 92.9%, respectively, using the 1987 criteria, while those using the 2010 criteria were 73.5 and 71.4%. van der Linden *et al.* [18] reported that both the sensitivity and specificity of the 2010 criteria were 74% when using DMARD-initiation within the first year as RA outcome in the Leiden Early Arthritis clinic. Our data were quite similar to their results. The sensitivity was better under the 2010 criteria, although the specificity, NPV and the likelihood ratio were better under the 1987 criteria. These results demonstrate that the 2010 criteria are superior to the 1987 criteria for the detection of RA in early stages, rather than for diagnoses. However, sensitivity under the new criteria decreased to 15.8% when both RF and anti-CCP were negative, which is considered to be a limitation of the new criteria. For example, a seronegative patient with 10 swollen/tender joints and elevated CRP and ESR for >6 weeks, who was strongly suspected to have a persistent and destructive disease (i.e. RA), could not achieve a total score of 6.

Eighteen RA patients and an additional eight patients without any swollen joints when first seen, were not classifiable as RA under the 2010 criteria at the point when the first laboratory and radiographic findings became available. Among these, while 19 patients had been treated with DMARDs before being subjected to the new criteria and could not be considered assessable because of improvement, the other seven patients who were just observed with or without NSAIDs came to be classifiable as having RA within 33 weeks (six within 12 weeks and one at 33 weeks). When we subjected the patients to the new criteria cumulatively over 12 weeks, the sensitivity increases up to at least 81.6%. It can be said that these criteria are useful to diagnose RA within 12 weeks, even

FIG. 2 (A) Scores of 313 subjects under the scoring system. The distribution of the scores at the point when first laboratory and radiographic findings were available is shown. The median scores were 7 and 2 in RA patients and non-RA subjects, respectively. (**B**) A ROC curve. A ROC curve was depicted to decide the best cut-off score. The ROC plot that was the closest to the upper left corner was a score of 5.



if we could not classify patients as having RA when first seen.

Meanwhile, except for cases with an arthritis similar to RA, NAD and OA subjects with one or two small swollen joints, non-specific high-titre RF positivity and mildly elevated ESR tended to be misclassified as having RA. If we were to classify such subjects as RA and start treatment with DMARDs, we might overtreat them. So we should be careful with this point when using the 2010 criteria.

The utility of the scoring system in various situations was also verified. Even if swollen joints and other diseases could not be accurately assessed, that is, if all patients with joint symptoms were to be submitted to the 2010 criteria, the sensitivity would be comparable and the specificity would be raised to 89.9%. Considering the result from the ROC curve, we could make presumptions about whether subjects with joint symptoms might be affected with RA if they were to attain a cut-off score of 5. Young *et al.* [19] reported that there has been little change in referral time from onset of symptoms to a rheumatologist over 25 years in a large RA inception register in the UK. It is important to avoid delay in consultation to rheumatologists as well as to make an early diagnosis of RA. If primary care physicians were to use the 2010 criteria, they might better refer patients to a rheumatologist or at least monitor them carefully under the UPIA recommendation [20] with a score of 5, so as not to miss RA patients.

There are some limitations to this study. One of these was the definition of the gold standard for RA. This definition contained risk of misdiagnosis. And the data used by rheumatologists in our institution to diagnose RA were partly corresponding to items of the new criteria, so the sensitivity might be highly overestimated. However, since the six rheumatologists who diagnosed the subjects in this study were all specialists in rheumatology, each with >10 years of clinical experience, almost all of the diagnoses were believed to be correct. Moreover, we determined the institution of not only MTX but also other DMARDs to be the gold standard. Since in our country, MTX is permitted for use by the Health, Labour and Welfare Ministry only after other DMARDs fail, only 44 (57%) of 76 patients had MTX initiated as their first treatment. Another limitation was that this study was a hospital-based study. Since our hospital is a major academic medical institute, there is a possibility that many of our subjects were more likely to have RA, and the PPV might be estimated as higher than it really is.

In conclusion, the present study showed that the 2010 classification criteria have high sensitivity and are useful for distinguishing early RA. However, it should be cautioned that the sensitivity decreased remarkably when both RF and anti-CCP were negative and that subjects with a small number of swollen joints, non-specific high-titre RF positivity and mildly elevated ESR were apt to be misclassified as having RA. If general physicians use the 2010 criteria to distinguish RA, a cut-off score of 5 would be better in order not to miss RA patients. Further studies with a larger cohort may be needed to optimize these criteria in the practical field.

Rheumatology key messages

- The 2010 classification criteria have high sensitivity and are useful for distinguishing early RA.
- The sensitivity of the 2010 classification criteria decreased remarkably when both RF and anti-CCP were negative.
- A cut-off score of 5 might be better in the practical field.

Disclosure statement: The authors have declared no conflicts of interest.

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An Allopurinol-Controlled, Multicenter, Randomized, Open-Label, Parallel Between-Group, Comparative Study of Febuxostat (TMX-67), a Non–Purine-Selective Inhibitor of Xanthine Oxidase, in Patients With Hyperuricemia Including Those With Gout in Japan

Phase 2 Exploratory Clinical Study

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Background: Allopurinol has been widely used for the treatment of hyperuricemia, however, it may be associated with various adverse effects. Febuxostat has been identified as a potentially safe and efficacious alternative.

Objectives: Febuxostat was administered to patients with hyperuricemia including gout in Japan to compare its efficacy and safety with those of allopurinol.

Methods: The starting dose of febuxostat and allopurinol was 10 and 100 mg/d, respectively, and was increased to the fixed maintenance dose of 40 or 60 mg/d for febuxostat and 300 mg/d for allopurinol for 16 weeks.

Results: The percent change in the serum uric acid level at 16 weeks compared with the baseline serum uric acid level was −42.96% ± 13.33% and −52.47% ± 9.79% for the febuxostat 40- and 60-mg/d groups, respectively, and −36.55% ± 18.59% for the allopurinol group, indicating that the hypouricemic effects of febuxostat increased in a dose-dependent manner and equaled to or surpassed those of allopurinol ($P = 0.0239$, 2-sample t test). The percentage of patients with serum uric acid levels of 6.0 mg/dL or less at 16 weeks was 88.9% and 100% for the febuxostat 40- and 60-mg/d groups, respectively, and 68.8% for the allopurinol group, showing higher achievements for the febuxostat groups compared with the allopurinol group. All adverse drug reactions were mild to moderate in severity, and there were no severe symptoms or reactions leading to drug discontinuation.

Conclusions: These results suggest that febuxostat is safe at doses of 40 and 60 mg/d and has equal or greater efficacy than 300 mg/d allopurinol.

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Although the incidence of gouty arthritis increases with serum uric acid levels,[1] it has been reported that progression from hyperuricemia to gouty arthritis generally requires 10 to 15 years. There are no subjective symptoms until the onset of gouty arthritis, however, intra-articular deposition of urate crystals can be progressing.[2] In Japan, asymptomatic hyperuricemia has been treated to prevent gout.[3] In addition, since Hall[4] noted the association of hyperuricemia with cardiovascular disease and hypertension in 1965, attention has been focused on the relationship between hyperuricemia and other diseases.[5–9] Tomita et al.[10] also reported in 2000 that the incidence of cardiovascular diseases, cerebrovascular diseases, renal failures, and others, increased significantly in the presence of hyperuricemia. Accordingly, the importance of proactive drug treatment of asymptomatic hyperuricemia has been gradually acknowledged not only to prevent gout but also from the standpoint of avoiding such risks as cardiovascular disease.[3]

To control hyperuricemia, uricosuric drugs and inhibitors of uric acid synthesis have been widely used. However, from a safety and efficacy standpoint, because uricosuric drugs reduce serum uric acid levels by inhibiting the tubular reabsorption of uric acid,[11] they should not be used for patients with excessive urate production, comorbid disorders such as urolithiasis, or deteriorating renal function. With regard to inhibitors of uric acid synthesis, a purine-like drug, allopurinol,[12] has been widely used. However, in some patients, it can cause a lethal adverse drug reaction, allopurinol hypersensitivity syndrome, which involves severe hepatic dysfunction such as fulminant hepatitis, mucocutaneous ocular syndrome (Stevens-Johnson syndrome), toxic epidermal necrosis (Lyell syndrome), and severe skin reactions such as dermatitis exfoliativa.[13] Allopurinol is metabolized by xanthine oxidase to an active metabolite, oxypurinol, which has an inhibitory effect on xanthine oxidase. Because oxypurinol is eliminated in urine via the kidneys in the same manner as uric acid, patients with impaired renal function are prone to prolonged excretion and elevated levels of circulating oxypurinol,[14] which has been reported to be closely involved with the occurrence of allopurinol hypersensitivity syndrome.[13] Therefore, development

of a new antihyperuricemic drug with superior safety and efficacy has been anticipated.

Febuxostat is a novel inhibitor of uric acid synthesis that does not have a purine in its chemical structure, which is completely different from that of allopurinol. It has been demonstrated that unlike allopurinol, febuxostat selectively and strongly inhibits both the oxidized and the reduced forms of xanthine oxidase at low concentrations.[15–17] Febuxostat has also demonstrated more potent hypouricemic effects than allopurinol in in vivo studies using rats and chimpanzees[15,18,19] and reduced serum uric acid levels in a dose-dependent manner in a clinical trial with hyperuricemia patients, including those with gout.[20] Its effects were significant compared with a placebo. Moreover, there were no adverse events that were clinically significant.

The phase 3 clinical study previously demonstrated that 40 mg/d febuxostat has more potent hypouricemic effects than 200 mg/d allopurinol. In this study, febuxostat was administered to patients with hyperuricemia including gout by gradually increasing the dose from a low level of 10 mg/d up to 40 or 60 mg/d to compare its efficacy with that of 300 mg/d allopurinol (gradually increased from 100 mg/d), with the primary endpoint defined as the percent change in serum uric acid level after 16 weeks compared with the baseline serum uric acid level.

MATERIALS AND METHODS

Subjects

Subjects were male and female patients aged 20 years or older in Japan who had hyperuricemia, including gout. The registration criteria were defined as follows: serum uric acid levels at the preregistration test greater than 7.0 mg/dL for patients with gout; 8.0 mg/dL or greater for patients with hyperuricemia who were receiving medication or therapy for urinary calculus, hypertension, hyperlipidemia, or abnormal glucose tolerance; and 9.0 mg/dL or greater for patients with hyperuricemia without complications. The study design was a randomized, open-label, parallel, between-group, comparative trial. The following patients were excluded from the study: patients with malignant tumors suspected of secondary hyperuricemia, severe cardiovascular diseases, deteriorating renal function (serum creatinine ≥1.5 mg/dL), and deteriorating liver function (either aspartate aminotransferase or alanine aminotransferase >2-fold higher than the upper limit of the facility standard) and patients developing gouty arthritis or recovering from gouty arthritis less than 2 weeks previously. In addition, drugs (excluding topical drugs) that affect serum uric acid levels were prohibited for 2 weeks before the preregistration test and throughout the study period. Registered patients were randomly assigned to the febuxostat 40- and 60-mg/d or allopurinol 300-mg/d groups through dynamic allocation based on serum uric acid levels at the preregistration test.

Study Drugs

Febuxostat 10- and 20-mg tablets were used as the investigational drugs, and allopurinol 100-mg tablets were used as control drugs.

Administration Method and Administration Period

A schedule for the increases in dose is shown in Figure 1. The initial oral dose of febuxostat was 10 mg/d and was increased in a stepwise manner to the fixed maintenance dose for each group (40 or 60 mg/d) at 2, 6, and 10 weeks, and the maintenance dose was maintained thereafter until 16 weeks. Administration of allopurinol was initiated at 100 mg/d once daily after breakfast and was gradually increased to 200 mg/d, twice daily after breakfast and dinner, at 2 weeks, and to the fixed maintenance dose of 300 mg/d, 3 times a day after breakfast, lunch, and dinner, at 6 weeks until 16 weeks.

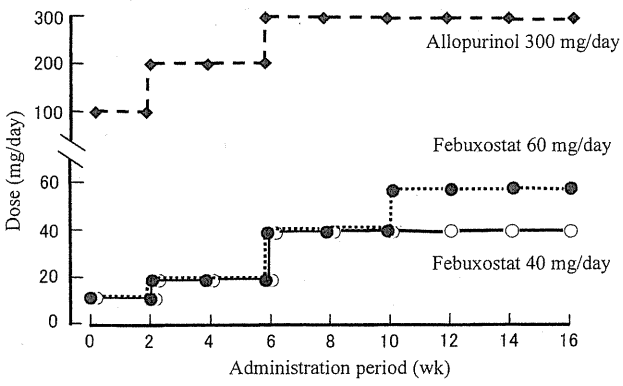

FIGURE 1. Timing of dose increases in each group.

Observations, Analyses, and Timing

Serum uric acid levels were measured before beginning drug administration and at 2, 6, 10, 14, and 16 weeks during the study. Hematological and blood biochemical examination, urinalysis, and measurement of vital signs (body temperature, blood pressure, and heart rate) were also conducted. In addition, a 12-lead electrocardiogram was conducted before beginning drug administration and at 16 weeks.

Efficacy Evaluation

Efficacy analysis was conducted for the full analysis set (FAS). Descriptive statistics and 95% confidence intervals for the primary efficacy endpoint, the percent change in serum uric acid levels at 16 weeks compared with the baseline serum uric acid level, were calculated for each febuxostat group and the allopurinol group. Percent change in serum uric acid level was compared between the allopurinol group and each febuxostat dose group, using 2-sample t test. The secondary endpoints were the percentage of patients with serum uric acid levels of 6.0 mg/dL or less at 16 weeks and the percent change in serum uric acid levels at each assessment point against the baseline serum uric acid level.

Safety Evaluation

The safety evaluation was conducted for the safety analysis set, and the incidences of adverse events and abnormalities in clinical parameters were calculated. Furthermore, the severity and seriousness of adverse events and drug causality were also evaluated for each group.

RESULTS

Disposition of the Subjects

Figure 2 shows the disposition of the subjects. Registered subjects were randomly assigned to the allopurinol group (20 patients), the febuxostat 40-mg/d group (10 patients), and the febuxostat 60-mg/d group (10 patients), and study drugs were administered to all subjects. The number of subjects who completed the study was 19 patients for the allopurinol group, 10 patients for the febuxostat 40-mg/d group, and 8 patients for the febuxostat 60-mg/d group.

Demographic and Other Baseline Characteristics

Of the 40 patients who received the study drugs, 2 patients without complete serum uric acid level data (inconsistently

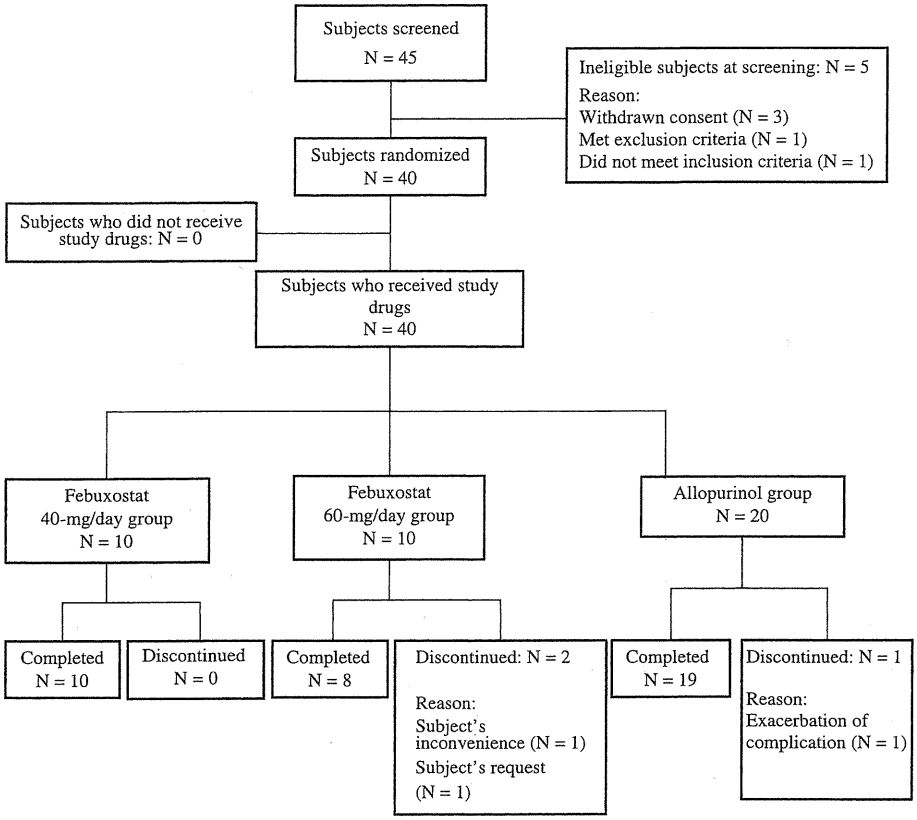

FIGURE 2. Disposition of subjects.

analyzed after the start of treatment) were excluded for the FAS. The FAS, composed of the remaining 38 patients, was subjected to analysis of efficacy. Table 1 shows demographic and other baseline characteristics of the patients. Although the percentage of patients with a clinical diagnosis of hyperuricemia was higher in the febuxostat 60-mg/d group, there were no differences in the

TABLE 1. Demographic and Other Baseline Characteristics (FAS)

Characteristic	Category	Febuxostat 40-mg/d Group	Febuxostat 60-mg/d Group	Allopurinol 300-mg/d Group
Sex	Male	10	9	19
	Female	0	0	0
Age, y	Mean	56.0	53.3	51.3
	SD	8.2	11.0	12.0
Height, cm	Mean	169.90	167.27	169.11
	SD	5.06	6.97	7.10
Weight, kg	Mean	69.84	68.09	73.05
	SD	5.52	9.72	12.31
Medical history of gout	Yes	8	4	17
	No	2	5	2
Serum uric acid levels before drug administration, mg/dL	Mean	8.64	8.48	8.34
	SD	0.77	1.15	1.16
Status of gouty tophus (n)	Yes	9	9	17
	No	1	0	2
Concurrent disease	Hypertension	6	3	7
	Hyperlipidemia	2	6	9
	Diabetes	1	0	1
	Hepatic disease	1	0	0
	Renal disease	0	0	0

mean values of serum uric acid levels before initiating drug administration among the groups. It was thus considered that these diagnoses had no impact on the efficacy assessment. With regard to other factors, no bias was observed among the groups.

Efficacy Evaluation

Serum Uric Acid Levels at Each Assessment Point

Figure 3 shows the time course of serum uric acid levels. Decreases in the serum uric acid levels after stepwise dose escalation were observed for all of the febuxostat and allopurinol groups. Serum uric acid levels (mean [SD]) at 16 weeks for the febuxostat 40- and 60-mg/d groups and the allopurinol group were 4.82 (0.89) mg/dL, 3.71 (0.59) mg/dL, and 5.29 (1.40) mg/dL, respectively.

Primary Endpoint

Figure 4 shows descriptive statistics for the percent change in serum uric acid levels (mean [SD]) after 16 weeks of treatment. The percent change for the febuxostat 40- and 60-mg/d groups and the allopurinol group was −42.96% (13.33%), −52.47% (9.79%), and −36.55% (18.59%), respectively. The hypouricemic effects of the febuxostat groups showed a tendency to increase in a dose-dependent manner. Moreover, the hypouricemic effects of the febuxostat groups were more potent than those of the allopurinol group, and there were significant differences in effects between the febuxostat 60-mg/d group and the allopurinol group ($P = 0.0239$, 2-sample t test).

Secondary Endpoints

Percentage of Patients With Serum Uric Acid Levels 6.0 mg/dL or Less at 16 Weeks

The percentage of patients achieving serum uric acid levels 6.0 mg/dL or less after 16 weeks of treatment was 88.9% (8/9 patients) for the febuxostat 40-mg/d group, 100% (8/8 patients) for the febuxostat 60-mg/d group, and 68.8% (11/16 patients) for the allopurinol group. These data suggest a greater achievement rate in febuxostat groups than allopurinol groups, although the difference was not statistically significant.

Percent Change in Serum Uric Acid Levels at Each Assessment Point

Table 2 shows the percent change in the serum uric acid levels at each assessment point. In all groups, the percent change in the serum uric acid levels gradually increased with the dose of study drugs. Because the percent change remained nearly constant in the febuxostat 40-mg/d group after 10 weeks (4 weeks after increasing the dose to 40 mg/d) and in the febuxostat 60-mg/d group after 14 weeks (4 weeks after increasing the dose to 60 mg/d), it was determined that the serum uric acid levels reached steady state within 4 weeks after a dose increment of febuxostat.

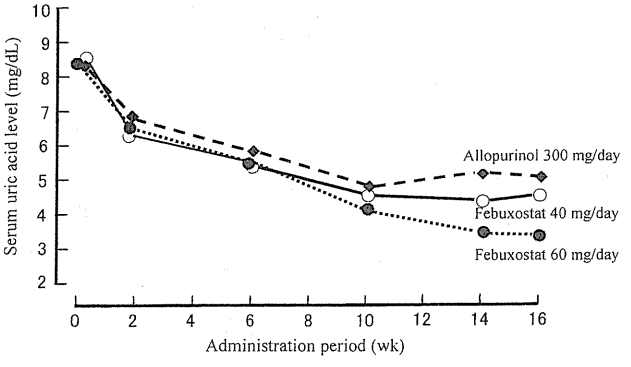

FIGURE 3. Time course of serum uric acid levels.

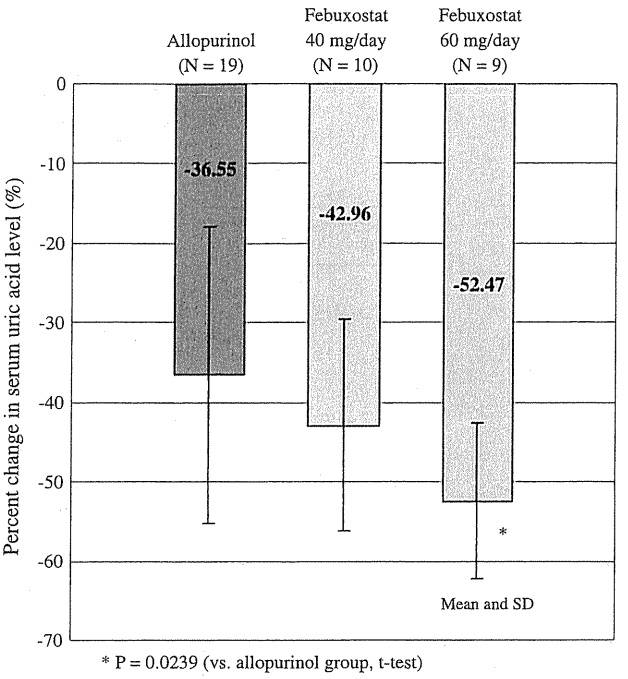

FIGURE 4. Percent change in serum uric acid levels 16 weeks after administration of febuxostat and allopurinol (FAS).

Safety

In this study, no patients withdrew from the study from registration to initiation of drug administration, and the safety assessment was conducted including all patients (40 patients).

Adverse Events

Thirty-four adverse events were observed in 13 patients in the febuxostat groups (40- and 60-mg/d groups) and 39 events in 16 patients in the allopurinol group. However, all adverse events were mild to moderate in severity, and no severe or serious adverse events were observed. Adverse events that were observed at high frequency included β_2-microglobulin urine increase in 3 patients (30%) in the febuxostat 40-mg/d group and in 1 patient (10%) in the 60-mg/d group, whereas in the allopurinol group, gouty arthritis was noted in 4 patients (20%) and blood creatine phosphokinase increased in 4 patients. In the febuxostat groups, the incidence of adverse events did not increase with stepwise dose escalation. In addition, the number of adverse events with unchanged outcome was 2 events (white blood cell count increase and intervertebral disk protrusion) in 2 patients in the allopurinol group and 1 event (β_2-microglobulin urine increase) in 1 patient in the febuxostat 40-mg/d group. However, none of the events were clinically significant, and drug causality was ruled out for all.

Adverse Drug Reactions

Adverse drug reactions for which drug causality could not be ruled out were observed in 14 events in 8 patients in the febuxostat groups and 9 events in 5 patients in the allopurinol

TABLE 2. Percent Change in Serum Uric Acid Levels at Each Assessment Point (FAS)

Administration Group		Assessment Point	No. Subjects	Mean (SD)	95% Confidence Interval	
					Lower Limit	Upper Limit
Allopurinol group		Week 2	18	−14.98 (6.95)	−18.44	−11.52
		Week 6	16	−26.87 (10.47)	−32.45	−21.29
		Week 10	16	−38.64 (17.77)	−48.10	−29.17
		Week 14	16	−33.81 (19.50)	−44.21	−23.42
		Week 16	16	−35.51 (18.61)	−45.43	−25.60
Febuxostat	40-mg/d group	Week 2	9	−26.65 (6.17)	−31.39	−21.90
		Week 6	10	−34.17 (8.42)	−40.19	−28.14
		Week 10	10	−45.05 (7.45)	−50.38	−39.73
		Week 14	9	−45.49 (10.01)	−53.19	−37.79
		Week 16	9	−43.79 (13.86)	−54.45	−33.14
	60-mg/d group	Week 2	9	−22.44 (8.99)	−29.35	−15.53
		Week 6	8	−31.04 (10.55)	−39.86	−22.23
		Week 10	8	−44.57 (6.01)	−49.60	−39.55
		Week 14	8	−53.87 (6.64)	−59.42	−48.32
		Week 16	8	−55.11 (6.13)	−60.24	−49.98

group. Among them, adverse drug reactions other than gouty arthritis observed in the febuxostat 40-mg/d group were depression, liver disorder, β_2-microglobulin urine increase, β-*N*-acetyl-D-glucosaminidase increase, and blood thyroid stimulation hormone increase, each in 1 event in 1 patient, and blood triglyceride increase in 2 events in 2 patients. The liver disorder and β-*N*-acetyl-D-glucosaminidase increase occurred in the same subject. In the febuxostat 60-mg/d group, alanine aminotransferase increase and β_2-microglobulin urine increase were each noted in 1 event in 1 patient, whereas in the allopurinol group, β_2-microglobulin urine increase and β-*N*-acetyl-D-glucosaminidase increase each occurred in 1 event in 1 patient (the same subject). All of these adverse drug reactions were mild in severity and disappeared without treatment; no serious adverse drug reactions were observed. Furthermore, the incidence of adverse drug reactions did not increase with stepwise dose escalation in any dose group.

Gouty Arthritis

Gouty arthritis occurred in 1 event in 1 patient in the 40-mg/d febuxostat group, 4 events in 1 patient in the 60-mg/d febuxostat group, and 7 events in 4 patients in the allopurinol group; drug causality could not be ruled out for any group. All of these events were mild to moderate in severity.

Other Data

Analysis of vital signs (blood pressure, heart rate, and body temperature) and 12-lead electrocardiogram results identified no clinically significant abnormal changes or abnormal findings.

DISCUSSION

Although allopurinol has been widely used as an inhibitor of uric acid synthesis for patients with gout and hyperuricemia, the risk of adverse drug reactions is high in patients with impaired renal function. It has thus been suggested to adjust dose levels for these patients according to the "Guidelines for the Management of Hyperuricemia and Gout" of the Japanese Society of Gout and Nucleic Acid Metabolism.[3] However, some reports indicate that satisfactory hypouricemic effects cannot be obtained if the dose of allopurinol is lowered.[21] Although a typical dose of allopurinol in Japan is defined as 200 to 300 mg/d, doses of 100 mg/d or less and 200 mg/d account for 60% to 70% and 20% to 30% of treatment in clinical practice, respectively, indicating that most treatments are performed using a dose of 200 mg/d or less.[22] In the phase 3 clinical study, febuxostat was demonstrated to have more potent hypouricemic effects than allopurinol. In this study, febuxostat was administered to patients with hyperuricemia including gout by increasing the dosage in a stepwise manner from a low level of 10 mg/d up to 40 or 60 mg/d to compare its efficacy with that of 300 mg/d allopurinol (increased from 100 mg/d), with the primary endpoint defined as the percent change in serum uric acid levels at 16 weeks compared with the baseline serum uric acid level.

In the febuxostat groups, the percent change in serum uric acid levels after 16 weeks of treatment increased in a dose-dependent manner and equaled or surpassed that of the allopurinol 300-mg/d group. Furthermore, the percentage of patients achieving serum uric acid levels 6.0 mg/dL or less was as high as ~90% for both febuxostat groups, compared with 74% for the allopurinol 300-mg/d group.

Regarding safety, there were no severe or serious adverse events observed in any treatment group. In addition, with regard to the incidence of adverse events, a tendency toward dose dependency was not observed between the febuxostat 40- and 60-mg/d groups. Events of gouty arthritis observed in this study were 1 event in 1 patient (10%) in the 40-mg/d febuxostat group, 4 events in 1 patient (10%) in the 60-mg/d group, and 7 events in 4 patients (20%) in the allopurinol group, and drug causality could not be ruled out for any patient. Except for gouty arthritis, all adverse drug reactions for which drug causality could not be ruled out were mild in severity and resolved without any treatment.

CONCLUSIONS

In the present study, febuxostat was demonstrated to be safe at dose increments up to 60 mg/d and to have the same or greater efficacy than 300 mg/d allopurinol.

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ORIGINAL ARTICLE

Magnetic resonance imaging (MRI) detection of synovitis and bone lesions of the wrists and finger joints in early-stage rheumatoid arthritis: comparison of the accuracy of plain MRI-based findings and gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI-based findings

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Abstract
Objective To explore whether synovitis and bone lesions in the wrists and finger joints visualized by plain magnetic resonance imaging (MRI)-based findings correspond exactly or not to those judged by gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI-based findings.

Methods Magnetic resonance imaging of the wrists and finger joints of both hands were examined in 51 early-stage rheumatoid arthritis (RA) patients whose median disease duration from the onset of articular manifestations to entry was 5 months, by both plain (T1 and short-time inversion recovery images) and Gd-DTPA-enhanced MRI (post-contrast fat-suppressed T1-weighted images) simultaneously. We focused on 15 sites per hand, to examine the presence of synovitis and bone lesions (bone edema and bone erosion). Gd-DTPA-enhanced MRI-based findings

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were considered "true" lesions, and we evaluated the accuracy of plain MRI-based findings in comparison to Gd-DTPA-enhanced MRI-based findings.

Results Synovitis, judged by plain MRI-based findings, appeared as false-positive at pretty frequency; thus, the specificity, positive predictive value and accuracy of the findings were low. The rate of enhancement (E-rate) in false-positive synovitis sites was significantly low compared with true-positive synovitis sites where Gd-DTPA enhancement appears. In contrast to synovitis, the false-positivity of bone lesions, judged by plain MRI-based findings, was very low compared with Gd-DTPA-enhanced MRI-based findings.

Conclusion Synovitis judged by plain MRI-based findings is sometimes considered false-positive especially in sites where synovitis is mild. However, plain MRI is effective in identifying bone lesions in the wrist and finger joints in early-stage RA.

Keywords Early-stage RA · Plain MRI · Gd-DTPA-enhanced MRI · Synovitis · Bone lesions

Abbreviations

ACR	American College of Rheumatology
CRP	C-reactive protein
E-rate	Rate of enhancement
Gd-DTPA	Gadolinium–diethylenetriamine pentaacetic acid
HLA-DRB1*SE	HLA-DRB1*shared epitope
RA	Rheumatoid arthritis
UA	Undifferentiated arthritis

Introduction

Magnetic resonance imaging (MRI) reveals joint inflammation and damage in early-stage rheumatoid arthritis (RA) [1–4] that take the form of synovitis and bone lesions, including bone edema and bone erosion [1–4]. As active synovial lesions in patients with RA are rich in vascularity, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI-based findings have become the gold standard to evaluate joint inflammation and damage in RA [1]. Accordingly, by assessing Gd-DTPA-enhanced MRI-based findings of the wrists and finger joints of both hands, we have determined that symmetrical synovitis and bone lesions are important predictors of the development of RA in patients with undifferentiated arthritis (UA) [5–8]. In these earlier studies, we did not specifically compare Gd-DTPA-enhanced MRI-based findings with plain MRI-based findings. However, Gd-DTPA-enhanced MRI is an expensive diagnostic tool compared to plain MRI, and Gd-DTPA can induce serious adverse events [9]. Thus, if plain MRI is sufficiently sensitive for the purpose, it should be possible to reduce both the cost and the adverse events associated with Gd-DTPA by using plain MRI.

The aim of the study reported here was to determine whether plain MRI-based findings are effective in evaluating joint inflammation and damage in early-stage RA in comparison to Gd-DTPA-enhanced MRI-based findings. Our results suggest that plain MRI is a sufficiently sensitive diagnostic tool to evaluate bone lesions, but that synovitis determined by plain MRI-based findings may on occasion appear as a false-positive, especially at sites where synovitis is mild.

Patients and methods

Patients

The Early Arthritis Clinic opened in 2001 as part of the Unit of Translational Medicine of the Department of Immunology and Rheumatology of the Graduate School of Biomedical Sciences of Nagasaki University. It is a regional center for the treatment of arthritis, with patients from the whole western part of Japan, Nagasaki Prefecture (approx. 450,000 inhabitants) being referred there for treatment. For our study, we recruited 51 early-stage RA patients from this clinic. The disease status of these patients was formally confirmed by a rheumatologist in our department, and a diagnosis of RA was based on the 1987 criteria for RA of the American College of Rheumatology (ACR) [10]. Baseline clinical manifestations and variables included sex, age, localization of arthritis, morning stiffness, number of tender joints, number of swollen joints, C-reactive protein level (CRP; measured by latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), immunoglobulin M-rheumatoid factor (IgM-RF) positivity (measured by latex-enhanced immunonephelometric assay; cut-off value 14 IU/ml; Dade Behring, Marburg, Germany), positive status for anti-cyclic citrullinated peptide (CCP) antibodies (measured by enzyme-linked immunosorbent assay; cut-off value 4.5 U/ml; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), HLA-DRB1 genotyping, and MRI findings for both the wrists and finger joints, as previously described [5–8, 11]. All variables were examined on the same day, as previously reported [5–8, 11]. Each patient provided a signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University.

MRI of wrists and finger joints

Magnetic resonance scan images of both the wrists and finger joints were acquired using a 1.5 T system (Signa; GE Medical Systems, Milwaukee, WI) with an extremity coil. T1-weighted spin-echo (TR 450 ms, TE 13 ms) images, short-time inversion recovery (STIR; TR 3000 ms, TE 12 ms, T1 160 ms) images, and Gd-DTPA-enhanced images were simultaneously acquired. The images were evaluated for bone edema, bone erosion, and synovitis in 15 sites in each finger and wrist: the distal radioulnar joint, the radiocarpal joint, the midcarpal joint, the first carpometacarpal joint, the second-fifth carpometacarpal joints (together), the first–fifth metacarpophalangeal joints, and the first–fifth proximal interphalangeal joints (PIP joints) separately (a total of 30 sites in both hands), as recently reported [5–8, 11]. The presence of synovitis, bone edema, and bone erosion was evaluated according to the methods described by Lassere et al. [12] and Conaghan et al. [13], by two experienced radiologists (M.U. and A.F.), and decisions were reached by consensus, as previously described [5–8, 11]. Since the focus of our study was to compare MRI-based findings and Gd-DTPA-enhanced MRI-based findings in terms of their accuracy in determining synovitis and bone change, we included bone edema and bone erosion as bone lesions in our study. Gd-DTPA-enhanced images were obtained by intravenous injection of 0.1 mmol/kg of Gd-DTPA (Magnevist; Bayer Schering Pharma, Berlin, Germany). A dynamic study was performed to evaluate the vascularity of the affected joints as a rate of enhancement (E-rate), which was determined by examining coronal sections taken at 4-s intervals over a 150-s time period with fast spoiled gradient recalled acquisition in the steady state (SPGR) sequences, as previously described [5–8, 11].

Comparison of plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings

Gd-DTPA-enhanced MRI-based findings are the gold standard for evaluating joint inflammation and damage by MRI in RA [1]. Thus, we assumed that Gd-DTPA-enhanced MRI-based findings represented "true" lesions and subsequently calculated the accuracy of plain MRI-based findings, comparing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Statistical analysis

Differences between the groups shown in Table 4 were examined for statistical significance using the Mann–Whitney U test. A P value of <0.05 was taken to indicate a statistically significant difference.

Results

Patient characteristics

Table 1 shows the baseline characteristics of the 51 patients with RA enrolled in our study. Since the median disease duration from the onset of articular manifestations to entry was 5 months, this study population was considered to have early-stage RA. The median Genant-modified Sharp score of the 51 patients at baseline was 0.49, which also identifies them as early-stage RA patients. The rates of seropositivity of IgM-RF and anti-CCP antibodies were 62.7 and 74.5%, respectively, and the rates of carriership of the HLA-DRB1*0405 allele and HLA-DRB1*shared epitope (SE) allele were 44.0 and 56.0%. These characteristics of autoantibodies and HLA-DR typing indicate that our study population manifested typical RA characteristics.

Synovitis and bone lesions of the wrists and finger joints of both hands according to plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings

Among the 1530 sites of interest, we were able to evaluate synovitis in 1416 sites on both plain MR and Gd-DTPA-enhanced MR scan images. Synovitis was considered positive in 65.6% of sites (929/1416) according to plain MRI-based findings, but was not found in 316 of these 929 sites by Gd-DTPA-enhanced MRI-based findings

Table 1 Demographic features of 51 early-stage rheumatoid arthritis patients

Demographic feature	Value
Gender (M:F, % F)	8:43 (84.3%)
Age (years)	52 (19–80)
Duration (months)	5 (1–28)
Distribution of arthritis	
Symmetric (%)	82.4
Only upper extremities (%)	27.5
Both upper and lower extremities (%)	72.5
Genant-modified Sharp score	0.49 (0–8.58)
Positivity of IgM-RF (%)	62.7
IgM-RF (IU/ml)	18.0 (4.5–395)
Positivity of anti-CCP antibodies (%)	74.5
Anti-CCP antibodies (IU/ml)	24.3 (0.6–2115.3)
Positivity of CRP (%)	70.0
CRP (mg/dl)	1.14 (0.03–11.13)
Carriership of HLA-DRB1*0405 (%)	44.0 (diploid: 8.0%)
Carriership of HLA-DRB1*shared epitope (%)	56.0 (diploid: 8.0%)

Values are given as the median with the range in parenthesis, unless otherwise stated

M Male, *F* female, *IgM* immunoglobulin M, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *CPR* C-reactive protein

Table 2 Comparison of plain MRI-based findings to Gd-DPTA-enhanced MRI-based findings

MRI findings	Gd-enhanced MRI		Total
	Synovitis (+)	Synovitis (−)	
Synovitis			
Plain MRI			
Synovitis (+)	613	316	929
Synovitis (−)	175	312	487
Total	788	628	1416
Bone lesions			
Plain MRI			
Bone lesions (+)	92	9	101
Bone lesions (−)	22	1378	1400
Total	114	1387	1501

Synovitis were evaluated in 1416 sites and bone lesions were evaluated in 1501sites as described in Patients and methods

Gd-DPTA Gadolinium–diethylenetriamine pentaacetic acid, *MRI* magnetic resonance imaging

Table 3 Sensitivity, specificity, PPV, NPV and accuracy of synovitis and bone lesions according to the plain MRI-based findings[a]

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Synovitis	77.8	49.7	66.0	64.1	65.3
Bone lesions	80.7	99.4	91.1	98.4	97.9

PPV Positive predictive value, *NPV* negative predictive value

[a] Gd-DTPA enhanced MRI-based findings were considered as gold standard; the accuracy of plain MRI-based findings were compared with Gd-DTPA-enhanced MRI-based findings

(Table 2). These data indicate that some synovitis that appears positive on a plain MR image scan is, in fact, false-positive. Bone lesions were visualized in 1501 sites by both plain and Gd-DTPA-enhanced MRI. In contrast to synovitis, the false-positive rate of bone lesions based on plain MRI findings was very low compared with that based on Gd-DTPA-enhanced MRI findings (Table 2). The rates of sensitivity, specificity, PPV and negative predictive value (NPV), and the accuracy of synovitis and bone lesion readings according to plain MRI were determined (Table 3).

The E-rate in sites of false-positive synovitis was significantly low compared with that in sites of true-positive synovitis

For the purposes of our study, the sites where plain MR scan images were positive for synovitis and Gd-DTPA-enhanced MR scan images were negative were considered

Table 4 Comparison of E-rate in sites of false-positive synovitis with sites of true-positive synovitis

MRI findings	N (sites)	E-rate (mean ± sd, median, range)	*P*-value
A. True positive; plain (+), enhanced (+)	366	8.1±5.1 (6.9, 1.2 – 50.1)	
B. False-negative; plain (-), enhanced (+)	57	6.8 ±2.2 (6.5, 3.4 – 14.6)	N.S.
C. False positive; plain (+), enhanced (-)	121	5.7±2.2 (6.0, 1.4 – 14.5)	§
D. True negative; plain (-), enhanced (-)	298	5.5±1.7 (5.5, 1.4 – 12.3)	N.S.

§ § § § §

We compared every E-rate by Mann–Whitney *U* test. *P* values are as follows: A vs B, 0.19; A vs C, 9.2×10^{-10}; A vs D, 5.2×10^{-8}; B vs C, 0.00096; B vs D, 5.3×10^{-6} and C vs D, 0.20. It is interesting to note that E-rate of false-negative synovitis sites tended to be low, however, there is no statistical significance as compared with true-positive sites (see A vs B). E-rate of false-negative synovitis sites was high as compared with false-positive synovitis sites (see B vs C)

§ *P* value <0.0001

to be false-positive sites; the sites for which positive results were obtained using both MRI imaging techniques were considered to be true positive sites. The severity of synovitis was compared by the E-rate of Gd-DTPA-enhanced MRI. As shown in Table 4, the E-rate of false-positive synovitis sites was significantly low compared with that of the true positive sites.

Discussion

Recent reviews have reported that plain MRI-based findings of bone lesions can be substituted for Gd-DTPA-enhanced MRI-based findings, although Gd-DTPA enhancement is recommended for the evaluation of synovitis [1]. Since the median disease duration from the onset of articular manifestations to entry in the 51 patients of our study cohort was 5 months, we suggest that our data reflect primarily rheumatoid joint damage, rather than secondary changes due to osteoarthritis. However, there have been few precise comparisons of plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings; i.e., both plain and Gd-DTPA-enhanced sequences of multiple sites in both hands examined simultaneously. Ostergaard et al. reported that Gd-DTPA injection is not important to qualify the MRI scores of bone erosion and bone edema, whereas it is indispensable to diagnose synovitis [14].

Our data also show that plain MRI-based findings are not sufficient alone to evaluate the presence of synovitis. The severity of synovitis, as determined by the E-rate in dynamic Gd-DTPA-enhanced MR scan images, is low in false-positive synovitis sites compared with true-positive

sites. We speculate that cartilage, synovial fluids, or fibrous tissues may be interpreted as synovial hyperplasia in these cases, and we must be aware of the superiority of Gd-DTPA-enhanced MRI over plain MRI in evaluating synovitis, especially in the case of less active lesions. The E-rate of false-negative synovitis sites tended to be low among our patients; however, there was no statistical significance relative to true-positive synovitis sites. Accordingly, the E-rate of false-negative synovitis sites was high as compared with that of false-positive synovitis sites. Since a previous study demonstrated that the E-rate of the wrist correlates with the clinical disease activity in patients with RA [15], we suggest that the E-rate could correlate well with the synovitis score based on the RA MRI scoring system (RAMRIS). Consequently, findings from Gd-DTPA-enhanced MRI are crucial to qualify the presence of synovitis correctly.

Nevertheless, plain MRI is an effective tool for evaluating bone lesions of the wrists and finger joints since false-positivity is very low for this evaluation. In addition to the wrists and metacarpophalangeal joints, we identified three PIP joints as being positively associated with bone lesions out of 114 sites which were identified by Gd-enhanced MRI. There was no false-positive result by plain MRI in these three PIP joints, indicating that plain MRI is able to accurately detect the bone lesions of smaller joints of PIP joints. A recent observation (unpublished data) by our group indicates that the E-rate of sites with bone lesions is significantly high compared with that of those without bone lesions [15]. These data suggest that synovial inflammation is obvious in bone lesion sites and, therefore, that false-positivity is low in these areas.

In summary, our present data confirm the recent results of Ostergaard et al. [14] that bone lesions can be correctly identified by plain MRI-based findings in early-stage RA, while synovitis cannot. Based on our present results, we are currently investigating longitudinal changes in bone lesions by plain MRI of the wrists and finger joints in early arthritis patients during therapeutic interventions. These studies are warranted to establish the value of plain MRI in clinical rheumatology.

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Conflict of interest None.

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