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Original Article

Association between matrix metalloprotease-3 levels and radiographic progression in patients with rheumatoid arthritis: A *post hoc* analysis from a Japanese Phase 3 clinical trial of peficitinib (RAJ4)

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ABSTRACT

Objectives: The current study assesses the utility of matrix metalloprotease-3 (MMP-3) as a biomarker for joint damage in patients with rheumatoid arthritis receiving peficitinib.

Methods: Rheumatoid arthritis patients with inadequate response to methotrexate were randomised to peficitinib 100 mg, peficitinib 150 mg, or placebo, combined with methotrexate, for 52 weeks; patients receiving placebo switched to peficitinib 100/150 mg at Week (W)12/28. This *post hoc* analysis investigated association between MMP-3 above/below upper limit of normal (ULN) at W12/28 and radiographic progression [modified total Sharp score (mTSS), joint space narrowing score, or erosion score >0.5] at W52 or swollen joint count 66 at W28, stratified by baseline glucocorticoid use and renal function.

Results: MMP-3 levels decreased in both peficitinib-treated groups but more slowly in patients with baseline glucocorticoids and those with radiographic progression at W52. There was no clear correlation between MMP-3 change from baseline (CFB) at W12, CFB in mTSS, joint space narrowing score, or erosion score at W52, or CFB in swollen joint count 66 at W28. More patients with MMP-3 ≤ULN versus >ULN at W12 had radiographic non-progression at W52. MMP-3 normalisation at W12 was significantly associated with mTSS non-progression at W52.

Conclusions: Normalisation of MMP-3 at W12 may be a predictor for subsequent non-progression of joint damage at W52.

KEYWORDS: Biomarker; matrix metalloprotease-3; peficitinib; radiographic progression; rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a degenerative autoimmune disease, in which chronic joint inflammation, destruction of cartilage, and bone erosion lead to joint deformity and physical disability [1]. Disease-modifying antirheumatic drugs (DMARDs) are the mainstay of RA treatment [2]. These can be classified into conventional synthetic (cs)DMARDs such as methotrexate (MTX), biologic (b)DMARDs such as tumour necrosis factor (TNF)α inhibitors, and targeted synthetic (ts)DMARDs such as the Janus kinase (JAK) inhibitors, namely tofacitinib, baricitinib, and peficitinib [2]. Guidelines from the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and Asia-Pacific League of Associations for Rheumatology all recommend the use of MTX and/or other csDMARDs as part of the first treatment strategy, followed by bDMARDs or tsDMARDs in patients with an inadequate response to csDMARDs or MTX [2–4].

Despite this variety of therapeutic approaches, patient response to treatment remains variable, e.g. only 60% of patients treated with bDMARDS achieve a 20% improvement according to ACR criteria (ACR20 response) [5]. In recent years, attention has focused on disease biomarkers as potential predictors of treatment response and to enable more targeted therapies [6]. One possible biomarker is matrix metalloprotease-3 (MMP-3), a proteolytic enzyme produced by synovial fibroblasts and chondrocytes, which degrades cartilage components including cartilage link protein and collagen [7]. Previous studies have shown an association between MMP-3 levels and disease activity, e.g. in a study of

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82 Japanese patients with RA, MMP-3 levels were strongly correlated with both inflammatory markers and the extent of joint destruction measured by Steinbroker stage [8]. In addition, a study of 59 Turkish patients with RA found a statistically significant correlation between serum MMP-3 levels and structural joint damage measured by the Larsen score [9]. Additionally, there is evidence that elevated MMP-3 levels are associated with glucocorticoid use in patients with RA [10, 11].

However, it is currently unclear whether MMP-3 is merely correlated with measures of joint damage or if it can be used as a predictor of these outcomes. In this paper, we report the results of a *post hoc* analysis of data from the RAJ4 study, a Phase 3 clinical trial that evaluated the efficacy and safety of peficitinib in Japanese patients with RA; the main efficacy and safety results for this study have been previously published [12]. Our aim was to explore the utility of MMP-3 as a predictive biomarker for joint damage and treatment response to peficitinib, by analysing the relationship between MMP-3 levels and radiographic progression.

Materials and methods

Ethics

The study was conducted in accordance with Good Clinical Practice, International Council of Harmonisation guidelines, and applicable laws and regulations. The study protocol and its amendments were reviewed and approved by an institutional review board at each study site. Written informed consent was obtained from each participant. The study was registered at ClinicalTrials.gov, NCT02305849.

Study design and patients

RAJ4 was a randomised, Phase 3, double-blind, placebo-controlled, parallel-group study of peficitinib, conducted at 161 centres in Japan [12]. The RAJ4 study design and eligibility criteria have been previously described (Supplementary Figure 1) [13]. Briefly, patient inclusion criteria were as follows: age ≥20 years old; RA <10 years as defined by 1987 ACR or 2010 EULAR criteria; RA class I, II, or III at screening according to the ACR 1991 revised criteria [14]; active disease [≥6/68 tender joint count (TJC68) and ≥6/66 swollen joint count (SJC66)]; C-reactive protein (CRP) ≥1.00 mg/dl at screening; bone erosion in ≥1 joint; and an inadequate response to MTX ≥8 mg/week for ≥28 days prior to baseline and a continuous administration for ≥90 days prior to screening. Exclusion criteria included treatment with bDMARDs (within specified periods prior to baseline) or other JAK inhibitors, infections, laboratory abnormalities, or a history of concurrent malignant tumour.

Eligible patients were randomised 1:1:1 to peficitinib 100 mg, peficitinib 150 mg, or placebo, orally once daily in combination with MTX (≤16 mg/week) over 52 weeks. At 12 weeks, patients in the placebo group with an inadequate response (<20% improvement from baseline in TJC68 and SJC66) were switched to peficitinib 100 or 150 mg. The remaining patients in the placebo group were switched to peficitinib 100 or 150 mg at Week (W)28. Blinding was maintained throughout.

Assessments and endpoints

Radiographic assessments of hands and feet were carried out at baseline, W12 (only for patients with an inadequate response), W28, W52, and early termination (ET) (for patients who discontinued before W28). The process of radiographic scoring has been described in detail previously [13]. Changes from baseline (CFBs) in joint space narrowing (JSN) score, erosion score (ES), and van der Heijde-modified total Sharp score (mTSS; sum of erosion and JSN scores) were calculated for each timepoint. Radiographic non-progression was defined as a CFB in mTSS, JSN score, or ES of ≤0.5.

Assessment of SJC66 and TJC68 was conducted at baseline and every 4 weeks thereafter until W52/ET [end of treatment (EOT)]. Blood samples for assessment of MMP-3 levels were taken at baseline, at W4, W8, W12, W28, and W52, at follow-up 28 days after EOT, and at ET if applicable. Samples were collected before study drug administration into a 2-ml sample tube containing disodium ethylenediaminetetraacetic acid and analysed using a latex agglutination turbidimetric immunoassay at LSI Medience Corporation, Tokyo, Japan. The normal range of MMP-3 was defined as 36.9–121.0 ng/ml (males) or 17.3–59.7 ng/ml (females) [15].

The primary efficacy endpoints for the main RAJ4 study were the proportion of patients with 20% improvement according to ACR criteria (ACR20 response rate) at W12/ET and mTSS mean CFB at W28/ET [12]. Endpoints for this *post hoc* analysis were the observed values and CFB in MMP-3 levels and the rates of radiographic non-progression in each treatment arm.

Statistical analyses

MMP-3 CFB to W52 was analysed overall and by sex, baseline glucocorticoid use (yes/no), renal function (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 versus ≥60 ml/min/1.73 m^2) and by categories of radiographic non-progression or progression in mTSS, JSN score, and ES. Correlation of the CFB in MMP-3 at W12 with CFB at W28 in SJC66 and TJC68 and the CFB at W52 in mTSS, JSN score, and ES was visualised using scatter plots and analysed using Spearman's rank correlation coefficient. Coefficients of >0.3 were considered to indicate notable correlation. The proportion of patients with radiographic non-progression at W52 was analysed by baseline glucocorticoid use (yes/no), renal function (eGFR <60 ml/min/1.73 m^2 versus ≥60 ml/min/1.73 m^2), and category of MMP-3 levels above or below the upper limit of normal (ULN) at W12 and W28.

The full analysis set (FAS) comprised all randomised patients who received at least one dose of study drug. Data were presented descriptively, and no hypothesis testing was conducted. For patients who discontinued before W28 or W52 or those who switched from placebo at W12, mTSS, ES, and JSN score were imputed using a linear extrapolation method, based on the scores at baseline and ET [12]. All outliers were included in the analyses, and no multiplicity adjustment was performed.

Multivariate logistic regression with backward variable selection (at the 0.15 significance level) was conducted to identify patient- and treatment-related characteristics associated with radiographic non-progression (mTSS CFB ≤0.5) at W52. In the backward selection, the following baseline characteristics were analysed: age (years), baseline weight (kg), duration from RA onset (years), baseline CRP (mg/dl), baseline disease activity score in 28 joints (DAS28)-CRP, baseline DAS28-erythrocyte sedimentation rate (ESR), baseline prednisone dose (mg/day), sex, baseline concomitant glucocorticoid flag,

Table 1.. MMP-3 levels at baseline, by glucocorticoid use.

Treatment arm	Patients without glucocorticoid use	Patients with glucocorticoid use
Placebo	274.05 (224.30)	292.30 (184.63)
Peficitinib 100 mg	308.77 (316.91)	319.93 (303.91)
Peficitinib 150 mg	339.34 (300.53)	302.07 (223.34)

Data are mean (SD).

prior anti-TNF use, prior bDMARD use, number of prior bDMARDs, MTX dose at baseline (mg/week), baseline mTSS, baseline anti-CCP antibody (U/ml), baseline rheumatoid factor (IU/ml), baseline eGFR (ml/min/1.73 m^2), and baseline MMP-3. Peficitinib dose (150 mg versus 100 mg) and MMP-3 at W12 were also included.

After backward selection, the selected variables included in the final multivariate logistics models were peficitinib dose (150 mg versus 100 mg), age (years), baseline weight (kg), duration of RA (years), baseline CRP (mg/dl), baseline DAS28-ESR, baseline mTSS, baseline anti-CCP antibody (U/ml), baseline MMP-3, and MMP-3 at W12. The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). *P* values <.15 were considered significant. All analyses were conducted using either SAS v9.4 or higher or R v4.2.1.

Results

Patient baseline characteristics

Of 780 patients screened, 518 were included in the FAS (peficitinib 100 mg, $n = 174$; peficitinib 150 mg, $n = 174$; placebo, $n = 170$). Patient demographics and baseline characteristics for the whole RAJ4 study population have been previously published [12] and were similar between treatment arms.

Radiographic progression

As previously described, CFBs in mTSS, JSN score, and ES were significantly reduced with peficitinib treatment compared with placebo (Supplementary Table 1) [12]. Similarly, the percentage of patients with non-progression, defined as mTSS CFB ≤0.5, was significantly higher in both peficitinib 100 mg and 150 mg groups versus placebo, at W28/ET and W52/ET (Supplementary Table 2) [12].

Change in MMP-3 levels

At baseline, mean (SD) MMP-3 levels were similar in patients with and without glucocorticoid use (Table 1). From W0 to W12, MMP-3 levels decreased in the peficitinib-treated groups but not in the placebo-treated group (Figure 1). A more gradual decline in MMP-3 in the peficitinib-treated groups continued to W52 and was observed in both males and females (Supplementary Figure 2). From W0 to W52, the mean change in MMP-3 was −196.97 ng/ml in the peficitinib 100 mg group and −188.68 ng/ml in the peficitinib 150 mg group (Figure 1).

Patients receiving glucocorticoids at baseline appeared to have a slower decline in MMP-3 levels between W0 and W12 compared with those not receiving glucocorticoids at baseline, although this difference was not substantial (Figure 2(a)). This pattern was observed in both peficitinib 100 mg and peficitinib 150 mg treatment arms.

The decrease in MMP-3 from W0 to W12 and W12 to W52 was similar in patients with radiographic progression (CFB >0.5 in mTSS, JSN score, or ES) and those without radiographic progression (CFB ≤0.5 in mTSS, JSN score, or ES) at W52 (Figure 2(b–d)). However, the decline in MMP-3 levels appeared slightly slower among those with radiographic progression (Figure 2(b–d)). There were no clear differences in MMP-3 CFB in patients with progression in JSN score versus those with progression in ES (Figure 2(c,d)). However, the number of patients with ES progression was low, particularly in the peficitinib 150 mg arm (Figure 2(d)).

In patients with normal renal function (eGFR ≥60 ml/min/1.73 m^2), decrease in MMP-3 levels was similar to peficitinib 100 mg and peficitinib 150 mg, regardless of baseline glucocorticoid use (Supplementary Figure 3). In patients with renal insufficiency (eGFR <60 ml/min/1.73 m^2) and without baseline glucocorticoid use ($n = 6$), a reduction in MMP-3 levels was observed with peficitinib 150 mg but not peficitinib 100 mg (Supplementary Figure 3). In patients with renal insufficiency and baseline glucocorticoid use ($n = 10$), no clear reduction in MMP-3 levels was observed with either peficitinib dose, and comparisons between treatment arms were precluded by small sample sizes (Supplementary Figure 3).

Correlation between MMP-3 and radiographic progression or disease activity

There was no clear correlation between MMP-3 CFB at W12 and CFB in mTSS, JSN score, or ES at W52. The Spearman's rank correlation coefficient for the association between these outcomes was highest in the placebo group for JSN score (0.2225) and overall mTSS (0.2029) and highest in the peficitinib 150 mg group for ES (0.1464) but remained below 0.3 for all radiographic progression measures in all three treatment arms (Supplementary Figure 4A–C).

There was no clear correlation between MMP-3 CFB at W12 and SJC66 CFB at W28. The Spearman's rank correlation coefficient was highest in the placebo arm (0.2097) and was <0.3 for all treatment arms (Supplementary Figure 4D). Similarly, no correlation with a coefficient >0.3 was observed between MMP-3 CFB at W12 and TJC68 at W28 (data not shown).

Proportion of patients with radiographic non-progression

For both peficitinib 100 mg and peficitinib 150 mg treatment arms, a greater proportion of patients with MMP-3 levels ≤ULN at W12 had radiographic non-progression (CFB ≤0.5 in mTSS, JSN score, or ES) at W52, compared with patients with MMP-3 levels >ULN at W12 (Figure 3). This pattern was observed regardless of whether patients were receiving glucocorticoids at baseline, although the difference between groups with MMP-3 levels above and below the ULN tended to be less notable among patients with baseline glucocorticoids than those without (Figure 4).

In patients not receiving baseline glucocorticoids, the difference between groups with MMP-3 levels above and below the ULN tended to be more notable for peficitinib 150 mg versus peficitinib 100 mg, particularly for JSN progression (Figure 4). In contrast, in patients with baseline glucocorticoids, differences between MMP-3 subgroups were more notable in those receiving peficitinib 100 mg versus 150 mg

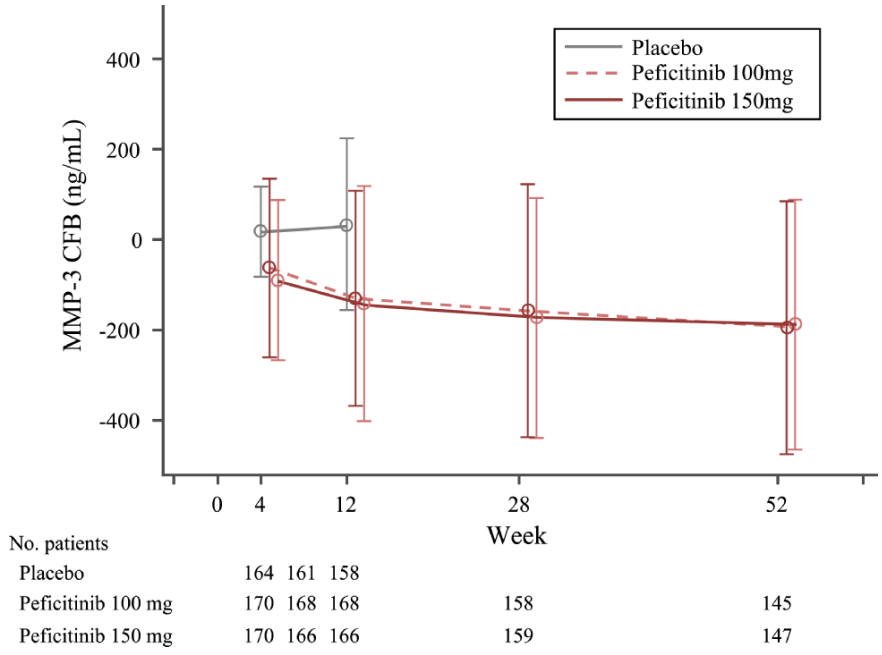

Figure 1. MMP-3 CFB to W52.

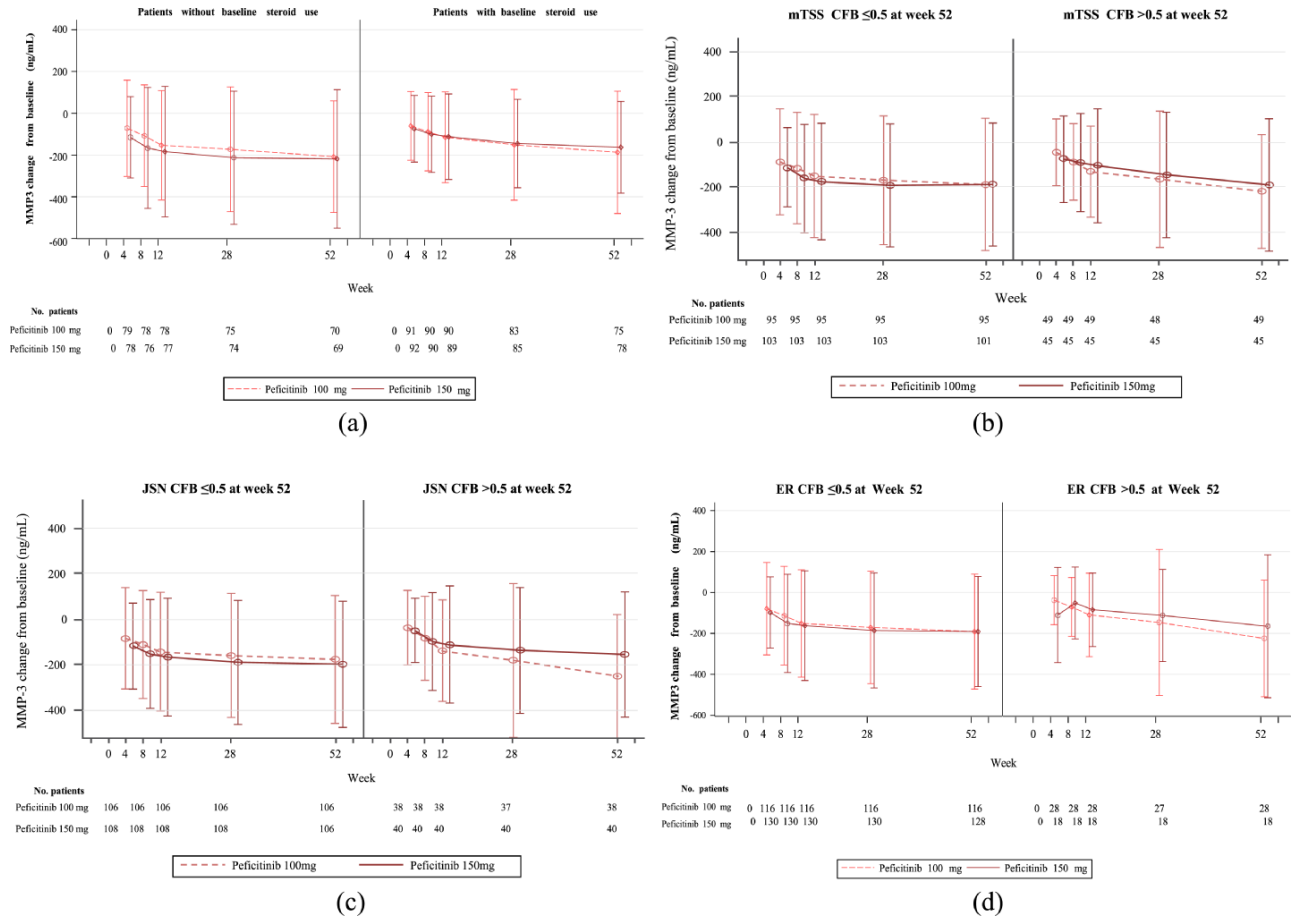

Figure 2. MMP-3 CFB to W52, stratified by (a) baseline glucocorticoid use and by non-progression/progression at W52 in (b) mTSS, (c) JSN score, and (d) ES.

Non-progression in mTSS, JSN score, or ES was defined as CFB ≤0.5.

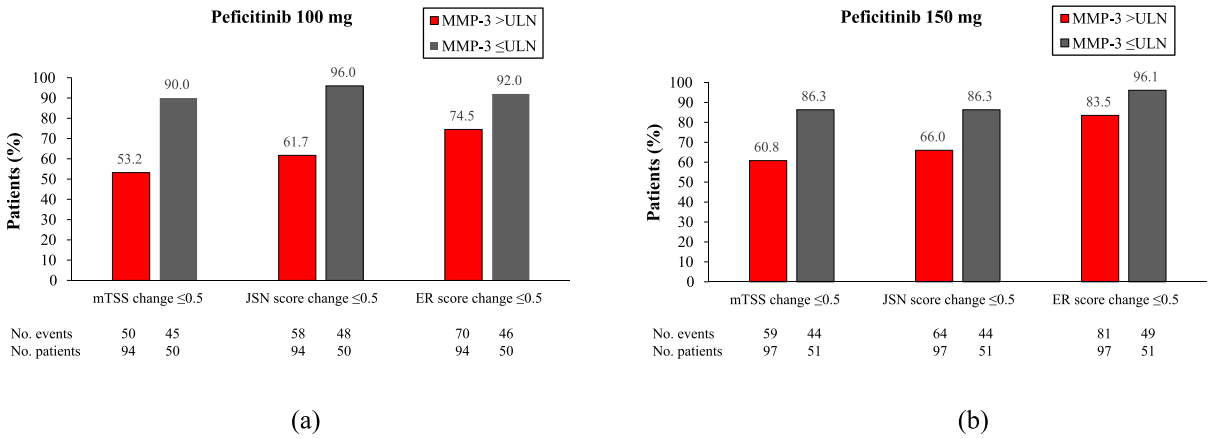

Figure 3. The proportion of patients achieving radiographic non-progression at W52, stratified by peficitinib dose and MMP-3 levels at W12. It excludes patients initially randomised to placebo. The ULN of MMP-3 was defined as 121 ng/ml (males) or 59.7 ng/ml (females).

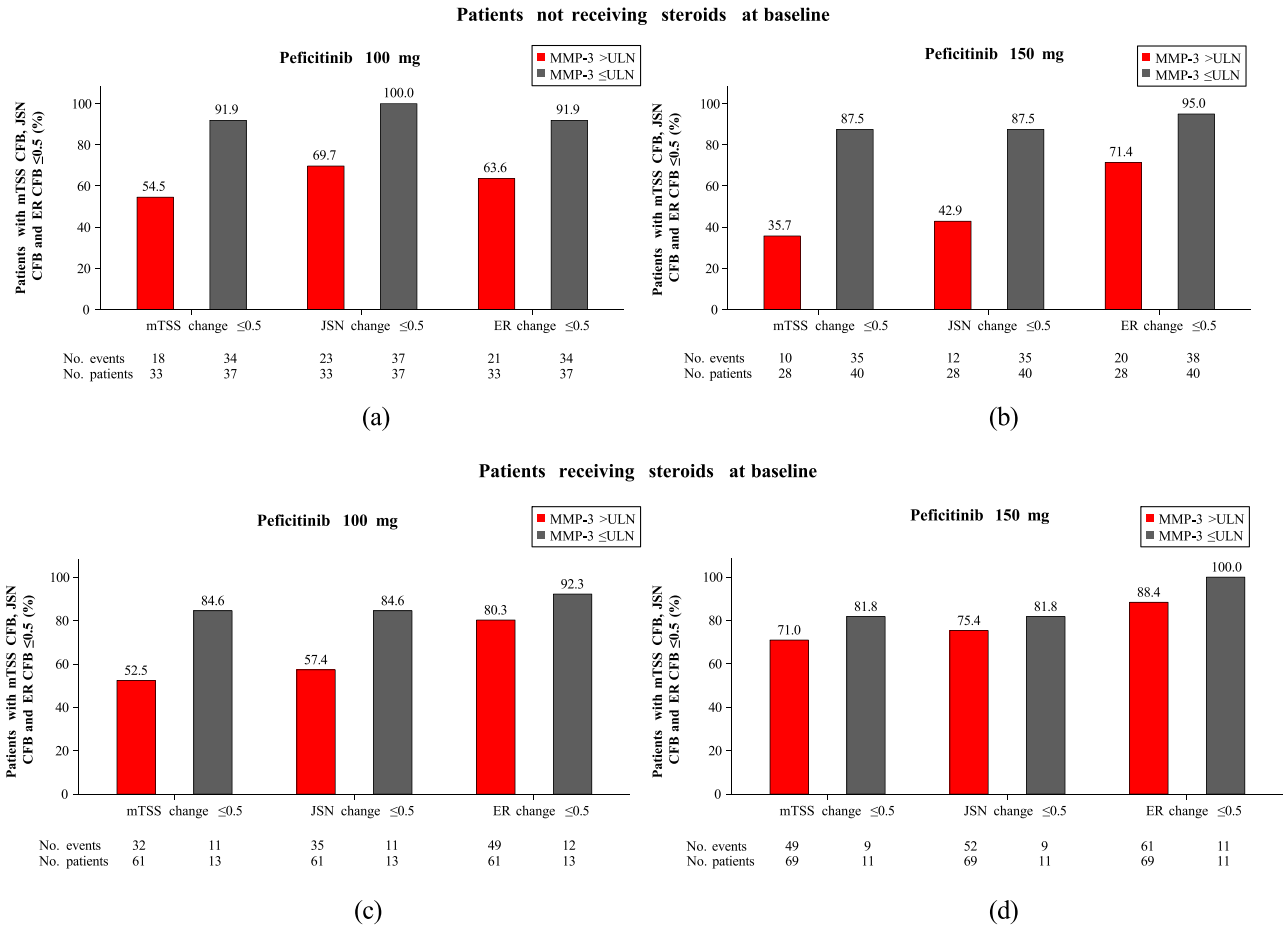

Figure 4. The proportion of patients achieving radiographic non-progression at W52, stratified by peficitinib dose, MMP-3 levels at W12 and baseline glucocorticoid use. It excludes patients initially randomised to placebo. The ULN of MMP-3 was defined as 121 ng/ml (males) or 59.7 ng/ml (females).

(Figure 4). In all MMP-3 and glucocorticoid subgroups examined, except for patients without baseline glucocorticoids receiving peficitinib 100 mg, the proportion of patients with JSN non-progression was smaller than the proportion with ES non-progression (Figure 4). Results for patients stratified by MMP-3 levels at W28 were similar to those at W12, although differences between MMP-3 subgroups tended to be less sizeable when stratified by levels at W28 (Supplementary Figure 5A and 5B) than at W12 (Figure 3 and Figure 4).

When stratified by baseline glucocorticoid use, renal function, and MMP-3 levels at W12, a greater proportion of patients with normal renal function and MMP-3 levels ≤ULN achieved radiographic non-progression at W52 versus patients with normal renal function and MMP-3 levels >ULN (Supplementary Figure 6A). This effect was seen regardless of baseline glucocorticoid use, for both peficitinib doses (Supplementary Figure 6A). Among patients with renal insufficiency, no difference in the proportion with radiographic

Table 2. Multivariate logistic regression analysis of the association between patient- or treatment-related characteristics and mTSS CFB ≤0.5 at W52.

Characteristics	OR	95% CI	*P* value
Peficitinib dose: 150 mg versus 100 mg	1.38	(0.79, 2.45)	.263
Age (years; continuous variable)	1.04	(1.01, 1.07)	.006*
Baseline weight (kg; continuous variable)	1.03	(1.01, 1.06)	.013*
Duration from RA onset (years; continuous variable)	1.11	(1.00, 1.23)	.055*
Baseline CRP (mg/dl; continuous variable)	0.80	(0.68, 0.93)	.005*
Baseline DAS28-ESR (continuous variable)	0.74	(0.54, 1.01)	.062*
Baseline mTSS (continuous variable)	0.99	(0.98, 1.00)	.120*
Baseline anti-CCP antibody (U/ml; continuous variable)	1.00	(1.00, 1.00)	.021*
MMP-3 at baseline (ng/ml; ≤ULN versus >ULN)	1.00	(1.00, 1.00)	.118*
MMP-3 at W12 (ng/ml; ≤ULN versus >ULN)	4.56	(2.21, 10.02)	<.001*

CCP, cyclic citrullinated peptide.
*$P < .15$ was considered significant. The table presents only statistically significant covariates identified during model selection.

non-progression at W52 was observed between those with MMP-3 levels ≤ULN and those with MMP-3 levels >ULN, for either peficitinib dose (Supplementary Figure 6B). However, the total number of patients with renal insufficiency was small, with only 1–3 patients in each comparison group (glucocorticoid/no glucocorticoid plus MMP-3 >ULN/≤ULN). The findings were similar when the proportion of patients with non-progression was stratified by baseline glucocorticoid use, renal function, and MMP-3 levels at W28 (Supplementary Figures 7A and 7B).

Association of patient characteristics with radiographic non-progression

Multivariate logistic regression analysis showed that the factors associated with mTSS non-progression at W52 were peficitinib dose (150 mg), older age, higher body weight, longer RA duration, lower baseline CRP, lower baseline DAS28-ESR, lower baseline mTSS, lower baseline anti-CCP antibody, higher baseline MMP-3, and MMP-3 ≤ULN at W12 (Table 2). Of these, MMP-3 ≤ULN at W12 had the most sizeable effect on mTSS non-progression (OR [95% CI]: 4.56 [2.21, 10.02]; $P < .001$) (Table 2). Although the threshold for statistical significance was not reached, there was a trend towards greater odds of mTSS non-progression with increased peficitinib dose (150 mg versus 100 mg) (OR [95% CI]: 1.38 [0.79, 2.45]; $P = .263$).

Discussion

Consistent with previous research [10, 11], this *post hoc* analysis of the RAJ4 clinical trial data showed that patients receiving glucocorticoids tended to have higher levels of MMP-3 than those not receiving glucocorticoids. Our findings indicate that MMP-3 may have some utility as a predictor of radiographic progression and treatment: a greater proportion of patients with MMP-3 levels ≤ULN at W12 and W28 achieved radiographic non-progression at W52 versus those with MMP-3 >ULN. In line with these observations, normalisation of MMP-3 levels at W12 was significantly positively associated with radiographic non-progression at W52, with the odds of non-progression over 4-fold higher in patients with MMP-3 ≤ULN than MMP-3 >ULN. However, the decrease in MMP-3 levels over the course of peficitinib treatment did not appear to differ notably between patients with and without radiographic progression, although any difference in trends was unclear possibly due to small numbers of patients, particularly the group with progression in ES in the peficitinib 150 mg arm.

In general, MMP-3 levels at W12 or W28 appeared to be predictive of radiographic non-progression in patients either with or without baseline glucocorticoid use, although the difference between MMP-3 subgroups was more substantial in patients without baseline glucocorticoids. Additionally, normalisation of MMP-3 at W12 had a minimal effect on the achievement of non-progression in patients receiving baseline glucocorticoids in the peficitinib 150 mg arm; the reason for this is unclear, particularly as baseline MMP-3 levels were similar between patients with and without glucocorticoids in each treatment arm. Among patients without baseline glucocorticoids who received peficitinib 150 mg, MMP-3 >ULN appeared to be a predictor of JSN score progression more markedly than of ES progression; this effect on JSN progression is consistent with the role of MMP-3 in accelerating cartilage destruction [9, 15].

Our results regarding the rates of non-progression are consistent with those from a previous study of patients with RA in Sweden, in which MMP-3 levels were downregulated in response to etanercept treatment [16]. More recently, Spigna *et al.* demonstrated a significant reduction in MMP-3 levels following combined MTX + bDMARD treatment [17]. Furthermore, Nawata *et al.* found that high MMP-3 levels were associated with progression in JSN score but not ES [18].

Our data also suggest that renal function may have an impact on the predictive utility of MMP-3 levels at W12 or W28. A difference in the proportion of patients with non-progression between the MMP-3 ≤ULN and MMP-3 >ULN groups was only observed among patients with normal renal function and not those with renal insufficiency. Previous research in patients with coronary artery disease showed an association between higher levels of circulating MMP-3 and a decline in eGFR [19]; it is therefore possible that renal insufficiency may confound the predictive effect of MMP-3 for non-progression in patients with RA. However, in our study, the numbers of patients with renal insufficiency were low, particularly once stratified by glucocorticoid use/non-use and MMP-3 levels, and it is not possible to draw firm conclusions from our data. Our correlation data were also not consistent with our results from either descriptive or logistic regression analysis; there was no clear correlation between MMP-3 CFB at W12 and CFB in mTSS or JSN score at W52 or CFB in SJC66 at W28. Across these outcomes, the placebo group showed the greatest tendency to correlate with disease activity.

This study is the first clinical trial of a tsDMARD to demonstrate that rapid reduction in MMP-3 levels is associated with radiographic non-progression. The most rapid improvements in MMP-3 levels were seen between W0 and W12, and this relatively early biomarker response, using levels at either W12 or W28, may assist in predicting and evaluating other peficitinib treatment outcomes. The limitations of the

study include the relatively short period of time that patients received peficitinib and also potentially restricted generalisability as only Japanese patients were included in the RAJ4 study. In addition, the current study does not assess the utility of CRP – for future research, it may be valuable to investigate the combination of CRP and MMP-3 as potential biomarkers.

In conclusion, MMP-3 levels within the normal range in the early stages of treatment (by W28) may be an indicator of the suppression of subsequent joint damage. However, evaluation of the relationship between joint damage and clinical symptoms or biomarkers like MMP-3 is challenging, and further research may be needed. In addition, our findings suggest that assessment of joint damage may be more complex than is currently determined by mTSS, SJC66 or TJC68.

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Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

T.T. received grants or contracts from AbbVie GK and Eisai Co. Ltd; consulting fees from AbbVie GK, Astellas Pharma Inc., Eli Lilly Japan K.K, and Gilead Sciences, Inc.; and payments or honoraria from AbbVie GK, Astellas Pharma Inc., Eisai Co., Ltd, Eli Lilly Japan, Gilead Sciences, Inc., and Pfizer Japan Inc. Y.T. received grants or contracts from Asahi-Kasei, AbbVie, Chugai, Eisai, Takeda, Daiichi-Sankyo and Boehringer-Ingelheim, and payments or honoraria from Gilead, AbbVie, Boehringer-Ingelheim, Eli Lilly, Mitsubishi-Tanabe, Chugai, Eisai, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Pfizer, and Astra-Zeneca. Y.M., D.K., Y.K. and W.T. are employees of Astellas.

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Data availability

Researchers may request access to anonymised participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

Author contributions

T.T., Y.T., Y.M., D.K., Y.K., and W.T. made a substantial contribution to study design. Y.K. and W.T. analysed the study data. T.T., Y.T., Y.M., D.K., Y.K., and W.T. interpreted the study data.

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