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Modern Rheumatology, **33**, 2023, 73–80
DOI: https://doi.org/10.1093/mr/roac021
Advance access publication date: 10 March 2022
Original Article

Post hoc analysis of clinical characteristics of patients with radiographic progression in a Japanese phase 3 trial of peficitinib and methotrexate treatment (RAJ4)

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ABSTRACT

Objective: To determine the efficacy of peficitinib in reducing joint damage and predictive factors affecting treatment response in Japanese patients with rheumatoid arthritis.

Methods: This *post hoc* analysis used data from a placebo-controlled, phase 3 trial (RAJ4) of peficitinib in patients with rheumatoid arthritis and inadequate response to methotrexate. Erosion and joint space narrowing (JSN) were assessed at baseline and at Week 28/early termination of treatment using the van der Heijde-modified Sharp method. A univariate logistic regression analysis of change from baseline in a modified total Sharp score identified predictive factors with significant treatment interaction; the effects of these factors on treatment response were further evaluated using a multivariate model.

Results: The analyses included 481 patients. For most joint groups, peficitinib demonstrated a reduced change from baseline at Week 28/early termination in erosion and JSN scores versus placebo; a numerically greater effect was observed with peficitinib 150 mg versus 100 mg. Baseline C-reactive protein (CRP) and prednisolone dose were identified as clinically significant negative predictive factors: the treatment effect decreased as CRP or prednisolone dose increased for both peficitinib doses.

Conclusions: Peficitinib 100 mg and 150 mg reduced joint damage versus placebo, across almost all joint groups. Higher baseline CRP and/or prednisolone dose were associated with reduced peficitinib efficacy.

ClinicalTrials.gov identifier: NCT02305849

KEYWORDS: JAK inhibitor; joint destruction; peficitinib; radiographic progression; rheumatoid arthritis

Introduction

The relationship between disease activity and the extent of joint structural damage in patients with rheumatoid arthritis (RA) is well established, and radiographic assessments can thus be considered an outcome measure of RA that correlates with cumulative joint inflammation [1, 2]. This inflammation is associated with largely nonreversible destruction of cartilage and erosion of bone [3], outcomes that are responsible for loss of function and reductions in patients' quality of life. Variations between ethnic populations are also observed, e.g. increased radiographic progression has been observed in Japanese populations [4–6] versus non-Asian populations [7].

Current RA management is founded on conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as the standard first-line treatment methotrexate (MTX) [8–10]. However, several biologic (b)DMARDs [11] and, more recently, targeted synthetic (ts)DMARDs [12] have also been developed for the treatment of RA. This last category includes the Janus kinase (JAK) inhibitors, which target the pro-inflammatory cytokine signalling that is a key feature of RA pathogenesis [13]. Peficitinib (ASP015K) is an orally bioavailable pan-JAK inhibitor (inhibiting JAK1, JAK2, JAK3, and tyrosine kinase 2), approved for use in Japan and Taiwan [14–17]. Previous phase 3 trials (the RAJ3 and RAJ4 studies) have demonstrated the efficacy and tolerability of both 100- and 150-mg once-daily doses of peficitinib [18, 19]. In particular, RAJ4 provided evidence of the structural efficacy of peficitinib: patients receiving peficitinib had

Received 2 December 2021; Accepted 4 March 2022

a significantly reduced change from baseline in the van der Heijde-modified total Sharp score (mTSS) at Week 28/early termination (ET), compared with placebo [19]. Sensitivity analyses of this endpoint produced results that were consistent with the primary analyses [19, 20]. The proportion of patients with change from baseline in mTSS of ≤0.5 at Weeks 28/ET and 52/ET was also significantly higher with both peficitinib doses versus placebo [19].

Here, we report the results of a *post hoc* analysis using data from the RAJ4 study to determine the extent to which peficitinib inhibited radiographic progression, both overall and by joint segment (groupings of hand and foot joints). This study also examined which baseline characteristics were either positive or negative predictive factors associated with response to peficitinib treatment, as measured by inhibition of radiographic progression, in Japanese patients with RA.

Materials and methods

Ethics

An Institutional Review Board at each study site reviewed and approved the protocol and amendments. The study was conducted in accordance with Good Clinical Practice and International Council on Harmonisation guidelines and applicable laws and regulations. Written informed consent was obtained from each participant.

Study design and population

RAJ4 was a randomized, placebo-controlled, double-blind, parallel-group, phase 3 study of peficitinib conducted at 161 centres in Japan. The study design has been described previously (Supplementary Figure S1) [19]. Patients were randomized (1:1:1) to receive peficitinib 100 mg, peficitinib 150 mg, or placebo, orally once daily in combination with MTX (≤16 mg/week) over 52 weeks.

Inadequate responders [<20% improvement from baseline in tender joint count (TJC) and swollen joint count (SJC)] in the placebo group were switched under blinded conditions at Week 12 to either peficitinib 100 mg or 150 mg (determined randomly at baseline); dosage was maintained until the end of treatment (EOT). The remaining patients in the placebo arm were switched at Week 28 under blinded conditions (determined at baseline) to peficitinib 100 mg/day or 150 mg/day.

Patients

Key eligibility criteria have been published previously [19] and included the following: age ≥20-year old; RA of <10 years classified according to 1987 American College of Rheumatology (ACR) or 2010 European Alliance of Associations for Rheumatology (EULAR) criteria; RA Class I, II, or III at screening according to the ACR 1991 revised criteria for a global functional status in RA [21]; active disease (≥6/68 TJC and ≥6/66 SJC); C-reactive protein (CRP) ≥1.00 mg/dL at screening; bone erosion in ≥1 joint (confirmed at the local site in the joints included in the mTSS); and an inadequate response to MTX. Exclusion criteria included treatment with bDMARDs (within specified periods prior to baseline), other JAK inhibitors, infections, laboratory abnormalities, or a history of or concurrent malignant tumour.

Assessments

Posteroanterior radiographs of both hands and dorsoplantar radiographs of both feet were taken at baseline, Week 12 (only for patients whose improvement in TJC and SJC from baseline was less than 20%), Week 28, Week 52, and at ET (for patients who discontinued prior to Week 28). The extent of erosion and of joint space narrowing (JSN) for each joint was assessed as described by van der Heijde *et al.* [22]. As previously detailed in [19], hand and foot radiographs were scored by two central readers independently (blinded to the order of the films and clinical information). The mean scores of both readers were then used for the analyses. Changes from baseline across all joints at Week 28/ET in erosion score, JSN score, and mTSS (sum of erosion and JSN scores) were calculated. Changes from baseline at Week 28/ET were also derived for erosion and JSN scores for each of four joint segments: proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints (including 1st interphalangeal joint of the hands for erosion score only), wrists, and feet. Rates of nonprogression, defined as change from baseline ≤0.5 in mTSS at Week 28/ET, were derived and summarized overall.

Objectives

The primary efficacy endpoints of the RAJ4 study were response rates according to ACR 20% improvement criteria (ACR20) at Week 12/ET, and mTSS change from baseline at Week 28/ET, as previously published [19]. The first aim of this *post hoc* analysis was to assess the extent of erosion and JSN occurring in each of the four joint segments, with peficitinib versus placebo treatment. The second aim was to determine the clinically important predictive factors (as defined by Lipkovich *et al.* [23]) influencing radiographic progression following peficitinib treatment.

Statistical analyses

In the main RAJ4 study, the full analysis set (FAS) comprised all randomized patients who received at least one dose of study drug [19]. For this *post hoc* analysis, inhibition of radiographic progression was assessed for all patients from the FAS who had available mTSS at baseline and at Week 28/ET (the mTSS patient subset). In the case of ET, linear extrapolation (LEP) was used for mTSS, erosion score, and JSN score to obtain scores for Week 28.

For the purposes of this study, mTSS was considered of greater clinical importance than its component erosion and JSN scores. The significance of the interaction between baseline variables and treatment was therefore investigated using a univariate logistic regression model of the change from baseline at Week 28/ET in mTSS only. Each demographic and baseline variable, the treatment group, and its interaction term were factors in the model. A set of 28 demographic and baseline variables was initially considered as potentially clinically important factors, from a predefined list of demographic and disease factors: 17 prespecified variables from the statistical analysis plan plus 11 exploratory RA severity variables (listed in Supplementary Table S1). Baseline prednisolone dose was recorded only for those patients who

were known to have received concomitant glucocorticoids at baseline.

Demographic and baseline variables that showed significant ($P < 0.15$) interaction with treatment groups for change from baseline in mTSS were used to define patient subgroups. The proportion of patients with nonprogression (change from baseline ≤ 0.5 at Week 28/ET) in mTSS, erosion score, and JSN score was calculated for each of these subgroups. The significant predictive factors for change from baseline in mTSS were then included as covariates in a multivariate logistic regression model, in which the covariate values analysed were those that corresponded to the first quartile, median, and third quartile of the observed patient values. The model was then used to calculate the odds ratio (OR) of mTSS change from baseline ≤ 0.5 at Week 28/ET with peficitinib versus placebo.

Statistical analyses were performed using SAS version 9.4 or higher.

Results

Patient baseline characteristics

As presented previously in [19], the FAS included 518 patients who were randomized and treated with the study drug (Table 1). Baseline mTSS, JSN, and erosion scores were similar across treatment arms (Table 1).

From the FAS, 481 patients had available mTSS at baseline and at Week 28/ET (LEP) and were included in the mTSS patient subset: 153, 164, and 164 in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively. Of the mTSS patient subset, 3.3% of patients had an mTSS score of 0 at baseline; this percentage was similar across treatment arms (Table 2).

Table 1. Patient demographics and baseline characteristics (mTSS patient subset[a]).

	Placebo ($N = 153$)	Peficitinib 100 mg ($N = 164$)	Peficitinib 150 mg ($N = 164$)	Peficitinib 100 mg + 150 mg ($N = 328$)	Total ($N = 481$)
Female, *n* (%)	110 (71.9)	111 (67.7)	118 (72.0)	229 (69.8)	339 (70.5)
Age (years), mean (SD)	54.8 (11.7)	58.5 (10.9)	56.0 (11.5)	57.3 (11.3)	56.5 (11.5)
RA duration (years),[b] mean (SD)	4.3 (3.0)	4.4 (3.0)	4.3 (3.1)	4.3 (3.0)	4.3 (3.0)
DAS28-CRP,[c] mean (SD)	5.4 (0.9)	5.2 (0.9)	5.4 (0.9)	5.3 (0.9)	5.3 (0.9)
CRP (mg/dL), mean (SD)	2.7 (2.2)	2.4 (2.1)	2.5 (2.2)	2.5 (2.1)	2.5 (2.2)
mTSS,[c] mean (SD)	29.8 (37.6)	25.5 (36.3)	25.0 (32.3)	25.2 (34.3)	26.7 (35.4)
Erosion score,[c] mean (SD)	11.6 (18.7)	10.4 (17.9)	9.8 (16.1)	10.1 (17.0)	10.6 (17.6)
JSN score,[c] mean (SD)	18.1 (20.7)	15.1 (19.9)	15.2 (18.1)	15.1 (19.0)	16.1 (19.6)
Prior biologic DMARD use, *n* (%)	37 (24.2)	32 (19.5)	26 (15.9)	58 (17.7)	95 (19.8)
Prior nonbiologic DMARD use, except for MTX, *n* (%)	87 (56.9)	99 (60.4)	89 (54.3)	188 (57.3)	275 (57.2)
MTX dose at baseline (mg/week), mean (SD)	9.8 (3.1)	10.0 (2.7)	9.9 (2.8)	9.9 (2.8)	9.9 (2.9)
Prior anti-TNF use, *n* (%)	34 (22.2)	23 (14.0)	19 (11.6)	42 (12.8)	76 (15.8)
Number of prior DMARDs including biologics, mean (SD)	1.9 (0.9)	1.9 (0.7)	1.8 (0.9)	1.8 (0.8)	1.9 (0.8)
Number of prior biologic DMARDs, mean (SD)	0.3 (0.6)	0.2 (0.4)	0.2 (0.6)	0.2 (0.5)	0.2 (0.6)
Baseline concomitant steroid, *n* (%)	75 (49.0)	87 (53.0)	87 (53.0)	174 (53.0)	249 (51.8)
Baseline prednisone dose (mg/day), mean (SD)	2.3 (2.8)	2.3 (2.7)	2.7 (3.1)	2.5 (2.9)	2.4 (2.9)
Baseline DAS28-ESR, mean (SD)	6.0 (0.9)	5.9 (1.0)	6.0 (1.0)	5.9 (1.0)	6.0 (1.0)
Baseline anti-CCP antibody (U/ml), mean (SD)	218.1 (185.6)	205.5 (190.0)	199.0 (177.8)	202.3 (183.7)	207.3 (184.3)
Baseline RF (IU/ml), mean (SD)	185.8 (337.0)	178.1 (288.6)	166.6 (224.4)	172.4 (258.2)	176.6 (285.4)
Baseline TJC (68 joints), mean (SD)	15.4 (9.5)	14.2 (8.8)	14.7 (7.9)	14.4 (8.3)	14.7 (8.7)
Baseline SJC (66 joints), mean (SD)	13.4 (6.9)	12.9 (6.9)	13.2 (7.0)	13.0 (6.9)	13.2 (6.9)
Baseline SGAP (100 mm VAS[d]), mean (SD)	56.7 (25.5)	52.0 (25.9)	55.0 (24.8)	53.5 (25.4)	54.5 (25.4)
Baseline SGA (100 mm VAS[d]), mean (SD)	57.4 (24.3)	52.5 (25.2)	55.4 (24.3)	54.0 (24.7)	55.0 (24.6)
Baseline PGA (100 mm VAS[d]), mean (SD)	60.7 (19.6)	59.1 (20.0)	61.0 (19.3)	60.0 (19.7)	60.2 (19.6)
Baseline HAQ-DI score,[e] mean (SD)	1.0 (0.7)	0.9 (0.7)	1.0 (0.6)	1.0 (0.6)	1.0 (0.6)
Baseline ESR (mm/h), mean (SD)	53.7 (27.6)	50.9 (25.9)	51.6 (27.3)	51.2 (26.6)	52.0 (26.9)
Estimated mTSS yearly progression, mean (SD)	9.0 (11.9)	6.9 (10.3)	7.4 (10.4)	7.1 (10.3)	7.7 (10.9)
Activity impairment due to RA, mean (SD)	51.7 (29.3)	49.0 (29.4)	50.7 (26.1)	49.8 (27.8)	50.4 (28.3)
RA class,[f] mean (SD)	1.9 (0.6)	1.9 (0.5)	2.0 (0.6)	1.9 (0.5)	1.9 (0.5)
RA stage,[g] mean (SD)	2.4 (0.7)	2.4 (0.7)	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)

[a]The mTSS patient subset comprised all patients from the FAS who had available mTSS at baseline and Week 28/ET.
[b]Duration of RA was calculated as (date of baseline mTSS taken—onset date of RA + 1)/365.25.
[c]Higher values indicate greater levels of disease activity.
[d]Possible VAS scores range from 0 to 100, with higher scores indicating greater disease activity.
[e]Possible HAQ-DI scores range from 0 to 3, with higher scores indicating greater disability.
[f]Defined according to the ACR 1991 revised criteria for global functional status in RA [21].
[g]Defined according to Steinbrocker's classification [26].
CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-CRP, disease activity score for 28 joints based on CRP; DMARD; disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde-modified total Sharp score; MTX, methotrexate; PGA, Physician's Global Assessment of Arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SGA, Subject's Global Assessment of Arthritis; SGAP, Subject's Global Assessment of Pain; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor.

Table 2. Proportions of patients with mTSS, erosion score, and JSN score ≥0 at baseline (mTSS patient subset[a]).

	Placebo ($N = 153$)	Peficitinib 100 mg ($N = 164$)	Peficitinib 150 mg ($N = 164$)	Peficitinib 100 mg + 150 mg ($N = 328$)	Total ($N = 481$)
Baseline mTSS score =0, *n* (%)	3 (2.0)	7 (4.3)	6 (3.7)	13 (4.0)	16 (3.3)
Baseline mTSS score >0, *n* (%)	150 (98.0)	157 (95.7)	158 (96.3)	315 (96.0)	465 (96.7)
Baseline erosion score =0, *n* (%)	16 (10.5)	16 (9.8)	27 (16.5)	43 (13.1)	59 (12.3)
Baseline erosion score >0, *n* (%)	137 (89.5)	148 (90.2)	137 (83.5)	285 (86.9)	422 (87.7)
Baseline JSN score =0, *n* (%)	15 (9.8)	24 (14.6)	24 (14.6)	48 (14.6)	63 (13.1)
Baseline JSN score >0, *n* (%)	138 (90.2)	140 (85.4)	140 (85.4)	280 (85.4)	418 (86.9)

[a]The mTSS patient subset comprised all patients from the FAS who had available mTSS at baseline and Week 28/ET.
ET, early termination; FAS, full analysis set; mTSS, van der Heijde-modified total Sharp score; JSN, joint space narrowing.

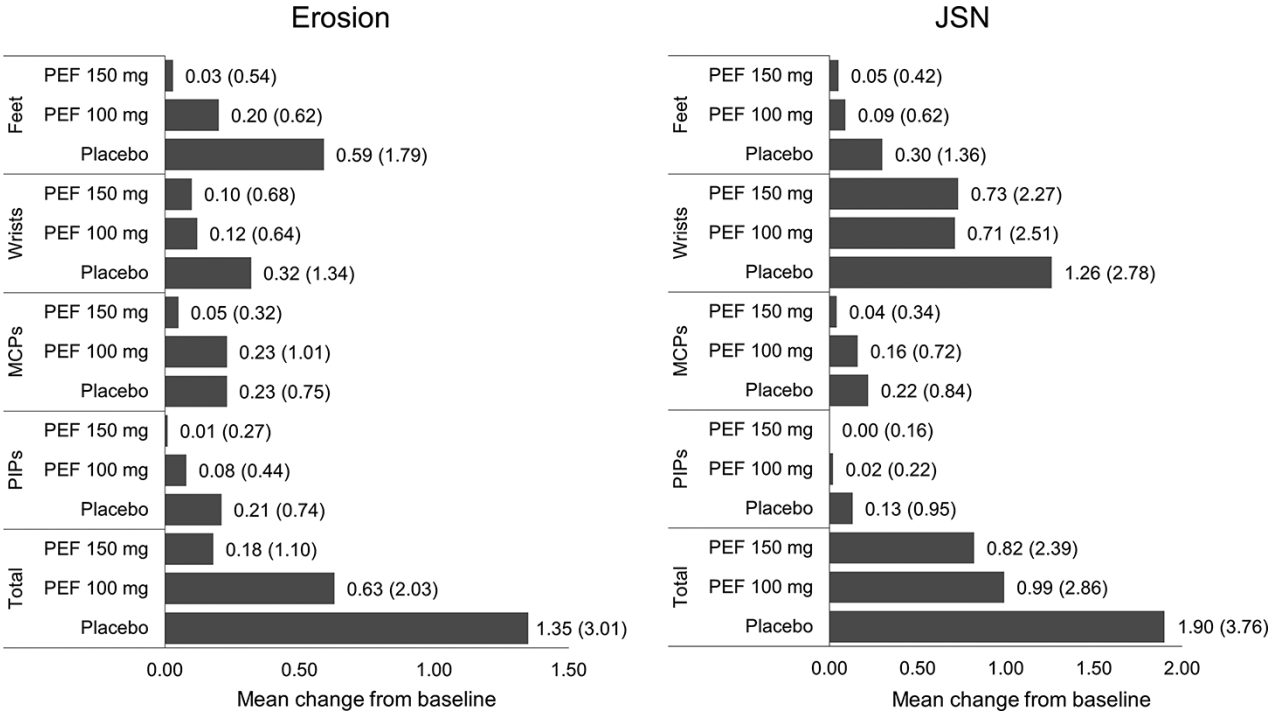

Figure 1. Change from baseline at Week 28/ET (LEP) for (a) erosion score and (b) JSN score, by joint segment (mTSS patient subset[a]).

[a]The mTSS patient subset comprised all patients from the FAS who had available mTSS at baseline and Week 28/ET. LEP, linear extrapolation: for subjects who discontinued at or before Week 28 or switched to receive peficitinib instead of placebo at Week 12 due to lack of efficacy, mTSS at Week 28 was extrapolated using the LEP method based on the mTSS at baseline and at ET or Week 12 or Week 28 (before switching). Values are mean (SD). ET, early termination; JSN, joint space narrowing; MCP, metacarpophalangeal joint; mTSS, van der Heijde-modified total Sharp score; PEF, peficitinib; PIP, proximal interphalangeal joint.

Change from baseline in mTSS, erosion score, and joint space narrowing score

As previously reported in [19], changes from baseline in mTSS, JSN score, and erosion score were significantly reduced in both peficitinib 100 mg and peficitinib 150 mg compared with placebo [Supplementary Figure 2(a)]. Cumulative probability plots for the change in mTSS, erosion score, and JSN score up to Weeks 28/ET visualized that both peficitinib groups were more efficacious than placebo for inhibition of radiographic progression; Supplementary Figure 2(b–d) [19].

Change from baseline in erosion and joint space narrowing scores by joint segment

Erosion scores

For overall erosion score at Week 28/ET (LEP) [Figure 1(a)], the mean (SD) change from baseline for patients receiving peficitinib 100 mg, peficitinib 150 mg, and placebo treatment was 0.63 (2.03), 0.18 (1.10), and 1.35 (3.01), respectively. For each individual joint segment assessed, change from baseline at Week 28/ET was numerically reduced for both peficitinib doses compared with placebo, except for peficitinib 100 mg in MCPs (Figure 1(a)). For each joint segment, a numerically greater effect was observed with peficitinib 150 mg versus 100 mg [Figure 1(a)].

Joint space narrowing scores

For overall JSN score at Week 28/ET (LEP) [Figure 1(b)], the mean (SD) change from baseline for patients receiving peficitinib 100 mg, peficitinib 150 mg, and placebo treatment was 0.99 (2.86), 0.82 (2.39), and 1.90 (3.76), respectively. For each individual joint segment assessed, change from baseline was numerically reduced for both peficitinib doses compared with placebo [Figure 1(b)]. For the majority of joint segments

Table 3. Clinically important predictive factors considered for multivariate analysis, and the proportion of patients with nonprogression (change from baseline ≤0.5) in mTSS at Week 28/ET (LEP) (mTSS patient subset[a]).

				Treatment difference versus placebo, %		
	Treatment arm	N	mTSS change from baseline ≤0.5 at Week 28/ET, *n* (%)	Difference,[b] %	95% CI,[c] %	*P* value for interaction with treatment groups[d]
Baseline CRP <median	Placebo	76	38 (50.0)			
	100 mg	89	69 (77.5)	27.5	(12.1, 42.9)	
	150 mg	79	64 (81.0)	31.0	(15.5, 46.5)	
Baseline CRP ≥median	Placebo	77	32 (41.6)			*P* = 0.075
	100 mg	75	41 (54.7)	13.1	(–4.0, 30.2)	
	150 mg	85	55 (64.7)	23.1	(6.9, 39.4)	
Concomitant glucocorticoid at baseline = no	Placebo	78	32 (41.0)			
	100 mg	77	57 (74.0)	33.0	(17.0, 49.0)	
	150 mg	77	57 (74.0)	33.0	(17.0, 49.0)	
Concomitant glucocorticoid at baseline = yes	Placebo	75	38 (50.7)			*P* = 0.108
	100 mg	87	53 (60.9)	10.3	(–6.3, 26.8)	
	150 mg	87	62 (71.3)	20.6	(4.6, 36.6)	
Prednisolone dose at baseline (mg/day) = none	Placebo	78	32 (41.0)			
	100 mg	77	57 (74.0)	33.0	(17.0, 49.0)	
	150 mg	77	57 (74.0)	33.0	(17.0, 49.0)	
Prednisolone dose at baseline (mg/day) ≤5 mg/day[e]	Placebo	60	29 (48.3)			
	100 mg	71	44 (62.0)	13.6	(–4.9, 32.1)	
	150 mg	66	49 (74.2)	25.9	(7.9, 44.0)	
Prednisolone dose at baseline (mg/day) >5 mg/day[e]	Placebo	15	9 (60.0)			*P* = 0.029
	100 mg	16	9 (56.3)	–3.8	(–44.9, 37.4)	
	150 mg	21	13 (61.9)	1.9	(–36.2, 40.0)	

[a]The mTSS patient subset comprised all patients from the FAS who had available mTSS at baseline and Week 28/ET.
[b]Difference in the proportion of subjects with mTSS change from baseline ≤0.5 (each peficitinib dose group minus placebo).
[c]CI was based on the normal approximation to the binomial distribution (continuity corrected).
[d]*P* values for interaction with treatment groups were based on univariate logistic models with treatment groups, each item, and its interaction term as factors.
[e]As the study protocol restricted prednisolone dose to a maximum of 10 mg/day, 5 mg/day was chosen as the cut-off point.
Continuous variables (instead of categorical) were used for both baseline CRP and baseline prednisolone. For CRP (mg/dL) and prednisolone (mg/day), continuous variables were used instead of categorical variables in the model. Clinically, important predictive factors were selected based on the results of univariate analyses and the clinical relevance of each factor considered. $P < 0.15$ was considered significant.
LEP, linear extrapolation: for subjects who discontinued at or before Week 28 or switched to receive peficitinib instead of placebo at Week 12 due to lack of efficacy, mTSS at Week 28 was extrapolated using the LEP method based on the mTSS at baseline and at ET or Week 12 or Week 28 (before switching).
CI, confidence interval; CRP, C-reactive protein; ET, early termination; FAS, full analysis set; JSN, joint space narrowing; mTSS, van der Heijde-modified total Sharp Score.

(excluding wrists), a numerically greater effect was observed with peficitinib 150 mg versus 100 mg [Figure 1(b)].

Predictive factors

Univariate analysis

From the univariate analysis of change from baseline in mTSS, the factors identified as having a significant ($p \leq 0.15$) interaction with treatment were baseline CRP level, baseline concomitant glucocorticoid (no/yes), and baseline prednisolone dose (Supplementary Table S1).

Patient subgroups were defined for the factors with a significant interaction with treatment: baseline CRP <median or ≥median; concomitant glucocorticoid at baseline: no or yes; and baseline prednisolone dose 0, ≤5, or >5 mg/day. The proportion of patients with nonprogression (change from baseline ≤0.5) in mTSS at Week 28/ET was then analysed for each of these subgroups (Table 3). The proportions of patients with nonprogression in erosion and JSN scores at Week 28/ET for each of these subgroups were also identified for reference [Supplementary Table S2(a,b)]. The proportion of patients with nonprogression in mTSS appeared lower among patients with CRP ≥median versus CRP <median, for each treatment arm (Table 3). The effect of concomitant glucocorticoid on rates of nonprogression in mTSS varied between treatment arms (Table 3). The proportion of patients with nonprogression in mTSS appeared to decrease with higher prednisolone doses among those receiving peficitinib 100 mg or 150 mg, but to increase with higher prednisolone doses among patients receiving placebo (Table 3). In general, the treatment effect was lower with the presence of a predictor of radiographic progression (CRP above median, baseline glucocorticoid use, or higher dose of prednisolone). This effect was observed for both doses of peficitinib.

Multivariate analysis

For change from baseline in mTSS at Week 28/ET, both baseline concomitant glucocorticoid (no/yes) and prednisolone dose were identified as significant predictive factors. As prednisolone dose and concomitant glucocorticoid at baseline had a high degree of correlation ($r = 0.81$), only one was selected for inclusion in the multivariate analysis. Baseline prednisolone dose was considered to have a greater clinical relevance than baseline concomitant glucocorticoid; therefore, baseline prednisolone dose and baseline CRP were selected as covariates for the multivariate logistic model. Baseline prednisolone dose was fixed at 0, 1.25, and 5 mg/day for the first quartile, median, and third quartile thresholds, respectively; baseline CRP was fixed at 1.10, 1.86, and 3.23 mg/dL

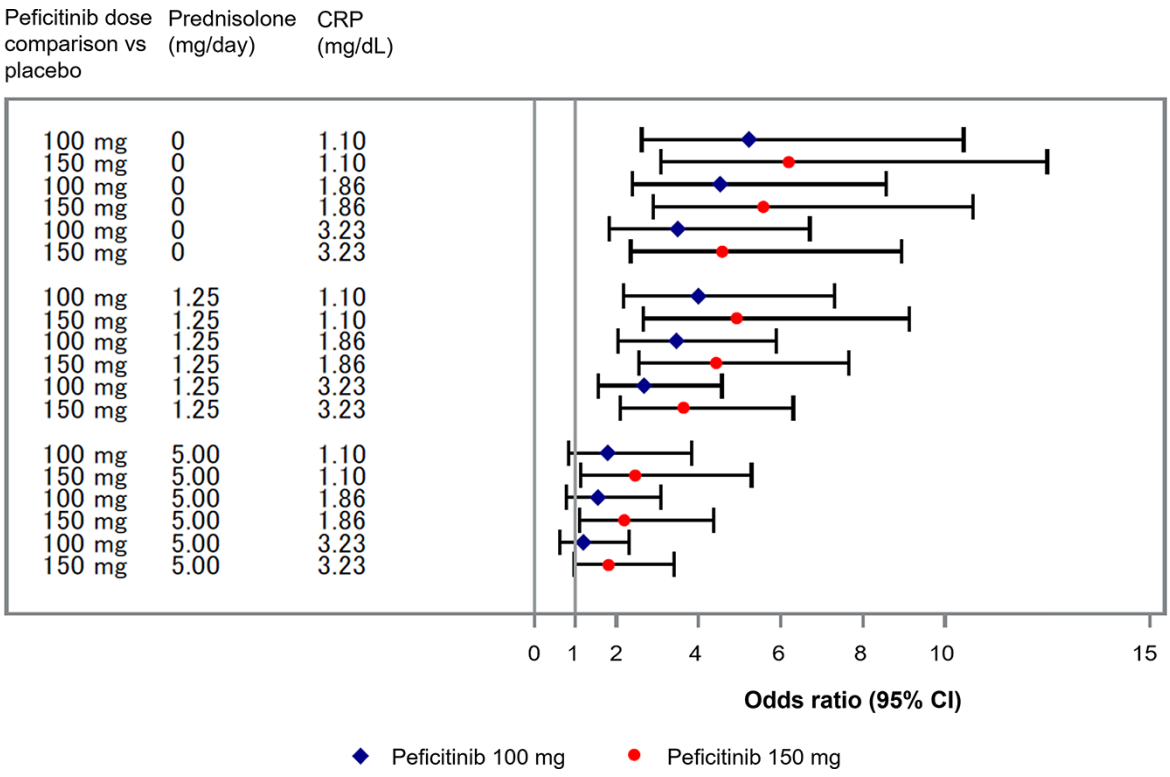

Figure 2. Probability of non progression (change from baseline ≤0.5) in mTSS, by baseline CRP and baseline prednisolone dose (mTSS patient subset[a]).

[a]The mTSS patient subset comprised all patients from the FAS who had available mTSS at baseline and Week 28/ET. OR (95% CI) calculated for the first quartile, median, and third quartile of the data for baseline CRP (mg/dL) and baseline prednisolone dose (mg/day). CI, confidence interval; CRP, C-reactive protein; ET, early termination; FAS, full analysis set; mTSS, van der Heijde-modified total Sharp score.

for the first quartile, median, and third quartile thresholds, respectively.

For the outcome of mTSS change from baseline ≤0.5 at Week 28/ET, the interaction effect of peficitinib with varying baseline CRP and baseline prednisolone dose is shown in Figure 2. For all covariate values analysed, an elevated treatment effect was observed for peficitinib 150 mg versus 100 mg. However, the treatment effect decreased as either baseline prednisolone dose and/or baseline CRP increased; this decrease was also observed for both peficitinib doses (Figure 2). Additionally, the 95% confidence intervals for each probability estimate also decreased with increasing covariate values (primarily due to reductions in the upper confidence limits); this decrease was also observed for both peficitinib doses (Figure 2).

Discussion

This *post hoc* analysis of findings from a phase 3 study in Japanese patients with active RA and an inadequate response to MTX (RAJ4) assessed the effect of peficitinib on the extent of erosion and JSN in separate joint segments of the hands and feet. Overall, treatment with peficitinib 100 mg and 150 mg resulted in a reduced change from baseline in both erosion and JSN scores versus placebo after 28 weeks of treatment. Additionally, there was a clear increase in the treatment effect from peficitinib 100 mg to 150 mg.

We also investigated the patient characteristics that were predictive, either positively or negatively, of a response to peficitinib treatment, as determined by the proportion of patients with nonprogression (change from baseline ≤0.5) in mTSS at Week 28/ET. Baseline CRP and baseline prednisolone dose were identified as clinically relevant factors with a statistically significant negative interaction ($p \leq 0.15$) with treatment: as either CRP levels or prednisolone dose increased, the treatment effect of peficitinib decreased. This relationship was observed regardless of which of these two factors was designated as the variable or fixed comparator. Although in all cases, the odds of nonprogression in mTSS was higher for peficitinib 150 mg than for 100 mg, the observed trend in reduction of treatment effect was consistent across both peficitinib doses and for all covariate values. Consequentially, patients with severe inflammation, or those who require high doses of glucocorticoids, may have a diminished response to peficitinib treatment. Other exploratory markers of RA severity, such as baseline RA class, baseline TJC or baseline SJC, did not demonstrate a similar interaction. Despite these findings, the overall results from both the peficitinib phase 3 trials (RAJ4 and RAJ3) demonstrated the efficacy of peficitinib in patient populations with mean baseline CRP 2.2–2.5 mg/dL [18, 19], and peficitinib remained efficacious versus placebo for almost all CRP and prednisolone dose categories analysed in this study. However, our findings may help identify patients who are at greater risk of inadequate response to peficitinib.

Numerous other published studies have also investigated the relationship between the treatment effect for other DMARDs and a variety of predictive factors, such as age, sex, TJC, SJC, or baseline RA seropositivity [3, 24, 25]. However, the significance and directionality of these factors appear to oppose the results observed in this study and varied widely

based on the patient population and DMARD treatment received. Landewé *et al.* [24] showed that the most significant predictors of the tofacitnib treatment effect in adults globally were baseline mTSS or erosion score; for these factors, the increased treatment effect was observed with increased covariate values. Other significant positive predictive factors noted were CRP levels, rheumatoid factor (RF) status, and anti-cyclic citrullinated peptide seropositivity. Similarly, Takeuchi *et al.* demonstrated that RF status, CRP, ESR, baseline JSN, and Health Assessment Questionnaire-Disability Index results were all significant positive predictors of etanercept efficacy in Japanese patients, while a higher tender joint count was a negative predictor [25]. The reasons for the difference between the results of our study and previous studies are uncertain; however, the number of patients in each of the baseline categories we investigated (CRP <median or ≥median; prednisolone dose 0 mg/day, ≤5 mg/day, or >5 mg/day) was low, particularly for prednisolone doses of >5 mg/day. These low numbers may have had an impact on the probability estimates derived from the multivariate analysis, which used three theoretical dosing thresholds for baseline CRP and baseline prednisolone dose, separately.

The strength of this study is that the range of variables included in the univariate analyses encompasses and expands upon those included in previous studies of predictive factors for treatment response to other DMARDs. Of the baseline characteristics investigated by Landewé *et al.* and Takeuchi *et al.*, each was included in this study, along with additional variables such as baseline prednisolone dose [3, 24, 25]. On the other hand, a wide range of variables could also increase the likelihood of incorporating false-positive results in the study outcomes. Other limitations (as previously published [19]) include a shorter duration of placebo compared with active treatment, which, although required for ethical reasons, makes comparisons and analyses difficult. Peficitinib doses >150 mg were not evaluated in the present study, and further evaluation may be required to confirm if 150 mg/day is the optimal dose from an efficacy perspective, particularly in non-Asian populations. The small size of the subgroups investigated in this study (most notably the baseline prednisolone dose >5 mg/day subgroup) may lead to overestimation of the interaction with the treatment effect. Lastly, this study enrolled patients who failed to respond to prior MTX, and our results may therefore not be generalizable to other patient populations.

Conclusions

Overall, treatment with peficitinib reduced the extent of joint damage compared with placebo, across all joint segments. Of the patient characteristics potentially influencing radiographic progression, baseline CRP and baseline prednisolone dose demonstrated a significant negative interaction with treatment: as either baseline CRP or prednisolone dose increased, a consistent reduction in the treatment effect was observed for both peficitinib 100 mg and 150 mg.

Acknowledgements

Medical writing support was provided by Glen Dorrington, PhD, and Iona Easthope, DPhil, of Cello Health MedErgy (Europe).

Supplementary data

Supplementary data are available at *Modern Rheumatology* online.

Conflict of interest

Y.T. reports speaking fees and/or honoraria from Gilead, AbbVie, Boehringer-Ingelheim, Eli Lilly, Mitsubishi-Tanabe, Chugai, Amgen, YL Biologics, Eisai, Astellas, Bristol-Myers Squibb, AstraZeneca, received research grants from Asahi-Kasei, AbbVie, Chugai, Mitsubishi-Tanabe, Eisai, Takeda, Corona, Daiichi-Sankyo, Kowa, Boehringer-Ingelheim, and consultancy fees from Eli Lilly, Daiichi-Sankyo, Taisho, Ayumi, Sanofi, GSK, and AbbVie. T.T. has received grants from Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd, Daiichi Sankyo Co. Ltd, Eli Lilly Japan, AbbVie GK, Asahi Kasei Pharma Corp., Mitsubishi Tanabe Pharma Co., Eisai Co. Ltd, AYUMI Pharmaceutical Corp., Nippon Kayaku Co. Ltd, and UCB Japan; speaking fees from AbbVie GK, AYUMI Pharmaceutical Corporation, Bristol-Myers K.K., Chugai Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Daiichi Sankyo Co. Ltd, Eisai Co. Ltd, Eli Lilly Japan, Gilead Sciences Inc., Sanofi K.K., and Janssen Pharmaceutical K.K.; consultancy fees from Chugai Pharmaceutical Co. Ltd, AbbVie GK, Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Gilead Sciences Inc., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., and Astellas Pharma, Inc. D.K., Y.K., M.F., H.I., and M.R. are employees of Astellas Pharma Inc. D.v.d.H. has received consultancy fees from AbbVie, Bayer, BMS, Cyxone, Eisai, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, and UCB Pharma. She is also the Director of Imaging Rheumatology BV.

Author contributions

D.K., Y.T., Y.K., M.F., H.I., and M.R. made contributions to the conception or design of the study; HI and MR made contributions to the acquisition of study data; Y.K. and M.F. made contributions to the analysis of the data; all authors made significant contributions towards the interpretation of data from the study. All authors read and approved the submitted version of the manuscript and agreed to be accountable for all aspects of the work.

Funding

This study was initiated and supported by Astellas Pharma Inc. Medical writing support was funded by Astellas Pharma Inc.

Data availability

Researchers may request access to anonymized 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.

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