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ORIGINAL ARTICLE

Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study

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Abstract

Objectives. To evaluate oral tofacitinib versus placebo for treatment of active rheumatoid arthritis in Japanese patients with inadequate response to disease-modifying antirheumatic drugs.
Methods. In this double-blind, placebo-controlled, randomized, parallel-group, 12-week, phase 2 study (clinicaltrials.gov NCT00687193), 317 patients received tofacitinib: 1, 3, 5, 10, or 15 mg as monotherapy or placebo twice daily (BID). Primary endpoint: response rate by American College of Rheumatology (ACR) ≥ 20% improvement criteria (ACR20) at week 12.
Results. ACR20 response rates: 37.7% (20/53), 67.9% (36/53), 73.1% (38/52), 84.9% (45/53), and 90.7% (49/54) with tofacitinib: 1, 3, 5, 10, and 15 mg BID, respectively, versus 15.4% (8/52) with placebo ($p < 0.01$; all doses). Dose-dependent ACR20 responses with tofacitinib versus placebo occurred from week 2 onward ($p < 0.05$). Changes from baseline in 28-joint disease activity score using erythrocyte sedimentation rate improved with tofacitinib versus placebo from week 4 ($p < 0.01$; all doses). Six tofacitinib patients experienced treatment-related serious adverse events (AEs). Most common treatment-emergent AEs: nasopharyngitis (10% vs 12%) and hyperlipidemia (5% vs 0%). Serum creatinine, hemoglobin, and total-, low-, and high-density lipoprotein-cholesterol levels increased with tofacitinib.
Conclusions. Tofacitinib produced dose-dependent ACR20 responses and reduced disease activity. The safety profile was consistent with that reported from global monotherapy trials.

Keywords

Japan, Monotherapy, Randomized controlled trial, Rheumatoid arthritis, Tofacitinib

History

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Introduction

Rheumatoid arthritis (RA) is a chronic, debilitating disease that negatively impacts on patient quality of life. Treatment options are based on disease-modifying antirheumatic drugs (DMARDs), typically starting with methotrexate [1–3]. Biologic DMARDs, such as tumor necrosis factor inhibitors (TNFis), are often used in patients with inadequate response to methotrexate (or other synthetic DMARDs). In Japan, the biologic DMARDs, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol (TNFi), tocilizumab and abatacept, have been approved for use in patients with active RA and an inadequate response to existing therapies [4–6]. However, not all patients achieve an adequate response with available synthetic or biologic DMARDs [7–11]. Therefore, there remains an unmet need for additional therapeutic options with alternative mechanisms of action.

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Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA [12,13]. Tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2, blocking signaling for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21 [14]. These cytokines are integral to lymphocyte activation and function, and inhibition of their signaling may modulate multiple aspects of the immune response [15].

Tofacitinib has demonstrated efficacy as monotherapy or in combination with DMARDs (mostly methotrexate) for the treatment of active RA in 6 phase 3 randomized controlled trials (RCTs) in various patient populations [16–21]. Furthermore, a phase 2 RCT in Japanese patients who had an inadequate response to methotrexate reported tofacitinib efficacy and safety in combination with stably dosed methotrexate [22]. Here, we evaluated multiple doses of tofacitinib monotherapy versus placebo for the treatment of RA in Japanese patients who have had an inadequate response to synthetic or biologic DMARDs.

Materials and methods

Patients

Key inclusion criteria included a diagnosis of RA based on the American College of Rheumatology (ACR) 1987 revised criteria [23]. Patients were required to have an active disease defined as ≥ 6 tender/painful joints and ≥ 6 swollen joints, and either erythrocyte sedimentation rate (ESR) above upper limit of normal (ULN) or

C-reactive protein (CRP) >7 mg/L. Patients were also required to have had an inadequate response to at least one synthetic or biologic DMARD, which had washed out ≥ 4 weeks prior to the first dose.

Key exclusion criteria included: cytopenias; estimated glomerular filtration rate <50 mL/min (Cockcroft–Gault calculation); total bilirubin, aspartate transaminase (AST), or alanine transaminase (ALT) $>2\times$ ULN; and evidence of active infection, including latent tuberculosis.

Study design and treatment

This was a 12-week, randomized, double-blind, placebo-controlled, parallel-group phase 2 study conducted at 47 centers in Japan from March 2009 to July 2010 (clinicaltrials.gov NCT00687193; Pfizer protocol A3921040). The study was performed in compliance with the 2008 update of the Declaration of Helsinki and the International Conference on Harmonisation's Good Clinical Practice Guidelines, and approved by the Institutional Review Boards at each study center. All patients provided written informed consent.

Based on a randomization table pre-prepared by the study sponsor's Global Clinical Data Service Department, patients were randomized (1:1:1:1:1:1) to tofacitinib: 1, 3, 5, 10, or 15 mg, or placebo, given orally twice daily (BID) for 12 weeks. The study sponsor, investigators, and patients were blinded to the identity of study medications.

Concomitant medications

No DMARDs were permitted as concomitant therapy during the study. Cytochrome P450 (CYP) 3A inducers and CYP3A4, 5, and 7 inhibitors were not permitted due to the potential for drug interactions, as tofacitinib metabolism is primarily mediated by CYP3A4 [24]. Stable doses of non-steroidal anti-inflammatory drugs, selective cyclo-oxygenase-2 inhibitors, or glucocorticoids (≤ 10 mg/day prednisone or equivalent) were permitted, provided they were stably dosed for ≥ 4 weeks before the first study drug dose.

Study assessments

The primary objective was to evaluate the dose–response relationship of the 5 tofacitinib doses compared with placebo; the primary efficacy endpoint was the response rate according to the ACR 20% improvement criteria (ACR20) compared with placebo at week 12. Secondary efficacy endpoints included ACR20 at all other timepoints, ACR50 and ACR70 response rates, change from baseline in 28-joint disease activity score using ESR (DAS28-4[ESR]), and proportions of patients achieving DAS-defined remission (DAS28-4[ESR] <2.6) [25]. Other secondary efficacy endpoints included selected patient-reported outcomes, namely the Health Assessment Questionnaire-Disability Index (HAQ-DI) [26], Medical Outcomes Study Short-Form (36-item) Health Survey (SF-36), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale [27]. ACR, DAS, and HAQ-DI assessments were performed at screening, baseline, and weeks 2, 4, 8, and 12. SF-36 was assessed at baseline and week 12, or early termination. FACIT-F was assessed at baseline, week 2, and week 12, or early termination.

Safety endpoints included the incidence and severity of adverse events (AEs), serious AEs, laboratory tests, and vital sign assessments. AEs were recorded at every visit from the first dose through the last visit, and mapped to preferred terms according to the Medical Dictionary for Regulatory Activities (version 13.0). Laboratory parameters were measured at a central laboratory, except ESR, which was measured locally. Hematologic, lipid, hepatic, and renal function tests were performed at baseline, weeks 2, 4, 8, and 12, or early termination.

Statistical analysis

The planned sample size of 50 patients per group (6 groups; total 300) had $\geq 80\%$ power, with a significance level of 5%, to detect a 30% difference from placebo in the ACR20 response rate, assuming the placebo response rate was 35%.

The primary analysis population and the safety analysis set for this study was the full analysis set (FAS; all patients who were randomized to the study and received ≥ 1 dose of study medication).

For the primary endpoint, pairwise comparisons of the tofacitinib doses versus placebo were conducted using a chi-squared test with two-sided significance level of 0.05. The type I error rate for the pairwise comparisons was protected using a step-down procedure. When the pairwise comparison of the higher tofacitinib dose group versus placebo was statistically significant, the step-down procedure continued to the next lower tofacitinib dose group versus placebo comparison.

For the secondary endpoints, response rates from binary endpoints were analyzed using the normal approximation to the binomial, comparing each dose of study treatment with placebo. For continuous measures, a longitudinal, mixed-effect, repeated-measures model was employed. Treatment, week, and treatment-by-week interaction were included as fixed effects, along with patients as a random effect. Estimates of mean and mean difference from placebo were derived from the model and contrasts with placebo were formed.

To address missing data, 3 types of imputation were employed: baseline observation carried forward, also known as non-responder imputation (NRI); last observation carried forward (LOCF); and data as is (no imputation). LOCF was used for the ACR20 primary analysis at week 12; additional analyses were performed as a measure of robustness of the results.

Post-hoc exploratory subanalyses were performed on the primary endpoint, ACR20 at week 12, and DAS28-4(ESR) remission rates, with respect to patient age, baseline DAS28-4(ESR), and RA disease duration.

Results

Patients

Of 383 patients screened, 318 were randomized; 317 patients received ≥ 1 dose of study medication and 299 patients (94.0%) completed the study (Figure 1). The patient demographics and disease characteristics at baseline were similar across treatment groups (Table 1).

Efficacy

The ACR20 response rates (FAS, LOCF) at week 12 (primary endpoint) were 20/53 (37.7%), 36/53 (67.9%), 38/52 (73.1%), 45/53 (84.9%), and 49/54 (90.7%) patients receiving tofacitinib: 1, 3, 5, 10, and 15 mg BID, respectively, and 8/52 (15.4%) patients receiving placebo ($p<0.0001$ vs placebo for all doses of tofacitinib except 1 mg BID, where $p<0.01$). The 12-week ACR response rates were similar when NRI was applied (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875).

Dose-dependent and statistically significant ACR20 responses were observed in all tofacitinib groups versus placebo from week 2, and were maintained throughout the 12-week period ($p<0.05$; Figure 2a). A dose-dependent relationship was also observed for ACR50 response rates over the course of 12 weeks, with significant improvements versus placebo for tofacitinib doses of ≥ 3 mg BID at all timepoints ($p<0.05$; Supplementary Figure 1a to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875). In addition, a dose-dependent rela-

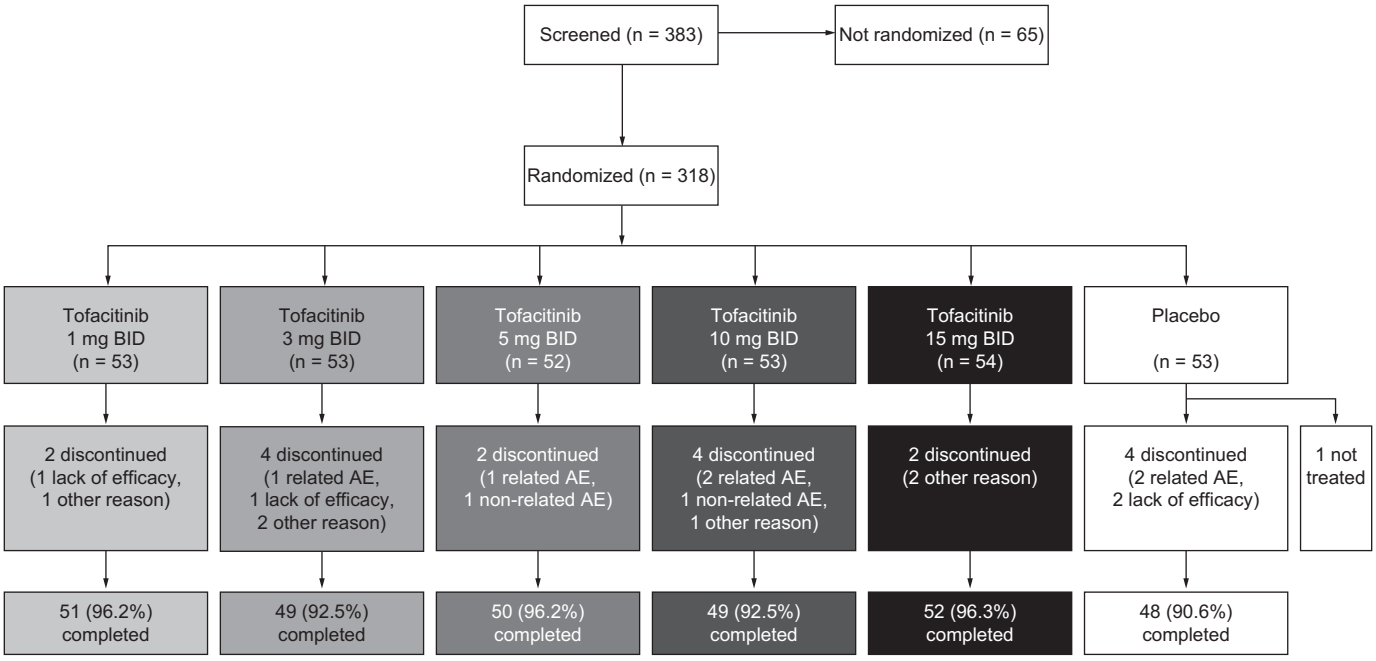

Figure 1. Patient disposition. AEs were categorized according to whether they were considered related to study drug or not. *AE* adverse event, *BID* twice daily.

tionship was seen for ACR70 response rates, with significant improvements versus placebo for tofacitinib doses of ≥5 mg BID at all timepoints, except at week 2 with tofacitinib: 5 mg BID; significant improvements in ACR70 were observed with tofacitinib: 3 mg BID at weeks 8 and 12 (Supplementary Figure 1b to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875). For the 1-mg BID dose, significant improvement versus placebo was only seen for ACR 50 response at week 8.

Disease activity decreased in a dose-dependent manner over the 12 weeks of treatment (Figure 2b). Mean changes from baseline in DAS28-4(ESR) and ESR showed significant improvement versus placebo from week 2 for all tofacitinib doses ($p < 0.01$), except 1 mg BID, which showed a statistical difference from placebo at week 4 for DAS28-4(ESR) and week 8 for ESR ($p < 0.01$; Supplementary Figures 2a and b to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875). The proportion of patients achieving DAS28-defined remission, DAS28-4(ESR) <2.6, was significantly greater for patients receiving tofacitinib: ≥5 mg BID compared with placebo at weeks 8 and 12 ($p < 0.05$; Figure 2c). The proportion of patients achieving low disease activity, defined as DAS28-4(ESR) ≤3.2, was significantly greater than placebo at weeks 4, 8, and 12 for those receiving tofacitinib: ≥5 mg BID ($p < 0.05$).

HAQ-DI values significantly improved from baseline compared with placebo from week 2 onward with tofacitinib doses of ≥3 mg BID ($p < 0.05$), and from week 8 onward with tofacitinib: 1 mg BID ($p < 0.0001$; Figure 2d). At week 12, a dose-dependent response was seen in the percentage of patients achieving a clinically meaningful decrease (≥0.22 units) in HAQ-DI from baseline ($p < 0.01$ vs placebo; Supplementary Table 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875).

SF-36 scores were significantly improved in patients receiving tofacitinib versus those receiving placebo. The mean change in SF-36 domain scores for physical function, role physical, bodily pain, and role-emotional were significantly higher for all tofacitinib doses versus placebo ($p < 0.05$). Mean changes in general health, vitality, social function, and mental health domain scores were significantly higher with tofacitinib: ≥3 mg BID versus placebo

Table 1. Patient baseline demographics and disease characteristics.

	Tofacitinib					
Characteristic, Mean	1 mg BID ($n = 53$)	3 mg BID ($n = 53$)	5 mg BID ($n = 52$)	10 mg BID ($n = 53$)	15 mg BID ($n = 54$)	Placebo ($n = 52$)
Age, years (SD)	53.3 (9.9)	52.8 (11.6)	52.6 (10.9)	54.7 (10.8)	53.6 (12.5)	53.3 (11.4)
Male, n (%)	11 (20.8)	6 (11.3)	8 (15.4)	9 (17.0)	10 (18.5)	9 (17.3)
Weight, kg (SD)	52.9 (9.4)	54.1 (10.2)	54.2 (6.6)	54.1 (10.0)	53.8 (9.9)	57.4 (11.7)
BMI, kg/m^2 (SD)	21.5 (3.2)	21.9 (3.8)	22.2 (2.9)	21.9 (3.9)	22.1 (3.2)	22.8 (3.8)
Duration of RA, years (range)	8.1 (0.5–39.0)	6.8 (0.6–28.0)	11.0 (0.4–34.0)	7.3 (0.5–45.0)	7.4 (0.5–38.3)	6.4 (0.5–38.0)
Tender joint count (SD)	13.55 (7.98)	17.26 (11.44)	18.58 (13.02)	17.13 (10.27)	17.35 (8.96)	15.10 (8.76)
Swollen joint count (SD)	11.30 (6.49)	14.64 (10.09)	15.31 (10.83)	13.77 (7.66)	14.48 (8.99)	11.96 (5.69)
PGA, mm (SD)	60.30 (22.40)	60.28 (19.92)	68.77 (22.28)	64.91 (21.25)	68.33 (18.79)	58.13 (25.27)
PtGA, mm (SD)	60.62 (22.19)	59.57 (18.83)	70.44 (19.85)	64.53 (22.51)	67.00 (19.97)	58.38 (21.83)
Patient pain assessment, mm (SD)	61.57 (17.37)	62.13 (18.09)	71.13 (17.54)	69.85 (15.21)	66.93 (17.60)	61.08 (16.79)
HAQ-DI (SD)	1.25 (0.59)	1.19 (0.64)	1.50 (0.69)	1.20 (0.65)	1.20 (0.69)	1.21 (0.69)
CRP, mg/L (SD)	30.21 (28.40)	25.65 (24.54)	35.61 (34.15)	26.88 (27.81)	27.37 (35.69)	24.01 (23.01)
DAS28-4(ESR) (SD)	6.04 (0.89)	6.08 (1.04)	6.41 (1.05)	6.06 (0.92)	6.20 (1.02)	5.83 (0.93)

BID twice daily, *BMI* body mass index, *CRP* C-reactive protein, *DAS28-4(ESR)* 28-joint disease activity score using erythrocyte sedimentation rate, *HAQ-DI* health assessment questionnaire-disability index, *PGA* physician global assessment, *PtGA* patient global assessment, *RA* rheumatoid arthritis, *SD* standard deviation.

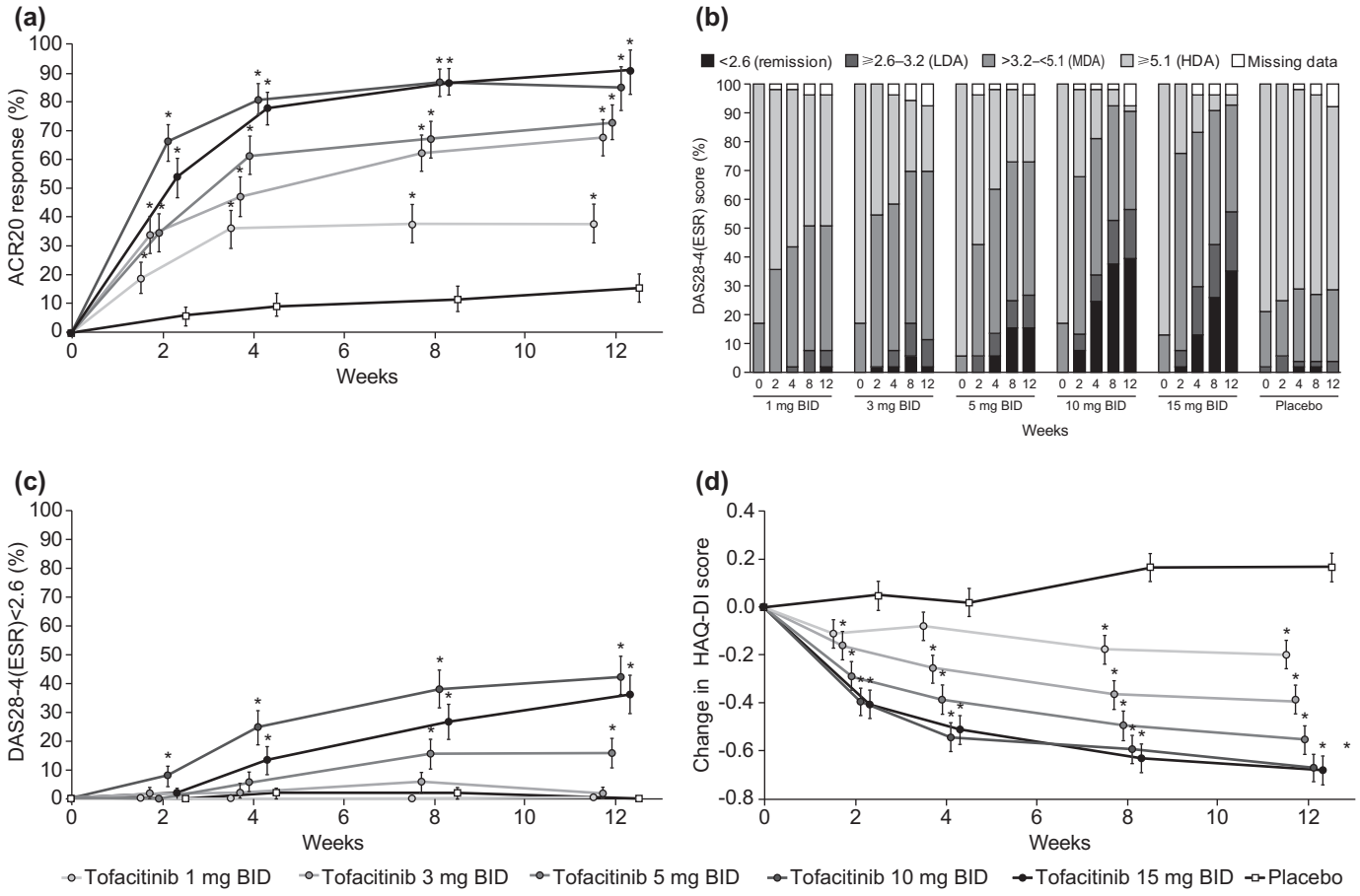

Figure 2. Response rates for patients receiving tofacitinib monotherapy or placebo over time. (a) ACR20 response (± SE), FAS, LOCF. (b) DAS28-4(ESR) < 2.6 (remission), 2.6–3.2 (LDA), > 3.2–< 5.1 (MDA), and ≥ 5.1 (HDA), FAS, no imputation. (c) DAS28-4(ESR) < 2.6 (remission) (± SE), FAS, no imputation. (d) Mean HAQ-DI (± SE) change from baseline, FAS. *$p < 0.05$ versus placebo. *ACR20* American College of Rheumatology 20% improvement criteria, *BID* twice daily, *DAS28-4(ESR)* 28-joint disease activity score using erythrocyte sedimentation rate, *FAS* full analysis set, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *HDA* high disease activity, *LDA* low disease activity, *LOCF* last observation carried forward, *MDA* medium disease activity, *SE* standard error.

($p < 0.05$). The proportion of patients achieving a clinically meaningful increase (≥ 2.5 points) from baseline was higher with all tofacitinib doses versus placebo in the SF-36 physical component score ($p < 0.001$), and was higher with ≥ 3 mg of tofacitinib BID versus placebo in the SF-36 mental component score ($p < 0.05$; Supplementary Table 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875).

Change in FACIT-F scores from baseline to week 12 were significantly greater (improved) in all tofacitinib groups versus placebo; mean score change (standard error): 2.51 (0.97), 5.44 (1.00), 7.52 (1.00), 8.51 (1.00), and 8.03 (0.97), with tofacitinib: 1, 3, 5, 10, and 15 mg BID, respectively, versus placebo –1.39 (1.01) ($p < 0.01$ for all tofacitinib doses vs placebo).

Exploratory subanalyses revealed significantly greater ACR20 response rates in patients receiving tofacitinib: ≥ 3 mg BID versus placebo at week 12 regardless of patient's age (18–44, 45–64, and ≥ 65 years), baseline DAS28-4(ESR) (score ≤ 5.1, > 5.1), and RA disease duration (< 2, ≥ 2 to < 7, ≥ 7 years). However, owing to low patient numbers in these subgroups, results must be interpreted with caution.

Safety

The incidence of treatment-emergent AEs was similar across treatment groups, with a slight trend toward higher incidence with increasing tofacitinib dose (Table 2). Eight patients discontinued due to AEs. There were no deaths in the study.

The most common all-causality AEs (in ≥ 10% of patients) were nasopharyngitis and abnormalities in laboratory tests including hyperlipidemia and increased low-density lipoprotein cholesterol (LDL-C); most AEs (Table 3) were mild in severity. In 4 patients, 6 severe AEs were reported: gastric ulcer perfo-

Table 2. Summary of safety data; all-causality TEAEs.

	Tofacitinib					
	1 mg BID ($n = 53$)	3 mg BID ($n = 53$)	5 mg BID ($n = 52$)	10 mg BID ($n = 53$)	15 mg BID ($n = 54$)	Placebo ($n = 52$)
TEAEs, n	37	31	42	62	50	41
Patients with ≥ 1 TEAE, n (%)	21 (39.6)	23 (43.4)	29 (55.8)	32 (60.4)	28 (51.9)	23 (44.2)
Patients with ≥ 1 TESAE, n (%)	0	3 (5.7)	2 (3.8)	2 (3.8)	1 (1.9)	1 (1.9)
Discontinuations due to AEs, n (%)	0	1 (1.9)	2 (3.8)	3 (5.7)	0	2 (3.8)
Deaths	0	0	0	0	0	0

AE adverse event, *BID* twice daily, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent serious adverse event.

Table 3. Most common all-causality treatment-emergent AEs occurring in ≥ 2% patients in any of the treatment groups.

	Tofacitinib					
AE, n (%)*	1 mg BID ($n = 53$)	3 mg BID ($n = 53$)	5 mg BID ($n = 52$)	10 mg BID ($n = 53$)	15 mg BID ($n = 54$)	Placebo ($n = 52$)
Nasopharyngitis	6 (11.3)	4 (7.5)	6 (11.5)	3 (5.7)	8 (14.8)	6 (11.5)
Hyperlipidemia	1 (1.9)	0	2 (3.8)	6 (11.3)	3 (5.6)	0
Headache	1 (1.9)	3 (5.7)	2 (3.8)	1 (1.9)	0	1 (1.9)
LDL-C increased	0	1 (1.9)	0	1 (1.9)	6 (11.1)	0
ALT increased	0	2 (3.8)	0	1 (1.9)	1 (1.9)	3 (5.8)
Constipation	1 (1.9)	0	1 (1.9)	0	3 (5.6)	2 (3.8)
Pharyngitis	0	0	0	3 (5.7)	2 (3.7)	1 (1.9)
Stomatitis	1 (1.9)	1 (1.9)	2 (3.8)	1 (1.9)	0	1 (1.9)
Abdominal discomfort	2 (3.8)	1 (1.9)	0	1 (1.9)	0	1 (1.9)
AST increased	0	1 (1.9)	0	1 (1.9)	0	3 (5.8)
Blood cholesterol increased	0	1 (1.9)	1 (1.9)	1 (1.9)	2 (3.7)	0
Fall	3 (5.7)	0	1 (1.9)	1 (1.9)	0	0
Herpes zoster	0	0	1 (1.9)	3 (5.7)	1 (1.9)	0
Hypercholesterolemia	0	2 (3.8)	0	3 (5.7)	0	0
Bronchitis	1 (1.9)	1 (1.9)	0	2 (3.8)	0	0
Contusion	2 (3.8)	1 (1.9)	0	0	1 (1.9)	0
Dental caries	0	0	2 (3.8)	1 (1.9)	0	1 (1.9)
Gingivitis	0	1 (1.9)	0	0	2 (3.7)	1 (1.9)
Hypertension	0	0	3 (5.8)	1 (1.9)	0	0
Upper respiratory tract infection	0	0	1 (1.9)	3 (5.7)	0	0
Diarrhea	1 (1.9)	0	0	0	0	2 (3.8)
Gastritis	0	1 (1.9)	0	0	2 (3.7)	0
RA	0	0	0	0	0	2 (3.8)
Upper respiratory tract inflammation	0	0	0	0	0	2 (3.8)

AE adverse event, *ALT* alanine transaminase, *AST* aspartate transaminase, *BID* twice daily, *LDL-C* low-density lipoprotein cholesterol.
*Preferred terms according to Medical Dictionary for Regulatory Activities version 13.0.

ration and rheumatoid vasculitis in the tofacitinib: 3 mg BID group (1 patient each); a fall and fracture of fibula and tibia in 1 patient receiving tofacitinib: 5 mg BID; herpes zoster in 1 patient receiving tofacitinib: 10 mg BID (the multidermatomal rash was widespread and was recorded as a serious AE, see below). No opportunistic infections were reported, including tuberculosis. Nine patients had serious AEs, of whom six had serious events considered treatment-related. The serious AEs were elevated creatine kinase, AST, and ALT levels leading to hospitalization for evaluation (3 mg BID); gastric ulcer perforation (3 mg BID); rheumatoid vasculitis (3 mg BID); and herpes zoster and post-herpetic nerve paralysis considered by the investigator to be attributed to the herpes zoster (5 mg BID), herpes zoster (10 mg BID), and herpes zoster oticus/Ramsay Hunt syndrome (15 mg BID). All patients with serious AEs were withdrawn from the study, and all serious AEs resolved, apart from the herpes zoster oticus and rheumatoid vasculitis; both patients were still recovering at the last follow-up date (98 days and 163 days after study withdrawal, respectively; Supplementary Text to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875).

Significant dose-dependent mean decreases in neutrophil and platelet counts, dose-dependent mean increases in LDL-C, high-density lipoprotein cholesterol (HDLC), and total cholesterol (TC) levels, and mean increases in hemoglobin and serum creatinine levels were observed with tofacitinib versus placebo (Table 4; Supplementary Figure 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.

Table 4. Mean changes in laboratory parameters from baseline at week 12.

	Tofacitinib					
	1 mg BID	3 mg BID	5 mg BID	10 mg BID	15 mg BID	Placebo
Parameter Mean change	$n = 51$	$n = 49$	$n = 50$	$n = 49$	$n = 52$	$n = 48$
Neutrophils, $\times 10^3/mm^3$	0.06	−0.98‡	−1.44‡§	−2.10‡	−1.66‡	0.47
HDL-C, mg/dL	5.04†	10.81‡	17.73‡	21.94‡	21.11‡	−0.94
LDL-C, mg/dL	3.21	11.77†	16.43‡	21.45‡	24.69‡	−0.24
TC, mg/dL	11.52†	25.44‡	35.83‡	50.35‡	51.31‡	−0.96
Hemoglobin, g/dL	0.15*	0.25†	0.48‡§	0.56‡	0.19*	−0.15
Serum creatinine, mg/dL	0.01	0.02*	0.04‡	0.05‡	0.06‡	−0.01
No. of patients (%)	$n = 53$	$n = 53$	$n = 52$	$n = 53$	$n = 54$	$n = 52$
Lymphocytes, $< 1000/mm^3$	11 (20.8)	6 (11.3)	11 (21.2)	12 (22.6)	16 (29.6)	18 (34.6)
Lymphocytes, $< 500/mm^3$	0	0	0	3 (5.7)	0	0
Neutrophils, $< 500/mm^3$	0	0	0	0	0	0
Hemoglobin, decrease of 2–3 g/dL from baseline or hemoglobin < 8 g/dL	0	0	0	0	0	0
AST or ALT > 3 × ULN	1 (1.9)	1 (1.9)	0	0	1 (1.9)	2 (3.8)

ALT alanine transaminase, *AST* aspartate transaminase, *BID* twice daily, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *ULN* upper limit of normal.
*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ versus placebo. §$n = 49$.

995875). Moderate-to-severe neutropenia (absolute neutrophil count [ANC] 500–1500/mm^3) occurred in 2 patients receiving tofacitinib: 3 mg BID and 5 patients receiving 15 mg BID. None of the patients had potentially life-threatening neutropenia (ANC $<$ 500/mm^3). None of the patients had a platelet count $<$ 75000/mm^3. Across all groups, 74 patients (23.3%) had their absolute lymphocyte counts decrease to $<$ 1000/mm^3 (Table 4). Three patients in the 10 mg BID group had more severe reductions ($<$ 500/mm^3; Table 4); none of these patients experienced severe infections, and all three had low lymphocyte counts at baseline. One patient receiving tofacitinib: 1 mg BID had mild iron deficiency anemia that was deemed to be treatment-related. The patient receiving tofacitinib: 3 mg BID who had a gastric ulcer perforation was first discontinued from the study due to a decrease of $>$ 30% from baseline in hematocrit level. The hemoglobin level recorded for this patient at discontinuation was 7.4 g/dL. No trends were seen in changes to hepatic enzymes. ALT or AST levels $>3\times$ ULN were observed in 3 patients receiving tofacitinib and 2 patients receiving placebo (Table 4). None of the patients were neutropenic at the last study date (Supplementary Text to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.995875).

Discussion

In Japanese patients with active RA, of mean duration: 6.4–11.0 years across groups, and inadequate response to DMARDs, tofacitinib doses from 1 to 15 mg BID for 12 weeks demonstrated significant improvement in signs and symptoms of RA compared with placebo. Dose-related efficacy was demonstrated for all tofacitinib doses versus placebo by statistically significantly greater rates of patients achieving ACR20, ACR50, ACR70 (at tofacitinib: $\geq$ 5 mg BID), and DAS28-defined remission (at tofacitinib: $\geq$ 5 mg BID). Moreover, significant improvements in physical function and other patient-reported outcomes, such as HAQ-DI, SF-36 physical component scores, and FACIT-F scores, represent improvements in function and quality of life measures among patients receiving tofacitinib at all doses.

The incidence of patients experiencing treatment-emergent AEs was similar between treatment groups, with a trend toward higher incidence with increasing tofacitinib dose. Dose-dependent mean changes in laboratory parameters, including decreases in ANC and increases in hemoglobin, cholesterol, and serum creatinine, were also observed with tofacitinib. There were 3 serious AEs of herpes zoster/herpes zoster oticus, and 1 serious AE of rheumatoid vasculitis. Some of the cytokines that are inhibited by tofacitinib play an important role in lymphocyte development and function [28], which suggests that immunosurveillance may be negatively impacted by tofacitinib; however, in most patients no decrease in lymphocyte levels was seen and none of the patients were neutropenic.

The efficacy of tofacitinib monotherapy was similar to a previously published clinical trial of tofacitinib with background methotrexate in 136 Japanese patients with active RA [22], in which 12-week ACR20 response rates (NRI) were 60.7–88.9% with 1–10 mg BID versus 14.3% with placebo ($p < 0.0001$ for all doses). Similar to the present study, nasopharyngitis was the most common AE. In that study, increases in serum creatinine were reported with tofacitinib versus placebo; the serum creatinine increases in the Tanaka et al.'s study and the present study were not considered clinically meaningful. That study also reported elevated levels of AST and ALT in all groups (including placebo), suggesting that the background methotrexate may have contributed to the elevated transaminase levels.

Tofacitinib efficacy was also similar to previously published RCTs of tofacitinib in global studies of patients with RA [29–31]. The global phase 2b study of tofacitinib monotherapy in 384 treated patients reported significantly greater 12-week ACR20 response rates of 39.2–71.9% (NRI) with doses of 315 mg BID versus 22.0% with placebo [29]. In addition, a global phase 3 study of tofacitinib monotherapy in 610 treated patients reported significantly greater 3-month ACR20 response rates of 59.8% and 65.7% with tofacitinib: 5 mg BID and 10 mg BID, respectively, versus 26.7% with placebo [16]. The above studies reported similar AEs to the present study, including headache, diarrhea, nausea, nasopharyngitis, upper respiratory tract infection, and urinary tract infection. One case of disseminated herpes zoster was reported in the global phase 3 study [16]. A similar percentage of patients in the global monotherapy studies discontinued due to an AE (0–10.8%) [16,29] compared with the present study (0–5.7%). The studies above also reported elevated lipid levels and a slight increase in mean serum creatinine levels with tofacitinib, similar to the present study.

In this study, tofacitinib was associated with increased levels of LDL-C, HDL-C, and TC. IL-6 signaling is implicated in the regulation of cholesterol levels, and an anti-IL-6 receptor monoclonal antibody, tocilizumab, has also been associated with elevated lipid levels in patients with RA [32–34]. As the mode of action of tofacitinib includes inhibition of IL-6 signaling [28], the changes in cholesterol levels in response to tofacitinib in patients with RA may involve a degree of IL-6 inhibition; however, further studies will be required to confirm the mechanism behind these lipid changes.

This study was limited by the 12-week study period; a long-term extension study including patients from the present study has recently been completed to evaluate longer-term safety and efficacy of tofacitinib in Japanese patients (NCT00661661). In addition, this study did not assess radiographic progression, which could have provided further insight into the effect of treatment on the disease process.

In conclusion, tofacitinib produced dose-dependent improvements in signs and symptoms, and disease activity in Japanese patients with RA. The safety profile was consistent with that reported from global monotherapy trials and other studies in Japanese patients.

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Appendix

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Conflict of interest

Y Tanaka has received consultancy fees, speaking fees, and honoraria from Abbvie, Chugai, Astellas, Takeda, Santen, MitsubishiTanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB Japan, GlaxoSmithKline, and Bristol-Myers-Squib.

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H Yamanaka has received consultancy fees, speaking fees, and honoraria from AbbVie, AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen Pharma, Mitsubishi Tanabe Pharma Corporation, Pfizer, and Takeda.

H Nakamura and S. Toyoizumi are employees of Pfizer Japan Inc, Tokyo, Japan.

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Supplementary material available online

Supplementary Tables 1–2, Figures 1–3 and Supplementary Text.