Efficacy and safety of tofacitinib in US and non-US rheumatoid arthritis patients: pooled analyses of phase II and III

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Abstract

Objective

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. This post-hoc pooled analysis assessed commonalities and differences in tofacitinib efficacy and safety for US versus rest of the world (ROW) populations.

Methods

Pooled phase (P) III data from patients receiving tofacitinib 5 or 10 mg twice daily (BID) or placebo were assessed for efficacy at Month 3 and for safety outcomes over 12 months. For adverse events of special interest, data on tofacitinib 5 or 10 mg BID or placebo were pooled from six PII and five PIII randomised studies.

Results

PIII data were available for 664 vs. 2447 and PII/PIII data for 943 vs. 3567 US vs. ROW patients, respectively. The US population had a higher proportion of Caucasians (81.5% vs. 54.4%), lower proportion of Asians (1.0% vs. 34.6%), and higher mean body weight (85.7 vs. 66.2 kg) and body mass index (31.5 vs. 25.6 kg/m^2) compared with ROW. At Month 3, PIII efficacy was similar between US and ROW as assessed by ACR 20/50/70 response rates, remission rates (DAS 28-4[ESR]<2.6), and HAQ-DI scores. Diarrhoea, peripheral oedema, and upper respiratory tract infection occurred in >5% of PIII patients in the US population. Incidence rates for adverse events of special interest were similar between the US and ROW PII/PIII populations.

Conclusion

Patients in the US achieved similar efficacy and safety with tofacitinib 5 and 10 mg BID compared with patients in ROW.

Key words

arthritis, rheumatoid, treatment efficacy, United States

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Introduction

In the US, rheumatoid arthritis (RA) affects an estimated 1.3 million adults (1). Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. It was approved by the US Food and Drug Administration in November 2012. The efficacy and safety of tofacitinib have been demonstrated in patients with active RA at doses of 5 mg and 10 mg twice daily (BID) in randomised Phase II (2-7) and Phase III (8-12) studies of up to 24 months' duration, and in ongoing long-term extension studies (13) up to 60 months of observation. Tofacitinib was associated with reductions in signs and symptoms, improvements in physical function, and reduction in progression of joint damage, with consistent safety signals in patients with RA worldwide.

This post-hoc analysis of pooled Phase II and III data evaluated the efficacy and safety of tofacitinib in patients in the US and the rest of the world (ROW; non-US).

Patients and methods

The population consisted of patients aged >18 years, with a diagnosis of active RA, and an inadequate response to a disease-modifying anti-rheumatic drug (DMARD) who participated in six Phase II randomised studies (NCT00147498, NCT00413660, NCT00550446, NCT00603512, NCT00687193, NCT01059864) (2-7) and five Phase III randomised studies (NCT00814307, NCT00847613 [1-year analysis used for all efficacy and safety data], NCT00960440, NCT00856544, NCT00853385) (8-12). Patients in the Phase II studies received doses of tofacitinib ranging from 1 to 30 mg BID or once daily, or placebo, as monotherapy or in combination with methotrexate. Patients in Phase III studies received study treatment as monotherapy or in combination with background nonbiologic DMARDs, mainly methotrexate. Patients randomised to placebo in Phase III studies advanced to tofacitinib 5 mg or 10 mg BID at Month 3 or 6.

The studies were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines established by the International Conference on Harmonisation, and local country regulations. The studies were approved by a central or local institutional review board or an independent ethics committee. All patients provided written informed consent.

For efficacy analyses, pooled Phase III data only were assessed at Month 3 for comparisons of tofacitinib 5 mg and 10 mg BID, and placebo, using descriptive statistics without missing data imputation. After the publication of one of the Phase III studies (11), one of its study sites (nine patients randomised) was found to be non-compliant to study procedures and those patients have been removed from the efficacy analyses presented.

Safety outcomes were assessed for pooled Phase III data of up to 12 months' duration in patients receiving tofacitinib or placebo. Patients who advanced from placebo to tofacitinib at either Month 3 or 6 were counted in the placebo group until advancement and were only counted in the tofacitinib group post-advancement. For adverse events (AEs) of special interest, patients receiving tofacitinib 5 mg or 10 mg BID were pooled from the six Phase II and five Phase III randomised studies; incidence rates (IRs; number of patients with events/100 patient-years) are presented for combined tofacitinib groups. Data collection and analyses for one Phase III study (NCT00847613) was still ongoing at the time of this analysis (*i.e.* databases not locked; some values may change from the final, locked databases).

Results

Patients

Data were included from 664 US and 2447 ROW patients in Phase III efficacy and safety analyses, and from 943 US and 3567 ROW patients in the Phase II/Phase III assessment of AEs of special interest (data cut-off April 2012).

Patients in the US and ROW (Phase II/Phase III) had similar demographics except that the US population had a higher proportion of Caucasian patients (81.5% *vs.* 54.4%), a lower proportion of Asian patients (1.0% *vs.* 34.6%), a higher mean body weight (85.7 kg *vs.* 66.2 kg) and body mass index (BMI; 31.5 *vs.* 25.6 kg/m^2), and a lower proportion of women

Table I. Patient demographic data and baseline characteristics for pooled data* from Phase II and III studies of tofacitinib in US and ROW patient populations.

	US (N=943)	ROW (N=3567)
Female, n (%)	743 (78.8)	3050 (85.5)
Race, n (%)		
Caucasian	769 (81.5)	1939 (54.4)
Black	91 (9.7)	41 (1.1)
Asian	9 (1.0)	1234 (34.6)
Hispanic	12 (1.3)	35 (1.0)
Other	62 (6.6)	318 (8.9)
Mean age, years (SD)	54.8 (11.1)	52.2 (11.9)
Mean weight, kg (SD)	85.7 (22.4)	66.2 (16.0)
Mean BMI, kg/m^2 (SD)	31.5 (7.8)‡	25.6 (5.5)‡
Mean height, cm (SD)	165.0 (9.7)‡	160.5 (8.6)‡

*Data as of April 19, 2012. ‡Evaluable patients: n=941 (US) and 3565 (ROW) for these measures. BMI: body mass index; N: number of patients; ROW: rest of the world; SD: standard deviation.

(78.8% *vs*. 85.5%) compared with ROW patients (Table I). Within the US and ROW Phase III populations a similar pattern was observed and the proportion of Caucasian and Asian patients was comparable between treatment subgroups (US Caucasian patients: 83.1%, 81.1%, 82.0%; ROW Caucasian patients: 58.7%, 55.3%, 55.5%; US Asian patients: 0.6%, 0.4%, 0.8%; ROW Asian patients: 31.7%, 33.7%, 32.5% for placebo, and tofacitinib 5 mg and 10 mg BID, respectively).

Pooled efficacy data from five Phase III studies of tofacitinib

Pooled efficacy data are summarised in Table II. At Month 3, efficacy — as measured by American College of Rheumatology (ACR) 20/50/70 response rates, remission rates (defined as <2.6 for 4-variable Disease Activity Score in 28 joints using the erythrocyte sedimentation rate [DAS28-4(ESR)<2.6]) and improvements from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score — observed in the tofacitinib 5 mg *vs*. the tofacitinib 10 mg dose group was similar in the US and ROW populations. In general, the placebo-adjusted statistics within each dose group were comparable between the two populations.

Adverse events occurring in five Phase III studies of tofacitinib

In Phase III studies of tofacitinib, patient-years of exposure for the US and ROW populations were 383.6 and 1714.6 with tofacitinib, and 44.3 and 158.3 with placebo, respectively. IRs were similar for the US compared with ROW for serious AEs, discontinuations due to AEs, and major adverse cardiovascular events (Table III).

No AEs occurred in >5% of patients in either group (tofacitinib 5 or 10 mg BID, and placebo) in the ROW population from Months 0 to 3, 3 to 6, or Month >6, while diarrhoea, peripheral oedema, and upper respiratory tract infection occurred in >5% of patients in the US population. During the first 3 months of treatment (before any patients in the placebo groups advanced to tofacitinib), diarrhoea and upper respiratory tract infection were reported in a higher proportion of US patients receiving tofacitinib compared with placebo (diarrhoea: 5.4% [27/504] *vs*. 1.3% [2/160] in the US population and 2.7% [52/1926] *vs*. 2.7% [14/521] in the ROW population; upper respiratory tract infection: 6.7% [34/504] *vs*. 4.4% [7/160] in the US population and 3.4% [66/1926] *vs*. 3.1 [16/521] in the ROW population for tofacitinib *vs*. placebo, respectively). In contrast, peripheral oedema was more common in US patients receiving placebo than those receiving tofacitinib (3.4% [17/504] *vs*. 5.6% [9/160] in the US population and 1.1% [21/1926] *vs*. 1.3% [7/521] in the ROW population for tofacitinib *vs*. placebo, respectively). The proportions of patients with these three events (diarrhoea, respiratory tract infection, and peripheral oedema) were similar between tofacitinib and placebo in the ROW population. During Months 3 to 6, the only AE that occurred in >5% of patients in either group was upper respiratory tract infection (URTI), which was reported by 5.7% (36/627) of the US population who received tofacitinib and 2.6% (59/2263) of the ROW population who received tofacitinib (no URTI cases in the small number of placebo-treated patients for Months 3 to 6 [US, n=37; ROW, n=184]). No AEs

Table II. Pooled efficacy from five Phase III studies (Month 0–Month 3) of tofacitinib in US and ROW patient populations (observed data)*.

	Placebo		Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo-adjusted tofacitinib 5 mg BID		Placebo-adjusted tofacitinib 10 mg BID	
	US (N=160)	ROW (N=472)	US (N=249)	ROW (N=903)	US (N=255)	ROW (N=897)	US	ROW	US	ROW
ACR20, %	24.0	30.1	53.3	60.9	63.4	67.5	29.3	30.8	39.4	37.4
ACR50, %	9.6	10.0	30.6	31.2	38.4	34.7	21.0	21.3	28.8	24.7
ACR70, %	3.4	2.8	15.3	11.5	18.1	16.3	11.9	8.8	14.7	13.5
DAS28-4 <2.6, %	<1.0	2.6	9.0	6.4	7.5	11.0	8.3	3.8	6.7	8.4
ΔHAQ-DI, LS mean	-0.16	-0.17	-0.42	-0.45	-0.50	-0.54	-0.26	-0.28	-0.34	-0.37

*N values represent the numbers of patients with available ACR data at Month 3.

Δ: change from baseline; ACR: American College of Rheumatology; BID: twice daily; DAS: disease activity score; HAQ-DI: Health Assessment Questionnaire-Disability Index; LS: least squares; N: number of patients; ROW: rest of the world.

Table III. Exposure estimates and incidence rates for pooled safety outcomes (Month 0 – Month 12) for five Phase III studies of tofacitinib in US and ROW patient populations.

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		All tofacitinib		Placebo*	
IR; number of patients with event/ 100 patient-years (95% CI) [n]	US (N=249)	ROW (N=967)	US (N=255)	ROW (N=959)	US (N=644)	ROW (N=2386)	US (N=160)	ROW (N=521)
Total patient-years of drug exposure	160.4	743.3	165.3	745.0	383.6	1714.6	44.3	158.3
Discontinuations due to AEs	13.2 (8.6, 20.3) [21]	10.0 (8.0, 12.6) [74]	14.6 (9.8, 21.8) [24]	10.1 (8.1, 12.7) [75]	12.9 (9.7, 17.0) [49]	9.1 (7.8, 10.7) [156]	13.6 (6.1, 30.3) [6]	12.1 (7.7, 18.9) [19]
SAEs	12.2 (7.8, 19.1) [19]	11.8 (9.5, 14.6) [85]	12.4 (8.0, 19.2) [20]	9.2 (7.2, 11.7) [67]	12.5 (9.4, 16.7) [47]	9.8 (8.4, 11.4) [164]	16.0 (7.6, 33.5) [7]	14.8 (9.8, 22.2) [23]
MACE	0.6 (0.1, 4.4) [1]	0.4 (0.1, 1.3) [3]	0.6 (0.1, 4.3) [1]	0.7 (0.3, 1.6) [5]	0.8 (0.3, 2.4) [3]	0.5 (0.3, 1.0) [9]	0 [0]	1.3 (0.3, 5.1) [2]

*Patients randomised to the placebo treatment group advanced to tofacitinib (5 mg or 10 mg BID) at either Month 3 or Month 6. Patients who advanced from placebo to tofacitinib were counted in the placebo group until advancement and were counted only in the 'All tofacitinib' group post-advancement.
AE: adverse event; BID: twice daily; CI: confidence interval; IR: incidence rate; MACE: major adverse cardiovascular event; N: number of patients; n: number of patients with events; ROW: rest of the world; SAE: serious adverse event.

occurred in >5% of patients in either the tofacitinib or placebo groups from Month 6 onwards.

Pooled safety data from Phase II and III studies of tofacitinib

The IRs for AEs of special interest in US and ROW patients are shown in Table IV. Although there were some numerical differences, 95% confidence limits (CIs) were largely overlapping. In the US population, there were no cases of opportunistic infections, tuberculosis [TB]), lymphoma, or serious herpes zoster (HZ) infection.

Discussion

In this pooled analysis, demographic differences were noted between the US and ROW populations, with the US population having a higher proportion of Caucasian patients and a lower proportion of Asian patients (as expected given the countries in which patients were enrolled), a higher mean body weight and BMI, and a lower proportion of female patients compared with the ROW population. In contrast with disease registries, where patients in the US generally have a lower mean baseline DAS28 score compared with those in other countries (14), baseline RA severity in the selected Phase III populations was similar between the US and ROW (mean baseline DAS28-4[ESR] score: 6.43 [US], 6.43 [ROW]).

In these Phase III studies, efficacy was similar between the US and ROW populations. Although ACR response rates at Month 3 for tofacitinib were slightly higher in the ROW compared with the US, particularly for ACR20, placebo-adjusted response rates were similar due to the slightly higher placebo response rate in the ROW population. DAS28-4-defined remission at Month 3 was achieved in numerically more patients treated with tofacitinib 5 mg BID in the US compared with the ROW, and in more patients treated with tofacitinib 10 mg BID in the ROW compared with the US. However, the results in the pooled Phase III population agree with the numerically higher rates with the 10 mg BID dose compared with the 5 mg BID dose observed in the individual studies at Month 3 (8, 9), and at the later time point of Month 6 (10-12). Improvements from baseline in HAQ-DI scores at Month 3 were similar between the US and ROW populations.

IRs for AEs of special interest were generally similar between the US and ROW populations and consistent with those published for established DMARDs. However, HZ infection was

Table IV. Adverse events of special interest and all-cause mortality in pooled safety data* from Phase II and III studies of tofacitinib in US and ROW patient populations.

	All patients receiving tofacitinib‡	
IR; number of patients with event/100 patient-years (95% CI) [number of patients with event]	US (N=943) (474.5 patient-years of exposure)	ROW (N=3567) (2068.7 patient-years of exposure)
Serious infection events	2.5 (1.4, 4.5) [12]	3.1 (2.4, 3.9) [63]
Opportunistic infections (excluding TB)	0 [0]	0.4 (0.2, 0.8) [8]
TB	0 [0]	0.3 (0.1, 0.6) [6]
All HZ	3.0 (1.8, 5.0) [14]	4.6 (3.7, 5.6) [93]
Serious HZ	0 [0]	0.4 (0.2, 0.8) [8]
All-cause mortality (30-day rule)§	0.8 (0.3, 2.2) [4]	0.3 (0.2, 0.7) [7]
Malignancies (excluding non-melanoma skin cancer)	0.6 (0.2, 2.0) [3]	0.6 (0.3, 1.0) [12]
Lymphoma	0 [0]	0.0 (0.0, 0.3) [1]¥

*Data as of April 19, 2012. ‡Includes patients receiving tofacitinib 5 mg and 10 mg twice daily. §Includes those events occurring within 30 days of last dose of study drug. ¥Actual values: 0.048 (0.007, 0.343): CI: confidence interval; HZ: herpes zoster; IR: incidence rate; N: number of patients; n: number of patients with events; ROW: rest of the world; TB: tuberculosis.

higher for tofacitinib in both populations than the rates reported in the literature for patients with RA treated with biologic and non-biologic DMARDs. There were no cases of opportunistic infections, TB, lymphoma, or serious HZ infection in the US population.

There was a relatively small sample size for the US population compared with that of the ROW population. As a consequence, any numerical differences in AEs between the US and ROW populations need to be considered within the context of the limitations of this post-hoc analysis which include differences in population sizes. In addition, varying background prevalences for diseases such as HZ and TB in different countries may impact on the results between geographic regions.

There are little data of comparative effectiveness and safety of medications across geographic populations in controlled trials and this is an attempt to bridge that gap. Although limited by differences in population size, this pooled analysis suggests that with tofacitinib, efficacy and safety (other than regional infections) are similar worldwide.

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