The JAK inhibitor tofacitinib for active rheumatoid arthritis: results from Phase III trials

Tofacitinib is a Janus kinase inhibitor that modulates the transcription of cytokine genes involved in immune regulation and hematopoiesis. This clinical trial report focuses on ORAL Solo, ORAL Standard, ORAL Step and ORAL Scan Phase III trials of the tofacitinib ORAL program. ORAL Solo shows an early and sustained clinical efficacy with tofacitinib monotherapy in rheumatoid arthritis (RA) patients with inadequate response to biologic or nonbiologic disease-modifying antirheumatic drugs. ORAL Standard demonstrates clinical response to tofacitinib plus methotrexate (MTX) in RA patients who had MTX-inadequate response. ORAL Step indicates rapid clinical response to tofacitinib plus MTX in TNF antagonist-inadequate response RA patients. ORAL Scan demonstrates that tofacitinib inhibits radiographic progression and improves clinical parameters in patients treated with tofacitinib and MTX. Upper respiratory tract infection, headache, diarrhea and nasopharyngitis were common adverse events. Tofacitinib is a new small molecule for the treatment of RA; long-term safety data and comparisons with other disease-modifying antirheumatic drugs will determine the role of tofacitinib in the treatment of RA.

KEYWORDS: CP-690,55 ■ JAK ■ ORAL trials ■ protein kinase inhibitor ■ rheumatoid arthritis ■ tofacitinib

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The advent of biologic therapies and new treat-to-target therapeutic strategies has changed the treatment paradigm of rheumatoid arthritis (RA) [1–6]. Nowadays, RA patients not fully responding to traditional disease-modifying antirheumatic drugs (DMARDs) are treated with biologic therapies that inhibit cytokines, modulate T cells or deplete B cells. Biologics are relatively effective for the treatment of RA; however, only half of patients achieve the intended remission or low disease activity [7]. In addition, biologics need special transport and storage conditions, are handled under restricted conditions and their cost of acquisition is high. The use of small molecules that block intracellular cytokine signaling pathways is a new approach for the treatment of RA. The small molecules are chemically synthesized and can be administered orally. Protein kinases are important enzymes in cell signaling. The Janus kinase (JAK) family (JAK1, JAK2, JAK3 and TYK2) has a critical role in intracellular signaling pathways of certain cytokines involved in immune regulation [8]. Tofacitinib (CP-690,550) is the first protein kinase inhibitor approved for the treatment of RA. It is a JAK inhibitor with functional selectivity for JAK1 and JAK3 over JAK2 [9]. It was first synthesized in 2000 by Pfizer, and was initially developed for immunosuppression in transplantation. Other drugs targeting the JAK family, such as: VX-509, a JAK3 inhibitor; baricitinib (LY-3009104), a specific JAK1 and JAK2 inhibitor; ASP015K, a JAK1 and JAK3 inhibitor [10]; and GLPG-0634, a JAK1 inhibitor [11], are also being developed for the treatment of RA.

Phase II studies

Dose-ranging Phase II trials for tofacitinib in RA consist of five randomized, double-blind, placebo-controlled studies. One Phase IIa proof-of-concept study (A3921019) [12] and one with tofacitinib monotherapy (A3921035), and one Phase IIb dose-ranging study with tofacitinib with background MTX (A3921025) [13,14], were conducted in a global population. Study A3921035 included an active control arm with adalimumab for the first 12 weeks, and study A3921025 had an arm with 20 mg once daily of tofacitinib. Phase IIb studies have also been undertaken in the Japanese population (A3921039, A3921035, A3921019 and A3921040) [15–17]. Design and primary efficacy results are shown in Table 1. All Phase IIb studies showed that ACR20 response rates were significantly greater than placebo for all tofacitinib doses ≥3 mg. Moreover, significant differences compared with placebo were detected at week 2 in A3921025 and A3921039. In study A3921035, ACR20 response at week 12 with adalimumab was no better than placebo,

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Table 1. Design, characteristics and results of Phase II studies.

ID number	Design	Patients	Doses	Duration (W)	Primary end point (%)	Ref.
A3921019 NCT00147498	Phase IIa Proof of concept Monotherapy	264 RA patients with prior inadequate response or intolerance to MTX, etanercept, adalimumab and infliximab	Tofacitinib 5, 15 or 30 mg b.i.d.	6	ACR20 5 mg b.i.d. W6, 70.5* ACR20 15 mg b.i.d. W6, 81.2* ACR20 30 mg b.i.d. W6, 76.8* ACR20 placebo W6, 29.2	[12]
A3921025 NCT00413660	Phase II Dose ranging On background MTX	507 RA patients with prior stable dose of MTX	Tofacitinib 1, 3, 5, 10 or 15 mg b.i.d. and 20 mg q.d.	24	ACR20 1 mg b.i.d. W12, 45.7 ACR20 3 mg b.i.d. W12, 52.9* ACR20 5 mg b.i.d. W12, 50.7* ACR20 10 mg b.i.d. W12, 58.1* ACR20 15 mg b.i.d. W12, 56.0* ACR20 20 mg q.d. W12, 53.8* ACR20 placebo W12, 33.3	[14]
A3921035 NCT00550446	Phase IIb Dose ranging Monotherapy	384 RA patients with failure with at least one DMARD except antimalarials	Tofacitinib 1, 3, 5, 10 or 15 mg b.i.d.; or adalimumab 40 mg sc. Q2W followed by tofacitinib 5 mg b.i.d. for 12 weeks	24	ACR20 1 mg b.i.d. W12, 31.5 ACR20 3 mg b.i.d. W12, 39.2* ACR20 5 mg b.i.d. W 12, 59.2* ACR20 10 mg b.i.d. W12, 70.5* ACR20 15 mg b.i.d. W12, 71.9* ACR20 adalimumab Q2W, W12, 35.9 ACR20 placebo W12, 22	[13]
A3921039 NCT00603512	Phase IIb Dose ranging On background MTX	140 Japanese RA patients with prior stable dose of MTX (maximum dose in Japan 8 mg/W)	Tofacitinib 1, 3, 5 or 10 mg b.i.d.	12	ACR20 1 mg b.i.d. W12, 64.3* ACR20 3 mg b.i.d. W12, 77.8* ACR20 5 mg b.i.d. W12, 96.3* ACR20 10 mg b.i.d. W12, 80.8* ACR20 placebo W12, 14.3	[17]
A3921040 NCT00687193	Phase IIb Dose ranging Monotherapy	317 Japanese RA patients inadequately responding to at least one DMARD	Tofacitinib 1, 3, 5, 10 or 15 mg b.i.d.	12	ACR20 1 mg b.i.d. W12, 37.7* ACR20 3 mg b.i.d. W12, 67.9* ACR20 5 mg b.i.d. W12, 73.1* ACR20 10 mg b.i.d. W12, 84.9* ACR20 15 mg b.i.d. W12, 90.7* ACR20 placebo W12, 15.4	[15,16]

**p < 0.05 vs placebo.*
b.i.d.: Twice daily; DMARD: Disease-modifying antirheumatic drug; ID: Identification; MTX: Methotrexate; Q2W: Every 2 weeks; q.d.: Once a day; RA: Rheumatoid arthritis; sc.: Subcutaneous; W: Week.

perhaps due to the unexpected high response rate in the placebo arm. Reported adverse events (AEs) in Phase II trials include headache, nausea, respiratory tract infection, diarrhea and anemia. A decrease in neutrophil count and an increase in high-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol levels were reported as dose-related AEs. Serious adverse events (SAEs) were uncommon and were not dose related [13,15]. The Japanese studies showed higher response rates than studies conducted in other patients [15].

Design of ORAL Phase III clinical trials

ORAL program trials

The ORAL clinical program involves six Phase III trials to assess the safety and efficacy of tofacitinib 5 and 10 mg twice daily (b.i.d.) as a monotherapy, or with background MTX or background traditional DMARD therapy (Table 2). The profile of targeted patients included patients naive to MTX (ORAL Start) [101], patients with an inadequate response (IR) to TNF antagonists (ORAL Step) [18], patients with an IR to MTX (ORAL Standard and ORAL Scan) [19,20] and patients with an IR to at least one nonbiologic or biologic DMARD (ORAL Solo and ORAL Sync) [21–24]. Active control arms with adalimumab and MTX were incorporated in ORAL Standard and ORAL Start, respectively. However, the ORAL Standard study was not designed to determine noninferiority or superiority between adalimumab and tofacitinib. In addition, ORAL Scan included progression of structural damage as a coprimary efficacy end point. This clinical trial report focuses on published results from the ORAL

Standard, ORAL Solo, ORAL Step and ORAL Scan studies [18,25–27].

In addition to the ORAL program, there are ongoing, open-label, long-term extension (LTE) studies (A3921024 and A3921041) that have enrolled patients who had previously participated in Phase II or III studies [28,29]. A3921041 is a LTE study of 404 Japanese patients from the A3921039 and A3921040 Phase IIb studies. A pooled data analysis was published in abstract format [30,31] and in the briefing document of the US FDA Advisory Committee Meeting on tofacitinib for the treatment of RA [102].

ORAL Standard design

The ORAL Standard trial (NCT00853385) was a 1-year, global, multicenter, double-blind, placebo- and adalimumab-controlled randomized Phase III trial with tofacitinib. Eligible patients were on background MTX and had an IR defined as the presence of at least six tender/painful joints (68-joint count) and at least six swollen joints (66-joint count), and an elevated erythrocyte sedimentation rate (ESR) or elevated C-reactive protein (CRP) levels. Current treatment with other antirheumatic agents, prior treatment with adalimumab, prior lack of response to TNF antagonists and history of class III or IV heart failure were among the exclusion criteria. Patients with evidence of active, latent or inadequately treated *Mycobacterium tuberculosis* infection were excluded. A total of 717 active RA patients with background MTX were randomized to receive 5 mg of tofacitinib b.i.d., 10 mg of tofacitinib b.i.d., 40 mg of adalimumab once every 2 weeks or placebo. At month 3, patients not achieving a 20% reduction in the number of swollen and tender joints in the placebo group were advanced to a prespecified tofacitinib dose (5 or 10 mg b.i.d.) in a blinded fashion. At month 6, all remaining placebo group patients were blindly advanced to their prespecified tofacitinib dose (either 5 or 10 mg of tofacitinib b.i.d.). Efficacy of tofacitinib was compared with placebo. Primary efficacy outcomes were: percentage of patients that met the criteria of ACR20

Table 2. Design, characteristics and results of Phase III studies.

Study	ID number	Design	Patients (n)	Primary end points (%)	Ref.
ORAL Standard	A3921064 NCT00853385	Phase III Placebo controlled and adalimumab arm IR to MTX On background MTX	717	ACR20 response at M6 vs placebo Mean change from baseline in HAQ-DI response at M3 vs placebo DAS28-ESR <2.6 at M6 vs placebo	[26]
ORAL Solo	A3921045 NCT00814307	Phase III Placebo controlled IR or intolerance to at least one traditional or biologic DMARD Monotherapy	610	ACR20 at M3 vs placebo Mean change from baseline in HAQ-DI response at M3 vs placebo DAS28-ESR <2.6 at M3 vs placebo	[25]
ORAL Step	A3921032 NCT00960440	Phase III Placebo controlled IR or intolerance to TNF inhibitors On background MTX	399	ACR20 at M3 vs placebo Mean change from baseline in HAQ-DI response at M3 vs placebo DAS28-ESR <2.6 at M3 vs placebo	[18]
ORAL Scan	A3921044 NCT00847613	Phase III Placebo controlled IR to MTX On background MTX	797	ACR20 at M6 vs placebo Mean change from baseline in SHS at M6 vs placebo Mean change from baseline in HAQ-DI response at M3 vs placebo DAS28-ESR <2.6 at M6 vs placebo	[35]
ORAL Sync	A3921046 NCT00856544	Phase III Placebo controlled IR to at least one traditional or biologic DMARD On background traditional DMARD	792	ACR20 response at M6 vs placebo Mean change from baseline in HAQ-DI response at M3 vs placebo DAS28-ESR <2.6 at M6 vs placebo	[24]
ORAL Start	A3921069 NCT01039688	Phase III MTX controlled MTX-naive patients Monotherapy	900 planned	Mean change from baseline in SHS at M6 vs MTX ACR70 at M6 vs MTX	[101]

DAS: Disease Activity Score; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; ID: Identification; IR: Inadequate response; M: Month; MTX: Methotrexate; SHS: Modified Sharp/van der Heijde score.

response at month 6; mean change from baseline to month 3 in Health Assessment Questionnaire Disability Index (HAQ-DI); and the percentage of patients achieving remission by Disease Activity Score (DAS)28-ESR criteria at month 6. Secondary efficacy outcomes included: percentage of patients who achieved ACR20, ACR50 and ACR70 response at different visits; and changes in HAQ-DI and DAS28-ESR compared with baseline. Incidence and severity of AEs were primary safety objectives.

ORAL Solo design

The ORAL Solo trial (NCT00814307) was a 6-month, global, multicenter, double-blind, placebo-controlled, randomized Phase III trial. All patients had an IR or intolerance to at least one DMARD (biologic or nonbiologic) and had discontinued all DMARD therapy prior to enrollment (antimalarial drugs were allowed). IR was defined as in the ORAL Standard trial. Patients with evidence of active, latent or inadequately-treated *M. tuberculosis* infections were excluded. A total of 611 patients were randomized to tofacitinib 5 mg b.i.d., 10 mg of tofacitinib b.i.d. or placebo. At month 3, patients treated with placebo were advanced to a prespecified tofacitinib dose (5 or 10 mg b.i.d.) in a blinded fashion. Rate of ACR20 response, change from baseline in HAQ-DI and percentage of patients achieving remission, measured by DAS28–4-ESR criteria, assessed at month 3 were the primary efficacy outcomes. Incidence and severity of AEs in tofacitinib-treated patients were also primary safety objectives. Secondary efficacy outcomes included percentage of patients achieving ACR20, ACR50 and ACR70 response at different time points, changes in HAQ-DI, DAS28-ESR and DAS28-CRP compared with baseline, and Functional Assessment of Chronic Illness Therapy score at month 3. *Post hoc* subgroup analyses were performed to assess efficacy in, for example, seropositive patients or patients with a prior IR to biologics [21].

ORAL Step design

The ORAL Step trial (NCT00960440) was a 6-month, global, multicenter, double-blind, placebo-controlled, randomized Phase III trial. Eligible patients were intolerant or had an IR to TNF antagonists. IR was defined as in the ORAL Standard and ORAL Solo studies. Patients with evidence of active, latent or inadequately-treated *M. tuberculosis* infection were excluded. A total of 399 patients were randomized to tofacitinib 5 mg b.i.d., 10 mg of tofacitinib b.i.d. or placebo. All patients receiving tofacitinib were also on background MTX. At month 3, placebo-treated patients were advanced to a prespecified dose of tofacitinib (5 or 10 mg b.i.d.) in a blinded fashion. ACR20 response rate, mean change from baseline in HAQ-DI and percentage of patients achieving remission, measured by DAS28–4-ESR criteria, assessed at month 3 were the primary efficacy outcomes. In addition, the incidence and severity of AEs in tofacitinib-treated patients compared with placebo were the primary safety objectives. Secondary efficacy end points included percentage of patients achieving ACR20, ACR50 and ACR70 response at different time points, changes in HAQ-DI, DAS28-ESR and DAS28-CRP compared with baseline, arthritis pain measured with a Visual Analogue Scale and Functional Assessment of Chronic Illness Therapy score at month 3. In all Phase III studies, no control for type 1 error was applied for secondary outcomes and *post hoc* analyses.

ORAL Scan design

The ORAL Scan trial (NCT00847613) was a 24-month, global, multicenter, double-blind, placebo-controlled, randomized Phase III trial. Data from a planned 12-month interim analysis have recently been reported [27]. All patients included had an IR to MTX. IR was defined as in the ORAL Standard trial. Patients with evidence of active, latent or inadequately-treated *M. tuberculosis* infection were excluded. Patients were randomized to tofacitinib 5 mg b.i.d., 10 mg of tofacitinib b.i.d. or placebo. At month 3, the placebo-treated nonresponder patients were blindly advanced to a prespecified dose of tofacitinib (5 or 10 mg b.i.d.). At month 6, all remaining placebo-treated patients were advanced in a blinded fashion. ACR20 response at month 6, change from baseline in total modified Sharp/van der Heijde score (SHS) at 6 months, change from baseline in HAQ-DI at month 3 and percentage of patients achieving remission, measured by DAS28-ESR criteria, assessed at month 6 were the primary efficacy outcomes. Incidence and severity of AEs in tofacitinib-treated patients were also primary safety objectives. Secondary efficacy outcomes included percentage of patients achieving ACR20, ACR50 and ACR70, changes from baseline in DAS28-ESR as well as patient-reported outcomes. Secondary radiographic end points included the rate of nonradiographic progressors (≤0.5 unit change from baseline in total SHS or erosion score), and changes from baseline in erosion score and joint space narrowing.

Results

ORAL Standard results

A total of 556 out of 717 randomized patients completed the 1-year study. ACR20 response rate at month 6, mean change from baseline in HAQ-DI scores at month 3, and percentage of patients achieving remission at month 6, were statistically significant for both doses of tofacitinib and adalimumab, compared with placebo (TABLE 3). ACR50 and ACR70 responses were significantly higher in all active-treatment groups than placebo over time. ACR20 and ACR50 responses with both tofacitinib doses were significantly higher than placebo at month 1. ACR50 and ACR70 response rates and changes from baseline in DAS28–4-ESR and HAQ-DI scores were sustained for the duration of the study. The most frequent AEs classified using the Medical Dictionary for Regulatory Activities terms were infections and infestations. SAEs and serious infectious AEs occurred more frequently in tofacitinib-treated patients than in placebo in the first 3 months. Two patients died: one from septic syndrome secondary to a respiratory infection in the 5-mg b.i.d. tofacitinib group, and the other patient died from cardiac arrest in the adalimumab group. There were two cases of pulmonary tuberculosis in the 10-mg b.i.d. tofacitinib group. Both patients had a negative QuantiFERON®-TB (Cellestis) test result at the start of study. Reductions in neutrophil counts were seen at month 3 in all active-treatment arms, but incidence of moderate-to-severe neutropenia was low. Higher changes than placebo in levels of LDL cholesterol and high-density lipoprotein cholesterol from baseline to month 3 were found in the tofacitinib groups. A total of 3.9% of patients in the 5-mg b.i.d. tofacitinib group, 6.5% in the 10-mg b.i.d. tofacitinib group, 0.93% in the placebo group and 0.1% in the adalimumab group had LDL cholesterol levels below 100 mg/dl at baseline increasing to 130 mg/dl or higher at month 3. Less than 2% of tofacitinib-treated patients had more than a threefold increase in the normal range of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. There was a small mean increase from baseline in serum creatinine level that was similar across all treatment groups.

ORAL Solo results

A total of 555 out of 611 randomized patients completed the 6-month study. Two of the primary efficacy end points assessed at month 3 (ACR20 response rate and mean change from baseline in HAQ-DI) were significantly greater for both doses of tofacitinib than placebo (TABLE 3). The percentage of patients with remission at month 3, defined by DAS28–4-ESR, was not significantly different between groups (TABLE 3). At month 3, the rate of patients with low disease activity, defined by DAS28–4-ESR, and mean changes from baseline in DAS28–4-ESR for both tofacitinib doses were significantly greater than placebo (TABLE 3). As early as week 2, significantly greater rates of ACR20 and ACR70 response were seen for tofacitinib 5 mg versus placebo, and ACR20, ACR50 and ACR70 responses were seen for tofacitinib 10 mg compared with placebo ($p < 0.001$, $p = 0.002$ and $p < 0.001$, respectively) [25]. *Post hoc* subgroup analysis did not find differences in ACR20 responses in seropositive and seronegative patients. Subgroup analysis in patients with an IR to biologic DMARDs found significant differences in the percentage of patients achieving ACR20 response at month 3 in the 10-mg tofacitinib group compared with placebo (42.9% in 5 mg of tofacitinib b.i.d., 62.5% in 10 mg of tofacitinib b.i.d. and 17.7% in placebo [$p = 0.06$ and $p < 0.001$ for respective comparisons with placebo]). The most common AEs were upper respiratory tract infection and headache. SAEs and serious infections were more frequent in patients treated with tofacitinib compared with placebo. One patient in the 10-mg tofacitinib b.i.d. group had tuberculous pleural effusion. The patient had no past history of tuberculosis or exposure to tuberculosis. The QuantiFERON-TB test result was indeterminate and the tuberculin skin test was negative. One case of disseminated herpes zoster was reported. Patients in tofacitinib-treated groups presented neutropenia more frequently than patients on placebo, but neutropenic patients did not have a higher rate of serious infection. The mean LDL cholesterol levels increased in months 0–3 by 3.5% with placebo, as compared with 13.6% with the 5-mg dose of tofacitinib and 19.1% with the 10-mg dose. Less than 1% of tofacitinib-treated patients had ALT or AST levels threefold higher than the normal range. Compared with baseline, three patients treated with tofacitinib had an increase in serum creatinine levels of 50% or more, but all levels remained within the normal range.

ORAL Step results

A total of 311 out of 399 TNF antagonist-IR randomized patients receiving background MTX completed the 6-month study. The TNF antagonist was discontinued before inclusion due to lack of efficacy, intolerance or both in 65.2,

Table 3. Results from ORAL Standard, ORAL Solo, ORAL Step and ORAL Scan trials.

Study	Efficacy (%)	Safety (%)	Ref.
ORAL Standard	ACR20 5 mg b.i.d. M6, 51.5*	AE 5 mg b.i.d. M0–3, 52.0	[26]
	ACR20 10 mg b.i.d. M6, 52.6*	AE 10 mg b.i.d. M0–3, 46.8	
	ACR20 ADA Q2W M6, 47.2*	AE ADA Q2D M0–3, 51.5	
	ACR20 placebo M6, 28.3	AE placebo M0–3, 47.2	
	HAQ-DI 5 mg b.i.d. M3, -0.6†*	AE 5 mg b.i.d. M3–6, 32.8	
	HAQ-DI 10 mg b.i.d. M3, -0.6†*	AE 10 mg b.i.d. M3–6, 30.8	
	HAQ-DI ADA Q2W M3, -0.5†*	AE ADA Q2D M3–24, 33.3	
	HAQ-DI placebo M3, -0.2†	AE placebo M3–6, 27.1	
	DAS28-ESR <2.6 5 mg b.i.d. M6, 6.2*	SAE 5 mg b.i.d. M0–3, 5.9	
	DAS28-ESR <2.6 10 mg b.i.d. M6, 12.5*	SAE 10 mg b.i.d. M0–3, 5.0	
	DAS28-ESR <2.6 ADA Q2W M6, 6.7*	SAE ADA Q2D M0–3, 2.5	
	DAS28-ESR <2.6 placebo M6, 1.1	SAE placebo M0–3, 1.9	
		SAE 5 mg b.i.d. M3–6, 4.9	
		SAE 10 mg b.i.d. M3–6, 3.5	
		SAE ADA Q2W M3–24, 2.9	
		SAE placebo M3–6, 3.4	
ORAL Solo	ACR20 5 mg b.i.d. M3, 59.8*	AE 5 mg M0–3, 51.0	[25]
	ACR20 10 mg b.i.d. M3, 65.7*	AE 10 mg M0–3, 56.7	
	ACR20 placebo M3, 26.7	AE placebo M0–3, 54.9	
	HAQ-DI 5 mg b.i.d. M3, -0.5†*	SAE 5 mg b.i.d. M0–3, 0.4	
	HAQ-DI 10 mg b.i.d. M3, -0.6†*	SAE 10 mg b.i.d. M0–3, 2.0	
	HAQ-DI placebo M3, -0.2†	SAE placebo M0–3, 4.9	
	DAS28-ESR <2.6 5 mg b.i.d. M3, 5.6	AE 5 mg M3–6, 39.9	
	DAS28-ESR <2.6 10 mg b.i.d. M3, 8.7	AE 10 mg M3–6, 41.2	
	DAS28-ESR <2.6 placebo M3, 4.4	AE placebo (5 mg) M3–6, 36.1	
		AE placebo (10 mg) M3–6, 39.3	
		SAE 5 mg b.i.d. M3–6, 2.1	
		SAE 10 mg b.i.d. M3–6, 2.4	
		SAE placebo (5 mg) M3–6, 1.6	
		SAE placebo (10 mg) M3–6, 0	
ORAL Step	ACR20 5 mg b.i.d. M3, 41.7*	AE 5 mg b.i.d. M0–3, 53.4	[18]
	ACR20 10 mg b.i.d. M3, 48.1*	AE 10 mg b.i.d. M0–3, 56.7	
	ACR20 placebo M3, 24.4	AE placebo M0–3, 56.8	
	HAQ-DI 5 mg b.i.d. M3, -0.4†*	AE 5 mg b.i.d. M3–6, 42.9	
	HAQ-DI 10 mg b.i.d. M3, -0.5†*	AE 10 mg b.i.d. M3–6, 43.3	
	HAQ-DI placebo M3, -0.2†	AE placebo M3–6, NA	
	DAS28-ESR <2.6 5 mg b.i.d. M3, 6.7*	SAE 5 mg b.i.d. M0–3, 1.5	
	DAS28-ESR <2.6 10 mg b.i.d. M3, 8.8*	SAE 10 mg b.i.d. M0–3, 1.5	

†*Mean change from baseline.*
**p < 0.05 vs placebo.*
ADA: Adalimumab; AE: Adverse event; b.i.d.: Twice daily; DAS: Disease Activity Score; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; M: Month; NA: Not applicable; Q2W: Every 2 weeks; SAE: Serious adverse event; SHS: Modified Sharp/van der Heijde score.

Table 3. Results from ORAL Standard, ORAL Solo, ORAL Step and ORAL Scan trials (cont.).

Study	Efficacy (%)	Safety (%)	Ref.
ORAL Step (cont.)	DAS28-ESR <2.6 placebo M3, 1.7	SAE placebo M0–3, 4.5	[18]
		SAE 5 mg b.i.d. M3–6, 3.8	
		SAE 10 mg b.i.d. M3–6, 4.5	
		SAE placebo M3–6, NA	
ORAL Scan	ACR20 5 mg b.i.d. M6, 51.5*	AE 5 mg b.i.d. M0–3, 48.9	[26]
	ACR20 10 mg b.i.d. M6, 61.8*	AE 10 mg b.i.d. M0–32, 54.1	
	ACR20 placebo M6, 25.3	AE placebo M0–3, 45.6	
	SHS 5 mg b.i.d. M6, 0.1†	AE 5 mg b.i.d. M3–6, 45.2	
	SHS 10 mg b.i.d. M6, 0.1†*	AE 10 mg b.i.d. M3–6, 35.1	
	SHS placebo M6, 0.5†	AE placebo M3–6, 25.9	
	HAQ-DI 5 mg b.i.d. M3, -0.4†	AE 5 mg b.i.d. M6–12, 51.7	
	HAQ-DI 10 mg b.i.d. M3, -0.5†*	AE 10 mg b.i.d. M6–12, 55.1	
	HAQ-DI placebo M3, -0.2†	AE placebo M6–12, NA	
	DAS28-ESR <2.6 5 mg b.i.d. M6, 7.2	SAE 5 mg b.i.d. M0–3, 3.7	
	DAS28-ESR <2.6 10 mg b.i.d. M6, 18.3*	SAE 10 mg b.i.d. M0–3, 3.2	
	DAS28-ESR <2.6 placebo M6, 1.6	SAE placebo M0–3, 3.1	
		SAE 5 mg b.i.d. M3–6, 5.3	
		SAE 10 mg b.i.d. M3–6, 2.2	
		SAE placebo M3–6, 6.2	
		SAE 5 mg b.i.d. M6–12, 4.0	
		SAE 10 mg b.i.d. M6–12, 2.8	
		SAE placebo M6–12, NA	

†*Mean change from baseline.*
**p < 0.05 vs placebo.*
ADA: Adalimumab; AE: Adverse event; b.i.d.: Twice daily; DAS: Disease Activity Score; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; M: Month; NA: Not applicable; Q2W: Every 2 weeks; SAE: Serious adverse event; SHS: Modified Sharp/van der Heijde score.

13.8 and 19.5% of patients, respectively. All three primary efficacy end points were met at month 3 for both doses of tofacitinib (Table 3). At month 3, rates of patients that achieved ACR50, ACR70, ACR/The European League Against Rheumatism Boolean-based remission criteria and remission defined by a simplified disease activity index were significantly higher in tofacitinib-treated patients than placebo. Significant differences were seen at week 2 in ACR20 and ACR50 response rates, and at week 4 in ACR70 response rates. Responses were sustained for the duration of the study. From baseline to month 3, the most frequent AEs in tofacitinib-treated patients were diarrhea, nasopharyngitis, headache and urinary tract infection. Rates of SAEs are shown in Table 3. Serious infectious AEs were only reported after month 3. One patient in the 10-mg tofacitinib group, who switched from placebo, died from pulmonary embolism. No tuberculosis infections were reported. Tofacitinib-treated patients had a greater decrease in neutrophil counts. A total of 7% of patients in the placebo group, 10.9% in the 5-mg b.i.d. tofacitinib group and 10% in the 10-mg b.i.d. tofacitinib group had LDL cholesterol levels below 2.59 mmol/l at baseline increasing to 3.7 mmol/l or higher at month 3. Elevations in ALT and AST levels that were more than threefold the normal limit were seen in <2% of patients. Mean changes from baseline in serum creatinine level were small and similar across all treatment groups.

ORAL Scan results

Overall, 797 patients were randomized. The rate of ACR20 response at month 3 for both doses of tofacitinib was significantly higher compared with placebo. The least squares mean changes in

total SHS at month 6 were higher in tofacitinib-treated patients than placebo, although they were only significant for the 10-mg b.i.d. dose. The least squares mean changes in the HAQ-DI score at month 3 and percentages of remission, defined as DAS28–4-ESR <2.6, at month 6 for the 10-mg tofacitinib dose were higher than placebo. Significance was not declared for the HAQ-DI score change and rate of patients achieving DAS28–4-ESR <2.6 for tofacitinib 5 mg b.i.d., owing to the step-down procedure applied for the primary efficacy end points (Table 3). Significantly higher rates of ACR20, ACR50 and ACR70 responses compared with placebo were seen for each tofacitinib dose at month 1. The proportion of patients with no progression in erosion score at month 12 was significantly higher in both tofacitinib treated groups compared with placebo, but not at month 6. Further statistical analyses, including SHS nonprogression data, can be found in the paper by van der Heijde *et al.* [27].

The most common AEs in all patients were infections and infestations, gastrointestinal disorders and abnormalities in laboratory measurements leading to investigations. The incidence of SAEs was similar in all treatment groups. There were seven opportunistic infections, including one lymph node tuberculosis. No patient was withdrawn owing to neutropenia. A total of 12.5% of patients in the 5-mg tofacitinib group, 18% in the 10-mg tofacitinib group and 1.7% in the placebo group had LDL cholesterol levels below 100 mg/dl at baseline increasing to 130 mg/dl or higher by month 3. Elevations in ALT or AST levels threefold higher than the upper limit of the normal range were rare. Five patients treated with tofacitinib had an increase in serum creatinine levels of 50% or more from baseline, but none of these patients had renal failure. There were six deaths; four in the tofacitinib 5-mg group, one in the tofacitinib 10-mg group and one in the placebo group.

Discussion

This clinical trial report shows that tofacitinib is effective in the control of signs and symptoms of RA across different populations of patients. In addition, tofacitinib improves function and halts the progression of radiographic joint damage [27]. For RA, the currently approved dose of tofacitinib by the FDA is 5 mg b.i.d.. The pooled analysis comparing 5- and 10-mg b.i.d. doses of tofacitinib from Phase III and LTE studies showed a greater likelihood of meeting the more stringent efficacy outcomes with 10-mg doses compared with with 5-mg doses [32]. However, this efficacy profile should be balanced against the different rates of dose-related AEs. Pooled analysis of the 5-and 10-mg b.i.d. tofacitinib doses demonstrated differences in safety, favoring 5 mg b.i.d. for serious infections in LTE studies but not in Phase III studies [32]. Overall, responses to tofacitinib did not appear to be different from the biologics used for the treatment of this condition [33]. However, the imputation of no response with advancement penalty analysis in ORAL trials of 12 months or greater duration makes it difficult to make comparisons with other trials. Although the ORAL Standard study design did not allow for formal comparison with adalimumab [19,26], numerically, tofacitinib efficacy did not differ from adalimumab. Tofacitinib presents unique characteristics that are worth commenting upon. Significant clinical responses occuring as early as 2 weeks were reported in ORAL Step with tofacitinib plus MTX [25], and at week 4 in ORAL Standard and ORAL Scan. Furthermore, tofacitinib monotherapy was effective in the control of signs and symptoms, and improving function in the severe biologic-IR patient population. ORAL Scan demonstrates that tofacitinib prevents the progression of radiographic joint damage [27]. In patients treated with traditional DMARDs, radiographic progression is not directly associated with improved clinical outcomes. On the contrary, in patients treated with biologics there is a dissociation between clinical and radiologic outcomes. This has to be carefully examined in patients treated with tofacitinib. ORAL Scan preliminary results at month 12 showed a significantly lower change from baseline in SHS in patients treated with 10 mg of tofacitinib in combination with MTX compared with placebo at month 6 [34]. Reported results at 2 years showed sustained inhibition of structural damage [35]. In a *post hoc* analysis of patients with a higher risk of radiographic progression, tofacitinib demonstrated inhibition of progression compared with placebo [36]. The ongoing ORAL Start study also includes radiographic outcomes, and it will show whether this radiographic efficacy is different from MTX in MTX-naive patients [37]. Safety is a major concern with innovative medicines. A meta-analysis of malignancies, serious infectious AEs and SAE rates in RA clinical trials did not show differences when comparing tofacitinib and biologics [38]. Nevertheless, serious infections are relevant [31]. A pooled analysis showed a lack of association between the occurrence of low

neutrophil counts in tofacitinib-treated patients and the rate of infections in the Phase III and LTE studies [102]. A total of 12 patients developed active tuberculosis, which occurred more frequently in patients receiving the higher doses of tofacitinib in tuberculosis-endemic regions. However, none of the patients with latent tuberculosis treated with isoniazid developed active tuberculosis [39]. This emphasized the need for careful evaluation and management of latent tuberculosis before starting tofacitinib. In addition, 239 patients treated with tofacitinib experienced herpes zoster in 5651 patient-years of exposure. Rates of herpes zoster were higher in tofacitinib-treated patients compared with placebo, although complicated herpes zoster was rare [40]. One case of herpes zoster was multidermatomal but no patients had visceral dissemination. Sixteen patients were hospitalized or received intravenous antiviral drugs. Rates of herpes zoster were similar with tofacitinib 5- and 10-mg b.i.d. doses. Lung cancer followed by breast cancer were the most common malignancies (excluding non-melanoma skin cancer) in the clinical trials with tofacitinib. Lymphoma was diagnosed in three patients. An integrated pooled analysis showed an IR of malignancies similar to published rates in RA patients treated with biologic and nonbiologic DMARDs [41]. The IR calculated for non-melanoma skin cancer was 0.37 (95% CI: 0.24–0.57), similar to patients treated with anti-TNF (0.47 [95% CI: 0.37–0.59]) [42].

Dose-dependent increase in LDL cholesterol levels and reduction in neutrophil counts were associated with tofacitinib treatment. Neutropenia could be due to the inhibition of granulocyte–macrophage colony-stimulating factor signaling via JAK2. Hypercholesterolemia has been proposed to occur as a result of inhibition of IL-6-dependent JAK1/2 signaling. Hypercholesterolemia occurs as a result of IL-6 receptor inhibition caused by tocilizumab. The effect of hypercholesterolemia in cardiovascular risk needs long-term evaluation [43]. Recommendations for the management of major AEs include the diagnosis and treatment of latent tuberculosis, caution in patients who have an increased risk of gastrointestinal perforation [44], and monitoring of laboratory parameters including lipids, hemoglobin, leukocytes, hepatic enzymes and renal function. With respect to pharmacologic interactions, combination therapy with MTX appears to be safe. Nevertheless, tofacitinib exposure is increased when it is coadministered with moderate CYP3A4 and potent CYP2C19 inhibitors, and exposure is decreased when it is coadministered with potent CYP3A4 inductors.

Conclusion

Tofacitinib is the first protein kinase inhibitor approved for RA. Results from Phase III trials show that 5 and 10 mg of tofacitinib b.i.d. in monotherapy or combined with MTX are significantly better than placebo in the reduction of signs and symptoms, improving function, structure preservation and preventing progression of radiographic joint damage. Efficacy is rapid and sustained in different populations of patients. Rates of serious infections do not differ from published rates for biologics. Rates of herpes zoster are increased in tofacitinib-treated patients compared with biologic and nonbiologic DMARDs. However, cases of serious herpes zoster were rare. Increase in cholesterol levels compared with baseline values and decrease in neutrophil counts are associated with tofacitinib. However, the dose-dependent mean decreases in neutrophils were similar with tofacitinib and adalimumab in the ORAL Standard study. Dose-related AEs may limit up-titration of tofacitinib in patients not responding to lower doses. Long-term safety is the main challenge for this new class of small molecules.

Future perspective

Information on safety and efficacy of tofacitinib from clinical trials is already available, but clinical trials are different from clinical practice and the decision on what type of patient should be treated with this drug is still open for debate. The long-term safety and the place of tofacitinib for the treatment of RA are among the several unanswered question regarding the use of this drug. JAK inhibitors other than tofacitinib are in development for the treatment of RA; interestingly, they have different main targets. Tofacitinib has functional selectivity for JAK1 and JAK3 over JAK2, baricitinib inhibits JAK1 and JAK2, ASP015K inhibits JAK1 and JAK3, GLPG-0634 inhibits JAK1, and VX–509 inhibits JAK3. Whether this has an impact on the efficacy and safety profiles of this new class of drugs will require further studies. Currently, clinical trials with tofacitinib for other inflammatory conditions, such as psoriasis and inflammatory bowel disease, are underway. They will ultimately demonstrate the role of tofacitinib in the treatment of immune-mediated chronic inflammatory diseases.

Financial & competing interests disclosure

JJ Gomez-Reino is on the Advisory Boards at and has received lecture fees and expert advice fees from Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Tofacitinib is the first protein kinase inhibitor approved for the treatment of a chronic inflammatory disease.
- Tofacitinib is an inhibitor of the Janus kinase (JAK) family that preferentially inhibits JAK3/JAK1 over JAK2 signaling.
- A Phase II proof-of-concept trial of tofacitinib monotherapy in rheumatoid arthritis (RA) showed significant efficacy at week 6 in comparison with placebo. Phase II dose-ranging trials of tofacitinib demonstrated that doses of 5 and 10 mg twice daily are efficacious and well tolerated for the treatment of RA.
- The ORAL clinical program involves six Phase III trials with tofacitinib as monotherapy, in combination with background methotrexate (MTX), and with other nonbiologic background disease-modifying antirheumatic drugs not including MTX. Full reports have been published for ORAL Standard, ORAL Solo, ORAL Step and ORAL Scan trials.
- ORAL Solo is a placebo-controlled trial of tofacitinib monotherapy in RA patients with an inadequate response (IR) to biologic or nonbiologic disease-modifying antirheumatic drugs. ORAL Solo showed significant clinical response and improvement in physical function at month 3 (primary end point).
- ORAL Standard is a placebo- and adalimumab-controlled trial of tofacitinib plus MTX in RA patients with an IR to MTX. ORAL Standard showed significant clinical response at month 6 and improvement in physical function at month 3 (primary end points).
- ORAL Step is a placebo-controlled trial of tofacitinib plus MTX in RA patients with an an IR to TNF antagonists. ORAL Step demonstrated an early and meaningful improvement in clinical response and physical function at month 3 (primary end point) that was sustained for 6 months.
- ORAL Scan is a placebo-controlled trial of tofacitinib plus MTX in RA patients with an IR to MTX. ORAL Scan demonstrated, and ORAL Start confirmed, that tofacitinib inhibits radiographic progression of structural damage, and provides significant clinical response at month 6 and improvement in physical function at month 3 (primary end points).
- Overall, rates of serious infections with tofacitinib are not different from the biologics used for the treatment of RA. Tofacitinib is associated with increased cholesterol levels over baseline and reduction in neutrophil counts.

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