CLINICAL INVESTIGATION

Review of tofacitinib in rheumatoid arthritis

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Lymphocytes play a central role in the pathogenesis of rheumatoid arthritis (RA) by releasing proinflammatory cytokines. JAK enzymes are cytoplasmic tyrosine kinases that modulate intracellular signaling transduction of the lymphocytes. JAK enzymes (JAK1, JAK2, JAK3 and TYK2) activate the signaling for gene transcription of proinflammatory cytokines, leading to joint inflammation and destruction. Tofacitinib is the first JAK inhibitor used for active RA. Its pharmacological characteristics, efficacy and safety are discussed in this review. Evidence from 11 controlled trials suggests that tofacitinib alone or combined with methotrexate is effective in patients with active disease who had failed or are intolerant to other RA therapies. Serious adverse events reported in the literature included serious infections and malignancies.

Keywords: CP-690550 • DMARD • janus kinase (JAK) inhibitor • rheumatoid arthritis • tasocitinib • tofacitinib • small-molecule

Approximately 9 million medical consultations and 250,000 hospitalizations per year in the USA are attributed to rheumatoid arthritis (RA) and its complications, leading to a great socioeconomic burden with a loss of US$17.6 billion in salaries and 2.5% of permanent disabilities per year [1,2].

Early RA diagnosis and treatment increases the probability of controlling the inflammatory process, slowing the disease progression, and improving the functional status and quality of life of the patients. Diseases modifying anti-rheumatic drugs (DMARDs) are the mainstream therapy for RA. Numerous DMARDs, both traditional and biologic, are currently available and have proven to be effective. Of the traditional group, methotrexate has proven to be more efficacious than other monotherapies [3–5].

For patients with inadequate response to traditional DMARDs, the newer biologic agents targeting proinflammatory cytokines (i.e., TNF-α, IL-1 and IL-6), B cells (CD20), or T-cell activation co-stimulatory signal (CTLA-4) can be used either alone or in combination with methotrexate. These agents have been shown to reduce the burden of synovitis, slow radiological disease progression and improve quality of life [6,7]. The currently available biologic agents in the USA are abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab.

Tofacitinib (CP-690,550) is the first oral small-molecule inhibitor that belongs to a novel class of drugs called JAK inhibitors; it is approved in the USA and many other countries (except EU) to treat adults with moderately to severely active RA who have had an inadequate response or intolerance to one or more DMARDs.

Tofacitinib, a JAK inhibitor

JAK are a family of intracellular, non-receptor tyrosine kinases (enzymes primarily expressed in hematopoietic and immunologic cell lineages that can transfer a phosphate group from ATP to a protein in a cell) that transduce cytokine-mediated signals via the JAK-STAT pathway [8]. This pathway transmits stimulation from chemical signals outside the cell, through the cell membrane, and onto gene

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promoters on the DNA in the cell nucleus, which causes DNA transcription and activity in the cell. The JAK-STAT system is a major signaling alternative to the second messenger system [9]. The JAK family includes four tyrosine kinases: JAK1, JAK2, JAK3 and TYK2. While JAK3 is primarily expressed in hematopoietic lineages, the others are universally expressed. JAK was shown to control signaling by IL-2, a key growth factor for T lymphocytes. Certain diseases can occur from changes in signaling of one of those tyrosine kinases, one example being the resulting myeloproliferative malignancies or certain leukemias after alterations of the JAK2 gene.

In 2003, tofacitinib (formerly known as tasocitinib, CP-690,550) was first introduced as an inhibitor of JAK 3 that could be used for prevention of organ allograft rejection [10,11]. Recent evidence suggests that tofacitinib also inhibits JAK1, JAK2 and TYK2, with less specificity for JAK2 and TYK2 [10,12–14].

Based on this, the effects of tofacitinib have been evaluated in different animal models (including inflammatory arthritis) and in patients with psoriasis, inflammatory bowel disease, dry eye disease and RA [15–27]. Ongoing clinical trials are being conducted to evaluate its efficacy and safety on ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis and ulcerative colitis [18,28,29].

For this review we searched MEDLINE, PubMed, clinical trials.gov and the abstract repository websites of the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR). We included terms related to 'RA', 'tofacitinib' and/or 'controlled trials'. From 488 potentially relevant citations, we found and summarize evidence from 11 randomized controlled trials (RCTs), and two long-term extension (LTE) studies.

Chemistry

Systematic name or chemical nomenclature according to the International Union of Pure Applied Chemistry is 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile. The drug substance tofacitinib citrate (CP-690,550-10) is highly soluble, not photosensitive, and has low permeability. The molecular formula is $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ (citrate salt) with a molecular weight of 504.50 g/mol (312.37 g/mol for free base). Tofacitinib tablets are packaged in 56, 60 and 180 tablets count. Two strengths are available (5 or 10 mg); each 5 mg tablet contains 8 mg tofacitinib citrate equivalent to 5 mg tofacitinib (dosage dependent on country-specific approval). The drug substance is manufactured by Pfizer Pharmaceuticals. The proposed shelf life for the drug product is 24 months when stored at 20–25°C [30].

Pharmacodynamics

The vital roles of JAK signaling have been shown in *in vitro* studies or mouse models with these kinases mutated or deleted.

In vitro studies

The inhibitory mechanisms of tofacitinib to both the innate and adaptive immune response in immune cells and in RA were studied using *in vitro* synovial macrophages, isolated murine and human T cells and several murine models of arthritis [12,31]. JAK inhibition by tofacitinib blocks signaling through the type I cytokine receptors containing the common γ chain for many cytokines, including IL-2, -4, -7, -9, -15 and -21, and through receptors for cytokines such as IL-6, IFN-γ and type 1 IFN [12,32]. A study in synovial macrophages isolated from RA patients reported significant decrease of IL-6 expression with tofacitinib [31]. Other studies have shown: disruption of γ-c cytokine signaling in CD4+ Th cells leading to inhibition of IL-4–dependent Th2 cell differentiation, interference with Th17 cell differentiation, blockage of the expression of IL-23 receptor and Th17 cytokines (IL-17A, IL-17F, IL-22) when naive T cells are stimulated with IL-6 and IL-23, and prevention of the activation of STAT1 and the differentiation of Th1 cells [12,33–35]. Also, tofacitinib partially blocks IL-12–driven phosphorylation of STAT4, suggesting a lower inhibitory efficacy of tofacitinib on TYK2 signaling than to other JAK signaling pathways [33–35]. TYK2 plays a restricted role in IFN-α signaling and is required for IL-12-mediated T-cell function through the activation of STAT4 [36]. In addition, tofacitinib has also shown inhibitory activity of the melatonin 3 receptor, VEGFR, CDPK-2 and LYN A kinase (Ki 2.3 μM) [37].

In vivo studies

In the murine model of K/BxN serum-induced arthritis, driven by the innate immunity and inflammatory cytokines such as IL-1β and TNF, tofacibinib significantly suppresses the arthritis symptoms and histologic changes, suggesting its effect through the innate immune mechanism [15]. Its efficacy in this disease model correlated with the specific inhibition of both JAK1 and JAK3 signaling pathways. Tofacitinib also modulates innate responses to lipopolysaccharide through a mechanism likely involving the inhibition of STAT1 signaling [11,12,15,35]. Other studies have found that inhibition of JAK can result in embryonic lethality, immunodeficiency, or impaired immune cell signaling and development [12,38,39]. Mice with germline deletion of JAK1 are perinatally lethal due to impaired lymphopoisis [40]. JAK2 knockout mice are embryonically lethal due to the lack of definitive erythropoi-

esis [41]. Mutation or depletion of JAK3 or TYK2 in humans and mice results in immunodeficiency and infections [42,43].

Carcinogenicity studies

In animals who recieved tofacitinib, the neoplastic findings observed were: benign angiomas, lipomas in the skin, interstitial cell adenomas in testis and pancreatic islet cell adenoma; and carcinoma in male rats and benign thymomas in thymus, uterine and cervical tumors (endometrial stromal polyps of the cervix) and malignant hibernomas in female rats. Lymphoma was observed in three monkeys who received higher dose (10 mg/kg/day). In addition, seroconversion for lymphocryptovirus was reported in mice, rats and monkeys. Furthermore, an increased risk of mortality in male rats was attributed to bacterial infections at the dose of 75 mg/kg/day and in females at the dose of 100 mg/kg/day between weeks 15 and 102 [37]. The reported developmental and reproductive toxicity in rats for tofacitinib (doses 10–100 times higher than those given to humans) was external, skeletal and visceral malformations in rabbits and external and skeletal malformations in rats. A natal study in rats showed reduced pup viability and weight gain. Thus, the drug is labeled as pregnancy category C. For genotoxicity, chromosomal aberrations were observed in an *in vitro* cytogenetic study in peripheral human lymphocytes.

Pharmacokinetics

The metabolic profile, routes of excretion and pharmacokinetics were evaluated in six healthy male subjects (ages between 18 and 55 years) [37]. After an oral administration of a single dose of 50 mg, plasma concentrations for both CP-690,550 and total drug radioactivity peaked at <2 h. The maximum concentration (C_{max}) values that tofacitinib achieved after the first dose administrated ranged from 331 to 480 ng/ml with a mean value of 397 ng/ml [37]. The area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) values for the parent drug ranged from 977 to 2060 ng·h/ml with a mean value of 1680 ng·h/ml. The mean terminal phase half-life ($T_{1/2}$) was estimated to be 3.2 h. Other parameters reported include: bioavailability 74%, protein binding 40% (binds predominantly to albumin) and 70% hepatic metabolism via CYP3A4 and CyP2C19. Volume of distribution after intravenous administration was 87 l. Approximately 95% of the administered dose was eliminated within 24 h, 30% through renal excretion [37]. Tofacitinib interactions include: increased exposure when co-administered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole); increased exposure when coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole); and decreased exposure when co-administered with potent CYP3A4 inducers (e.g., rifampin) [37]. Regarding general toxicology, side effects include suppression of the immune and hematopoietic systems (suppression of myeloid and erythroid bone marrow production), reduced or atrophied lymphoid organs and reductions in circulating red and white blood cells. In patients with moderate to severe renal or hepatic impairment, dose needs to be reduced to 5 mg once daily [37].

Clinical efficacy

Here we review data from 11 RCTs, five Phase II [25–27,44,45] of 3–6 months durations and six Phase III [20–24,46,47] of 6–12 months durations, with a total of 1612 and 4271 participants, respectively (Tables 1 & 2). All studies included adult patients with a diagnosis of RA based on the 1987 revised criteria established by the ACR. Most were multicenter studies and all were fully supported by Pfizer Pharmaceutical. Nine of the studies included patients who have previously failed both biologic and traditional DMARDs, one included patients who only failed traditional DMARDs [26], and one included patients who had not previously received methotrexate or therapeutic doses of methotrexate [46,47]. Four studies provided data on tofacitinib monotherapy [24,26,44,45] and the remaining permitted methotrexate at stable doses or other DMARDs as background [20–23,25], one study did not report sufficient details on concomitant therapies [47]. Tofacitinib doses used were 1 mg to 30 mg twice daily in Phase II studies and 5 mg or 10 mg twice daily in Phase III studies. Outcome measures in all trials included the ACR 20, 50 and 70 response core sets including the Disability Index of the Health Assessment Questionnaire (HAQ-DI) and the EULAR response based on the disease activity score (DAS) among others, with the ACR 20 response as primary endpoint in most. Only two studies reported on radiographic progressions and all reported safety outcomes including withdrawals and adverse events.

In this review we summarize the results of four outcomes: ACR 50, DAS28 score results (as mean change from baseline or percent of patients achieving disease remission DAS <2.6), radiographic progression measured by the total Sharp score and disability index measured by the HAQ (Tables 3 & 4). We have chosen to report on the ACR 50 response rate because it is a more clinically meaningful threshold for patients compared to ACR 20 [48]. The lower sensitivity of the ACR 50 to identify some control patients with a response to treatment is compensated by the other outcome measures we reported on [49,50].

Table 1. Trial characteristics: Phase II studies.

Study/year	Setting					Comparison		Funding	Outcomes		
	Sites	Location	Age range (yrs)	DD (yrs)	Groups	Active groups	Control		Primary	Secondary	Ref.
Kremer 2009 (NCT00147498)	60	USA, Canada, Brazil, Mexico, Austria, Spain, Germany, Italy, Belgium, Norway and Slovakia	47.9–51.8	8.7–10.2	4	Tofacitinib + PDN	PBO + PDN	Pfizer	ACR 20 at week 6	ACR 50, 70, DAS28, HAQ DI, safety, pharmacokinetics	[44]
Kremer 2012, A3921025 (NCT00413660)	72	USA, Europe and Latin America	51–56	7.5–11.8	7	Tofacitinib + MTX	PBO + MTX	Pfizer	ACR 20 at week 12	ACR 50, 70, DAS28, HAQ DI, SF-36, FACIT-F, safety	[25]
Fleischmann 2012, A3921035 (NCT00550446)	63	USA, Europe, Latin America, Republic of Korea	52–55	7.7–10.8	5	Tofacitinib + MTX	PBO + MTX	Pfizer	ACR 20 at week 12	ACR 50, 70, DAS28, HAQ DI, safety	[26]
Tanaka 2011, A3921039 (NCT00603512)	19	Japan	50–53.3	5.7–8.7	6	Tofacitinib + PDN	PBO + PDN	Pfizer	ACR 20 at week 12	ACR 50, 70, DAS28, HAQ DI, SF-36, safety	[27]
Tanaka 2011, A3921040 (NCT00687193)	NR	Japan	52.6–54.7	6.4–11.0	7	Tofacitinib + HCQ/PDN; ADA + HCQ/PDN	PBO + HCQ/PDN	Pfizer	ACR 20 at week 12	ACR 50, 70, DAS28, HAQ DI, safety	[45]

ACR 20, 50, 70: American College of Rheumatology improvement criteria – 20, 50, 70% response rates; ADA: Adalimumab; DD: Disease duration; DAS28: Disease activity score in 28 joints; FACIT-F: The Functional Assessment of Chronic Illness Therapy-Fatigue Subscale; HAQ DI: Health Assessment Questionnaire disability index; HCQ: Hydroxychloroquine; MTX: Methotrexate; NR: Not reported; PBO: Placebo; PDN: Prednisone; SF-36: The Short Form 36 health survey.

Table 2. Trial characteristics: Phase III studies.

Study/year	Setting					Comparison			Outcomes		
	Sites	Location	Age range (yrs)	DD (yrs)	Groups	Active groups	Control	Funding	Primary	Secondary	Ref.
Burmester 2011 (ORAL-Step; NCT00960440)	82	Australia, Taiwan, Republic of Korea, Europe, USA, Canada, Brazil	54.3–55.4	11.3–13	3	Tofacitinib + MTX	PBO + MTX	Pfizer	ACR 20, HAQ DI, DAS28 at 12 weeks	ACR 50, 70, SDAI, FACIT-F, safety†	[22]
Fleischmann 2012 (ORAL-Solo; NCT00814307)	94	USA, Latin America, Europe, Asia	49.7–52.4	7.7–8.6	3	Tofacitinib + HCQ/ PDN	PBO + HCQ/PDN	Pfizer	ACR 20 at week 12	ACR 50, 70, DAS28, HAQ DI, FACIT-F, safety	[24]
Kremer 2013 (ORAL-Sync; NCT00856544)	NR	Australia, Asia, Latin America, Europe, USA	50.8–53.3	8.1–10.2	3	Tofacitinib + DMARDs	PBO + MTX	Pfizer	HAQ DI at 12 weeks, ACR 20, and DAS28 at 24 weeks	ACR 20, 50, 70, FACIT-F, safety	[20]
Lee 2012 (ORAL-Start; NCT01039688)‡	151	North America, Latin America, Europe, Asia, Australia	48.8–50.3	2.7–3.4	3	Tofacitinib	MTX	Pfizer	ACR 70 and radiographic at 24 weeks	ACR 20, 50, DAS28, HAQ DI, safety	[46,47]
Van der Heijde 2013, Phase III, A3921044 (ORAL-Scan; NCT00847613)‡	111	North America, South America, Europe, Asia, Australia	52–53.7	8.8–9.5	3	Tofacitinib + MTX	PBO + MTX	Pfizer	HAQ DI at 12 weeks, ACR 20, and radiographic at 24 weeks	ACR 50, 70, DAS28, HAQ DI, radiographic, safety	[21]
Van Vollenhoven 2012 (ORAL-Standard; NCT00853385)§	115	North America, South America, Asia, Australia, Europe, USA	51.9–55.5	6.9–9.0	4	Tofacitinib + MTX; ADA + MTX	PBO + MTX	Pfizer	HAQ DI at 12 weeks, ACR 20, and DAS28 at 24 weeks	ACR 50, 70, safety	[23]

†Additional outcomes included SF-36, MOS Sleep Scale, EuroQoL EQ-5D, RA Healthcare Resource Utilization Questionnaire and Work Limitations Questionnaire Safety assessments.
‡24-month study. Results are from interim analyses.
§Patients were excluded if current treatment was other than methotrexate or if they have failed to TNF-α inhibitors. All patients were adalimumab-naive.
ACR20, 50, 70: American College of Rheumatology improvement criteria – 20, 50, 70% response rates; ADA: Adalimumab; DD: Disease duration; DAS28: Disease activity score in 28 joints; DI: Disabilty index; FACIT-F: The functional assessment of chronic illness therapy-fatigue subscale; HAQ DI: Health Assessment Questionnaire disability index; HCQ: Hydroxychloroquine; MOS: Medical outcomes study; MTX: Methotrexate; NR: Not reported; PBO: Placebo; PDN: Prednisone; SDAI: Simplified disease activity index (criteria recommended by the American College of Rheumatology and the European League Against Rheumatism); SF-36: The Short Form 36 health survey.

ACR 50 improvement criteria.

In patients who failed biologic and traditional DMARDs, higher ACR 50 response rates were observed for tofacitinib monotherapy 3 mg (26.4%), 5 mg (31.1–46.2%), 10 mg (36.8–69.8%), 15 mg (52–72.2%) and 30 mg (38%) compared with placebo (7.7–12.5%) after 6-24 weeks [24,44,45]. Similarly, after 12–24 weeks, ACR 50 response rates were higher when tofacitinib

Table 3. Clinical efficacy: Phase II studies.

Study	Duration	Groups	n	ACR50	DAS28†	Radiographic progression (mTSS)	HAQ†	Ref.
Biologics (TNFi and/or non-TNFi) and DMARD failure#								
Kremer 2009, (NCT00147498)#	3 months (6 weeks treatment + 6 weeks follow-up	5 mg + PDN	61	32%	-2.0	NM	-0.6	[44]
		15 mg + PDN	69	52%	-2.3	NM	-0.7	
		30 mg + PDN	69	50%	-2.8	NM	-0.7	
		PBO + PDN	65	8%	-1.2	NM	-0.3	
Kremer 2012, A3921025 (NCT00413660)	6 months (24 weeks)	1 mg + MTX	71	28%	12.9%	NM	-0.3‡	[25]
		3 mg + MTX	68	26%	22%	NM	-0.5‡	
		5 mg + MTX	71	32%	31%	NM	-0.6	
		10 mg BID + MTX	74	36%	31%	NM	-0.5	
		15 mg + MTX	75	42%	29.3%	NM	-0.5	
		20 mg QD + MTX	80	38%	21.3%	NM	-0.5‡	
		PBO§ + MTX	69	22%	10.1%	NM	-0.4	
Tanaka 2011, A3921039 (NCT00603512)	3 months (12 weeks)	1 mg + MTX	28	32.1%	-1.8	NM	-0.4	[27]
		3 mg + MTX	27	44.4%	-1.9	NM	-0.4	
		5 mg + MTX	27	74.1%	-2.4	NM	-0.5	
		10 mg + MTX	26	46.2%	-2.7	NM	-0.6	
		PBO + MTX	28	10.7%	-0.7	NM	-0.1	
Tanaka 2011, A3921040 (NCT00687193)	3 months (12 weeks)	1 mg + PDN	51	13.2%	5.9%	NM	-0.2	[45]
		3 mg + PDN	49	26.4%	2.0%	NM	-0.4	
		5 mg + PDN	50	46.2%	16.0%	NM	-0.6	
		10 mg + PDN	49	69.8%	42.9%	NM	-0.7	
		15 mg + PDN	52	72.2%	40.4%	NM	-0.7	
		PBO + PDN	48	7.7%	2.1%	NM	0.2	

†Values are mean change (between baseline and end point) or percentage of patients achieving remission (DAS<2.6).
‡Assessment performed at 12 weeks.
§Placebo group at 12 weeks was switched to either 5 or 10 mg of tofacitinib.
¶Intolerant or inadequate response to methotrexate (and/or other DMARDs) and TNFi (and/or other biologic agents).
#Adalimumab was given for 12 weeks and then patients were switched to tofacitinib.
ACR 50: American College of Rheumatology improvement criteria 50% response rate; ADA: Adalimumab; BID: Twice a day; DAS28: Disease activity score in 28 joints (in most studies DAS was based on C-reactive protein (CRP) levels, except for Fleischmann 2012 [24,26], Tanaka 2011 [45], Kremer 2013 [20]); DMARDs: Disease modifying anti-rheumatic drugs; HAQ DI: Health Assessment Questionnaire (lower scores indicate less disability); HCQP: Hydroxychloroquine; mg: Milligrams; Mtss: Modified total sharp score (lower scores indicate no progression); MTX: Methotrexate; n: Number; NM: Not measured; PBO: Placebo; PDN: Prednisone; QD: Once a day; TNFi: Tumor necrosis factor alpha inhibitor.

Table 3. Clinical efficacy: Phase II studies (cont.).

Study	Duration	Groups	n	ACR50	DAS28†	Radiographic progression (mTSS)	HAQ†	Ref.
DMARD failure								
Fleischmann 2012, A3921035 (NCT00550446)	6 months (24-weeks)	1 mg + HCQ/PDN	54	7.4%	7.7%	NM	-0.3‡	[26]
		3 mg + HCQ/PDN	51	27.5%	5.9%	NM	-0.4‡	
		5 mg +HCQ/PDN	49	34.7%	12.5%	NM	-0.5‡	
		10 mg + HCQ/PDN	61	44.3%	14.8%	NM	-0.7‡	
		15 mg + HCQ/PDN	57	54.4%	19.3%	NM	-0.8‡	
		ADA¶ + HCQ/PDN	63	18.9%‡	3.9%	NM	-0.4‡	
		PBO§ + HCQ/PDN	59	10.2%	3.6%	NM	-0.3‡	

†Values are mean change (between baseline and end point) or percentage of patients achieving remission (DAS<2.6).
‡Assessment performed at 12 weeks.
§Placebo group at 12 weeks was switched to either 5 or 10 mg of tofacitinib.
¶Intolerant or inadequate response to methotrexate (and/or other DMARDs) and TNFi (and/or other biologic agents).
#Adalimumab was given for 12 weeks and then patients were switched to tofacitinib.
ACR 50: American College of Rheumatology improvement criteria 50% response rate; ADA: Adalimumab; BID: Twice a day; DAS28: Disease activity score in 28 joints (in most studies DAS was based on C-reactive protein (CRP) levels, except for Fleischmann 2012 [24,26], Tanaka 2011 [45], Kremer 2013 [20]); DMARDs: Disease modifying anti-rheumatic drugs; HAQ DI: Health Assessment Questionnaire (lower scores indicate less disability); HCQP: Hydroxychloroquine; mg: Milligrams; Mtss: Modified total sharp score (lower scores indicate no progression); MTX: Methotrexate; n: Number; NM: Not measured; PBO: Placebo; PDN: Prednisone; QD: Once a day; TNFi: Tumor necrosis factor alpha inhibitor.

was used in combination with methotrexate or other DMARDs versus control [20–23,25,27]. Only one study evaluated tofacitinib in methotrexate-naive patients or with prior of use of subtherapeutic methotrexate doses [46,47] and found higher ACR 50 response rates for tofacitinib 5 mg and 10 mg combined with methotrexate (46.6 and 56.2%, respectively) compared with methotrexate alone (27.2%). These ACR 50 response rates have been further analyzed in two meta-analyses [35,51]. One meta-analysis found that the risk ratio (RR) for tofacitinib (monotherapy or in combination therapy) versus control was 2.9 (95% CI 2.0–4.2) and 3.3 (95% CI 2.3–4.7) at 5mg and 10mg doses respectively [35]. The other meta-analysis studied tofacitinib 5 mg dose as monotherapy or in combination therapy separately and found RR versus control of 3.4 (95% CI 2.3–5.0) 2.8 (95% CI 1.8–4.5), respectively [51].

DAS 28

The reported mean change of DAS 28 score were similar to the above ACR 50 response rates, with benefits seen in most used doses of tofacitinib. This was true for both groups of tofacitinib alone (DAS reduction of 2.0–2.8) or in combination therapy (DAS reduction of 1.8–2.7) compared with control groups (DAS reduction of 1.2 and 0.7) [27,44]. The proportion of patients achieving disease remission (DAS 28 <2.6) was also higher for most tofacitinib doses in patients previously failed traditional DMARDs alone or in combination with biologics compared to control [20–26,45,46]. For methotrexate-naive patients or with prior subtherapeutic methotrexate doses usage, disease remission rates ranged between 14.6% and 21.6% for the tofacitinib 5 mg and 10 mg groups respectively compared with 7.6% for methotrexate at 24 weeks. In a meta-analysis, the pooled RR to achieve disease remission for tofacitinib monotherapy versus placebo was 3.0 (95% CI 1.5–6.0) and for tofacitinib plus DMARD versus DMARD was 4.7 (95% CI 2.0–11.1) [51].

The radiographic progression measured by the modified Total Sharp Score [52] was evaluated only in two Phase III trials [21,46], one for tofacitinib 5 mg or 10 mg as monotherapy versus methotrexate in methotrexate-naive patients and the other for the same doses in combination with methotrexate in DMARDs failure patients; both showed significantly less radiographic progression with tofacitinib compared with the control groups (Tables 3 & 4).

Table 4. Clinical efficacy: Phase III studies.

Study	Duration	Groups	n	ACR50	DAS28†	Radiographic progression (mTSS)	HAQ†	Ref.
Biologics and DMARD failure††								
Burmester 2011 (ORAL-Step; NCT00960440)	6 months (24 weeks)‡	5 mg + MTX	132	26.5%	6.7%	NM	-0.4¶	[22]
		10 mg + MTX	133	27.8%	8.8%	NM	-0.5¶	
		PBO§ + MTX	131	8.4%	1.7%	NM	-0.2¶	
Fleischmann 2012 (ORAL-Solo; NCT00814307)	6 months (24 weeks)‡	5 mg + HCQ/PDN	243	31.1%	5.6%	NM	-0.5¶	[24]
		10 mg + HCQ/PDN	245	36.8%	8.7%	NM	-0.6¶	
		PBO§ + HCQ/PDN	122	12.5%	4.4%	NM	-0.2¶	
Kremer 2013 (ORAL-Sync; NCT00856544)	12 months (52 weeks)‡	5 mg + DMARDs	315	27.3%	8.0%	NM	-0.4¶	[20]
		10 mg + DMARDs	318	33.0%	9.0%	NM	-0.5¶	
		PBO§ + DMARDs	159	9.4%	2.5%	NM	-0.2¶	
Van der Heijde 2013, Phase III (ORAL-Scan; NCT00847613)	6 and 12 months (24 and 52 weeks)	5 mg + MTX	321	32.4%	7.2%	0.12¶	-0.5¶	[21]
		10 mg + MTX	316	43.7%	16.0%	0.06¶	-0.6¶	
		PBO§ + MTX	160	8.4%	1.6%	0.47¶	-0.2¶	
Van Vollenhoven 2012 (ORAL-Standard; NCT00853385)#	6 and 12 months (24 and 52 weeks)	5 mg + MTX	204	36.7%	7.3%	NM	-0.6‡,¶	[23]
		10 mg + MTX	201	34.7%	12.5%	NM	-0.6‡,¶	
		ADA + MTX	204	27.6%	6.2%	NM	-0.5‡,¶	
		PBO§ + MTX	108	12.3%	1.1%	NM	-0.2 ‡,¶	
MTX-naive or subtherapeutic MTX doses								
Lee 2012 (ORAL-Start; NCT01039688)	6 and 12 months (24 and 52 weeks)	5 mg	371	46.6%	14.6%	-0.18¶	-0.8¶	[46,47]
		10 mg	395	56.2%	21.6%	-0.04¶	-0.9¶	
		MTX	186	27.2%	7.6%	0.84¶	-0.6¶	

†Percentage of patients achieving remission (DAS <2.6).
‡Assessment performed at 12 weeks.
§Placebo group at 12 weeks was switched to either 5 or 10 mg of tofacitinib.
¶Adalimumab was given for 12 weeks and then patients were switched to tofacitinib.
#Least-squares mean changes (group means after having controlled for a covariate).
††Intolerant or inadequate response to methotrexate (and/or other DMARDs) and TNFi (and/or other biologic agents).
ACR 50: American College of Rheumatology improvement criteria 50% response rate; ADA: Adalimumab; BID: Twice a day; DAS28: Disease activity score in 28 joints (in most studies DAS was based on C-reactive protein (CRP) levels, except for Fleischmann 2012 [24,26], Tanaka 2011 [45], Kremer 2013 [20]); DMARDs: Disease modifying anti-rheumatic drugs; HAQ DI: Health Assessment Questionnaire (lower scores indicate less disability); HCQ: Hydroxychloroquine; mg: Milligrams; mTSS: Modified Total Sharp Score (lower scores indicate no progression); MTX: Methotrexate; n: Number; NM: Not measured; PBO: Placebo; PDN: Prednisone; QD: Once a day.

Functional status outcomes measured by HAQ-DI are also reported in Tables 3 & 4. Overall, a significant improvement was observed in patients with prior failure to biologic and traditional DMARDs who received tofacitinib monotherapy or in combination with other DMARDs. Similarly, the disability scores for methotrexate-naive patients receiving tofacitinib were lower compared with control [46].

All the above evidence support the efficacy of tofacitinib at approved dose of 5 mg or 10 mg by mouth twice daily for the treatment of RA either alone or in combination with methotrexate.

Clinical effectiveness

Beyond RCTs there are few studies currently available addressing the clinical effectiveness of tofacitinib. Yamanaka *et al.* 2011 [53]. A LTE study published as a conference abstract recruited Japanese patients that completed Phase II trials of tofacitinib either as monotherapy [45] or combined with methotrexate [27] (clinicaltrials.gov identifier: NCT00661661). In this LTE, 404 patients received tofacitinib 5 mg twice daily or were advanced to 10 mg twice daily if considered having an inadequate response. The ACR 20 response rate was reported 80% at 144 weeks (data available only for 85 patients).

Connell *et al.* (2011) [54,55] also published two conference abstracts (no clinicaltrials.gov identifier provided) results including 1070 patients who received tofacitinib 5 or 10 mg twice daily. At 104 weeks (data available only for 207 patients), 55% of the patients maintained an ACR 50 response, DAS score was reduced from baseline by 2.86 points and disability scores decreased from baseline by 0.70 points. At four years, the ACR50 response rate was 50% and the DAS28 remission rates was 22% compared to 48% and 20% rates at 4 weeks respectively. Similarly, there was an observed persistent mean reduction in HAQ-DI after 4 years of treatment (0.8) [56]. One pooled analysis of the two LTE studies after 5 years of follow-up was provided a posteriori by the drug manufacturer including in total 4102 patients treated with tofacitinib 5 mg or 10 mg. Over time, sustained ACR response rates and remission rates (measured by DAS28-4ESR<2.6) were observed.

Those are emerging positive data but further post-marketing and LTE studies are needed to confirm the effectiveness of tofacitinib in the daily clinical practice. These studies would also address the safety issues discussed below.

Withdrawals, safety & tolerability

Table 5 shows the rates observed in each trial for total withdrawals, withdrawals due to lack of efficacy or due to adverse events, total adverse events, serious adverse events, infections and serious infections.

Withdrawals

In the RCTs, no statistically significant differences were found in the rate of withdrawals due to any cause between tofacitinib monotherapy or combined with DMARD compared with controls at 6-24 weeks[35]. In LTE studies, discontinuation rates due to adverse events ranged from 4.7% to 6.7% and discontinuation due to serious infections were 1.2% at 104-144 weeks [53,55]. However, in a study reporting pooled data from the two LTE studies, the total discontinuation rate was 20.8% after five years of follow-up. Half of the discontinuations (10.7%) were due to adverse events, with the most common causes being infections, abnormal laboratory tests and neoplasias (benign, malignant or unspecified) [56].

Total adverse events

No statistically significant differences were found in the rate of total adverse events between tofacitinib monotherapy or combined with DMARD compared with controls [35]. Connell *et al.* reported about 929 treatment-related adverse events at 104 weeks, most common were infections (18.4%), gastrointestinal disorders (10.2%) and laboratory abnormalities (7.4%) [54]. Total adverse events rates ranged from 64% at 144 weeks to 76.8% at 5 years in the LTE studies [53,56].

Infections

In the RCTs, no statistically significant differences were found in the rate of infections between tofacitinib monotherapy or combined with DMARD compared with controls at 6-24 weeks [35]. The most commonly reported infections were respiratory and urinary tract infections, nasopharyngitis, influenza and herpes zoster [35]. However, LTE studies data showed the rate of serious infections was 18% (2.62/100 patient-years at 2 years and 3.1/100 patient-years at 5 years) [54,56], and in its pooled report of the two LTE studies [53,54], Wollenhaupt *et al.* reported that the most commonly adverse events were infections (39.7 and 50.8% at 3 and 4 years respectively), including influenza, tuberculosis, herpes zoster and sepsis [56-59]. In its health technology report on tofacitinib, The European Medicines Agency (EMA) determined that patients receiving the drug were at an increased risk of infections (based on the evidence submitted by the manufacturer). Opportunistic infections of concern included tuberculosis, severe pneumonia, and herpes zoster infections [60]. In addition, tofacitinib was associated with an increased neutropenia, life-threatening lymphopenia and decreased CD4/CD8 and CD56 counts.

Serious adverse events

Serious adverse events were less likely to occur in the tofacitinib monotherapy group (RR 0.13; 95% CI 0.03-0.56) when compared with control [51] at 6-24 weeks. The rates of serious adverse events in RCTs ranged from 0 to 3.8% for tofacitinib 5 mg alone compared to 1.5 to 5.9% for placebo. However, no differences were found between tofacitinib combined with DMARD compared with DMARD alone. Similarly the rates of serious adverse events between tofacitinib and adalimumab were similar across groups [51]. Serious adverse event rate in LTE studies was reported at 25.5% at 2 years and at 11.1/100 patient-years at 5 years [54,56].

Laboratory abnormalities

Three meta-analyses have pooled the incidence of laboratory abnormalities in 9–10 RCTs [35,51,61]. In two of these, compared with controls, patients in the tofacitinib monotherapy group were more likely to have an increased total cholesterol (mean difference (MD) 12; 95% CI 11–13), an increased LDL (MD 11.8; 95% CI 10.1–13.5), an increased HDL (MD 10; 95% CI 7.3–12.7) and an increased ratio of total cholesterol to HDL (MD 13; 95% CI 11.8–14.2) [35,51]. In addition,compared with DMARD alone, patients

Table 5. Safety outcomes in clinical trials: 6–24 weeks.

Study	Groups	n	Withdrawals			Total AEs (%)	Infections (%)	Serious AEs (%)	Serious infections (%)	Ref.
			Total	Lack of efficacy (%)	AEs (%)					
Week 6										
Kremer 2009, [NCT00147498]	5 mg + PDN	61	3	1	1	59	24.6	0	0	[44]
	15 mg + PDN	69	9	1	3	75	30.4	1.4	1.4	
	30 mg + PDN	69	17	1	5	69	30.4	1.4	0	
	PBO + PDN	65	17	8	1	65	26.2	1.5	0	
Week 12										
Tanaka 2011, A3921039 (NCT00603512)	1 mg + MTX	28	2	0	0	39.3	10.7	3.6	0	[27]
	3 mg + MTX	28	4	1	2	48.1	11.1	3.7	0	
	5 mg + MTX	28	4	0	4	77.8	3.7	3.7	0	
	10 mg + MTX	28	5	0	4	43.1	26.9	7.7	0	
	PBO + MTX	28	5	1	2	35.7	17.9	0	0	
Tanaka 2011, A3921040 (NCT00687193)	1 mg + PDN	53	NR	NR	0	39.6	NR	0	NR	[45]
	3 mg + PDN	53	NR	NR	1.9	43.4	NR	5.7	NR	
	5 mg + PDN	52	NR	NR	3.8	55.8	NR	3.8	NR	
	10 mg + PDN	53	NR	NR	5.7	60.4	NR	3.8	NR	
	15 mg + PDN	54	NR	NR	0	51.9	NR	1.9	NR	
	PBO + PDN	52	NR	NR	3.8	44.2	NR	1.9	NR	
Week 24										
Burmester 2011 (ORAL-Step; NCT00960440)†	5 mg + MTX	133	3	0	2	53.4	13.5	1.5	0	[22]
	10 mg + MTX	134	4	0	1	56.7	9.7	1.5	0	
	PBO + MTX	132	6	2	2	56.8	13.6	4.5	0	
Kremer 2012, A3921025 (NCT00413660)	1 mg + MTX	71	9	2	2	59.2	14.3	2	0	[25]
	3 mg + MTX	68	11	0	3	69.1	20	7.3	3.6	
	5 mg + MTX	71	15	1	1	66.2	22.5	5.6	1.4	
	10 mg BID + MTX	74	8	0	4	67.6	17.6	1.4	1.4	
	15 mg + MTX	75	15	0	7	76	18.7	8	0	
	20 mg QD + MTX	5	14	1	80	61.2	19.4	3	1.5	
	PBO‡ + MTX	69	15	5	3	56.9	5.9	0	0	
Fleischmann 2012, A3921035 (NCT00550446)	1 mg + HCQ/PDN	54	14	4	2	51.4†	29.7†	5.4†	5.9†	[26]
	3 mg + HCQ/PDN	51	8	2	0	52.9†	20.6†	2.9†	0	
	5 mg + HCQ/PDN	49	6	1	1	55.1†	34.7†	0	0	
	10 mg + HCQ/PDN	61	6	1	1	59.0†	34.4†	1.6†	0	
	15 mg + HCQ/PDN	57	5	0	2	61.4†	33.3†	7.0†	1.8†	
	ADA§ + HCQ/PDN	53	16	5	3	50.9†	18.9†	1.9†	0	
	PBO‡ + HCQ/PDN	59	16	4	0	47.1†	17.6†	5.9†	2.9†	

†Assessment performed at 12 weeks.
‡Placebo group at 12 weeks was switched to either 5 or 10 mg of tofacitinib.
§Adalimumab was given for 12 weeks and then patients were switched to tofacitinib.
¶Data reported separately by background DMARD.
ADA: Adalimumab; AE: Adverse events; BID: Twice a day; DMARDs: Disease modifying anti-rheumatic drugs; HCQ: Hydroxychloroquine; mg: Milligrams; MTX: Methotrexate; n: Number; NR: Not reported; PBO: Placebo; PDN: Prednisone; QD: Once a day.

Table 5. Safety outcomes in clinical trials: 6–24 weeks (cont.).

Study	Groups	n	Withdrawals			Total AEs (%)	Infections (%)	Serious AEs (%)	Serious infections (%)	Ref.
			Total	Lack of efficacy (%)	AEs (%)					
Fleischmann 2012 (ORAL-Solo; NCT00814307)	5 mg + HCQ/PDN	243	11	1	3	51.0†	11.5	0.4†	0	[24]
	10 mg + HCQ/PDN	245	27	1	9	56.7†	13.1	2.0†	0.4†	
	PBO‡ + HCQ/PDN	122	17	7	5	54.9†	14.8	4.9†	0	
Week 52										
Kremer 2013 (ORAL-Sync; NCT00856544)	5 mg + DMARDs	315	54	16	14	52.7†	NR¶	2.5†	0.6†	[20]
	10 mg + DMARDs	318	66	12	20	54.4†	NR¶	2.9†	1.3†	
	PBO‡ + DMARDs	159	21	6	5	61.0†	NR¶	3.8†	0	
Van Vollenhoven 2012 (ORAL-Standard; NCT00853385)§	5 mg + MTX	204	54	6	24	52.0†	12.7†	5.9†	1.5†	[23]
	10 mg + MTX	201	43	7	24	46.8†	12.4†	5.0†	2.0†	
	ADA + MTX	204	42	6	22	51.5†	13.2†	2.5†	0	
	PBO‡ + MTX	108	22	6	7	47.2†	1.9†	1.9†	0.9†	
Week 104										
Lee 2012 (NCT01039688)	5 mg	371	NR	4.0%	3.5	70.1%	31.8%	NR	6.5%	[46]
	10 mg	395	NR	1.8%	4.3	74.4%	38.7%	NR	6.1%	
	MTX	186	NR	9.7%	5.9	69.9%	27.4%	NR	7.0%	
Van der Heijde 2013, Phase III (ORAL-Scan; NCT00847613)	5 mg + MTX	321	71	3	26	48.9%	12.5%	3.7%	0.6%	[21]
	10 mg + MTX	316	51	7	36	54.1%	13.6%	3.2%	0.6%	
	PBO‡ + MTX	160	32	4	11	45.6%	8.8%	3.1%	0	

†Assessment performed at 12 weeks.
‡Placebo group at 12 weeks was switched to either 5 or 10 mg of tofacitinib.
§Adalimumab was given for 12 weeks and then patients were switched to tofacitinib.
¶Data reported separately by background DMARD.
ADA: Adalimumab; AE: Adverse events; BID: Twice a day; DMARDs: Disease modifying anti-rheumatic drugs; HCQ: Hydroxychloroquine; mg: Milligrams; MTX: Methotrexate; n: Number; NR: Not reported; PBO: Placebo; PDN: Prednisone; QD: Once a day.

receiving tofacitinib combined with DMARD were more likely to have a reduced neutrophil count, 10^{-3}/µl (MD -0.52; 95% CI -0.90– -0.15), an increased serum creatinine (MD 0.05; 95% CI 0.03–0.06), an increased total cholesterol (MD 25.3; 95% CI 13.5–37.2), an increased HDL (MD 10.2; 95% CI 7.1–13.3), an increased LDL (MD 13.5; 95% CI 8.7–18.3), an increased Apo B (MD 0.13; 95% CI 0.02–0.24), higher rates of ALT>1*ULN (RR 1.7; 95% CI 1.0–2.7), and higher rates of AST>1*ULN (RR 2.3; 95%CI 1.2–4.2) [35,51]. When compared with adalimumab, patients in the tofacitinib group had more change in neutrophil count, 10^{-3}/µl (MD 0.53; 95% CI 0.16–0.90), an increased serum creatinine (MD 0.03; 95% CI 0.00–0.06), an increased HDL (MD 8.1; 95% CI 3.7–12.5), an increased LDL (MD 8.9; 95% CI 3.2–14.7), and higher rates of AST>1*ULN (RR 9.7 95% CI 1.3–74.1). A subsequent study by Pfizer using atorvastatin concomitantly with tofacitinib effectively reduced the elevation of lipids associated with tofacitinib treatment [62].

In long term follow-ups up to 5 years, laboratory abnormalities remain a concern [56–59]. Decreased hemoglobin was observed in 2.5%, 3.5% and 12.7% (1% life-threatening) at 3, 4 and 5 years respectively [56]. Similarly, increased aminotransferases values three times upper limit of normal were observed in 1.2% of the patients at five years [56]. Moderate to severe neutropenia was also reported in 0.5% of the patients at 3 years and 0.7% at 4 or 5 years. Increased creatinine of at least to 33% from baseline was observed in 12.2% of the patients, while a 50% or more increase was found in 3.2% of the patients at 3 and 5 years.

Malignancies

We used the EMA and US FDA review documents and the drug's insert to report data on malignancies. After 12 months, 11 solid cancers and one lymphoma were reported in 3328 patients receiving tofacitinib (monotherapy or combined), while none of the 809 patients receiving control (placebo or DMARD)

reported a malignancy [37]. In addition, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was reported in five out of 218 *de-novo* renal transplant patients receiving tofacitinib versus none of the 111 patients treated with cyclosporine [37]. At two and three years, the incidence rates for malignancies, including lymphomas and lymphoproliferative disorders were 1.9 and 1.6, respectively for tofacitib and 1.6 for adalimumab. The most frequently observed malignancies were lung cancer, breast cancer and lymphomas [60]. At five years, 1.4% of the patients discontinued the drug due to neoplasms (benign, malignant and unspecified). The incidence rate for malignancies excluding non-melanoma skin cancers was 1/100 patient-years and for the non-melanoma skin cancers was 0.5/100 patient-years. [56]. Similar rates have been reported for other targeted therapies [63]. Pooled data from RCTs and LTE studies revealed that in 5674 patients receiving tofacitinib there were 105 malignancies (excluding non-melanoma skin cancer) and 38 non-melanoma skin cancer reported. The standardized incidence rates for all malignancies (excluding non-melanoma skin cancer) and for lymphoma were 1.1 and 2.6 respectively[64,65].

Regulatory affairs

On November 6, 2012 the FDA approved tofacitinib (brand name Xeljanz) to treat adults with moderately to severely active RA who have had an inadequate response to, or who are intolerant to methotrexate. The FDA approval was based on safety and efficacy evidence of seven clinical trials in adult patients with moderately to severely active RA. According to the FDA's pharmacology review, patients on tofacitinib monotherapy or combined with DMARDs showed greater improvement in clinical response and physical functioning compared with patients treated with placebo or DMARDs alone. However, tofacitinib was associated with an increased risk of serious infections (including opportunistic infections, tuberculosis), cancers and lymphoma. Therefore, the FDA requested Pfizer to include a Boxed Warning regarding these safety risks. In addition, increases in cholesterol and liver enzyme tests and decreases in blood counts were also observed. The manufacturer will submit a risk evaluation and mitigation strategy at 18 months, 3 years and 7 years from the date of approval to inform healthcare providers and patients about the serious risks associated with treatment. Contrastingly, on April 25, 2013 the EMA, European Committee for Medicinal Products for Human Use (CHMP) rejected the application for marketing authorization of tofacitinib based on the evidence of five Phase III studies of safety and efficacy involving over 3300 patients with RA at 12–24 weeks. The CHMP had major concerns about the safety profile of tofacitinib and whether the risks associated could be managed successfully in medical practice. Specifically, the risk and type of serious infections, certain cancers, gastro-intestinal perforations, liver damage and abnormal lipid profile. Also the CHMP considered that evidence was not sufficient to demonstrate a clinically important reduction in disease activity and structural damage with the 5 mg dose in patients who had failed to at least two other DMARDs. The application was resubmitted in July 2013 and the company removed statements of efficacy on structural damage with the 5 mg dose. However, the committee considered that the benefits did not outweigh the concerns about safety. Currently in Europe, Pfizer continues providing the drug to patients enrolled in clinical trials and considers requests for compassionate use on an individual basis in accordance with local regulations.

Conclusion

Traditional or biologic DMARDs do not fully control the disease activity in many RA patients. Tofacitinib is a novel small-molecule oral agent that has been added to the arsenal of DMARDs used to treat patients with active RA and an inadequate response to methotrexate and or other biologic DMARDs. Tofacitinib is a JAK inhibitor that selectively blocks signaling pathways that modulates cytokines at the basis of RA pathogenesis. In animal models JAK inhibition reduced signs of arthritis resulting in joint inflammation reduction [12,15]. After its approval for RA treatment, tofacitinib is currently being evaluated in clinical trials for psoriasis, spondyloarthritis and inflammatory bowel disease. Evidence from five Phase II and six Phase III trials suggests that tofacitinib is clinically efficacious in improving signs and symptoms of RA including physical function, disease activity and slowing structural damage at 12–24 weeks. Tofacitinib's potential side effects include the risk of serious infections and certain laboratory abnormalities (i.e., mild to moderate anemia, moderate to severe neutropenia, liver enzyme abnormalities, increased lipids and increased creatinine levels). The true risk of malignancies is yet to be determined over the longer term in real-life conditions.

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Executive summary

Mechanism of action

- Tofacitinib is an oral JAK inhibitor that blocks JAK-1, JAK-2, JAK 3 and TYK2. Preferentially inhibits JAK 3 and/or JAK 1 blocking signaling through the common γ-chain-containing receptors to cytokines relevant for lymphocyte function such as IL- 2, 4, 7, 9, 15 and 21.

Chemistry

- Tofacitinib is provided as 5 mg and 10 mg tablets.

Pharmacokinetic properties

- Rapid absorption following oral administration, with an absolute bioavailability of 74%.
- Volume of distribution after intravenous administration is 87 l. The protein binding of tofacitinib is approximately 40%. Tofacitinib binds predominantly to albumin.
- The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. 70% hepatic metabolism and 30% renal excretion. 95% of the administered dose is expected to be eliminated within 24 h.
- Concentrations are dose proportional. There is a linear relationship between body weight and volume of distribution, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. In patients with moderate to severe renal or hepatic impairment dose needs to be reduced to 5 mg once daily.

Clinical efficacy

- The ACR 50 response of patients treated with tofacitinib monotherapy and tofacitinib plus DMARDs was significantly better than patients treated with placebo or DMARD alone from 6–104 weeks.
- Clinical remission (DAS28 < 2.6) was more likely achieved by patients treated with tofacitinib monotherapy and tofacitinib plus DMARDs compared with patients treated with placebo or methotrexate monotherapy at 6–24 weeks.
- Mean progression of structural damage was lower in patients treated with combined tofacitinib plus methotrexate than with methotrexate alone at 24–104 weeks.
- All doses of tofacitinib alone of combined in 11 trials showed statistically significantly greater improvement in the disability index of the HAQ from baseline to the end of follow-up (6–104 weeks) compared with control groups.

Withdrawals, safety & tolerability

- Most common side effects:
  - Infections (respiratory tract infections, urinary tract infections, influenza, herpes zoster);
  - Abnormal laboratory test (lymphocytes, neutrophils, liver enzymes and lipids);
  - Anemia;
  - Diarrhea;
  - Nausea and vomiting;
  - Headache;
  - Abdominal pain.

Potential risks

- Serious infections such as tuberculosis, sepsis and opportunistic infections.
- Malignancies and lymphoproliferative disorders.
- Birth defects (animal studies).

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