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Rheumatoid Arthritis (J Kay, Section Editor)

JAK Inhibitors for Rheumatoid Arthritis

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Abstract

Although biologic therapies have changed expectation and outcomes for rheumatoid arthritis, the optimal therapy for this disease has yet to be determined. There are still a significant number of patients who do not respond satisfactorily to currently available therapies. The Janus kinase inhibitors represent a new class of therapies for rheumatoid arthritis. Tofacitinib is the first drug in this class to have demonstrated efficacy and a reasonable safety profile, and other examples, such as baracitinib, are in the late stages of development. These drugs work uniquely by inhibiting intracellular pathways thought to be important in the pathogenesis of rheumatoid arthritis. They are available as oral agents, which is also different than the currently available biologics. Tofacitinib has been carefully evaluated in multiple phase 3 clinical trials, and although safety concerns cannot fully be answered until the drug is studied over longer periods of time, the data to date suggest that this drug—and perhaps other JAK inhibitors—may represent an important addition to the therapeutic armamentarium. Further study and experience will better define when these drugs should be used and in which patients.

Opinion statement

Janus kinase (JAK) inhibitors are a novel approach to the treatment of rheumatoid arthritis (RA). They specifically inhibit some of the intracellular mechanisms involved in the immune-pathogenesis of the disease. An example of a JAK inhibitor is tofacitinib, which has demonstrated efficacy in multiple clinical trials, with a safety profile not substantially different from the biologic agents currently available. Baracitinib has also demonstrated efficacy in phase 3 clinical trials which are to be published soon. Other JAK inhibitors are also currently being evaluated. Their mechanism of action and oral route of

administration is unique compared to biologic therapies to date, and their place in the rheumatologist's armamentarium has yet to be determined.

Introduction

Biologics have changed the landscape of therapy for rheumatoid arthritis (RA). While they have substantially improved outcomes in patients with RA who are disease-modifying antirheumatic drug (DMARD) incomplete responders (IRs), they require administration via the subcutaneous or intravenous routes. Recently, a new class of oral DMARDs has been developed which inhibit Janus kinase enzymes.

JAK enzymes are constitutively bound to the intracellular domains of cytokine receptors. When extracellular cytokines and growth factors bind to these receptors, JAKs are phosphorylated, leading to activation of signal transducers and activators of transcription (STATs). The result is modulation of a variety of signaling cascades involved in innate and acquired immunity and hematopoiesis, including many thought to be involved in the pathogenesis of rheumatoid arthritis [1••, 2, 3••].

There at least four JAK enzymes, JAK1, JAK2, JAK3, and Tyk2, and they are associated with receptors in pairs [1••, 2, 3••]. JAK3 is expressed mostly in lymphoid cells and binds primarily with the gamma chain of the IL-2 family of receptors, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. JAK1 is also expressed in lymphoid cells, but also more widely, including the central nervous system, and is associated with the beta chain of the IL-2 family of receptors and also with other cytokine receptors including interferon-gamma and IL-6, IL-10, IL-12, and IL-23. JAK2 is expressed on a wide variety of cells, inhibits signaling by erythropoetin and growth hormone, and is important in controlling the production of blood cells from hematopoetic stem cells, and JAK2 mutations are associated with myeloproliferative syndromes. Tyk2 also has somewhat ubiquitous expression and is a component of alpha and beta-interferon signaling as well as IL-6, IL-10, IL-12, and IL-23 transduction.

Tofacitinib

Tofacitinib is a selective JAK inhibitor with higher affinity for JAK3 and JAK1 than JAK2 with limited affinity for Tyk2 [4]. Tofacitinib significantly inhibited JAK1/JAK2, JAK1/JAK3, and JAK2/JAK3 combinations in in vitro assays [4]. Tofacitinib represents the first drug in a new class of nonbiological DMARDs.

Immunologic effects

Multiple in vitro studies demonstrate the immunosuppressive effects of tofacitinib [1••, 2, 3••, 5–12]. In studies of mouse and human T cells, tofacitinib inhibited several signaling pathways, including IL-2-induced phosphorylation of a variety of STATs, IL-6-induced phosphorylation of STATs, and other downstream effects of JAK3 as well as JAK1 and JAK2 [5–7]. In in vitro studies of rheumatoid synoviocytes, tofacitinib inhibited IL-6-induced expression of the acute-phase serum amyloid A, which is known to induce the synthesis of other pro-inflammatory cytokines, and inhibited TNF-induced expression of multiple lymphocyte attracting cytokines and chemokines [9]. In CD4 T cells from RA patients, tofacitinib inhibited the proliferation of these cells and the synthesis and transcription of IL-17 and TNF-gamma (but not IL-6 or IL-8) [2, 5–10].

In in vivo animal models of RA, tofacitinib reduced acute-phase reactants, synovitis, cell influx, and cartilage damage in a dose-dependent manner [11]. The drug also suppressed innate immune responses to lipopolysaccharide, including the synthesis of TNF and other inflammatory cytokines [11]. When synovium and cartilage from a human RA patient was implanted into SCID mice, tofacitinib treatment suppressed proliferation of RA-derived synovium into the cartilage allowing preservation and reduced IL-6, IL-8, and MMp-3 levels [12].

Pharmacokinetics

Tofacitinib is rapidly absorbed after oral administration with plasma concentrations increasing in a dose-dependent manner with peak plasma concentrations achieved within 0.5–1 h, and steady-state level is reached in 24–48 h [4]. After a 10 mg dose was administered to healthy volunteers, the bioavailability of the drug was 74.1 % [4]. Following intravenous administration, the volume of distribution was 87 l, evenly distributed between plasma and red blood cells. Protein binding is approximately 40 %, primarily to albumin [4].

8pt?>Tofacitinib is primarily metabolized by cytochrome CYP3A4 (P450) and to a much lesser extent by CYP2C19 [4]. The elimination half-life is approximately 3 h. Hepatic metabolism accounts for 70 % of clearance, with renal clearance accounting for the other 30 %. The pharmacokinetics of tofacitinib are not apparently affected by age, body weight, gender, or race [4]. In patients with moderate or severe renal or modest hepatic impairment, dose reduction to 5 mg daily is recommended [4]. The safety of tofacitinib in severe hepatic dysfunction is uncertain, and the drug is not recommended in this situation [4]. Currently, the drug is not recommended in patients with positive hepatitis B or C serologies [4].

Tofacitinib has no apparent impact on the pharmacokinetics of concomitant methotrexate (MTX), oral contraceptives, or metformin [4]. If coadministered with ketoconazole or fluconazole, the dosage of tofacitinib should be reduced to 5 mg once daily [4]. Coadministration with rifampin in healthy volunteers reduced tofacitinib levels [4].

Regulatory agency approval

At the time of this writing, tofacitinib is FDA-approved in the USA for the treatment of adults with moderate to severe RA who have had an incomplete response to methotrexate, either as monotherapy or in combination with other DMARDs [4]. The approved oral dose is 5 mg twice daily. The drug is also approved for use in Canada, Switzerland, Japan, Russia, and many other countries. The European Medicines Agency did not grant tofacitinib marketing approval in Europe. The 10-mg twice daily dose has not been approved because of concerns regarding safety issues.

Clinical efficacy

Phase 2 clinical trials

Kremer et al. reported a phase 2a dose-finding trial of 264 RA patients who were MTX or TNF inhibitor (TNFi) IRs or who were intolerant to these drugs [13]. Patients were randomized to placebo or 5, 15, or 30 mg of tofacitinib twice daily

without background therapy for 6 weeks, with an additional 6 weeks of follow-up after treatment. The American College of Rheumatology 20 % response rate (ACR20) was 26.9, 70.5, 81.2, and 76.8 %, respectively, at 6 weeks in the four arms of the trial ($P>0.001$ all doses). Adverse events (AEs) in the placebo and 5 mg groups were similar, with higher rates in the higher dosage groups. The most common AE was headache (24.6 %), with gastrointestinal disorders, and nervous system disorders noted in >5 % of patients. Abnormal laboratory findings included cholesterol and creatinine level increases, as well as leukopenia and anemia. The infection rate was essentially similar across groups, with no opportunistic infections or deaths. Three serious adverse events (SAEs) occurred: infectious gastroenteritis in one patient receiving 15 mg twice daily, severe leukopenia in one patient receiving 30 mg twice daily, and one patient with staphylococcal aureus pneumonia in one patient receiving placebo.

A later phase 2a study by Tanaka et al. included 140 RA patients who MTX IRs but who remained on background MTX and were given placebo or tofacitinib 1, 3, 5, or 10 mg twice daily for 12 weeks [14]. ACR20 response rates were 14.3, 64.3, 77.8, 96.3, and 80.8 %, respectively, in the five treatment groups ($P<0.0001$ all doses). Significant improvements in ACR50, ACR70, and Health Assessment Questionaire-Disability Index (HAQ-DI) were also demonstrated in the 5 and 10 mg groups. Nasopharyngitis and transaminase abnormalities were seen in all groups. Dose-dependent decreases in neutrophil counts were seen and judged as mild to moderate. Mild anemia and elevated cholesterol levels were reported. Infections were essentially equal across all groups. There were two SAEs (dyspnea, gastroenteritis) which resolved with active drug withdrawal.

Fleischmann et al. reported a phase 2b dose-finding study which included adalimumab as an active comparator [15]. In this study, 384 RA patients who were DMARD IRs were randomized to placebo, tofacitinib 1, 3, 5, 10, 15 mg twice daily, or adalimumab 40 mg every 2 weeks without background therapy for 24 weeks. Compared to placebo, significant improvement in the ACR20 was achieved 22.0, 31.5, 39.2, 59.2, 70.5, and 71.9, respectively, at week 12 ($P=0.256$ for 1 mg group, $P<0.05$ for 3 mg group, <0.0001 for others). The ACR20 response rate for the adalimumab group was 35.9 % ($P=0.105$). The ACR20 response rates were sustained through 24 weeks. AEs were noted at 7.4 % in the tofacitinib groups versus 3.4 % in the placebo group, with diarrhea 4.8 versus 1.7 % and bronchitis 4.4 versus 1.7 %. Serious AEs were seen in 2.9 % of the tofacitinib group, with severe anemia the most common. AEs, infections but not SIEs, anemia, and liver function abnormalities were numerically higher in the 10 mg twice daily tofacitinib group.

In the largest phase 2b study by Kremer et al., 507 RA patients who were MTX IRs were randomized to placebo or tofacitinib 1, 3, 5, 10, and 15 mg twice daily or 20 mg daily with background MTX for 24 weeks [16]. The ACR20 responses were 33.3, 45.7, 52.9, 50.7, 58.1, 56, or 53.8 % at week 12 ($P<0.05$ for 3 mg and higher doses), and these response rates were sustained through 24 weeks. AEs in >10 % of any tofacitinib group included diarrhea, upper respiratory tract infections, urinary tract infections, arthralgia, and headache. There were less common increases in transaminases, cholesterol, and creatinine, and decreases in hemoglobin and neutrophils. Again, infections but not SIEs, and laboratory abnormalities were numerically higher in the two highest tofacitinib dose groups. There were 21 SAEs reported.

Phase 3 clinical trials: primary clinical endpoints, other outcomes, and safety results (see Table 1)

In the first phase 3 trial, the ORAL Solo study, Fleischmann et al. studied 610 RA patients who were MTX IRs randomized 4:4:1:1 to tofacitinib as monotherapy 5 or 10 mg twice daily, placebo crossed over to tofacitinib 5 mg twice daily at 3 months, or placebo for 6 months [17•]. At month 3, the ACR20 response rates were higher in the tofacitinib groups compared to both combined placebo groups: 59.8 versus 65.7 versus 26.7 %, respectively ($P<0.001$ for both comparisons). Similarly, reductions in HAQ-DI were greater in the tofacitinib groups: −0.50 versus −0.57 versus −0.19 points, respectively ($P<0.001$). The percentage of patients achieving remission defined by a disease activity score DAS28-4(ESR) <2.6 was not significantly higher in the tofacitinib groups compared to placebo. Common AEs included headache and upper respiratory tract infections. Serious infections were noted in six tofacitinib patients. Tofacitinib was associated with elevations of low-density lipoprotein cholesterol, transaminases, and reductions in neutrophil counts, all in <20 % of patients. The 10 mg twice daily tofacitinib group had numerically more AEs, SIEs, and anemia than the 5 mg twice daily group. There were 32 SAEs in 24 patients across all groups.

In the second important phase 3 trial, the ORAL Standard study, Van Vollenhoven et al. studied 717 RA MTX-IR patients who continued MTX and were randomized 4:4:4:1:1 to tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo crossed over to tofacitinib 5 mg twice daily at 3 months, or placebo for 12 months [18•]. At month 6, the ACR20 response rates were higher in the tofacitinib groups and the adalimimab group compared to both combined placebo groups: 51.5 versus 52.6 versus 47.2 versus 28.3 %, respectively ($P<0.001$ for all comparisons). Similarly, HAQ-DI reductions were greater in the tofacitinib and adalimumab groups: −0.55, −0.61, and −0.49 versus −0.24, respectively ($P<0.001$). The percentage of patients achieving a DAS28-4(ESR) was higher in the tofacitinib and adalimumab groups: 6.2, 12.5

Table 1. The six phase 3 tofacitinib clinical studies

Name of study, author (ref)	General description	ACR20/50/70 % for 5 mg BID vs PBO% vs other%
ORAL Solo, Fleischman et al. [17•]	Tofa vs PBO in MTX-IR monotherapy	59.3/31.1/15.4 vs 26.7/12.5/5.8 at 3 months
ORAL Standard, von Vollenhoven et al. [18•]	Tofa vs adalimumab vs PBO in MTX-IR, on MTX	51.5/NA vs 28.3/NA vs 47.2 ADA at 6 months
ORAL Step, Burmester et al. [19•]	Tofa vs PBO in TNF-IR, on MTX	41.7/26.5/13.6 vs 24.4/8.4/1.5 at 3 months
ORAL Scan, Van der Heijde et al. [20•]	Tofa vs PBO in TNF-IR, on MTX + X-ray	51.5/32.4/14.6 vs 25.3/8.4/1.3 at 6 months, mTSS change not sig
ORAL Sync Kremer et al. [21•]	Tofa vs PBO in DMARD-IR on DMARD	21.2/NA vs 30.8/NA (ACR20) at 6 months
ORAL Start Lee et al. [22•]	Tofa vs MTX, MTX-naive + X-ray	NA/25.5 (ACR70) vs NA/12.0 mTSS change 0.2 vs 0.8 at 6 months

Tofa tofacitinib, *PBO* placebo, *MTX-IR* MTX inadequate responders, *ADA* adalimumab, *NA* data not shown, *X-ray* radiographic scores, *mTSS* modified Sharp/van der Heijde score

and 6.7 versus 1.1 %, respectively (for data with) ($P<0.05$ for 5 mg group, $P<0.001$ for 10 mg group). AEs were more common in the tofacitinib groups, but were not described. Tofacitinib was associated with elevations of high- and low-density lipoprotein cholesterol (HDL, LDL), transaminases and reductions in hemoglobin and neutrophil counts. SAEs were more common in the first 3 months in the tofacitinib patients compared to the adalimumab or placebo patients. There were two cases of tuberculosis in the 10 mg tofacitinib group.

Bermester et al. published the next phase 3 trial, the ORAL Step study [19•]. In this study, 399 RA patients who were IRs to TNF inhibitors were randomized 2:2:1:1 to tofacitinib 5 or 10 mg, placebo to tofacitinib at 3 months, or placebo for 6 months while maintained on MTX. At month 3, the ACR20 response rates were higher in the tofacitinib groups compared to both placebo groups: 41.7 versus 48.1 versus 24.4 % for both combined placebo groups ($P=0.0024$ for 5 mg group, $P<0.0001$ for 10 mg group). Similarly, HAQ-DI reductions were greater in the tofacitinib groups: −0.43 and −0.46 versus −0.18, respectively ($P<0.001$ for both groups), DAS28<2.6. The percentage of patients achieving a DAS28 <2.6 was higher in the tofacitinib groups: 6.7 and 8.8 versus 1.7 % ($P=0.0496$ for 5 mg group, $P<0.0105$ for 10 mg group). AEs were more common in the tofacitinib groups, including diarrhea (4.9 %), nasopharyngitis (4.1 %), headaches (4.1 %), and urinary tract infections (3.0 %), although nausea (6.8 %) was slightly higher in the placebo groups. Tofacitinib was associated with increases in HDL and LDL cholesterol and decreases in neutrophil counts. Tofacitinib was associated with increases in SAEs, equally reported in all groups.

Van der Heijde et al. reported the results of the ORAL Scan phase 3 trial which evaluated 797 RA patients who were MTX IRs but remained on MTX and who were randomized 4:4:1:1 to tofacitinib 5 and 10 mg twice daily, placebo to tofacitinib 5 mg twice daily at 3 months or placebo with interim results reported at 12 months for a 24-month study [20•]. At month 6, the ACR20 response rates were higher for the tofacitinib groups versus both combined placebo groups: 51.5 versus 61.8 versus 25.3 % ($P<0.0001$ for both). Similarly, the least squares mean (LSM) reductions in the HAQ-DI were greater in the tofacitinib groups: −0.40 and −0.54 versus −0.15 (P for 5 mg group not stated, $P<0.0001$ for 10 mg group). At month 6, the percentage of patients achieving a DAS28-4(ESR) was 7.2 and 16.0 versus 1.6 % (P value not declared for 5 mg group, $P<0.001$ for 10 mg group). Also at month 6, radiographic scores were reported: LSM changes in total modified Sharp/van der Heijde score (mTSS) for the tofacitinib groups were 0.12 and 0.06 versus 0.47 for the placebo group ($P=0.0792$ for 5 mg group and $P<0.05$ for the 10 mg group), statistically significant for the 10 mg but not the 5 mg dose. Tofacitinib in both doses resulted in less erosion and joint space narrowing (JSN) at 12 months, but statistically significant change only in JSN not erosion ($P<0.05$ for former). The radiographic changes in all groups were quite small. Treatment emergent AEs, SAEs, and serious infections were similar across groups. Tofacitinib was associated with increases of LDL cholesterol and decreases of neutrophils. Despite the presence of MTX, increases in transaminases >3× normal were uncommon.

The ORAL Sync study reported by Kremer et al. involved 792 RA patients with incomplete responses to a variety of DMARDs [21•]. They were randomized 4:4:1:1 to tofacitinib 5 or 10 mg twice daily, placebo to tofacitinib 5 or 10 mg twice daily at 3 months for 12 months. At month 6, the ACR20 response rates were higher for the tofacitinib groups versus both combined placebo

groups: 52.1 versus 56.6 versus 30.8 % ($P<0.001$ for both groups). At month 3, the reductions in the HAQ-DI were greater in the tofacitinib groups: −0.44 and −0.53 versus −0.16 ($P<0.001$ for both groups). At month 6, the percentage of patients achieving a DAS28-4(ESR) was higher in the tofacitinib groups: 8.5 and 12.5 versus 2.6 % ($P<0.005$ for 5 mg group, $P<0.001$ for 10 mg group). AEs and SAEs were higher in the placebo group compared to the tofacitinib groups with the latter reported at 10.9 events per 100 patient-years for placebo versus 6.9 and 7.3 for the 5 and 10 mg tofacitinib groups, respectively. In the tofacitinib groups, there were two cases of tuberculosis, two cases of nontuberculous opportunistic infection, three cardiovascular events, and four deaths, not obviously related to dose. Also, in the tofacitinib groups, there were decreases in neutrophils, increases in hemoglobin and HDL and LDL cholesterols, and small increases in transaminases and creatinine.

The most recent phase 3 trial, the ORAL Start trial, was reported by Lee et al. and included 958 RA patients who were MTX-naive and were randomized 2:2:1 to receive tafacitinib monotherapy 5 or 10 mg twice daily or MTX at a dose that was increased to 20 mg over 8 weeks for 24 months [22•]. At month 6, the different primary clinical endpoint ACR70 response rates were higher for the tofacitinib groups versus MTX: 25.5 and 37.7 versus 12.0 % ($P<0.001$ for both). Also, at 6 months, the mean changes in the van der Heijde modified total Sharp score were smaller in the tofacitinib groups versus MTX: 0.2 and 0.1 versus 0.8 ($P<0.001$ for both), but the changes in all groups were quite small. AEs and SAEs were similar across groups, but serious infections were more common in the tofacitinib groups, not obviously related to dose. Herpes zoster was reported in 4.0 % of the tofacitinib patients versus 1.1 % in those receiving MTX. Cancer (three cases of lymphoma) developed in five tofacitinib patients versus one MTX patient. In the tofacitinib groups, increases in creatinine and LDL and HDL cholesterols were noted, numerically more common in the tofacitinib 10 mg twice daily group.

Phase 3 clinical trials: other secondary clinical and longer-term outcomes

In the ORAL Solo trial, ACR50/70 response rates and changes in FACIT-fatigue scores were significantly higher for both tofacitinib groups compared to placebo at 3 months [17•]. With regard to improvements in the HAQ-DI scores, a 0.30 point difference was selected as an endpoint, higher than the minimal significant clinical change of 0.22, and the LSM changes in the scores from baseline were significantly higher for the tofacitinib groups compared to placebo. Similarly, improvements in the ACR50/70 response rates were significantly higher for tofacitinib versus placebo at 6 months in the ORAL Standard, Step, Scan, and Start studies [18•, 19•, 20•, 22•]. In all the phase 3 clinical trials, the improvement noted in the tofacitinib groups were sustained throughout the duration of the trials [17•, 18•, 19•, 20•, 21•, 22•].

Phase 3 clinical trials: overall safety

Tofacitinib was reasonably well tolerated in all the clinical trials. In the ORAL Standard study, the combination of tofacitinib plus MTX resulted in discontinuation of treatment due to side effects during months 0–3 in 6.9 % of the tofacitinib 5 mg group, 5 % of the tofacitinib 10 mg group, 4.9 % of the adalimumab group, and 2.8 % of the placebo group [18•]. In the ORAL Start

study, discontinuation of treatment due to side effects during months 0–12 was lower in the tofacitinib groups compare with the MTX group, 3.5 and 4.3 versus 5.9 %, respectively [22•].

Although the incidence of AEs was similar between tofacitinib groups and placebo during the placebo-controlled periods of the phase 3 trials, the incidence of SAEs was higher in the ORAL Solo and Standard studies [17•, 18•]. The incidence of serious infections was higher with tofacitinib than placebo. The most frequent AEs in the patients treated with tofacitinib include infections (upper respiratory tract infections most commonly), gastrointestinal symptoms (particularly diarrhea), headache, and laboratory abnormalities including neutropenia and hypercholesterolemia. In the ORAL Standard study, during months 0–3, AEs were reported in 52 % of the 5 mg group, 46.8 % of the 10 mg group, 51.5 % of the adalimumab group, and 47.2 % of the placebo group [18•]. In the ORAL Start study, gastrointestinal AEs were reported in 21 % of the 5 mg tofacitinib group, 25.1 % of the tofacitinib 10 mg group, and 34.3 % of the MTX group [22•]. The side effect profile of the drug appears to be similar to that of the other biologics used in RA.

As mentioned the rate of infections, particularly serious infections was higher in the tofacitinib-treated patients. In the ORAL Standard study, serious infections were reported in 3.4 % of the tofacitinib 5 mg group, 4.0 % of the 10 mg tofacitinib group, and 1.5 % of the placebo group [18•]. In this study and others, the incidence rate of herpes zoster infection was higher in the tofacitinib groups. A later review of the phase 2, phase 3, and long-term extension (LTE) studies concluded that increased rates of herpes zoster were observed in patients treated with tofacitinib compared with those treated with placebo, particularly in patients from Asia, although complicated herpes zoster was rare [23]. The crude herpes zoster incidence rate across all reviewed studies was 4.4 per hundred patient-years (95 % CI 3.8–4.9) [23].

With regard to opportunistic infections, in the ORAL Scan study, seven opportunistic infections were reported, four of these in the tofacitinib 10 mg group, including tuberculosis, candidiasis, cytomegalovirus, and one case of pneumocystis jiroveci pneumonia which resulted in death [20•]. In the phase 3 trials, five cases of tuberculosis were identified, all in the tofacitinib 10 mg groups, three pulmonary, and two extrapulmonary (bone marrow and lymph node) [24]. In the latest review of infections, all all-cause mortality in all phase 2, phase 3, and LTE studies of tofacitinib in RA through April, 2012, higher rates of serious infections with tofacitinib were confirmed, including herpes zoster, and 16 cases of tuberculosis and 25 cases of other opportunistic infections, with slightly higher rates in patients who were male and older than 65 [24]. In the LTE study population (not the P3 population), the rates of infections were 26.3 events per 100 patient-years (CI 24.6–28.1) in the tofacitinib 5 mg twice daily groups compared to 45.0 events per 100 patient-years in the 10 mg twice daily tofacitinib groups (CI 42.6–54.5), and also in the LTE population the estimated risk of SIEs in the 10 mg twice groups was twice that of the tofacitinib 5 mg twice daily groups.

The pooled analysis by Cohen et al. also reported an all-cause mortality rate of 0.30 events per 100 patient-years within the initial 30 days after a tofacitinib dose [24]. There were two deaths reported in the phase 2 trials, 14 deaths in the phase 3 trials (12 in 10 mg groups), and 31 deaths in LTE trials. In the phase 3 trials, six deaths were from infection, two from cardiac causes, one from cancer,

one from trauma, three from noncardiovascular causes ("other"), and one was unknown. Even after adjudication, the causes of death other than infection were concluded to be consistent with those expected in patients with active RA [24]. The mortality rates were also concluded to be consistent with those in active RA, particularly active RA treated with biologics [24].

In a recent review of malignancies across the entire tofacitinib in RA clinical development program through 2013, lung cancer was reported most frequently (24 cases), followed by breast cancer (19 cases) and lymphoma (10 cases) [25]. The overall standardized incidence rate per 100 patient-years for all malignancies (excluding nonmelanomatous skin cancer and specific malignancies were both comparable to reported data for other biologic agents and more moderate to severe RA independent of treatment) [25]. Whether or not the mechanism of action of tofacitinib might lead to the development of malignancy, e.g., lymphoma, remains a potential concern and one which will require long-term safety studies.

Another review of safety across open-label, long-term extension studies concluded there were 11 potential cases of lower gastrointestinal perforation in tofacitinib patients compared to none in the placebo patients [26]. Risk factors included prior history of diverticulosis, concomitant corticosteroids, and NSAIDs. The incidence rate of perforation with tofacitinib was estimated to be twice that of placebo-treated RA patients.

As mentioned, laboratory changes in tofacitinib-treated patients were relatively common. The frequency of these changes in months 0–3 was similar to those reported after 3 months. The most common abnormalities reported were neutropenia, hyperlipidemia, and elevated transaminases, with a numerical increase in the 10 mg twice daily tofacitinib groups. Most of the neutropenia cases were mild-moderate and not associated with serious infections. Cohen et al. reported the rates of neutropenia of any severity (as defined by OMERACT criteria) at month 12 as <1 % of patients treated with tofacitinib 5 mg twice daily, 1.9 % of patients treated with tofacitinib 10 mg twice daily, compared to <1 % in patients receiving adalimimab [24]. They noted no further decreases in neutropenia in the LTE studies and no obvious relationship between neutropenia and serious infections.

Also in the report by Cohen et al., in the phase 3 trials, mean lymphocyte counts were <2 × 10 cubed/mm cubed which meets criteria for lymphopenia, and 25 % of these were defined as moderate to severe (0.5–1.5) [24]. Lymphocyte counts decreased by approximately 10 % from baseline to month 12 and was not obviously related to tofacitinib dose. Only when lymphocyte counts decreased to <0.5 did the rate of serious infections increase which occurred in 5 of 2340 phase 3 patients and 17 of 4088 patients in the LTE studies included in the review. Lymphopenia and neutropenia are presumably related to JAK2 inhibition of granulocyte-macrophage colony-stimulating factors [24].

In the phase 3 trials, hemoglobin levels remained stable, although there was a slight trend for increase in patients treated with tofacitinib 5 mg twice daily. In the ORAL Step study, mean hemoglobin levels increased by 1.1 g/L in the 5 mg tofacitinib group, essentially were unchanged in the 10 mg tofacitinib groups, and decreased slightly (0.10 g/L) in the placebo group [19•]. Anemia was explained by JAK2 inhibition and interference with erythropoietin, but this effect would

need to be balanced by potential increases in hemoglobin in those RA patients whose disease improved with treatment.

Dose-dependent increases in total cholesterol, LDL, and HDL were reported in tofacitinib-treated patients in the phase 3 trials in months 0–3 and remained stable through the trials. In the ORAL Standard study, LDL cholesterol concentrations increased by 12.2 % in the tofacitinib 5 mg group, 18.9 % in the tofacitinib group, 3.6 % in the adalimumab group, and 0.26 % in the placebo group [18•]. The long-term significance, if any, of these elevations will require careful study in tofacitinib-treated patients over much longer periods of time. Although the causes of these cholesterol changes remain uncertain, decreased IL-6 levels were observed in animal models of arthritis when treated with tofacitinib, and cholesterol increases have been seen in human RA patients treated with the IL-6 receptor antagonist tocilizumab, suggesting a possible effect of tofacitinib on IL-6 in the clinical trials [24].

Elevations of transaminases were noted in the tofacitinib-treated patients compared to placebo. These changes were almost all mild-moderate. In the ORAL Step study, alanine aminotransferase levels greater than the upper limit were reported in 13.6 % of the tofacitinib 5 mg group, 20.3 % of the tofacitinib 10 mg group, and 13 % of the placebo group [19•]. In the ORAL Start study, increases in transaminases to three or more times the upper limit of normal was infrequent and similar across both tofacitinib and methotrexate groups [22•]. The potential causes of the transaminitis also remain uncertain, although the before-mentioned potential effects of tofacitinib on IL-6 may also be relevant.

A recent review of changes in serum creatinine in the tofacitinib RA clinical trials concluded that tofacitinib has a small and reversible effect on renal function [27]. In the phase 3 trials, least square mean serum creatinine differences from placebo at 3 months were 0.02 and 0.04 mg/dL for tofacitinib 5 and 10 mg twice daily, respectively. Confirmed serum creatinine >33 % increases were reported in 1.4 and 1.9 % of patients receiving tofacitinib 5 and 10 mg twice daily, respectively. These elevations usually occurred within the first 3 months, plateaued, and then remained normal throughout the phase 3 and LTE studies. Another recent trial with a specific interest in renal function and tofacitinib also reported small increases in mean serum creatinine levels in patients receiving the drug, with return to normal upon drug discontinuation [28]. Phase 3 data also demonstrated that patients with higher baseline C-reactive protein (CRP) levels or greater CRP decreases following tofacitrinib treatment had the largest increases in serum creatinine. The mechanism explaining these changes, however, remain unknown. Acute renal failure occurred infrequently was usually observed in patients with concomitant illnesses, and generally responded to appropriate management.

Conclusion

Tofacitinib has demonstrated clinical efficacy in more than 5000 patients in phase 2 and 3 clinical trials. The benefit is usually rapid and usually sustained, and meaningful improvement in signs and symptoms, RA disease activity indices, and function. The potential inhibition on radiographic progression has been assessed in two phase 3 clinical trials, with the 5 mg twice daily dosage inhibition of structural damage was statistically significant in one of these. The

safety profile of tofacitinib appears reasonable and not that different from the biologics used to treat RA, with the exception of increased herpes zoster infections. Laboratory abnormalities such as neutropenia, hyperlipidemia, and transaminitis are usually mild, but require regular monitoring. As with other new therapies, tofacitinib will initially be used mostly in RA patients who are TNFi failures, but because of its oral route of administration, the drug has the potential for rapidly increasing use, depending on the results of ongoing studies of the long-term effects on clinical parameters, radiographic progression, and safety.

Baricitinib

Baricitinib is a potent inhibitor of JAK1 and JAK2, and, as discussed previously, has the ability to block downstream inflammatory activity. It is administered orally, once daily. Clinical trials for RA are ongoing, and the drug has not yet been submitted for approval from regulatory agencies.

Immunologic activity

Baricitinib selectively and reversibly inhibits JAK1 and JAK2 through binding and intracellular mechanisms similar to those described for tofacitinib. As a result, cytokines such as IL-6, IL-12, and IL-23, as well as granulocyte-macrophage colony-stimulating factor and interferon-gamma may be inhibited as downstream effects. In animal models of inflammatory arthritis, baricitinib was shown to have significant anti-inflammatory effects, but also led to preservation of cartilage and bone, with no detectable suppression of humoral immunity or adverse hematologic effects [29].

Pharmacokinetics

Following oral administration in healthy human volunteers, baricitinib attained a peak plasma concentration within 1.5 h and demonstrated dose linear and time invariant pharmacodynamics, with low oral dose clearance of approximately 17 L/h and minimal systemic accumulation following repeat oral dosing [30]. Mean renal clearance was approximately 2 L/h [30]. The pharmacokinetics correlated well with plasma concentrations [30].

Phase 2 clinical trials

A preliminary report of a phase 2a clinical trial in patients with active RA despite DMARD or biologic therapy was reported by Greenwald et al. [31]. In this study, 127 long-standing RA patients were randomized to placebo, or 4, 7, or 10 mg of baricitinib in combination with DMARDs but not any biologic therapy. ACR20 response rates were 32 versus 52, 59, and 53 %, respectively. The percentages of patients achieving a DAS28<2.6 were 16 versus 23, 25, and 17 %, respectively. Treatment emergent AE rates were fairly similar across groups with headache and diarrhea reported most commonly. There were two cases of herpes zoster. Increases in HDL and LDL cholesterols were observed.

In a phase 2b trial by Keystone et al., 301 RA patients with active RA despite MTX were randomized 2:1:1:1:1 to receive placebo or 1, 2, 4, or 8 mg of baricitinib once daily for 12 weeks while continuing their DMARD medications [32]. After 12 weeks, patients receiving placebo or 1 mg of baricitinib were

changed to baricitinnib 2 or 4 mg daily, and these and all other baricitinb patients were followed for an additional 12 weeks. At the primary endpoint of 12 weeks, ACR20 response rates were significantly higher in the combined baricitinib 4 and 8 mg groups compared to placebo: 76 versus 41 % ($P<0.01$). Also at week 12, significant differences between these groups were observed for ACR50/70 response rates, DAS28<2.6 rates, CDAI, and SDAI response rates. Patients in the 2, 4, and 8 mg groups maintained or improved all measures through 24 weeks. AEs were similar across groups. Three serious infections were observed in the baricitinib groups. There were no cases of herpes zoster or opportunistic infections. Mild decreases in hemoglobin and neutrophil counts were seen as were increases in HDL and LDL cholesterol, transaminase, and creatinine levels.

Phase 3 clinical trials

Preliminary data from two phase 3 clinical trials were recently presented in abstract form. In one, the RA-BUILD study, 684 RA patients with active disease despite DMARD treatment were randomized 1:1:1 to placebo or baricitinib 4 or 8 mg once daily for 24 weeks [33]. Placebo patients were switched to active treatment at 16 weeks. Significantly higher ACR20 response rates compared to placebo were observed in both baricitinib groups: 40 versus 66 and 62 %, respectively ($P<0.001$ for both). Significant improvements in both baricitinib groups were also seen in ACR50/70 response rates, DAS28<2.6 percentages, HAQ-DI, CDAI and SDAI responses rates which were sustained through week 24. Slowing of radiographic progression was also observed, with changes in mTSS of 0.33 and 0.15 in the baricitinib 2 and 4 mg groups versus 0.7 in the placebo group respectively at 24 weeks. Weekly assessments early in this trial, demonstrated rapid improvements in many patients, some as early as week 1. TEAE and SAE rates and serious infections were similar across groups. There were no serious infections. Laboratory abnormalities were similar to those seen in the phase 2 studies.

Preliminary results from the other phase 3 trial, the RA-BEACON study, were also recently presented [34]. In this study, 527 RA patients with an inadequate response to 1 or more TNFi were randomized 1:1:1 to placebo or baricitinib 2 or 4 mg once daily in addition to background nonbiologic DMARDs for 24 weeks. Significantly higher ACR20 response rates compared to placebo were observed in both baricitinib groups: 27 versus 49 and 55 %, respectively ($P<0.001$ for both). Improvements, often but not always statistically significant, were observed in the baricitinb groups in ACR50/70 response rates, DAS<2.6 percentages, HAQ-DI, CDAI and SDAI response rates. Improvements were seen early, some as early as week 1. Treatment benefit was sustained at 24 weeks in the 4 mg dose only. More TAEs were seen in the baricitinib groups, including infections, but SAEs were similar across groups. There were no opportunistic infections. Laboratory abnormalities were similar to those seen in the phase 2 studies.

The phase 3 studies await formal publication, and long-term studies to assess more fully the potential efficacy and safety of baricitinib in RA are also anticipated. To date, the data suggest that baracitinib may be another viable treatment option in a competitive marketplace.

Other JAK inhibitors in development

A number of small molecule JAK inhibitors are in clinical development for the treatment of RA [35]. These compounds have differing degrees of specificity to the four characterized JAKs. There are published phase 2 data available for three other JAK inhibitors: decernotinib (JAK3), filgotinib (JAK1), peficitinib (JAK3), and INCB-039110 (JAK1) [35]. A randomized, double-blind, placebo-controlled, 12-week dose-ranging phase 2b study of decernotinib as monotherapy in active RA demonstrated that the drug was efficacious in improving signs and symptoms at doses of 50–150 mg twice daily [36]. Infections and increases in transaminase and lipid levels were noted. In abstract form, a phase 2b 24-week study of decernotinib in combination with background methotrexate in RA also demonstrated significant efficacy [37]. Also in abstract form, two phase 2b, randomized, double-blind, parallel-group, placebo-controlled study of peficitinib demonstrated efficacy at 12 weeks in RA patients both on and not on methotrexate [38, 39]. There are preclinical or very early clinical data published for ABT-494, INCB-047986, and AC410 [33]. Which products will be available for clinical use in the future requires further study of long-term safety and the sustainability of efficacy. Whether or not more specific JAK selectivity is important clinically also needs to be evaluated. JAK inhibitors for RA are already a reality, but their position in the current therapeutic armamentarium remains to be determined.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Cohen has nothing to disclose

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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