# Promise and pitfalls of kinase inhibitors for rheumatoid arthritis

Over the last 15 years outcomes for patients with rheumatoid arthritis have dramatically improved. The move towards early aggressive treatment and the development of biologic therapies targeting cytokines and T/B cells involved in the pathogenesis of the disease has resulted in fewer patients progressing to disability and greater numbers of patients with low disease activity or in remission. Even with these improvements many patients continue with active disease, since the biologic therapies are only available through intravenous or subcutaneous administration and are expensive. Investigation of small molecular therapies that inhibit signal transduction resulting in reduced inflammatory cytokine production has been ongoing for the last decade. Original efforts targeting downstream proteins involved in signal transduction were unsuccessful; however, recent efforts in targeting the upstream Jaks and Syk have demonstrated efficacy and acceptable safety in rheumatoid arthritis randomized clinical trials. This review will summarize the recently published or presented data on the kinase inhibitors under development for rheumatoid arthritis.

**KEYWORDS: fostamatinib ■ Janus kinase ■ spleen tyrosine kinase ■ tofacitinib**

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Advances in treatment for rheumatoid arthritis (RA) over the last 15 years have resulted in dramatic improvements in the quality of life for RA patients. Treatment has shifted from 'empiric' therapies, such as gold and penicillamine and subsequently methotrexate (MTX), to therapies that target molecules/cells involved in disease pathogenesis. 'Targeted' therapies utilize discoveries from basic research that identified molecules pivotal to the chronic inflammatory process, allowing for the development of molecules that could inhibit these 'proinflammatory' molecules. This resulted in the development of the multiple biologic therapies currently available for the treatment of RA.

We have learned a number of lessons regarding optimal management of RA over the last two decades. Intervening earlier in disease before joint damage occurs and targeting disease remission or low disease activity has been clearly shown to prevent or reduce structural damage and improve physical function and health-related quality of life [1,2]. Using biologics in combination with MTX has resulted in improvements in the signs and symptoms of disease in up to 60% of patients, as determined by the American College of Rheumatology (ACR) composite response scores, and resulted in remission in 10–30% of patients depending on disease duration, with patients with earlier disease deriving the most benefit [3,4]. The safety profiles of these molecules have been well delineated and for most RA patients the benefits of treatment far outweigh the risks.

Even with these advances challenges in treatment persist. We presently lack biomarkers to guide our treatment decisions and initial choice of therapy is purely empirical. The hope for 'personalized medicine' in RA has yet to be realized. Biologics are large proteins that require parenteral administration and are costly, with average prices for a treatment in the range of US$35,000 per year. In randomized clinical trials (RCTs) more than half the patients demonstrate less than a 50% response by ACR criteria and only 20–30% demonstrate a good European League Against Rheumatism response [5,6]. Loss of efficacy or toxicity over time occurs with only 50% of patients still on treatment with etanercept after 10 years and fewer on infliximab [7,8]. In the clinic we frequently find ourselves cycling through different therapies when response to treatment is lost or adverse events (AEs) develop.

Over the last two decades, identification of molecules involved in signal transduction after ligand binding to receptors on inflammatory cells has progressed (Figure 1). This work has resulted in the development of various inhibitors to these peptides integral to signal transduction, with the potential that inhibition might abrogate the inflammatory process. This has ushered in the era of 'small molecules', which can be administered orally, and have the potential to be less costly and have similar efficacy to the biologic therapies.

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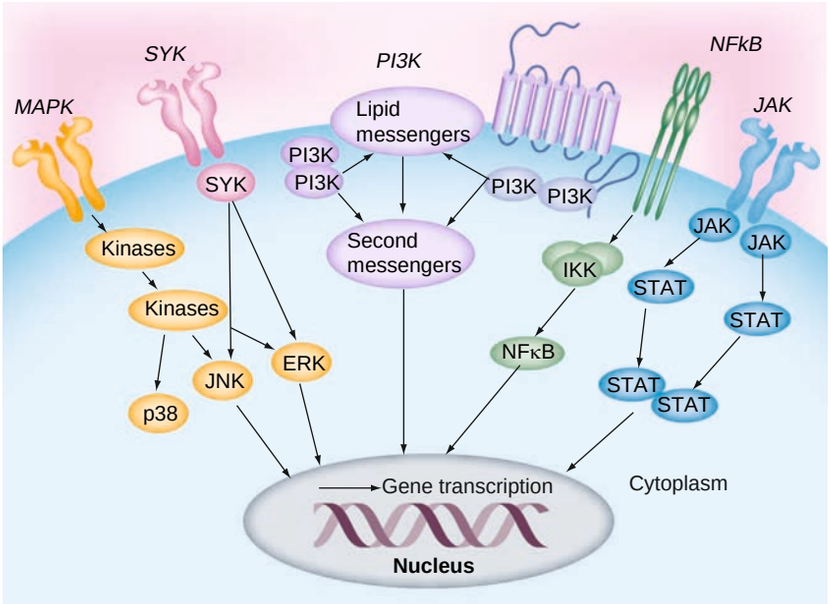



**Figure 1. Signaling pathways involved in proinflammatory cytokine production after receptor/ligand binding.**
Image courtesy of Dr Gary Firestein.

The first of these molecules targeted in RA was p38MAPK. Preclinical models demonstrated that antagonism of this kinase demonstrated significant benefit in rodent arthritis models [9,10]. p38MAPK is a downstream kinase involved in signal transduction and a key regulator of proinflammatory cytokine production. Unfortunately, several RCTs involving different molecules blocking the p38α isoform failed to demonstrate significant efficacy and all had a similar toxicity profile of CNS (dizziness), skin (pustular/acneiform eruption) and hepatic (transaminitis) AEs [11–13]. Attempts to decrease CNS penetration of the molecule or increase efficacy or safety were unsuccessful. In some of the studies a biologic effect was demonstrated by early suppression of CRP that was not persistent and often reversed by 2–4 weeks into the study. This suggested there were other more upstream pathways involved in signal transduction after ligand binding that remained functional even if this pathway was blocked.

Another downstream kinase MEK was targeted in RA utilizing a small molecule that targeted MEK1/2 after preclinical studies demonstrated a benefit. MEK1/2 is another kinase involved in signal transduction, resulting in the generation of proinflammatory cytokines. A Phase II RCT failed to demonstrate a benefit as determined by ACR response or change in Disease Activity Score 28 (DAS28)-4 (CRP) score and the molecule is no longer in development [14].

As a result of these failed RCTs, targeting upstream molecules involved in signal transduction has progressed rapidly. Building on the success of targeting protein tyrosine kinases in oncology, RCTs of inhibitors to the tyrosine kinases, Jak and Syk, have been ongoing (Table 1). Results have been either presented or published on the early-phase RCTs and Phase II/III RCTs of these kinase inhibitors, with several trials still ongoing. One of these molecules, tofacitinib (TOFA), is presently undergoing review by regulatory agencies for approval for RA treatment. In this article, data on the kinase inhibitors that are in development for RA and that have data available in the public domain will be reviewed.

## Jaks

Protein kinases modify protein function by transferring phosphate groups from ATP or GTP to the free hydroxyl groups of amino acids. A total of 518 protein kinases have now been identified and the majority are serine/threonine kinases. Of these kinases, 90 are protein tyrosine kinases that have been divided into two groups: receptor tyrosine kinases and nonreceptor tyrosine kinases. Receptor tyrosine kinases include EGF and PDGF. There are 32 cytoplasmic protein tyrosine kinases. Two subclasses of these kinases – Jak and Syk – have been identified as potential targets for inhibition in inflammatory diseases [15].

The Jak family of tyrosine kinases bind the cytoplasmic region of type I and II transmembrane cytokine receptors. After receptor–ligand interaction various Jaks are activated, resulting in phosphorylation of the cytoplasmic tail of the receptor-activating STATs, which act as transcription factors. Jaks consist of four enzymes: Jak1, Jak2, Jak3 and Tyk2. Jak1, Jak2 and Tyk2 are expressed on multiple cell types and Jak3 is primarily expressed in hematopoietic cells. Knocking out the *Jak1* and *Jak2* genes results in embryonic death. Knockout mice for *Jak3* exhibit severe combined immunodeficiency, and this syndrome in humans has been demonstrated to be related to Jak3 deficiency [16].

Jak3 and Jak1 are activated following ligand binding of the transmembrane receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, all of which share a common γ-chain receptor [17]. Jak3 and Jak1 are required for signaling through the γ-chain cytokine receptors. These interleukins play a pivotal role in lymphocyte activation, function and proliferation. Jak-3 knockout mice have defects in T and B lymphocytes and natural killer cells with no other defects reported, suggesting

a limited role of Jak3 in the development or function of nonimmunologic tissues.

Jak1 and Jak2 are also receptor-associated tyrosine kinases involved in signal transduction and are being considered as targets for inhibition in RA. GM-CSF, IL-3 and IL-5 signal through Jak2. Il-6, IL-10, IL-11, IL-19, IL-20, Il-22 and IFN-γ signal through Jak1 and Jak2. Inhibition of these inflammatory cytokines could potentially have benefit for RA patients. Concerns exist with specific inhibition of Jak2 as growth hormones, prolactin, erythropoietin and thrombopoietin also signal through this kinase. Jak2 inhibitors are undergoing extensive evaluation in myelodysplastic syndromes, such as myelofibrosis, polycythemia vera and essential thrombocytosis, with recent US FDA approval of a Jak1/2 inhibitor, ruxolitinib, for intermediate- and high-risk myelofibrosis [18].

Since ATP is ubiquitous, there were concerns that it would be difficult, if not impossible, to develop protein tyrosine kinase inhibitors with acceptable safety. It was thought that inhibition of multiple kinases involved in cellular signaling would most certainly have untoward side effects. The safety of imatinib and sumatinib for oncology indications demonstrated that safe use of tyrosine kinase inhibitors was possible even without the specificity originally thought necessary [19].

This experience in oncology led to investigation of Jak inhibitors for RA. All of the Jaks are inhibited by these molecules at nanomolar concentrations, although at varying concentrations. Multiple Jak inhibitors are under investigation with the Jak1/3 inhibitor TOFA being developed by Pfizer (NY, USA) now in Phase III trials and others in earlier phases of development. Jak1/2 inhibitors are in development for RA in Phase II trials and several other Jak inhibitors are in preclinical or early-phase trials for RA. To date, Tyk2 has not been targeted in RA clinical trials [20].

## TOFA

TOFA is a Jak1/3 inhibitor under development in RA, transplantation, psoriasis and inflammatory bowel disease. TOFA has been demonstrated *in vitro* cellular assays to inhibit Jak1, Jak2 and Jak3, and to a lesser extent Tyk2, with functional selectivity for Jak1/3 and Jak1/2 signaling over Jak2/2 [21]. Inhibition of Jak1/3 by TOFA will inhibit signaling for cytokines that bind receptors that utilize the common γ-chain receptor and recent data suggest that IL-17 production by Th17 cells is also inhibited [22–24].

This inhibition will result in suppression of inhibition of multiple cytokines involved in the disease process. The drug is administered orally and is rapidly absorbed with a half-life of approximately 3 h, resulting in the need for twice-daily (b.i.d.) dosing. The drug is cleared by both hepatic (70%) and renal metabolism (30%).

**Table 1. Protein tyrosine kinase inhibitors in randomized clinical trials for rheumatoid arthritis with data in the public domain.**

| Nomenclature | Method of action |
|---|---|
| Tofacitinib | Jak1/3 inhibitor |
| LY3009104 | Jak1/2 inhibitor |
| VX-509 | Jak1/3 inhibitor |
| Fostamatinib | Syk inhibitor |

## RCTs: efficacy

Six RCTs evaluating TOFA in RA have been presented as abstracts or published [25–30]. The initial three trials were dose-ranging trials evaluating TOFA as a monotherapy or in combination with MTX, with adalimumab (the placebo) as a comparator in one trial.

The initial RCT was a 6-week, dose-ranging study of 5, 15 and 30 mg TOFA b.i.d. as a monotherapy or placebo in 264 RA patients with active disease who had failed MTX or biologic therapy [25]. The primary end point was the ACR20 response at 6 weeks and was met by 70, 81 and 77% of the patients in the 5, 15 and 30 mg TOFA cohorts, respectively, compared with 29% in the placebo group ($p < 0.0001$). Response was seen as early as 1 week. A statistically significant difference in ACR50 and ACR70 response and change in DAS28 score was also seen in all active treatment cohorts compared with placebo. In addition, differences were noted in the important patient-reported outcomes of pain, physical function and disability as measured by Health Assessment Questionnaire – Disability Index (HAQ-DI), and both the physical and mental components of the SF-36 domains.

The second study was a 24-week, Phase IIb dose-ranging study evaluating TOFA at 1, 3, 5, 10 and 15 mg b.i.d. or 20 mg once-daily (q.d.) compared with placebo in 507 RA patients with active disease despite MTX therapy [26]. Patients remained on a stable background MTX of 7.5–25 mg/week. The primary end point was ACR20 response at week 12. At week 12 all nonresponders were reassigned to 5 mg b.i.d. treatment for the remaining 12 weeks of the study. The 3, 5, 10 and 15 mg b.i.d. and 20 mg q.d. TOFA cohorts achieved the primary end point at week 12; the 5 and 15 mg b.i.d., and 20 mg q.d. cohorts achieved ACR50/70 response and

DAS28 response at week 12 compared with placebo. The highest response rates were seen in the 10 and 15 mg b.i.d. groups. Efficacy was maintained with each of these doses until week 24. Only the 1 mg cohort failed to separate from the placebo cohort.

The third RCT was a Phase IIb dose-ranging RCT study of 386 RA patients comparing 1, 3, 5, 10 and 15 mg b.i.d. TOFA monotherapy, adalimumab monotherapy 40 mg every 14 days administered subcutaneously and placebo [27]. This was not a formal noninferiority trial and adalimumab was evaluated as an active comparator to assess efficacy of TOFA. This was a 12-week placebo-controlled study. At 12 weeks the adalimumab patients and nonresponders to 1-mg and 3-mg TOFA and placebo were reassigned to TOFA 5 mg b.i.d. for weeks 12–24.

The primary end point was the ACR20 response at 12 weeks. Patients had longstanding disease (7.7–10.8 years) and had failed 1.5–1.9 previous disease-modifying anti-rheumatic drugs (DMARDs). A small percentage had failed biologics. Response to TOFA was rapid and statistical differences were seen as early as week 2 for doses of ≥3, 5, 10 and 15 mg. At these doses, TOFA met the primary end point at week 12, as well as ACR50/70 response and DAS28 response; efficacy was maintained through to week 24 at these doses. Adalimumab was superior to placebo for ACR20/50/70 responses and similar to the response for TOFA 5 and 10 mg b.i.d.

Based on the results from the Phase II studies, the 5 mg b.i.d. and 10 mg b.i.d. dosages of TOFA were determined to be the doses to move forward to Phase III studies. The results of a 12-month Phase III trial in RA patients with active disease were reported at the 2011 European League Against Rheumatism meeting [28]. A total of 792 patients with active disease (disease duration: 8.1–10.2 years) despite having received at least one DMARD, primarily MTX, were randomized to receive 5 mg or 10 mg TOFA b.i.d. or placebo. The primary end point was the ACR20 response and DAS28 (erythrocyte sedimentation rate [ESR]) response at 6 months. Both the 5 mg b.i.d. (ACR20 53%, ACR50 33% and ACR70 13%) and 10 mg b.i.d. (ACR20 58%, ACR50 37% and ACR70 16%) were statistically superior to placebo (ACR20 31%, ACR50 13% and ACR70 3%) at month 6 for ACR responses (Figure 2). DAS28(ESR) scores of <2.6, considered to be indicative of remission, were reported in 11% of the 5 mg cohort, 14.8% of the 10 mg cohort and 2.7% of the placebo cohort. Differentiation from placebo was seen as early as week 2.

At the 2011 ACR annual meeting Van der Heijde *et al.* reported the 12 month results from a 2-year Phase III RCT evaluating 887 patients with RA with an inadequate response to MTX [29]. The study was designed to evaluate the impact of TOFA on radiographic progression and patients enrolled were required to have at baseline at least three erosions by x-ray or to be seropositive for rheumatoid factor or anti-citrullinated protein antibody. These features, along with elevated acute phase reactants, are associated with greater risk of structural progression. Patients received 5 or 10 mg b.i.d. or placebo in combination with MTX.

Enrolled patients had longstanding disease (mean 8.8–9.5 years) and at baseline had modified Total Sharp Score (30.1–37.3). At month 3 patients who were nonresponders were randomized in a blinded fashion to TOFA and at 6 months all placebo patients were randomized to TOFA. Only 22.8% of the patients were enrolled from North America.

At 6 months ACR20 was achieved by 25.3% of placebo patients, 51.5% of patients on 5 mg b.i.d. TOFA and 61.8% of the 10 mg TOFA-treated patients, both of which were statistically superior to placebo. As seen in the previous

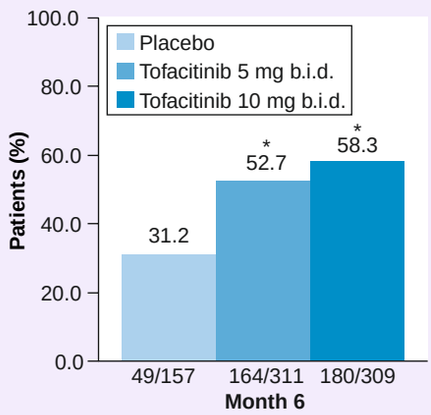



**Figure 2. American College of Rheumatology 20 response rates from a Phase III randomized clinical trial of tofacitinib in rheumatoid arthritis patients with active, disease despite background disease-modifying antirheumatic drugs.**
*p < 0.0001 versus placebo.
ACR20: American College of Rheumatology 20; b.i.d.: Twice daily; DMARD: Disease-modifying antirheumatic drug; NRI: Nonresponder imputation.

studies, response was rapid with statistically superior ACR response for TOFA compared with placebo by 4 weeks. At month 6 the modified Total Sharp Score progressed 0.47 in the placebo group, 0.12 in the 5-mg TOFA patients and 0.06 in the 10-mg TOFA patients (FIGURE 3). Radiographic progression was much less than predicted for all groups based on the patient's previous rate of progression. The difference from placebo was statistically significant for the 10-mg cohort, but not for the 5-mg cohort.

In addition, the 10-mg TOFA cohort demonstrated a statistically superior improvement in HAQ-DI score at month 3 of 0.54 compared with placebo at 0.15. The 5-mg cohort demonstrated an improvement in HAQ-DI of 0.4, but this did not achieve statistical significance owing to the statistical analysis, which did not allow for evaluation if the preceding coprimary end point was not achieved. More patients on TOFA 10 mg achieved DAS28 remission (18.3%) than placebo (1.6%), which was statistically significant. Out of all the patients on TOFA 5 mg, 7.2% achieved DAS28 remission, which was not statistically different from placebo based on the statistical analysis utilized.

At the 2011 ACR meeting, Burmeister *et al.* presented the results of a 6-month trial of TOFA in patients with inadequate response or intolerance to at least one TNF inhibitor [30]. Patients enrolled were on background MTX and received TOFA 5 or 10 mg b.i.d. or placebo. All placebo patients were blindly advanced to 5 or 10 mg b.i.d. TOFA at 3 months. A total of 399 RA patients with longstanding disease with mean baseline DAS28-4 ESR scores of 6.29–6.84 were randomized in to the protocol. A third of the patients had failed two or more TNF inhibitors.

Both doses of TOFA were statistically superior to placebo for the primary end point of ACR20 at 3 months (TOFA 5 mg b.i.d. 41.7%, TOFA 10 mg b.i.d. 48.1% and placebo 24.4%). Both doses of TOFA were statistically superior to placebo for the ACR50 and ACR70 responses. At month 3, 6.7% of the 5 mg b.i.d. TOFA and 11.2% of the 10 mg b.i.d. TOFA patients achieved a DAS28-4 ESR of less than 2.6 compared with 1.2% of the placebo cohort ($p < 0.05$). Significant improvement in the HAQ-DI was seen for the TOFA patients.

The safety and tolerability of TOFA and the durability of clinical response for up to 36 months in a long-term extension study of patients who had completed the RCTs was reported at the 2011 ACR meeting [31]. A total of 3227 patients

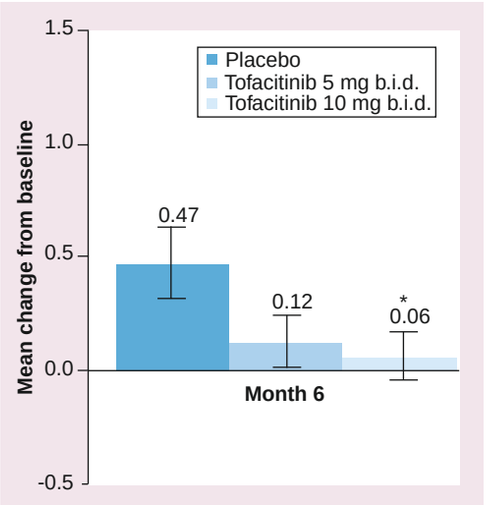



**Figure 3. Tofacitinib radiographic outcome in the 12-month study of rheumatoid arthritis patients with active disease, despite methotrexate, as measured by the Modified Total Sharp score.**
*p = 0.038.
b.i.d.: Twice daily.

were treated for a total duration of 3118 patient-years; mean (maximum) duration of treatment was 349 (1456) days. A total of 441 patients (13.7%) discontinued from the long-term extension studies: 223 (6.9%) owing to AEs and 42 (1.3%) owing to insufficient clinical response. ACR20, ACR50 and ACR70 response rates were consistent over time between month 1 and 36. At month 1, ACR20, ACR50 and ACR70 response rates for patients initially treated with TOFA 5 or 10 mg b.i.d. were 71.0, 47.3 and 26.3%, respectively; corresponding rates at month 36 were 72.7, 52.3 and 35.2%, respectively.

## Safety

Similar AEs were reported across the clinical trials and it was noted in the Phase II trials that the frequency of these events was dose-related. Based on the toxicity profile and the above noted efficacy results, doses above 10 mg b.i.d. were not continued on to Phase III RCTs. The most common AEs were nasopharyngitis, upper respiratory infections, urinary tract infections (UTIs), headache, infections and gastrointestinal complaints. These occurred numerically more commonly in the TOFA-treated patients but were rarely a reason for study discontinuation.

Several laboratory AEs of special interest potentially related to the mechanism of action were noted. A reduction in overall neutrophil counts similar to that seen with TNF and IL-6 inhibitors was reported. Rare (1–2%) cases of

neutrophil counts below 2000 were seen but no cases of grade 4 neutropenia (<500) have been reported. No relationship between neutropenia and infection has been reported. This neutropenia could be related to the reduction in IL-6 through TOFA-mediated Jak1 inhibition.

Rare cases of anemia were seen in the clinical trials, possibly related to Jak2 inhibition as erythropoietin signals through this Jak. This was primarily seen in the Phase II RCTs at doses of TOFA greater than 10 mg b.i.d, with minimal changes in the red blood cell counts reported in the Phase III trials.

Liver function test elevations were seen more commonly with TOFA compared with the placebo groups. More frequent elevations were reported in combination with MTX than monotherapy. Rare patients had transaminase elevations of more than three-times the upper limit of normal, requiring dose modification. These elevations resolved with dose modification or drug discontinuation and no cases of hepatic failure have been reported.

A peculiar elevation in serum creatinine levels has been reported in the RCTs. These were generally in the range of less than 30% and not associated with other signs and symptoms of renal injury. A rare patient had to discontinue the RCTs due to protocol-mandated discontinuation for creatinine elevation of ≥50%. The mechanism for this elevation is unclear and studies are ongoing to explore the mechanism of this elevation.

Approximately 15% of patients in the RCTs had an increase in total cholesterol that occurred early and plateaued by 3 months. In general, both the low-density lipoprotein and high-density lipoprotein levels were elevated with no change in the ratio. A study with atovarstatin demonstrated responsiveness of the elevated cholesterol to intervention [32]. This increase in cholesterol is similar to that reported for tocilizumab and suggests that suppression of IL-6 by TOFA Jak1 inhibition may be playing a role here.

An analysis of infections and all-cause mortality was presented at the 2011 ACR meeting in 2011 [33]. A total of 3315 patients from the RCTs and 3227 patients in the long-term follow-up studies were included in the analysis, representing 2098 and 3118 patient-years of exposure to TOFA, respectively. The majority of these patients were on 5 mg b.i.d. TOFA. Out of all the patients enrolled in the trials, 59.1% were from Latin America, South America, Asia or eastern Europe.

Serious infectious episodes were reported in 2.91 per 100 patient-years for the pooled TOFA cohort compared with a rate of 1.48 per 100 patient-years in the placebo cohort and 1.68 per 100 patient-years in the adalimumab cohort. In the RCTs there was no difference in the frequency of serious infections for the 5-mg and 10-mg TOFA cohorts with monotherapy or combination therapy. In the long-term follow-up studies more serious infectious episodes were seen in the 10-mg TOFA cohort compared with the 5-mg cohort.

Herpes zoster was reported more frequently in the TOFA-treated patients in the range of approximately 4 per 100 patient-years compared with 1.49 and 2.81 in the placebo and the adalimumab groups, respectively. This rate is higher than previously reported with other biologic therapies for RA. All-cause mortality was not different from placebo and adalimumab and was similar to that reported in RCTs of approved biologic therapies.

Ten cases of tuberculosis (TB) were reported with only one case reported in North America. The rate of TB reported was similar to the background prevalence of TB in the countries where the cases were reported. There were 20 patients with other opportunistic infections. These included esophageal candidiasis (seven), cytomegalovirus infection/viremia (four), *Pneumocystis jiroveci* pneumonia (three), non-TB mycobacterium lung infection (two) and one case each of cryptococcal pneumonia, cryptococcal meningitis, multidermatomal herpes zoster and BK encephalitis.

The development program of TOFA was recently reviewed by a FDA advisory committee. The committee voted for approval of TOFA for RA patients failing one or more DMARDs. During the presentation, data on malignancy, including lymphoma, were displayed [101]. The standardized incidence ratio based on comparison with the Surveillance Epidemiology and End Result database for malignancies (excluding nonmelanoma skin cancer) was 1.18 (95% CI: 0.91–1.51). There were six patients with lymphoma reported up to January 2012; the incidence rate across all RA studies was 0.07 events per 100 patient-years. The standardized incidence ratio for TOFA was 2.2 (95% CI: 0.81–4.79), consistent with that reported for other biologic therapies.

The safety issues noted were not unexpected for a potent immunomodulator and similar to what we have seen with marketed cytokine inhibitors. Laboratory monitoring similar to what is presently being utilized for MTX will be indicated in view of the transaminase elevations, reductions

in neutrophil counts and necessity to monitor serum creatinine. The issue of herpes zoster and possibly other viral infections noted in the RCTs will require pharmacovigilance to determine patients at greatest risk for these AEs and possible risk-mitigation efforts such as pretreatment vaccination for varicella zoster virus.

## Other Jak inhibitors

At the 2011 ACR meeting Fleischmann *et al.* presented the results of a Phase II RCT evaluating a Jak inhibitor with selectivity for Jak3 from Vertex [34]. This was a 12-week dose-ranging study of the Jak inhibitor VX-509 as monotherapy. The coprimary end points at 12 weeks were ACR20 response and change in DAS28-CRP.

A total of 204 patients were enrolled and treated with 25, 50, 100 or 150 mg of drug or placebo; all administered b.i.d. Mean disease duration was 7.8 years and mean baseline DAS28 score was 6.1. All doses of 50 mg and higher achieved statistically significant differences in ACR20 response and change in DAS28-CRP. Doses of 100 and 150 mg b.i.d. achieved statistically significant ACR50 and ACR70 responses compared with the placebo cohort. DAS28-CRP remission was achieved in 35 and 37% of the VX-509 100 and 150 mg groups, respectively, compared with 7% for placebo (both $p = 0.003$).

AEs led to discontinuation in 7.9% of VX-509 subjects and 4.8% of placebo subjects. Infections were the most common AE, occurring with similar frequency in placebo (17%) and VX-509 subjects (12–25%). Serious AEs occurred in 4.9% of VX-509 and 2.4% of placebo subjects, with serious infection in 3.1% of VX-509 subjects (100 mg, n = 3; 150 mg, n = 2, including one case of TB) and none in placebo. Two deaths occurred in the VX-509 group (100 mg): one due to subarachnoid hemorrhage and one due to pneumonia. Transaminase elevations were seen in 5.5% of VX-509 subjects and 4.9% of placebo subjects. Most were grade 1. There were dose-related reductions in platelets (within normal ranges) and a dose-related increase in low-density lipoprotein and high-density lipoprotein. There were no effects on hemoglobin, neutrophils or renal function.

A Jak1/2 inhibitor originally from Incyte (London, UK) is continuing in clinical trials. A small Phase IB study of 16 RA patients who were treated with 15 mg b.i.d. INCB018424 or placebo and followed for 28 days [35]. Efficacy was reported for the active compound and pharmacodynamics analysis demonstrated inhibition of IL-6-induced STAT3 phosphorylation. At the 2010 ACR meeting results of a Phase II 24-week dose-ranging trial evaluating INCB28050, a second Jak1/2 inhibitor from Incyte, was reported [36]. All three doses of oral INCB28050 (4, 7 and 10 mg q.d.) achieved the primary end point, ACR20 at week 12. Results seen at 12 weeks for placebo were 32% for ACR20, 13% for ACR50 and 3% for ACR70, and for patients treated with INCB28050 the results were 59% for ACR20, 35% for ACR50 and 16% for ACR70, which achieved statistical significance. This molecule continues under development by Lilly (IN, USA) with Phase III trials to begin later this year.

Other Jak inhibitors are in early phase study or in preclinical evaluation. What competitive advantage these molecules may have remains to be determined pending the results of RCTs.

## Syk inhibitors

Syk is a nonreceptor protein tyrosine kinase that is involved in signal transduction in immune cells bearing Fcγ-activating receptors, including macrophages, mast cells, B cells, neutrophils and synoviocytes. Syk plays a critical role in B-cell receptor signaling and also plays an important role in both the maturation and survival of the B-cell lineage. Syk-deficient murine models demonstrate a developmental block at the transitional B-cell stage and an absence of B cells in peripheral lymphoid organs. At the 2011 ACR meeting, Wei *et al.* presented data demonstrating that patients with refractory B-cell lymphoma treated with a Syk inhibitor had impaired B lymphocyte development at the transitional B-cell stage without mature B-cell populations being affected [37].

Syk binds to the cytoplasmic region of receptors that contain the immune-receptor tyrosine-based activation motif; receptor binding leads to immune-receptor tyrosine-based activation motif phosphorylation activating Syk, which activates downstream MAPKs, PI3K and phospholipase Cγ, resulting in MMP and IL-6 production. Syk has been detected in RA synovial tissue primarily in the intimal lining [38].

Fostamatinib (FTB) is an oral agent that is converted to an active metabolite, R406, and inhibits Syk activity. FTB is being investigated in lymphoid malignancies and immune thrombocytopenic purpura. FTB has been investigated in three Phase II RA RCTs and is now being studied in Phase III RCTs [39–41].

## Efficacy

The initial study was a 12-week placebo-controlled dose-ranging study in 189 patients with active RA (**Figure 4**) [39]. Patients received 50,

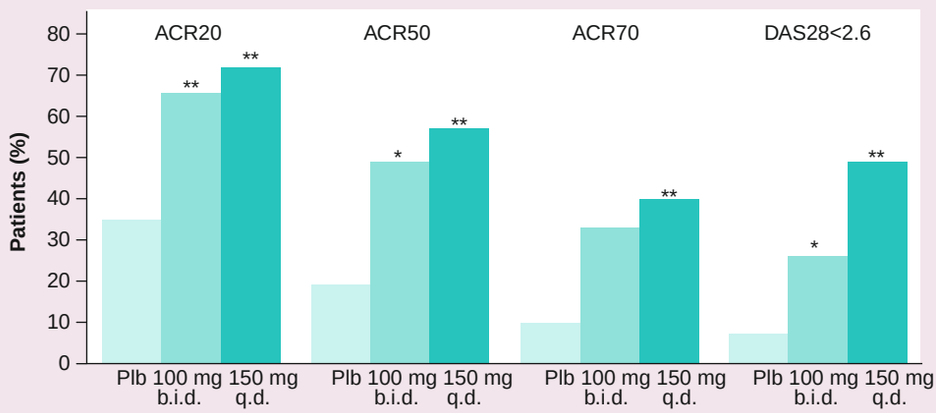
100 and 150 mg b.i.d. or placebo. Patients were allowed concomitant nonsteroidal anti-inflammatory drugs and prednisone, as well as stable sulfasalazine, hydroxychloroquine, minocycline or doxycycline but no other DMARDs. The primary end point was the ACR20 response at week 12. Out of all the patients, 65% in the 100-mg group ($p = 0.008$) and 72% in the 150-mg group ($p < 0.001$) met the primary end point, compared with 38% on placebo (Figure 3). Statistically significant differences were reported for the ACR50 and ACR70 response rates and DAS remission at the 100 and 150 mg b.i.d. doses. Response was seen as early as 1 week after the start of treatment, and at week 12 a significant decrease from baseline in levels of IL-6 and MMP-3 was seen at the two highest dose cohorts.

A second placebo-controlled 6-month RCT was conducted in 457 RA patients with active disease despite MTX evaluating the 100 and 150 mg b.i.d. doses of FTB [40]. The primary end point was the ACR20 response at 6 months, which was achieved by 66 and 57% of the patients in the 100- and 150-mg groups, respectively, compared with 35% of the placebo patients. Statistically significant improvements were reported in ACR50/70 and DAS remission for the 100-mg cohort and ACR50 and DAS remission for the 150-mg group. Response was seen again as early as week 1 and plateaued by week 6. Patients who had previous exposure to anti-TNF inhibitors were less likely to respond to FTB.

A third placebo-controlled 12-week RCT was conducted in 219 patients who had failed biologic DMARDs with the primary end point being the ACR20 response at 12 weeks [41]. A subset of patients had MRIs of the hands and wrists evaluated. In this study, FTB failed to achieve the primary end point as no statistical difference was seen between the two groups. Significant improvement in CRP and ESR was seen in the actively treated groups compared with the placebo, and improvement in MRI synovitis scores was noted in the FTB-treated patients. A subanalysis showed that patients enrolled in the trial on the basis of elevated levels of CRP demonstrated a statistically superior response that was different from placebo, whereas for those enrolled with an elevated ESR, placebo was superior to FTB.

## Safety

In these three RCTs AEs reported due to FTB were similar. Diarrhea, headache, dizziness, hypertension, elevated liver function tests and neutropenia were reported more frequently in the FTB patients than in the placebo-treated




| Treatment | n | ACR20% | ACR50% | ACR70% | DAS28<2.6% |
|---|---|---|---|---|---|
| Placebo | 153 | 35% | 19% | 10% | 7% |
| 100 mg q.d. | 152 | 65%** | 49%* | 33% | 26%* |
| 150 mg b.i.d. | 152 | 72%** | 57%** | 40%** | 49%** |

**Figure 4. American College of Rheumatology response rates to fostamatinib in a methotrexate inadequate responder Phase II placebo-controlled dose-ranging randomized clinical trial.**
*$p < 0.01$ (compared to placebo); **$p < 0.001$.
ACR: American College of Rheumatology; DAS: Disease Activity Score; b.i.d.: Twice daily; Plb: Placebo; q.d.: Once daily.
Data taken from [40].

patients. In general, these AEs were managed with dose reduction or drug withdrawal with reversibility. Increases in systolic and diastolic blood pressure were more common for patients with pre-existing hypertension and 6% of the FTB-treated patients required antihypertensive treatment, with 1% of the placebo patients requiring intervention. In the TNF incomplete responder study there were more serious AEs (SAEs) occurring in the FTB group (n = 13) than the placebo group (n = 1). The most common SAE was infection in three FTB patients, and one placebo patient died of septic shock.

At the 2011 ACR meeting safety data from the three RCTs and the long-term open-label trial were presented [42]. This analysis included 803 patients with 1038 patient-years of FTB exposure (mean exposure: 1.3 years). SAEs, serious infectious episodes, treatment discontinuations and dose reductions for FTB were higher in the TNF incomplete responder group versus all other groups. The most common AEs were diarrhea (27.4%), hypertension (22.5%) and UTIs (12.7%). The most common SAEs (rate per 100 patient-years) were infective events (3.4) and gastrointestinal events (1.8). The most common serious infectious episodes (rate per 100 patient-years) were pneumonia (1.0), UTIs (0.4), and cellulitis (0.3). The discontinuation rate on FTB treatment was highest in the first 6 months. Primary reasons for treatment discontinuations were lack of efficacy in the TNF incomplete responder study and AEs (most commonly diarrhea, neutropenia or increased transaminases). Blood pressure ≥160/100 mmHg and ≥180/110 mmHg for patients on FTB versus placebo were 22.9 versus 24.8 per 100 patient-years and 4.9 versus 2.8 per 100 patient-years, respectively. Neutrophil counts of less than 1500 and less than 1000 $mm^3$ for patients on FTB versus placebo were 9.9 versus 3.7 per 100 patient-years and 2.2 versus 0 per 100 patient-years, respectively.

Based on the two positive trials and the subanalysis that suggests benefit in postbiologic-treated RA patients with elevated CRP levels, this molecule is now being investigated in Phase III trials. These studies are enrolling and no additional data have been presented to date. Other sponsors are moving forward with molecules targeting Syk in RA.

## Future perspective

Based on the results published to date, it is hoped that we will have a small molecule available for oral therapy approved for RA later this year. Where the Jak inhibitor will fit in to the armamentarium of treatment remains to be determined; however, a clear benefit similar to parenteral biologic therapies has been demonstrated, as well as a safety profile similar to what we have seen with other biologics. The increased rates for

### Executive summary

***Inhibition of signal transduction of proinflammatory cytokines***

- Treatment for rheumatoid arthritis (RA) has evolved over the last 15 years with early aggressive treatment and the development of newer biologic therapies targeting cytokines or T/B cells involved in the pathogenesis of RA.
- Even with these therapies, many RA patients continue to have active disease and biologics are expensive and must be administered either by subcutaneous injection or intravenously.
- Targeting peptides involved in signal transduction of inflammatory cytokines has been ongoing for the last 10 years, initially targeting p38MAPK with insufficient efficacy and unacceptable toxicity.
- Targeting upstream protein tyrosine kinases such as the Jaks and Syk, required for signal transduction for several inflammatory cytokines, has proven a successful strategy in RA randomized clinical trials.

***Jak inhibitors***

- Tofacitinib is a Jak1/3 inhibitor that has been evaluated in six randomized clinical trials of RA patients and demonstrated to be effective in improving signs and symptoms of disease as determined by the American College of Rheumatology response and change in Disease Activity Score 28 and improvement in health-related quality of life and disability as determined by Health Assessment Questionnaire – Disability Index scores.
- Tofacitinib 10 mg twice-daily has been demonstrated to slow radiographic progression, and patients treated with the 5 mg twice-daily dose demonstrated less radiographic progression compared with placebo that did not achieve statistical significance.
- Acceptable safety has been reported, similar to that reported for biologic disease-modifying antirheumatic drugs in randomized clinical trials and observational databases. Herpes zoster was reported more frequently on tofacitinib than that reported with approved biologic therapies.

***Syk inhibition***

- Fostamatinib is a Syk inhibitor that has been demonstrated to be effective in improving signs and symptoms of disease and improving health-related quality of life and physical function in dose-ranging trials of RA patients with active disease despite methotrexate.
- The adverse event profile of fostamatinib included diarrhea, headache, dizziness, hypertension, elevated liver function tests and neutropenia.

herpes zoster and possibly other viruses seen to date and the impact on opportunistic infections will need to be closely monitored. The safety profile will become better delineated with greater exposure to these therapies but clearly additional treatments are necessary for patients who suffer from this lifelong affliction. Hopefully, this is the beginning of novel approaches utilizing small molecules to target inflammatory mediators critical to the development and persistence of RA.

**Financial & competing interests disclosure**

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

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