

JAK: no longer 'just another kinase'

The four JAKs, named JAK1, JAK2, JAK3 and Tyk2, form a group of nonreceptor protein tyrosine kinases, important for the regulation and development of immune and hematopoietic cells. Numerous cell receptors can activate JAK autophosphorylation to promote DNA transcription. Because of their ubiquitous presence in mammalian cells and the severe morbidity associated with either increased or decreased activity, numerous regulatory systems are in place to ensure their proper function. Currently, pharmacologic biologic blockade of JAK proteins is being evaluated for treatment in immune and hematologic disease as well as transplantation.

KEYWORDS: JAK ■ kinase ■ LY3009104 ■ rheumatoid arthritis ■ tofacitinib ■ Tyk2

Background & physiology of JAK proteins

■ Discovery of JAK proteins

With the advent of the human genome screening in the past two decades, thousands of discoveries have resulted from PCR-based screens, among them several tyrosine kinases in the JAK–STAT pathway [1]. These were initially named 'just another kinase' but later renamed Janus kinase in reference to the two-faced Roman god of gateways (FIGURE 1) to describe the structure of an active tyrosine kinase domain adjacent to another tyrosine kinase domain (these may autophosphorylate).

Janus kinases or JAKs are a family of four tyrosine kinase proteins, JAK1, JAK2, JAK3, and Tyk2 (the Tyk2 system was the first described). These are small molecules that range between 120 and 130 kDa in size, and each has seven distinct regions of homology within the tyrosine kinase domain responsible for the enzymatic activity of JAK (FIGURE 2) [2]. The JAK kinases function through the JAK–STAT pathway which mediates the signals from many different receptors on the cell surface to promote a different section of DNA transcription (TABLE 1).

While JAK 3 is found largely in hematopoietic cells, JAK1, JAK2, and Tyk2 are pervasive in mammalian cells [3]. The transduction of a signal from the cell surface begins with a ligand attaching to its receptor on the cell surface. The dimerization of the cell surface receptor brings together two inactive JAKs intracellularly. Once the two JAKs are brought into close proximity of each other, each kinase phosphorylates and activates the other. The autophosphorylation

attracts a STAT protein which attaches to the phosphorylated sites of the cytokine receptors. The STAT protein is then phosphorylated by a JAK, which allows two STAT monomers to dimerize. The dimerized STAT complex imports into the cell nucleus, binds to its recognized DNA target, and promotes transcription of that specific gene [4]. There are only seven known mammalian STAT proteins despite hundreds of cytokines which signal through a STAT pathway. Thus, specificity in targeting gene transcription is partially obtained by having groups of cytokines associating with only a specific STAT protein. Though still largely unknown, the remaining specificity required may depend on the other transcription factors and signaling molecules triggered concurrently [2]. The use of the JAK–STAT pathway is ubiquitous, and cytokines, interferons and growth factors utilize the JAK–STAT pathway to effect cellular DNA activation. Disruption or genetic defects in the JAK–STAT pathway can result in cell growth dysregulation (cancer) or immune disorders (TABLE 1) [5,6].

Because the JAK–STAT pathway is so pervasive in mammalian cells and because dysfunction in the pathway has such grave consequences, the suppressor of SOCS proteins help to fastidiously regulate JAK–STAT function through negative feedback mechanisms. One SOCS protein has a domain which acts as an E3 ubiquitin ligase, tagging the signaling molecule for a degradation pathway. Other domains of the SOCS proteins can either degrade proteins directly or act as a pseudosubstrate for JAK and thus inhibit the pathway through obstruction [3].

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Figure 1. Depiction of the two headed Roman god Janus.

The JAK–STAT pathway is also subject to regulation through crosstalk of different cytokines generated in certain inflammatory responses. One such example occurs during the acute phase response which triggers the proinflammatory p38-MAPK pathway.

This pathway eventually phosphorylates the gp130 receptor leading to internalization and degradation of the receptor thereby, leading to decreased signaling through the JAK1 pathway [7].

The JAK/STAT pathway has only recently received attention for researchers in rheumatoid arthritis (RA). STAT-3 is constitutively activated in RA and STAT-1 target genes are expressed in RA synovium. Furthermore, numerous pro-inflammatory cytokines known to activate RA, including IL-6, IL-15, granulocyte-macrophage colony-stimulating factor and interferons each utilize a JAK/STAT pathway [8]. Blocking RA cytokines, with inhibition of JAK/STAT pathways, has the potential to offer novel therapy for RA.

■ JAK1

The JAK1 protein is ubiquitous in mammalian cells as it transmits signals for both type II cytokine receptors, which include IL-10R, IL-19R, IL-20R and IL-22R, and the GP130 subunit receptors IL-6R and IL-11R. When the cytokine

docks onto its receptor, JAK1 autophosphorylates and depending on cell type, interacts with a specific STAT protein to cause transcription of a specific section of the cell genome. This is the mechanism utilized by type I cytokine receptors which include the common γ chain containing receptors IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R (FIGURE 3). Similarly, JAK 1 is known to activate the cell signal for the IL-6 superfamily, which includes IL-6R, IL-11R, LIF-R, OSM-R, cardiotrophin-1R, neurotrophin-1R and leptin-R. Furthermore, JAK 1 transduces the signals for interferons both type I and type II. Because JAK 1 plays such a critical role in response for so many major cytokine receptor families, deletion of JAK 1 in mice is lethal.

■ JAK2

Receptors for hormone cytokines including receptors for growth hormone, prolactin, erythropoietin and thrombopoietin largely signal through JAK2. JAK2 is also responsible for receptor signaling from IL-3 receptor or granulocyte-macrophage colony stimulating factor, both used for hematopoietic cell development [9]. Like JAK1, JAK2 is used for signal transduction by some of the cytokine type II family of receptors (IL-10R, IL-19R, IL-20R and IL-22R) and the GP130 receptor family (IL-6R and IL-11R), though not to the same extent that these receptors use JAK1. Deletion of JAK2 in mice is lethal, and gain of function mutations in JAK2 have been found in some types of leukemia, polycythemia vera, essential thrombocythemia and myeloproliferative diseases [10]. An activating mutation in JAK2 of valine to phenylalanine at position 617 is found in most cases of polycythemia vera or essential thrombocythemia. This mutation is thought to constitutively activate JAK2 by disrupting its ability to be inhibited [11].

■ JAK3

JAK3 is found almost exclusively in immune cells, including B cells, T cells, natural killer cells and monocytes [11–13]. In these cells, JAK3 transduces the signal for type I cytokines, those with the common γ chain (IL-2R, IL-4R, IL-7R, IL-9R, IL-15R and IL-21R). Mutations in JAK3 have been found to be clinically relevant as a possible cause of autosomal recessive severe combined immunodeficiency disease (SCID) as these patients lack both T cells and natural killer cells [6,10]. Pharmacologic inhibition of JAK3 may be beneficial in treatment for chronic lymphocytic leukemia, for RA and for renal allograft rejection [5,14,15].

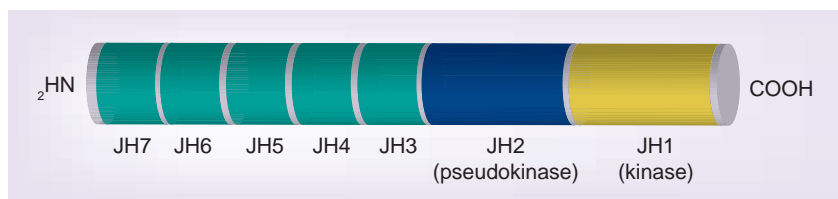


Figure 2. Common Janus kinases structure with a seven-domain homology.

Table 1. Function and significance of Janus kinases.

Tyrosine kinase	Interaction	Clinical significance
JAK1	γ chain-type 1 cytokines γ chain-type 2 cytokines Gp130 IFN-type I IFN-type II	Knockout of this gene is lethal
JAK2	γ chain-type 2 cytokines GM-CSF Epo-R Prolactin Gp130	Knockout of this gene is lethal Mutation of JAK2 ^T found in leukemia, polycythemia vera, thrombocythemia and myeloproliferative disorders
JAK3	γ chain-type 1 cytokines	Mutations in JAK3 causes SCID
Tyk2	γ chain-type 1 cytokines γ chain-type 2 cytokines IFN-type I IL-12	Mutation in Tyk2 causes hyperimmunoglobulin E Tyk2 deficient mice were resistant to experimental rheumatoid arthritis

^TMutation of valine to phenylalanine at the 617 position of JAK2 increases sensitivity to growth factors such as erythropoietin and thrombopoietin.
 SCID: Severe combined immunodeficiency disease.

■ **Tyk2**

Tyk2 was the first tyrosine kinase described in the JAK family. Many receptor families which signal through either JAK1 or JAK2 will also signal through Tyk2. Type I interferon receptors use a combination of JAK1 and Tyk2, and p40 containing cytokines IL-12 and IL-23, use JAK2 and Tyk2 together [3]. Tyk2 is thought to play an important role in antiviral immunity as IL-12 is responsible for Th1 generation of T cells, the subset of T cells most prominent in fighting viral infections and intracellular pathogens. Mutations of this gene has been used to generate a mouse asthma model as it perturbs the balance of T-cell differentiation to favoring Th2 dominance with a subsequent increase in IL-4 production and immunoglobulin E levels [2]. In addition to the known role of IL-12 in protection against infection, IL-12 also promotes the manifestation of autoimmune disease which is also Th1 mediated. The B10.Q/J strain of mice, known to be highly sensitive to *Toxoplasma gondii*

infection, were found to also have a decreased susceptibility to collagen-induced arthritis (an autoimmune model of arthritis). Upon further study, this strain of mice were found to have a genetic mutation in Tyk2, thus delineating a role of Tyk2 in both protective immunity and autoimmune pathology [16].

Clinical evaluation of JAK inhibitors in inflammatory arthritis

■ **Tofacitinib (previously known as tasocitinib): a JAK3 inhibitor**

After evaluation of JAK inhibitors in Phase I trials in humans showed no serious untoward reactions, dose ranging Phase II trials began in 2005 [101]. Tofacitinib, initially known as CP-690,550 is an oral JAK inhibitor thought to block predominately JAK3 which is expressed almost exclusively on immune cells. Tofacitinib has a selectivity for JAK3 inhibition relative to other JAK kinases. In cell-based assays, tofacitinib demonstrated a potency to inhibit JAK3

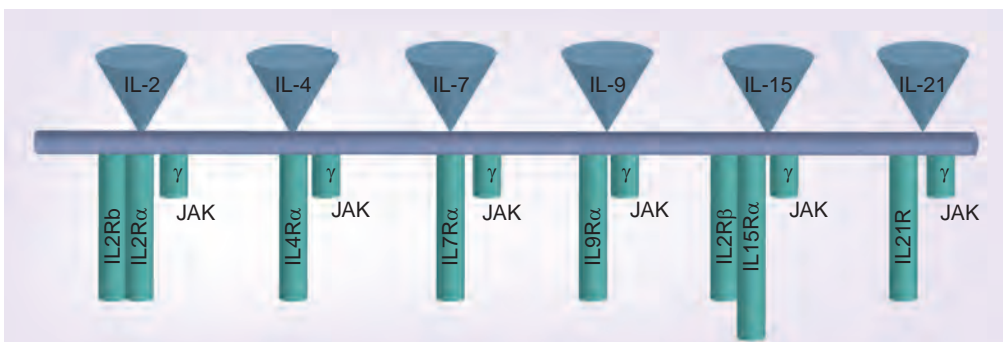


Figure 3. Janus kinase 1 transmits the cell signal for type I cytokines with a common γ chain. This includes activating the signal for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21.

with an inhibitory concentration (IC_{50}) of 1 nM versus an IC_{50} for JAK1 of 26–63 nM and IC_{50} for JAK2 of 129–501 nM [17]. In rodent models of collagen-induced arthritis and adjuvant-induced arthritis, there was a greater than 90% reduction in clinical disease with a dose of 15 mg/kg/day. In these rodent models, histology showed inflammation was reduced to baseline levels with the 15 mg/kg/day dose as well [18]. In Phase I trials with RA patients, the pharmacokinetic profile was found to be linear with a half-life of approximately 3 h and the 24-h area dose under the curve was twofold in humans compared with the rodent models.

For human trials, much smaller doses of tofacitinib 5, 15 and 30 mg b.i.d were evaluated.

In this 6-week dose-ranging study, 264 subjects from 11 different countries in North or South America or Europe were randomized to placebo or tofacitinib at 5, 15 or 30 mg b.i.d [14]. To enroll, subjects had to have established RA based on the American College of Rheumatology (ACR) 1987 revised criteria and a functional class of I, II or III. All subjects at screening and baseline had active disease defined as ≥ 9 tender joints and ≥ 6 swollen joints (based on a 68 or 66 joint count respectively), at least 45 min morning stiffness, a Westergren sedimentation rate ≥ 28 mm/h or a C-reactive protein (CRP) of ≥ 10 mg/l. All subjects had prior inadequate control with methotrexate or anti-TNF therapy (adalimumab, etanercept or infliximab). All prior disease-modifying antirheumatic drug (DMARD) or biologic therapy was withdrawn for at least 4–8 weeks prior to the tofacitinib study. The only background rheumatoid therapy permitted during the study was NSAID, acetaminophen, low-dose prednisone of ≤ 10 mg/day and opioids. The subjects were given placebo or tofacitinib for 6 weeks and then given no RA therapy for an additional 6 week follow-up safety period. The efficacy data was collected on the first 6 weeks and the safety data collected over the 12-week period.

The 264 subjects were randomized into four groups of 61–69 subjects, 85% were female with an average age of about 50 years, and 95% were Caucasian or of Hispanic background. The RA disease duration averaged 10 years and approximately 80% were enrolled with active disease despite prior methotrexate, and only 15% with active RA despite a combination of methotrexate and an anti-TNF (a very few had been treated with prior anti-TNF only). Up to 94% of the subjects were rheumatoid factor positive and two-thirds were on background glucocorticoids at baseline and through the study.

Efficacy analysis found a statistically significant dose response for tofacitinib for the ACR 20, ACR 50 and ACR 70 analysis (representing a 20, 50 and 70% improvement, respectively for the ACR criteria (FIGURE 4)). Remarkably, significant response was noted as early as 1 week after beginning the oral treatment. At 6 weeks, the ACR 20 ranged between 70–81%, the ACR 50 ranged between 30–50%, and the ACR 70 ranged from 12–25%. The placebo responses were as low as 7%, possibly because no background DMARD or biologic RA therapy was allowed.

There was statistical significance found for each component of the ACR response criteria, for each of the tofacitinib doses in a dose-dependent manner by 6 weeks. This includes number of tender joints, swollen joints, the subjects visual assessment score of pain as well as a visual assessment of RA disease activity, the physicians visual score for global RA disease activity, the health activity questionnaire (D1), and the change in laboratory CRP. Interestingly, a dose-dependent response was noted in the DAS28 measurement but did not reach statistical significance. In general, there was very active RA disease at baseline reflected by a DAS28 score of about 6.0, and the response was numerically superior with each dose escalation of tofacitinib; improving to 4.8, 4.2, 3.4 or 3.1 corresponding to a dose of tofacitinib of 0, 10, 30 or 60 mg daily. Similarly, the European League Against Rheumatism (EULAR) moderate or good response based on DAS28 was numerically superior in a dose dependent manner but did not reach statistical significance. This may be owing to the heavy reliance of DAS28 on the CRP laboratory data whereas the ACR response criteria include more clinical response elements in addition to the CRP.

Regarding the safety data, there were dose-related increases in adverse events as well. There were 3, 9 and 17 subjects who withdrew from the study in the 5, 15 and 30 mg b.i.d dose groups. Treatment emergent adverse events were reported in 59, 75 and 77% of the three tofacitinib groups increasing with the dose administered. Up to 17% of the subjects receiving 60 mg/day tofacitinib had an increased incidence of anemia, neutropenia, lymphopenia and thrombocytopenia and three subjects had to be withdrawn from the study. In the 15 mg b.i.d group, one subject was withdrawn owing to severe leukopenia and one other for moderate leukopenia and neutropenia. In laboratory analysis, there was a dose-dependent decrease in neutrophils

and hemoglobin correlating with the tofacitinib dose. This suggests that JAK2 may also have been inhibited since JAK2 has more hematopoietic regulatory functions. Tofacitinib inhibits JAK3 with a 20-fold preference over JAK2 in cell assays, but *in vivo* the effects may be different [13]. There was a doubling in incidence of headache in the 60 mg/day dose compared with placebo or either of the lower tofacitinib dosages, and one subject withdrew from the study owing to severe headache. There was no difference in infections between placebo and any of the tofacitinib dose groups over this short 6-week exposure. All but one of the reported adverse events in all categories resolved with cessation of study drug (one subject had ongoing myocardial ischemia despite withdrawal of the study drug and appeared unrelated to the study).

The safety laboratory testing during the 6-week study found a dose related elevation in total cholesterol, an increase in high density lipoprotein cholesterol, and an increase in low density lipoprotein cholesterol. The mechanism of this is unknown and the effect with more time of exposure is unknown. Increases in lipid levels have been reported with use of other biologic agents in RA and long term effects are still unclear [19,20]. There were no reported effects on liver transaminases. There was an increase in mean serum creatinine up to 5% starting in week 1. These were small increases with a maximum increase of 0.25 mg/dl but creatinine continued to be elevated in a few subjects at the 12-week final laboratory check point. There was no demonstrated change in hypertension in the 6-week treatment period.

In other tofacitinib trials, studies evaluating tofacitinib in patients with hepatic impairment and evaluation of tofacitinib with rifampin or ketoconazole have been completed (upregulating or inhibiting the cytochrome p450 enzymes respectively; NCT00969813 [102], NCT01204112 [103] and NCT01202240 [104]). A protocol evaluating cholesterol in subjects with RA taking atorvastatin along with tofacitinib is also ongoing (NCT01059864 [105]) and another protocol evaluating cholesterol metabolism in active RA patients given tofacitinib is planned (NCT01262118 [106]). Most Phase III protocols going forward are utilizing 5 mg b.i.d or 10 mg b.i.d and results presented at meetings show promising efficacy results. At 6 months, and for some subjects followed-up to 24 months, with background methotrexate in the majority of subjects, the ACR20 response is above 65%, the ACR50 response above 40%, and the ACR70

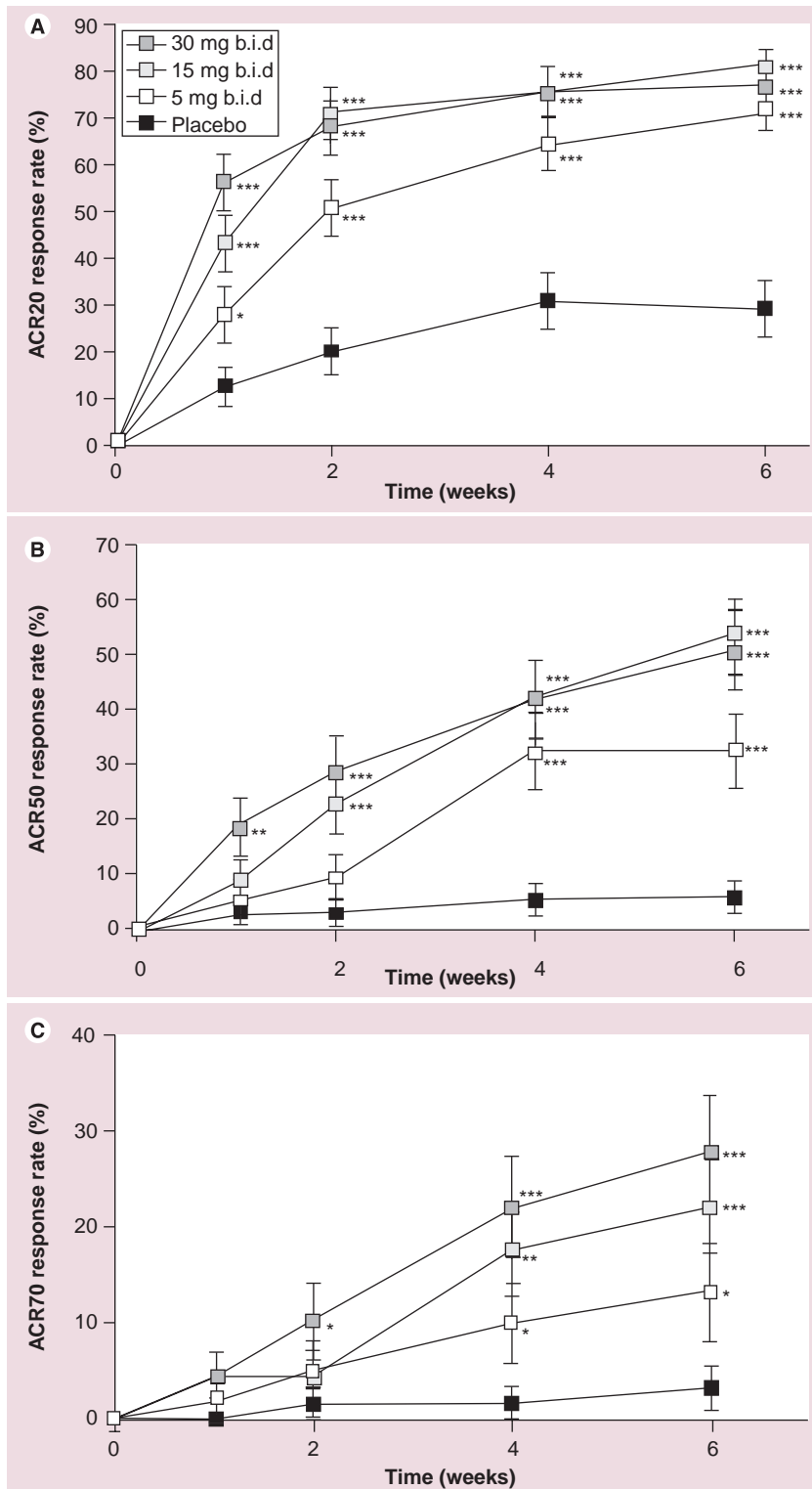


Figure 4. Mean \pm SEM response rate in patients with active rheumatoid arthritis who were treated with 5 mg, 15 mg or 30 mg tofacitinib twice daily or placebo. (A) ACR20 Response rate. (B) ACR50 response rate. (C) ACR70 response rate.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, versus placebo.

ACR20: American College of Rheumatology 20% improvement criteria; ACR50: American College of Rheumatology 50% improvement criteria; ACR70: American College of Rheumatology 70% improvement criteria; b.i.d: Twice daily.

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response above 20%. The efficacy parameters appear to improve with time and new safety issues did not arise [21–23].

■ LY3009104: a JAK1 & JAK2 inhibitor

This JAK1/2 inhibitor, also known as INCB 28050, has yet to register a generic name. A similar JAK1/2 inhibitor, ruxolitinib, is being evaluated for the treatment of myelofibrosis and psoriasis [24]. The inhibition of JAK1 and JAK2 each decrease signals from IL-6 (gp130 receptors) as well as IL-12 and IL-23 [25]. Such blockade mimics current approved therapy such as tocilizumab (anti-IL6) for RA or ustekinumab (anti-IL23) for psoriasis. The choice to preferentially inhibit JAK1 and JAK2 but not JAK3 was a hypothesis that there would be less immune suppression by sparing JAK3 (since JAK3 predominates in immune cells). The inhibitory concentration IC_{50} for LY3009104 against JAK1 or JAK2 is 6 nM and greater than 600 nM for JAK3 or other kinases. The JAK3 sparing effect of this compound is based on clinically relevant doses in human trials. The half-life with this JAK1/2 kinase inhibitor is 8 h, compatible with once a day oral dosing.

To test the hypothesis that inhibition of JAK1/2 would be efficacious in immune arthritis, LY3009104 was tested in rodent models of RA including adjuvant arthritis and collagen-induced arthritis [26]. These preclinical models demonstrated, in addition to anti-inflammatory properties such as reduced clinical signs of arthritis, cartilage and bone protective effects using micro-CT analysis. (FIGURE 5: These figures are from the adjuvant induced arthritis model). The highly efficacious results in preclinical models of RA led to human trials.

In a Phase II trial of RA, 125 subjects were randomized to placebo, 4, 7 or 10 mg LY3009104 once a day for 12 weeks [27]. There was an additional 12 week blinded extension where all subjects were on active drug and no placebo for additional safety data. All subjects remained on background therapy, which included about 75% on methotrexate and 40% on corticosteroids. Therefore, the addition of the JAK1/2 inhibitor would have to show an effect beyond these proven RA therapies. Despite the background ongoing therapies, these subjects demonstrated active rheumatoid disease with similar characteristics between groups; 15 tender joints, 12 swollen joints and 30–50% had been treated in the past with anti-TNF therapies. Approximately 80% female, the subjects had to qualify for the study with a Westergren sedimentation rate

≥ 28 or a CRP ≥ 7 mg/l. The baseline DAS was 5.8. The baseline health assessment questionnaire measurement was 1.6.

The primary outcome measure was an ACR20 response by week 12. By 2 weeks (the first data point), clinical response was documented and by 12 weeks, ACR20 was statistically significant with 52–59% of the subjects responding to study drug compared with a 32% placebo response rate. The ACR20 response on study drug improved to over 70% by 24 weeks. There was no significant dose response as the 4 mg/day dose reached similar efficacy end points when compared with the 7 mg/day or 10 mg/day dose groups. There were no lower doses tested. The ACR50 reached at 12 weeks was 35% compared with a placebo response rate of 13%. The ACR50 on study drug at 24 weeks rose to a 44% response rate. The ACR70 response rate was up to 16% at 12 weeks and 30% at 24 weeks. The efficacy response seen in the placebo subjects after week 12 when they were blindly crossed over to active treatment was similar to the active treated subjects randomized to study drug in the first 12 weeks. The efficacy response also was similar between those subjects who had used anti-TNF biologic therapy in the past and subjects who were naive to prior biologic therapies. At 24 weeks, the ACR20 response was about 70% and the ACR50 response about 40% in either group.

The CRP was dramatically reduced by week 2 (the first data point in the trial) for any dose of LY3009104. The CRP remained suppressed throughout the 24 weeks. There was no dose-response in this measurement and both 4 mg/day and 10 mg/day appeared equally efficacious. Similarly, the individual parameters of number of swollen joints, number of tender joints, physician's global assessment of disease and subject's global assessment of disease all showed improvement by week 2 with no difference between doses of study drug. By week 24, the health assessment questionnaire improved 36% for all active treatment groups combined. By week 24, the DAS-CRP improved by 42% for all active treatment groups combined and the DAS improvement was statistically superior to placebo at week 12 for any study dose (FIGURE 6). At 24 weeks, using the Outcome Measures in Rheumatology (OMERACT) criteria for a good response (DAS-CRP < 3.2), there was a 48–65% good response in the active groups. At 24 weeks, using the OMERACT criteria for a remission (DAS-CRP < 2.6), there was a 30–48% remission rate on active treatment with the JAK1/2 inhibitor.

Safety concerns were addressed for the first 12 weeks compared with placebo and then all subjects were on active study drug between week 12 and week 24 for additional safety data. In the first 12 weeks, compared with placebo, there was no difference for the number of upper respiratory infections, sinusitis, bronchitis or cough. Also there was no change in the number who complained of headache between placebo and the active treatment arms. Gastrointestinal complaints, diarrhea or nausea, did not change compared with placebo but two subjects did withdraw from the study who were on the active study drug (one with nausea and one with mouth ulceration). One infection of interest did occur only in the study drug group; there were five cases of herpes zoster simplex. Two of the herpes zoster cases occurred in the first 12 weeks (none in the placebo group) and three more cases occurred between the 12–24 week period when all subjects were on study drug. Two of the subjects were withdrawn from the study and treated for zoster, while three of the subjects continued on study drug and were treated for zoster without complication. The primary investigator caring for the subject was permitted to decide with the subject whether to continue on study drug. There was no zoster prophylaxis in the study protocol. Since JAK1 and JAK2 are both involved in interferon cell signaling, the inhibition of these kinases might increase the risk of reactivation of herpes zoster. There were no serious infections, no fungal infections and no tuberculosis during the study.

Safety laboratory testing revealed dose-related and consistent effect decreasing hemoglobin. The decrease was mild and one subject was withdrawn from the study for a reduction in hemoglobin (this subject was on the 10 mg/day dose). In general, the reduction in hemoglobin was about 2% on the 4 mg/day dose, 3.5–4% on the 7 mg/day dose and 8% on the 10/day dose. This occurred by week 12 and stabilized through week 24. The lower hemoglobin appeared to plateau on each dose of JAK1/2 inhibitor and might be expected when JAK2 is inhibited given its function in activation of erythropoietin. The absolute reticulocyte count had a similar normal reaction and it had a corresponding dose response to study drug. The reticulocyte count was 2–14% at the 4 mg/day dose, 8–15% at 7 mg/day dose and 17–24% at the 10 mg/day dose. This reticulocyte response appears to be compensatory and may account for the fact that the hemoglobin value resets on the JAK1/2 inhibitor. The absolute neutrophil

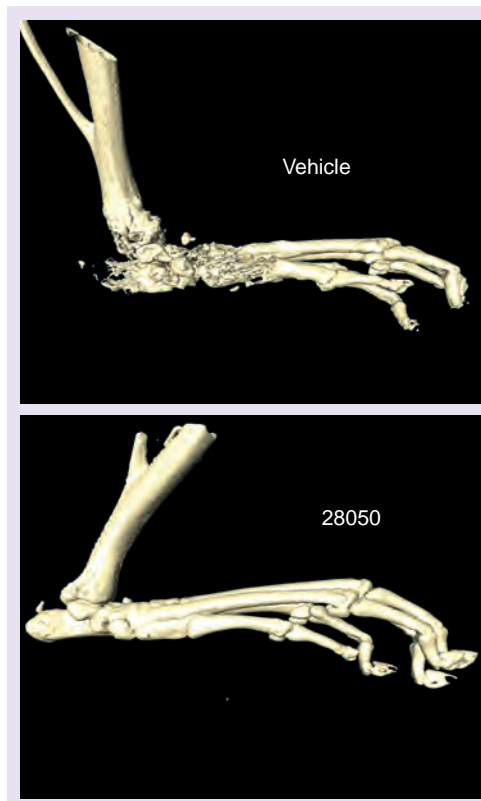


Figure 5. Micro-CT images of arthritic rat ankles.

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count had no response to JAK1/2 inhibition at these doses. The platelet count increased in a dose related manner; platelets increased 10–35% corresponding to increased study drug dose and the platelet count appeared to plateau after 12 weeks with no further increase. The platelet count increased despite the background methotrexate in 70% of the subjects.

There was no effect on creatinine on any dose of the JAK1/2 inhibitor study drug compared with placebo over all 24 weeks. There were also no effects on liver transaminases. There was a modest increase of total cholesterol, HDL, and LDL. The HDL rose 15–25% and the LDL increased 7–21%. There was no clear dose response and the effect on cholesterol did not change after week 12–24. The HDL:LDL ratio actually improved between 12–19%. The pathophysiology of the cholesterol effect is unclear, but as discussed earlier, IL-6 and TNF treatment based biologic therapies also affect cholesterol by poorly understood mechanisms.

Other programs are now underway to evaluate LY3009104 with rheumatoid arthritis (clinicaltrials.gov NCT01185353 [107]).

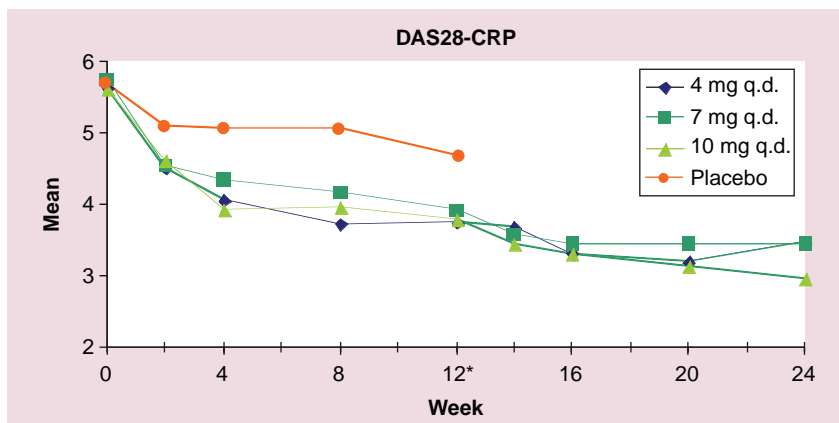


Figure 6. DAS28-CRP response on the JAK1/2 inhibitor LY3009104 over 24 weeks. All active doses were statistically superior to placebo at 12 weeks. * $p < 0.05$. CRP: C-reactive protein.

Future perspective

The future use of small molecules to inhibit JAK proteins in RA and likely other immune disease appears certain [3]. These JAK inhibitors are oral, once daily or twice a day and are well tolerated in studies to date. The rapid response with marked improvement in laboratory and clinical measurements in week 1 and week 2 is very gratifying and novel when compared with other current therapeutic choices. It is unclear whether efficacy will equal other biologic choices until there is a study with an active biologic treatment arm. As discussed, JAK inhibitors may achieve remission in a third to one half of subjects in a short period of time. However, safety concerns regarding changes in cholesterol lipid profiles, possibly decreased hemoglobin levels, elevation in creatinine and increases in herpes zoster need to be further evaluated. It also remains to be discovered if there is clinical import to inhibition of JAK1, JAK2, JAK3 or Tyk2 in control of immune disease or risks related to safety. Inhibition of each of these JAK proteins is proceeding.

Emerging clinical research has demonstrated the integral role of JAK proteins in the pathogenesis of psoriasis. As of 2010, two oral JAK inhibitor drugs, ruxolitinib and tofacitinib, have shown rapid and promising efficacy in Phase I/II trials with psoriasis patients. Studies show skin clearing within 1 week of beginning treatment [28,29]. Ruxolitinib has completed Phase II clinical trials supplied as a topical cream [108].

This article of JAK kinases illustrates the numerous permutations that can arise in immunology: many different cell types, four different JAK kinases which vary by cell type, seven different STAT proteins which also differ by cell type and each JAK–STAT combination activates transcription of a different part of DNA. In addition to these multiple outcomes, there has been the name/renaming malady common to immunology that can make reviews in immunology a challenge. To help anyone interested in new developments, results reporting is a new component of clinicaltrials.gov. All studies registered on the clinicaltrials.gov database after 2008 have US FDA Amendments Act mandates to submit results independent of journal publication. The goal is to promote the flow of information and outcomes, whether positive or negative, whether collected in the USA or abroad. However, results reporting for interventional drugs or biologics are only required after FDA approval for any use [30].

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Executive summary

Intracellular JAKs

- There are four described JAKs: JAK1, JAK2, JAK3 and Tyk2.
- These small molecules are part of the JAK–STAT pathway.
- There are four forms of JAK tyrosine kinases and seven different STAT proteins which are produced in different combinations in different cell types.
- JAK2 gain-of-function mutations increase response to erythropoietin and thrombopoietin.

JAK inhibitors in rheumatoid arthritis have shown efficacy in human clinical trials

- Tofacitinib has shown efficacy in an oral twice daily regimen.
- LY3009104 has shown efficacy in an oral once a day regimen.

Safety issues with JAK inhibitors in human trials

- Small elevations in cholesterol and lipid levels have been dose related.
- A dose-related decrease in hemoglobin and neutrophil count has been noted.
- Some cases of simple herpes zoster have occurred in the clinical trials above the rate seen in the placebo group.

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