World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5312/wjo.v5.i4.496

World J Orthop 2014 September 18; 5(4): 496-503
ISSN 2218-5836 (online)

TOPIC HIGHLIGHT

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Protein kinase small molecule inhibitors for rheumatoid arthritis: Medicinal chemistry/clinical perspectives

Charles J Malemud, David E Blumenthal

Charles J Malemud, David E Blumenthal, The Arthritis Research Laboratory, Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, Cleveland, OH 44106-5076, United States
Charles J Malemud, David E Blumenthal, Department of Anatomy, Case Western Reserve University, Cleveland, OH 44106-5076, United States
Charles J Malemud, David E Blumenthal, School of Medicine, Division of Rheumatology, Veteran's Administration Medical Center, Cleveland, OH 44106, United States
Author contributions: Malemud CJ and Blumenthal DE solely contributed to this paper.
Supported by A contract from Genentech/Roche Group and the Case Western Reserve University School of Medicine Visual Sciences Research Core, No. P30 EY-011373
Correspondence to: Charles J Malemud, PhD, Department of Medicine, Division of Rheumatic Diseases, The Arthritis Research Laboratory, Foley Medical Building, 2061 Cornell Road, Cleveland, OH 44106-5076,
United States. cjm4@cwru.edu
Telephone: +1-216-8447846 Fax: +1-216-8442288
Received: January 11, 2014 Revised: June 5, 2014
Accepted: June 20, 2014
Published online: September 18, 2014

Abstract

Medicinal chemistry strategies have contributed to the development, experimental study of and clinical trials assessment of the first type of protein kinase small molecule inhibitor to target the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway. The orally administered small molecule inhibitor, tofacitinib, is the first drug to target the JAK/STAT pathway for entry into the armamentarium of the medical therapy of rheumatoid arthritis. The introduction of tofacitinib into general rheumatologic practice coupled with increasing understanding that additional cellular signal transduction pathways including the mitogen-activated protein kinase and phosphatidylinositide-3-kinase/Akt/mammalian target of rapamycin pathways as well as spleen tyrosine kinase also contribute to immune-mediated inflammatory in rheumatoid arthritis makes it likely that further development of orally administered protein kinase small molecule inhibitors for rheumatoid arthritis will occur in the near future.

Key words: Clinical trials; Protein kinase; Signal transduction; Small molecule inhibitor; Rheumatoid arthritis

Core tip: Signal transduction is a regulator of gene expression in cells. Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling is activated by pro-inflammatory cytokines which contributes to immune-mediated inflammation in rheumatoid arthritis. Medicinal chemistry was employed to develop JAK small molecule inhibitors for determining their clinical efficacy in active rheumatoid arthritis patients. Tofacitinib, a JAK small molecule inhibitor, is now generally used to treat moderate to severe rheumatoid arthritis patients who have not adequately responded to disease-modifying anti-rheumatic drugs or various biologic agents. The clinical efficacy of JAK small molecule inhibitors provides the impetus for future drug discovery targeted at other signal transduction pathways in rheumatoid arthritis.

Malemud CJ, Blumenthal DE. Protein kinase small molecule inhibitors for rheumatoid arthritis: Medicinal chemistry/clinical perspectives. *World J Orthop* 2014; 5(4): 496-503 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i4/496.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i4.496

INTRODUCTION

Medical therapeutic intervention of rheumatoid arthritis

(RA) was dramatically altered with the introduction of biologic drugs with monoclonal antibody or fusion protein structures[1-5] into the armamentarium of disease-modifying anti-rheumatic drugs (DMARDs), which had previously included, non-steroidal anti-inflammatory drugs, immunosuppressive drugs, (*e.g.*, glucocorticoids, methotrexate, sulphasalazine), anti-malarial agents (*e.g.*, hydroxychloroquine), and modifiers of DNA synthesis (*e.g.*, leflunomide)[6-10] or various combinations of these DMARDs. Among the biological drugs chosen for development for RA were those whose mechanism of action was attributed to their capacity to neutralize the downstream effects of the elevated levels of the pro-inflammatory cytokines in RA sera and synovial fluid[11-15], tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6[16-18], among other interleukins[11-13] as well as possessing activity towards the inhibition of proliferation and dysfunctional RA T-cells and B-cells[19-23].

However, the general requirement that the biologic drugs need to be employed in RA therapy for long periods of time has caused problems inherent in their chronic use, including, but not limited to, the elevated relative risk for developing cancers and infections, inadequate drug responses and drug refractoriness and death as well as the potential for antibodies to be produced that are directed against the monoclonal antibodies or fusion proteins themselves[24-27] thus neutralizing their effectiveness. These crucial considerations have resulted in the contention that there needs to be continual identification of novel therapeutic targets coupled to drug development for intervention in RA and autoimmune diseases in general[28,29].

IDENTIFICATION OF PROTEIN KINASES AS POTENTIAL DRUG TARGETS FOR RA

The JAK/STAT pathway

A central theme for considering which component of RA pathology should be targeted for novel drug development first involves identifying a pathway(s) that is involved in the aberrant cell and humoral-mediated immune response and inflammation which regulate abnormal survival of T-, B-cells, macrophages and synoviocytes as well as the loss of chondrocyte viability and vitality, all of which are characteristic elements of RA progression[29]. In that regard, the Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway perfectly fits this viewpoint because JAK/STAT signaling has been shown to regulate so many of the diverse cellular functions critical to RA pathogenesis and progression, including, cell survival and proliferation, immune cell-fate determination and apoptosis[26,28,30,31]. There are 4 members of the JAK family, namely, JAK1, JAK2, JAK3 and TYK2[32] and 7 STAT proteins, STAT1-4, STAT5A, STAT5 and STAT6[33].

The elevated gene expression of several pro-inflammatory cytokines, including interferon-γ (INF-γ), IL-2, IL-6, IL-7, IL-7 receptor, *IL-17*, *IL-15*, *IL-19*, *IL-21*, *IL-23* genes as well as other genes and transcription factors germane to RA pathology are all regulated by phosphorylated (*i.e.*, activated) STAT proteins[33-37]. In addition, there are several STAT-target genes relevant to cell differentiation, survival, apoptosis and cytokine signaling (*e.g.*, cyclin D1, c-Myc, Bcl-xL, Mcl-1, survivin, MKP-1, TNFRSF13b and SOCS-3), all of which play important roles in RA. For example, the complex interaction involving IL-7 and IL-7R appears to be critical for regulating the T-cell receptor-γ-locus *via* phosphorylated STAT5 and histone acetylase. Thus, the findings reported by Hartgring *et al*[38] that RA synovial fluid contained elevated levels of IL-7R made the *IL-7R* gene an even more attractive target for SMI drug development, perhaps through the inhibition of STAT5 activation.

Tofacitinib (CP-690,550)

The development and FDA approval of the first small molecule inhibitor (SMI) of a protein kinase, for use in the therapy of moderate-to-severe active RA in which methotrexate did not work well, arose from a series of sequential optimization protocols involving pyrrolopyrimidine based-JAK3 inhibitors[39], which eventually resulted in the drug CP-690,550, now called tofacitinib[40]. The efficacy of this drug for RA was established in numerous RA clinical trials[41,42] (see below) and tofacitinib has now entered general rheumatology practice.

Ruxolitinib (INCB018424)

Ruxolitinib/INCB018424 now referred to as ruxolitinib is a JAK1 and JAK2 SMI[43]. The results of studies conducted on normal volunteers[44] and RA patients[44] concluded that ruxolitinib was generally safe and well-tolerated and also exhibited acceptable oral bioavailability with dose-proportional systemic pharmacokinetics and pharmacodynamics with low oral dose clearance and a small volume of distribution. Additional results from that study showed that ruxolitinib inhibited the phosphorylation of STAT3 in whole blood that was correlated with the plasma levels of the drug. Additional clinical trials involving patients with mild-to-moderate psoriasis[43] or active RA[45] administered ruxolitinib have now been conducted. In the RA trial, Williams *et al*[45] showed that ruxolitinib achieved an American College of Rheumatology (ACR)-70 criteria in 33% of patients compared to 0% in the placebo arm. Pharmacokinetic analysis determined that ruxolitinib inhibited JAK1 and JAK2 and also reduced plasma levels of IL-6 and CD40, the latter a co-stimulatory protein found on antigen-presenting cells. Ruxolitinib was also a potent p-STAT3 SMI in *ex vivo* studies conducted on blood cells obtained from RA patients.

Pre-clinical studies and development of JAK SMIs

Clinical trials are presently being conducted with RA and psoriasis patients to determine the clinical efficacy of several JAK SMIs, including INCB020850 (specificity, JAK1

Table 1 Janus kinase small molecule inhibitors in development

SMI	JAK Specificity/other kinase inhibitory activity	Ref.
SAR302503 (Fedratinib)	JAK2	[46]
CEP701 (Lestaurtinib)	JAK2	[47]
SB1518 (Pacritinib)	JAK2/FLT3[1]	[48]
XL-019	JAK2	[48]
LY2784544	JAK2/V617F[2]	[49,50]
AZD1480	JAK2	[51]
NS-108	JAK2/Src[3]	[52]
BMS-911453	JAK2	[53]

[1]FLT3: Fms-like tyrosine kinase 3; a receptor-type tyrosine-protein kinase; [2]V617F: A point mutation in JAK2 (V617F) identified in the hematopoietic cells of patients with several chronic myeloproliferative disorders; [3]Src: V-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog; JAK: Janus kinase; SMI: Small molecule inhibitor.

= JAK2), INCB39110 (JAK1 > JAK2), LY3009104 (specificity, similar to INCB020850), PF-956980 (specificity, JAK3) and CYT387 (specificity, JAK1/JAK2; with activity towards TYK2 as well). Clinical studies in normal volunteers and patients with various malignancies are also being conducted with the ultimate goal of developing additional JAK SMIs for use in clinical therapy (Table 1).

According to the PubMed Central database at the time of this writing there are as yet no published Phase 3 RA or psoriasis clinical trials results for INCB020850, INCB39110, LY3009104 or PF-956980. However, Kyttaris[54] recently reviewed the status of the JAK3-selective SMI, VX-509, which showed "promising" results in a Phase 2b clinical trial. In that regard, Genovese *et al*[55] recently reported the results of a 12-24 wk placebo-controlled double-blind phase 2 clinical trial involving RA patients maintained on a stable dose of methotrexate. VX-509 administered orally at 100, 150 and 200 mg QD was employed. The subjects receiving VX-509 showed statistically significant ACR20, ACR50 and ACR70 responses *vs* placebo (*i.e.*, methotrexate) as well as a statistically significant improvement from baseline in the DAS-28-CRP, Health Assessment Questionnaire-D1 (HAQ-D1) and Clinical Disease Activity Index *vs* placebo. However, the adverse event rates were higher in the VX-509 arm, most notably the incidence of infection relative to the placebo.

In a recent preclinical evaluation comparing the effects of tofacitinib with INCB028059 on STAT protein activation, Migita *et al*[56] showed that both tofacitinib and INCB028050 suppressed activation of JAK1/JAK2/JAK3 as well as inhibiting phosphorylation of STAT1/STAT3/STAT5 while also reducing monocyte chemotactic protein-1 (MCP-1) and serum amyloid A1/2 (SAA1/2) levels by oncostatin-stimulated RA synovial fibroblasts. However, another JAK SMI, PF-956980, only inhibited the activation of STAT1/STAT5 and MCP-1, but not SAA1/2.

The efficacy of a JAK3-selective SMI in RA compared to several of the JAK1/JAK2 SMIs now in development for treatment of myeloproliferative diseases and malignancies (Table 1) may be a more desirable result because JAK3 is known to be less involved in hematopoietic cell development than is JAK2[57].

THE MAPK, PI3K/AKT/MTOR AND SYK PATHWAYS

MAPK and PI3K/Akt/mTOR

Signal transduction pathways other than JAK/STAT which are relevant to RA are the mitogen-activated protein kinase (MAPK) and phosphatidylinosotide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PI3K/Akt/mTOR) pathways and intracellular signaling involving spleen tyrosine kinase (Syk)[58,59]. There is strong evidence for "cross-talk" between the JAK/STAT, MAPK and PI3K/Akt/mTOR pathways[26]. There are also many overlapping characteristics in the cellular events that promote the abnormal survival of cancer cells when compared to cells involved in the RA synovial joint which also involve MAPK and PI3K/Akt/mTOR signaling. Thus, it was not surprising that future drug development for RA has taken a page from those experimental interventions which particularly focus on inhibiting the proliferation of cancer cells. In that regard, insights gleaned from studies of MEK1/2, the upstream activator of extracellular signal-regulated kinase1/2 (ERK1/2) and mTOR activity[60] in mutant BRAF-metastatic melanoma[61,62] and other experimental models of malignancy may shed light on whether or not these molecules may be eventually applied to RA.

In that regard, the MEK1/2 SMI, AZD6244 (selumetinib) when used in combination with the mTORC1/mTORC2 SMI, AZD8055, showed significant anti-tumor activity in nude mouse xenograft models of human lung adenocarcinoma and colorectal carcinoma[60], whereas the MEK1/2 inhibitor, AZD6244, sensitized apoptosis-resistant NRAS-mutant lines of melanoma cells to undergo apoptosis. This was correlated with negative regulation of the Wnt/β-catenin signaling *via* ERK1/2 and increased levels of the downstream scaffolding protein, AXIN1[61]. Of note, a Phase 2 trial of selumetinib in patients with the BRAFV600E/K-mutated type of melanoma[62] resulted in tumor regression in 3 of 5 patients with BRAF-mutated low p-Akt activity. However, no response was observed in the AZD6244 treatment group with high p-Akt activity. These results provide a rationale for the dual targeting of MEK1/2 and p-Akt, especially in those melanoma patients with documented high p-Akt activity.

Although there was persuasive pre-clinical data supporting the targeting of p38 kinase-α in RA[63], the results from several clinical trials in which the efficacy of pamapimod was compared to methotrexate in RA patients was disappointing in favor of methotrexate. Thus it is unlikely that pamapimod will be further developed for treating RA[64-66] although the jury is still out, so to speak, regarding whether or not VX-702, another p38 kinase SMI should be further developed and assessed for clinical efficacy in RA patients[67].

SyK signaling

The clinical trial evidence is somewhat stronger, but not persuasive, for promoting the further development of the SyK inhibitor, fostamatinib (R-788)[68], although in 3 RA clinical trials with this drug, the ACR20 response rate ranged from only 35%-38%[69,70]. Moreover, in one of these clinical trials the ACR20 response in the fostamatinib (100 mg twice daily group) was 38%, compared to 35% in the placebo group after 3 mo and no significant differences were achieved in the ACR20, ACR50, or ACR70 response levels at that time.

Protein kinase C-θ

There is also increasing evidence for targeting protein kinase C-θ in RA[71]. This is because protein kinase C-θ is known to play an integral role in regulating T-cell viability and cytoskeletal reorganization by regulating the activities of Vav, PI3K and Rac1 (guanyl-nucleotide exchange factor)[72,73].

THE CLINICAL PERSPECTIVE

Data on the efficacy and safety of tofacitinib in RA was presented to the FDA in May 2012[74]. In November 2012, tofacitinib was approved for use in the US for the treatment of adults with moderately to severe active RA with an inadequate response to, or intolerance to methotrexate. Assessment of the efficacy in RA clinical trials has become fairly standardized[75] and the outcome measures used in the tofacitinib studies were similar to those used in previous clinical trials of biologic drugs for RA. The raw data included a measurement of the tender joint count and the swollen joint count by an examiner, the patient's assessment of pain on a visual analog scale, the patient's global assessment of disease activity on a visual analog scale, an examiner's global assessment of disease activity on a visual analog scale, the patient's assessment of physical function using the HAQ[76], blood testing to determine erythrocyte sedimentation rate (ESR) or CRP, and radiographs of the hands and feet[76]. In most RA studies the raw data is further "manipulated" to produce composite measures of drug efficacy. The ACR has defined the ACR20 response rate as a measure of efficacy in RA to be $\geqslant$ 20% improvement in tender joint count, $\geqslant$ 20% improvement in swollen joint count, and $\geqslant$ 20% improvement in 3 out of 5 of the following parameters: patient pain assessment, patient global assessment, physician global assessment, patient self-assessment of disability and blood acute phase reactant (ESR or CRP)[77]. In the Phase 3 tofacitinib clinical trials, approximately 25%-30% of study patients achieved an ACR20 efficacy when placebo was added to their prior therapy with methotrexate or to another oral immunosuppressant. This was a result that was similar to that previously reported in clinical trials with biologic therapies for RA[74]. In order to demonstrate efficacy that is less likely to be achieved by placebo alone, ACR50 and ACR70 data are also commonly reported, representing $\geqslant$ 50% and $\geqslant$ 70% improvement in the composite ACR score, respectively. Thus, the tender joint count of 28 joints, swollen joint count in 28 joints, serum ESR or CRP and the patient's global assessment of disease activity can be entered into a formula to generate a DAS28-4 score ranging from 0 to 10[78]. If the patient's global assessment of disease activity is omitted, the resulting score is a DAS28-3. A DAS score of $\leqslant$ 2.6 is considered to represent clinical remission, although such a DAS28 score does not necessarily represent a cessation of all joint inflammation. However, DAS28 efficacy measurements are potentially relevant to clinicians, since the DAS28 can be used to track efficacy in clinical practice and a DAS28 $\leqslant$ 2.6 is often the therapeutic goal in treat-to-target clinical trials. Radiographs are also assessed to determine joint space narrowing and the presence of periarticular erosions, which are used to calculate a radiographic score. The method of Sharp as modified by Van der Heijde is commonly employed[79]. This method generates a joint space narrowing score and an erosion score as secondary endpoints, which are combined to generate the primary endpoint, the total Sharp score[76]. Although the publication of this type of radiographic data has become standard over the past 15 years, there are some methodological flaws in this analysis. When efficacy of a new pharmaceutical is assessed, the study population usually adds the new drug to a stable dose of an oral immunosuppressant such as methotrexate. The efficacy data of this population is compared to a group randomized to receive a stable dose of oral immunosuppressant plus placebo. As a result, both groups of subjects receive medication with potential efficacy in RA, and the rise in the modified Sharpe/Van der Heijde score can be slow to rise, even in the placebo group. Therefore, to discern a meaningful difference between the new drug and placebo it may become necessary to choose study subjects with a high risk for the rapid accumulation of joint damage (for example, high serum levels of rheumatoid factor or anti-cyclic citrullinated peptide antibody), to continue to collect radiographic data for 1-2 years or more, or more often to enroll larger numbers of patients.

Ultrasound and Magnetic Resonance Imaging have been proposed as potential substitutes for radiography. However, issues of standardization, reproducibility, potential cost and correlation with other clinical outcome measures are still being worked out, but clinical trials employing these imaging techniques are beginning to appear in published reports.

The dose of tofacitinib used to treat RA in the US is 5 mg orally twice daily. The subjects enrolled in the 5 phase 3 clinical trials were those patients who had experienced an inadequate response to prior treatment with methotrexate, another oral immunosuppressant, or a TNF inhibitor[74]. Most of the study subjects were given either tofacitinib or placebo under a double-blind study design while continuing a stable dose of methotrexate or other oral immunosuppressant. In one of these studies, subjects on a stable dose of methotrexate were given subcutaneous injections (either adalimumab or placebo) plus a pill (placebo pill to recipients of adalimumab, placebo or tofacitinib to recipients of placebo injections). A small

number of subjects were enrolled in a 3 mo study of tofacitinib *vs* placebo without therapy with another immunosuppressant, but there were ethical concerns about randomizing patients with active RA to a study arm in which they were to receive no treatment. In most RA trials the new drug is compared to an active immunosuppressant commonly used in RA (usually methotrexate). The outcome data demonstrated statistically significant efficacy for tofacitinib 5 mg twice daily *vs* placebo as determined by the following outcome measures: ACR20, ACR50, ACR70, DAS-4 (ESR) $\leqslant$ 2.6, DAS-4 (ESR) improving $\geqslant$ 1.2, and HAQ-Disability Index. When compared to 199 subjects receiving adalimumab, 40 mg by subcutaneous injection every 14 d, plus methotrexate plus placebo pills, tofacitinib plus placebo injection plus methotrexate was not inferior using the following outcome measures: ACR20, ACR50, ACR70, DAS-4(ESR) $\leqslant$ 2.6, DAS-4(ESR) improving $\geqslant$ 1.2, HAQ-Disability Index. One of these 5 studies also provided radiographic outcome data. Only 20% of the subjects receiving a stable dose of methotrexate plus placebo demonstrated worsening of the radiographic score at 1 year. In the tofacitinib 5 mg twice daily plus methotrexate treatment group there was a trend toward decreased progression of the total Sharp score, but the difference did not meet statistical significance at either 6 or 12 mo.

Tofacitinib was the first JAK SMI submitted to the FDA for approval in the treatment of RA. As a result the safety assessment was broad in scope, with data collected on mortality, total adverse effects, serious adverse effects, infections, malignancies other than non-melanoma skin cancer, cardiovascular events, and bowel perforations, with monitoring of cell counts, creatinine, liver enzymes, creatinine phosphokinase, and lipid levels in the blood. Data was available for the blinded placebo controlled phase of the study and also the unblinded long-term extension clinical trial. Treatment with tofacitinib was associated with drug dose-dependent neutropenia and lymphopenia, a rise in total HDL and LDL cholesterol, but without associated cardiovascular events, and a rise in serum creatinine[74]. The increased LDL cholesterol improved after the addition of atorvastatin. Overall, the rates per 100 patient-years for all-cause mortality, serious infections, malignancy other than non-melanoma skin cancer, lymphoma, lung cancer, myocardial infarction and gastrointestinal perforation were similar to those reported in published clinical trials of biologic therapies for RA[80]. However, the rate of Herpes zoster infection was higher in the subjects treated with tofacitinib than the infection rates for Herpes zoster reported in prior clinical trials of biologic drugs for RA. After review of the clinical trial data, tofacitinib was considered to be sufficiently safe and effective to be approved for use in the US for moderate to severe active RA not responsive to methotrexate. Of note, post-FDA approval monitoring of the long term safety of tofacitinib is ongoing.

Published RA treatment trials of other small molecule inhibitors have employed a study design similar to those used to assess the safety and efficacy of tofacitinib. As stated above, a phase 2 clinical trial of fostamatinib in RA has now been concluded. Outcome criteria included ACR20, ACR50, ACR70, and DAS28 as measures of efficacy[81]. Imaging outcomes in that study were assessed by MRI. Patient-reported quality of life was assessed using the HAQ-Disability Index, multiple domains of the SF-36 questionnaire, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire[82]. A 12 wk trial of pamapimod *vs* placebo added to a stable dose of methotrexate used ACR20, ACR50, ACR 70, DAS28, change in mean serum CRP, HAQ-DI, SF-36, and FACIT-F as efficacy outcome measures[83]. Clinical trials of other small molecule inhibitors currently under development are likely to have a similar study design.

CONCLUSION

The development of SMIs of the JAK/STAT (including the newly developed JAK3 SMI, VX-509)[84], MAPK, PI3K/Akt/mTOR and SyK signaling pathways has recently been the target of additional pre-clinical experimental arthritis studies and RA clinical trials assessment. The phase 3 clinical trial data for the JAK SMI, tofacitinib, illustrates the therapeutic potential of this class of SMI drug. For example, by comparison with the relative ease of storage and oral administration of these SMI drugs, the treatment of RA with biologic drugs such as the TNF blockade drugs, etanercept, adalimumab, golimumab, certolizumab, the T-cell co-stimulator inhibitor, abatacept, and the IL-6/IL-6R neutralizing monoclonal antibody, tocilizumab, requires that the medication be shipped by rapid delivery, stored at 2 ℃-8 ℃ and maintained in a cool storage temperature during travel. Administration of these drugs also requires mastery of the correct injection technique, and safe and proper disposal of hypodermic needles. Therefore, if the efficacy and safety of protein kinase SMIs proves to be comparable to the injectable types of biologic drugs, many RA patients may prefer the convenience of an oral medication. However, the relatively short half-life of tofacitinib means that twice daily dosing will be necessary to achieve optimal clinical efficacy. This can be an advantage to the RA patient if the patient develops an infection such that the treating clinician may wish to reverse the immunosuppressive effect of the drug. Thus, at present, treatment with tofacitinib is a therapeutic option for moderate-to-severe RA where disease progression cannot be controlled with methotrexate.

Although SMIs have been primarily targeted to inhibit the activity of JAKs, specific members of the MAPK pathway (*e.g.*, p38-α) and PI3K/Akt/mTOR signaling pathways were also shown to be relevant to the pathogenesis of immune-mediated inflammation associated with RA. Therefore, there are likely to be signaling components of the MAPK pathway, such as the upstream protein kinase, MEK1/2, whose activity is required for phosphorylation of ERK1/2 that may be targeted for further drug development[57]. In addition, since one tar-

get of STAT activation is it's potential to increase the expression of anti-inflammatory cytokines, such as, IL-4 and IL-10[37] and the signaling pathways these cytokines activate, it appears justified to consider developing SMIs that inhibit those protein kinases which can suppress the expression of anti-inflammatory cytokine genes.

However, as an example of the continuing SMI drug development for JAKs in RA, Baricitinib, (formerly known as LY3009104/INCB028050) an inhibitor of JAK1 and JAK2 is presently under investigation in clinical trials in RA with the results from an open extension of the phase 2b trial having been recently reported[85] with additional studies entering the recruitment phase[86]. In the open-extension phase 2b trial, among all patients, the proportions of patients achieving ACR20, ACR50, ACR70, clinical disease activity index (CDAI) Remission, simplified disease activity index (SDAI) Remission, DAS28CRP $\leqslant$ 3.2, DAS28CRP < 2.6, DAS28ESR $\leqslant$ 3.2, DAS28CRP < 2.6 or the ACR/European League Against Rheumatism (EULAR) Boolean remission at the start of the open label extension (week 24) were similar or increased at week 52.

The ultimate place of protein kinase SMIs in RA therapy is not yet known. It is likely to be determined by the following conditions; more patient-years of follow-up to better understand the long-term efficacy and safety of this drug class as well as head-to-head safety and efficacy comparisons with conventional and biologic DMARDs already in use including cost issues relative to other RA treatment options

REFERENCES

1 **Malemud CJ**, Reddy SK: Targeting cytokines, chemokines and adhesion molecules in rheumatoid arthritis. *Curr Rheumatol Rev* 2008; **4**: 219-234 [DOI: 10.2174/157339708786263933]

2 **Gibbons LJ**, Hyrich KL. Biologic therapy for rheumatoid arthritis: clinical efficacy and predictors of response. *BioDrugs* 2009; **23**: 111-124 [PMID: 19489652 DOI: 10.1155/2010/529376]

3 **Feely MG**, Erickson A, O'Dell JR. Therapeutic options for rheumatoid arthritis. *Expert Opin Pharmacother* 2009; **10**: 2095-2106 [PMID: 19606939 DOI: 10.1007/s11095-011-0396-7]

4 **Taylor PC**. Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases. *Curr Opin Pharmacol* 2010; **10**: 308-315 [PMID: 20172761 DOI: 10.1186/1476-4598-12-98]

5 **Geyer M**, Müller-Ladner U. Actual status of antiinterleukin-1 therapies in rheumatic diseases. *Curr Opin Rheumatol* 2010; **22**: 246-251 [PMID: 20150813 DOI: 10.1097/BOR.0b013e3283373fa0]

6 **Kumar P**, Banik S. Pharmacotherapy options in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord* 2013; **6**: 35-43 [PMID: 23997576 DOI: 10.4137/CMAMD.S12606]

7 **Braun J**. Methotrexate: optimizing the efficacy in rheumatoid arthritis. *Ther Adv Musculoskelet Dis* 2011; **3**: 151-158 [PMID: 22870474 DOI: 10.1177/1759720X11408635]

8 **Meier FM**, Frerix M, Hermann W, Müller-Ladner U. Current immunotherapy in rheumatoid arthritis. *Immunotherapy* 2013; **5**: 955-974 [PMID: 23998731 DOI: 10.2217/imt.13.94]

9 **Taherian E**, Rao A, Malemud CJ, Askari A: The biological and clinical activity of anti-malarial drugs in autoimmune disorders. *Curr Rheum Rev* 2013; **9**: 45-62 [DOI: 10.2174/1573397111309010001]

10 **Finckh A**, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. *Ann Rheum Dis* 2009; **68**: 33-39 [PMID: 18230627 DOI: 10.1136/ard.2007.085696]

11 **Petrovic-Rackov L**, Pejnovic N. Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis. *Clin Rheumatol* 2006; **25**: 448-452 [PMID: 16362448 DOI: 10.1007/s10067-005-0106-0]

12 **Hartgring SA**, Bijlsma JW, Lafeber FP, van Roon JA. Interleukin-7 induced immunopathology in arthritis. *Ann Rheum Dis* 2006; **65** Suppl 3: iii69-iii74 [PMID: 17038478 DOI: 10.1136/ard.2006.058479]

13 **Lotito AP**, Silva CA, Mello SB. Interleukin-18 in chronic joint diseases. *Autoimmun Rev* 2007; **6**: 253-256 [PMID: 17317618 DOI: 10.1016/j.autrev.2006.08.010]

14 **Paunovic V**, Carroll HP, Vandenbroeck K, Gadina M. Signalling, inflammation and arthritis: crossed signals: the role of interleukin (IL)-12, -17, -23 and -27 in autoimmunity. *Rheumatology* (Oxford) 2008; **47**: 771-776 [PMID: 18238793 DOI: 10.1093/rheumatology/kem352]

15 **Astry B**, Harberts E, Moudgil KD. A cytokine-centric view of the pathogenesis and treatment of autoimmune arthritis. *J Interferon Cytokine Res* 2011; **31**: 927-940 [PMID: 22149412 DOI: 10.1089/jir.2011.0094]

16 **Upchurch KS**, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology* (Oxford) 2012; **51** Suppl 6: vi28-vi36 [PMID: 23221584]

17 **Mertens M**, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. *J Rheumatol* 2009; **36**: 1118-1125 [PMID: 19447938 DOI: 10.3899/jrheum.090074]

18 **Tanaka T**, Kishimoto T: Immunotherapy of tocilizumab for rheumatoid arthritis. *J Clin Cell Immunol* 2013; **S6**: 001 [DOI: 10.4172/2155-9899]

19 **Ostör AJ**. Abatacept: a T-cell co-stimulation modulator for the treatment of rheumatoid arthritis. *Clin Rheumatol* 2008; **27**: 1343-1353 [PMID: 18670735 DOI: 10.1007/s10067-008-0964-3]

20 **Laganà B**, Vinciguerra M, D'Amelio R. Modulation of T-cell co-stimulation in rheumatoid arthritis: clinical experience with abatacept. *Clin Drug Investig* 2009; **29**: 185-202 [PMID: 19243211 DOI: 10.2165/00044011-200929030-00005]

21 **Vicente Rabaneda EF**, Herrero-Beaumont G, Castañeda S. Update on the use of abatacept for the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol* 2013; **9**: 599-621 [PMID: 23899231 DOI: 10.1586/1744666X.2013.811192]

22 **Caporali R**, Caprioli M, Bobbio-Pallavicini F, Bugatti S, Montecucco C. Long term treatment of rheumatoid arthritis with rituximab. *Autoimmun Rev* 2009; **8**: 591-594 [PMID: 19393205]

23 **Blüml S**, McKeever K, Ettinger R, Smolen J, Herbst R. B-cell targeted therapeutics in clinical development. *Arthritis Res Ther* 2013; **15** Suppl **1**: S4 [PMID: 23566679 DOI: 10.1186/ar3906]

24 **Malemud CJ**. Defining novel targets for intervention in rheumatoid arthritis: An overview. *Curr Rheum Rev* 2008; **4**: 214-218 [DOI: 10.2174/157339708786263889]

25 **Malemud CJ**. Molecular mechanisms in rheumatic diseases - Rationale for novel drug development - Introduction. Anti-Inflammatory *Anti-Allergy Agents Med Chem* 2011; **10**: 73-77 [DOI: 10.2174/18715211179508298]

26 **Malemud CJ**, Pearlman E. Targeting JAK/STAT signaling pathway in inflammatory diseases. *Curr Signal Transduct Ther* 2009; **4**: 201-221 [DOI: 10.2174/157436209789057467]

27 **Malemud CJ**. Dysfunctional immune-mediated inflammation in rheumatoid arthritis dictates that development of anti-rheumatic disease drugs target multiple intracellular signaling pathways. *Anti-Inflammatory Anti-Allergy Agents Med Chem* 2011; 10: 78-84 [DOI: 10.2174/187152111795508315]

28 **Seavey MM**, Dobrzanski P. The many faces of Janus kinase. *Biochem Pharmacol* 2012; **83**: 1136-1145 [PMID: 22209716 DOI: 10.5530/pc.2011.1.2]

29 **Malemud CJ**. Targeted drug development for arthritis.

Future Med Chem 2012; **4**: 701-703 [PMID: 22530633 DOI: 10.4155/fmc.12.38]
30 **Norman P**. Selective JAK1 inhibitor and selective Tyk2 inhibitor patents. *Expert Opin Ther Pat* 2012; **22**: 1233-1249 [PMID: 22971156]
31 **Gomez-Puerta JA**, Mócsai A. Tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. *Curr Top Med Chem* 2013; **13**: 760-773 [PMID: 23574525]
32 **Leonard WJ**, O'Shea JJ. Jaks and STATs: biological implications. *Annu Rev Immunol* 1998; **16**: 293-322 [PMID: 9597132]
33 **Ivashkiv LB**, Hu X. Signaling by STATs. *Arthritis Res Ther* 2004; **6**: 159-168 [PMID: 15225360 DOI: 10.1186/ar1197]
34 **O'shea JJ**. Targeting the Jak/STAT pathway for immunosuppression. *Ann Rheum Dis* 2004; **63** Suppl 2: ii67-ii71 [PMID: 15479876 DOI: 10.1136/ard.2004.028290]
35 **Walker JG**, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. *J Rheumatol* 2005; **32**: 1650-1653 [PMID: 16142855 DOI: 10.1136/ard.2005.050385]
36 **Malemud CJ**. Inhibitors of JAK for the treatment of rheumatoid arthritis: rationale and clinical data. *Clin Invest* 2012; **2**: 39-47 [DOI: 10.4155/CLI.11.169]
37 **Malemud CJ**. Suppression of pro-inflammatory cytokines via targeting of STAT-responsive genes. In: El-Shemy H. Drug discovery. (Ed), Rijeka: InTech Publishing, 2012: 373-411 [DOI: 10.5772/52506]
38 **Hartgring SA**, van Roon JA, Wenting-van Wijk M, Jacobs KM, Jahangier ZN, Willis CR, Bijlsma JW, Lafeber FP. Elevated expression of interleukin-7 receptor in inflamed joints mediates interleukin-7-induced immune activation in rheumatoid arthritis. *Arthritis Rheum* 2009; **60**: 2595-2605 [PMID: 19714586 DOI: 10.1002/art.24754]
39 **Flanagan ME**, Blumenkopf TA, Brissette WH, Brown MF, Casavant JM, Shang-Poa C, Doty JL, Elliott EA, Fisher MB, Hines M, Kent C, Kudlacz EM, Lillie BM, Magnuson KS, McCurdy SP, Munchhof MJ, Perry BD, Sawyer PS, Strelevitz TJ, Subramanyam C, Sun J, Whipple DA, Changelian PS. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem* 2010; **53**: 8468-8484 [PMID: 21105711 DOI: 10.1021/jm1004286]
40 **Vijayakrishnan L**, Venkataramanan R, Gulati P. Treating inflammation with the Janus kinase inhibitor CP-690,550. *Trends Pharmacol Sci* 2011; **32**: 25-34 [PMID: 21144599 DOI: 10.1016/j.tips.2010.10.004]
41 **Coombs JH**, Bloom BJ, Breedveld FC, Fletcher MP, Gruben D, Kremer JM, Burgos-Vargas R, Wilkinson B, Zerbini CA, Zwillich SH. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2010; **69**: 413-416 [PMID: 19587388 DOI: 10.1136/ard.2009.108159]
42 **Tanaka Y**, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res* (Hoboken) 2011; **63**: 1150-1158 [PMID: 21584942 DOI: 10.1002/acr.20494]
43 **Mesa RA**. Ruxolitinib, a selective JAK1 and JAK2 inhibitor for the treatment of myeloproliferative neoplasms and psoriasis. *IDrugs* 2010; **13**: 394-403 [PMID: 20506062 DOI: 10.1182/blood-2011-11-395228]
44 **Shi JG**, Chen X, McGee RF, Landman RR, Emm T, Lo Y, Scherle PA, Punwani NG, Williams WV, Yeleswaram S. The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. *J Clin Pharmacol* 2011; **51**: 1644-1654 [PMID: 21257798 DOI: 10.1177/0091270010389469]
45 **Williams W**, Scherle P, Shi P, Newton R. McKeeve E, Fridman J, Burn T, Vaddi K, Levy R, Moreland LA: . A randomized placebo-controlled study of INCB018424, a selective janus kinase 1&2 (JAK1&2) inhibitor in rheumatoid arthritis (RA). *Arthritis Rheum* 2008; **58**: S431
46 **Gotlib J**. JAK inhibition in the myeloproliferative neoplasms: lessons learned from the bench and bedside. *Hematology Am Soc Hematol Educ Program* 2013; **2013**: 529-537 [PMID: 24319228]
47 **Furqan M**, Mukhi N, Lee B, Liu D. Dysregulation of JAK-STAT pathway in hematological malignancies and JAK inhibitors for clinical application. *Biomark Res* 2013; **1**: 5 [PMID: 24252238 DOI: 10.1186/2050-7771-1-5]
48 **Gowin K**, Emanuel R, Geyer H, Mesa RA. The new landscape of therapy for myelofibrosis. *Curr Hematol Malig Rep* 2013; **8**: 325-332 [PMID: 24101258 DOI: 10.1007/s11899-013-0178-x]
49 **Rosenthal A**, Mesa RA. Janus kinase inhibitors for the treatment of myeloproliferative neoplasms. *Expert Opin Pharmacother* 2014; **15**: 1265-1276 [PMID: 24766055 DOI: 10.1517/14656566.2014.913024]
50 **Ma L**, Clayton JR, Walgren RA, Zhao B, Evans RJ, Smith MC, Heinz-Taheny KM, Kreklau EL, Bloem L, Pitou C, Shen W, Strelow JM, Halstead C, Rempala ME, Parthasarathy S, Gillig JR, Heinz LJ, Pei H, Wang Y, Stancato LF, Dowless MS, Iversen PW, Burkholder TP. Discovery and characterization of LY2784544, a small-molecule tyrosine kinase inhibitor of JAK2V617F. *Blood Cancer J* 2013; **3**: e109 [PMID: 23584399 DOI: 10.1038/bcj]
51 **Lee JH**, Park KS, Alberobello AT, Kallakury B, Weng MT, Wang Y, Giaccone G. The Janus kinases inhibitor AZD1480 attenuates growth of small cell lung cancers in vitro and in vivo. *Clin Cancer Res* 2013; **19**: 6777-6786 [PMID: 24158701 DOI: 10.1158/1078-0432.CCR-13-1110]
52 **Nakaya Y**, Shide K, Niwa T, Homan J, Sugahara S, Horio T, Kuramoto K, Kotera T, Shibayama H, Hori K, Naito H, Shimoda K. Efficacy of NS-018, a potent and selective JAK2/Src inhibitor, in primary cells and mouse models of myeloproliferative neoplasms. *Blood Cancer J* 2011; **1**: e29 [PMID: 22829185 DOI: 10.1038/bcj.2011.29]
53 **Tam CS**, Verstovsek S. Investigational Janus kinase inhibitors. *Expert Opin Investig Drugs* 2013; **22**: 687-699 [PMID: 23432430 DOI: 10.1517/13543784.2013.774373]
54 **Kyttaris VC**. Kinase inhibitors: a new class of antirheumatic drugs. *Drug Des Devel Ther* 2012; **6**: 245-250 [PMID: 23055694 DOI: 10.2147/DDDT.S25426]
55 **Genovese MC**, van Vollenhoven R, Bloom BJ, Jiang JG, Kinnman N: A phase 2b, 12-week study of VX-509, an oral selective Janus kinase 3 inhibitor, in combination with background methotrexate in rheumatoid arthritis. *Arthritis Rheum* 2013; **65**: 3320
56 **Migita K**, Izumi Y, Torigoshi T, Satomura K, Izumi M, Nishino Y, Jiuchi Y, Nakamura M, Kozuru H, Nonaka F, Eguchi K, Kawakami A, Motokawa S. Inhibition of Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway in rheumatoid synovial fibroblasts using small molecule compounds. *Clin Exp Immunol* 2013; **174**: 356-363 [PMID: 23968543 DOI: 10.1111/cei.12190]
57 **Malemud CJ**. The discovery of novel experimental therapies for inflammatory arthritis. *Mediators Inflamm* 2009; **2009**: 698769 [PMID: 20339519 DOI: 10.1155/2009/698769]
58 **Bonilla-Hernán MG**, Miranda-Carús ME, Martin-Mola E. New drugs beyond biologics in rheumatoid arthritis: the kinase inhibitors. *Rheumatology* (Oxford) 2011; **50**: 1542-1550 [PMID: 21622522]
59 **Shaw HM**, Nathan PD. Vemurafenib in melanoma. *Expert Rev Anticancer Ther* 2013; **13**: 513-522 [PMID: 23617343 DOI: 10.1586/era.13.24]
60 **Holt SV**, Logie A, Davies BR, Alferez D, Runswick S, Fenton S, Chresta CM, Gu Y, Zhang J, Wu YL, Wilkinson RW, Guichard SM, Smith PD. Enhanced apoptosis and tumor growth suppression elicited by combination of MEK (selu-

metinib) and mTOR kinase inhibitors (AZD8055). *Cancer Res* 2012; **72**: 1804-1813 [PMID: 22271687 DOI: 10.1158/0008-5472.CAN-11-1780]
61 **Conrad WH**, Swift RD, Biechele TL, Kulikauskas RM, Moon RT, Chien AJ. Regulating the response to targeted MEK inhibition in melanoma: enhancing apoptosis in NRAS- and BRAF-mutant melanoma cells with Wnt/β-catenin activation. *Cell Cycle* 2012; **11**: 3724-3730 [PMID: 22895053 DOI: 10.4161/cc.21645]
62 **Catalanotti F**, Solit DB, Pulitzer MP, Berger MF, Scott SN, Iyriboz T, Lacouture ME, Panageas KS, Wolchok JD, Carvajal RD, Schwartz GK, Rosen N, Chapman PB. Phase II trial of MEK inhibitor selumetinib (AZD6244, ARRY-142886) in patients with BRAFV600E/K-mutated melanoma. *Clin Cancer Res* 2013; **19**: 2257-2264 [PMID: 23444215 DOI: 10.1158/1078-0432.CCR-12-3476]
63 **Cohen S**, Fleischmann R. Kinase inhibitors: a new approach to rheumatoid arthritis treatment. *Curr Opin Rheumatol* 2010; **22**: 330-335 [PMID: 20164774 DOI: 10.1097/BOR.0b013e3283378e6f]
64 **Doggrell SA**, Christensen AM. Does the p38 MAP kinase inhibitor pamapimod have potential for the treatment of rheumatoid arthritis? *Expert Opin Pharmacother* 2010; **11**: 2437-2442 [PMID: 20666701 DOI: 10.1517/14656566.2010.507631]
65 **Cohen SB**, Cheng TT, Chindalore V, Damjanov N, Burgos-Vargas R, Delora P, Zimany K, Travers H, Caulfield JP. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. *Arthritis Rheum* 2009; **60**: 335-344 [PMID: 19180516 DOI: 10.1002/art.24266]
66 **Genovese MC**. Inhibition of p38: has the fat lady sung? *Arthritis Rheum* 2009; **60**: 317-320 [PMID: 19180514 DOI: 10.1002/art.24264]
67 **Damjanov N**, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. *Arthritis Rheum* 2009; **60**: 1232-1241 [PMID: 19404957 DOI: 10.1002/art.24485]
68 **Morales-Torres J**. The status of fostamatinib in the treatment of rheumatoid arthritis. *Expert Rev Clin Immunol* 2012; **8**: 609-615 [PMID: 23078058 DOI: 10.1586/eci.12.63]
69 **Nijjar JS**, Tindell A, McInnes IB, Siebert S. Inhibition of spleen tyrosine kinase in the treatment of rheumatoid arthritis. *Rheumatology* (Oxford) 2013; **52**: 1556-1562 [PMID: 23861534 DOI: 10.1093/rheumatology/ket225]
70 **Scott DL**. Role of spleen tyrosine kinase inhibitors in the management of rheumatoid arthritis. *Drugs* 2011; **71**: 1121-1132 [PMID: 21711059 DOI: 10.2165/11591480-000000000-00000]
71 **Altman A**, Villalba M. Protein kinase C-theta (PKC theta): a key enzyme in T cell life and death. *J Biochem* 2002; **132**: 841-846 [PMID: 12473184]
72 **Chand S**, Mehta N, Bahia MS, Dixit A, Silakari O. Protein kinase C-theta inhibitors: a novel therapy for inflammatory disorders. *Curr Pharm Des* 2012; **18**: 4725-4746 [PMID: 22830352]
73 Tofacitinib FDA Briefing Package May 9, 2012. Available from: URL: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm302956.htm
74 **Kirkham JJ**, Boers M, Tugwell P, Clarke M, Williamson PR. Outcome measures in rheumatoid arthritis randomised trials over the last 50 years. *Trials* 2013; **14**: 324 [PMID: 24103529 DOI: 10.1186/1745-6215-14-324]
75 **Fries JF**, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; **23**: 137-145 [PMID: 7362664]
76 **van der Heijde D**, Simon L, Smolen J, Strand V, Sharp J, Boers M, Breedveld F, Weisman M, Weinblatt M, Rau R, Lipsky P. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a round-table discussion. *Arthritis Rheum* 2002; **47**: 215-218 [PMID: 11954017]
77 **Felson DT**, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, Katz LM, Lightfoot R, Paulus H, Strand V. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; **38**: 727-735 [PMID: 7779114]
78 **Prevoo ML**, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; **38**: 44-48 [PMID: 7818570]
79 **van der Heijde D**. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 1999; **26**: 743-745 [PMID: 10090194]
80 Tofacitinib Pfizer Briefing Package May 9, 2012. Available from: URL: http://www.fda.gov/downloads/AdvisoryCommittees/.../Drugs/.../UCM302960
81 **Genovese MC**, Kavanaugh A, Weinblatt ME, Peterfy C, DiCarlo J, White ML, O'Brien M, Grossbard EB, Magilavy DB. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. *Arthritis Rheum* 2011; **63**: 337-345 [PMID: 21279990 DOI: 10.1002/art.30114]
82 **Weinblatt ME**, Kavanaugh A, Genovese MC, Jones DA, Musser TK, Grossbard EB, Magilavy DB. Effects of fostamatinib (R788), an oral spleen tyrosine kinase inhibitor, on health-related quality of life in patients with active rheumatoid arthritis: analyses of patient-reported outcomes from a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2013; **40**: 369-378 [PMID: 23378467 DOI: 10.3899/jrheum.120923]
83 **Alten RE**, Zerbini C, Jeka S, Irazoque F, Khatib F, Emery P, Bertasso A, Rabbia M, Caulfield JP. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. *Ann Rheum Dis* 2010; **69**: 364-367 [PMID: 19357113 DOI: 10.1136/ard.2008.104802]
84 Oral selective JAK3 inhibitor VX-509 showed statistically significant signs and symptoms of rheumatoid arthritis after 12 weeks of study. Available from: URL: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=798474]
85 Abstracts from the European Workshop for Rheumatology Research, 20–22 February 2014, Lisbon, Portugal. *Ann Rheum Dis* 2014; **73** Suppl 1: A1-98 [PMID: 24489135 DOI: 10.1136/annrheumdis-2013-205124.71]
86 A randomized, double-blind, placebo-and active-controlled, phase 3 study evaluating the efficacy and safety of Baricitinib in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate therapy. Available from: URL: http://Clinicaltrials.gov/NCT01710358Clinicaltrials.gov/NCT01710358

P- Reviewer: Chen Q, Lee WH, Mattei JP, Mosca JD, Yazisiz V
S- Editor: Wen LL **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com