

# Kinase inhibitors: a new class of antirheumatic drugs

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**Abstract:** The outlook for patients with rheumatoid arthritis has improved significantly over the last three decades with the use of disease-modifying antirheumatic drugs. However, despite the use of methotrexate, cytokine inhibitors, and molecules targeting T and B cells, a percentage of patients do not respond or lose their response over time. The autoimmune process in rheumatoid arthritis depends on activation of immune cells, which utilize intracellular kinases to respond to external stimuli such as cytokines, immune complexes, and antigens. In the past decade, small molecules targeting several kinases, such as p38 MAPK, Syk, and JAK have been developed. Several p38 MAPK inhibitors proved ineffective in treating rheumatoid arthritis. The Syk inhibitor, fostamatinib, proved superior to placebo in Phase II trials and is currently under Phase III investigation. Tofacitinib, a JAK1/3 inhibitor, was shown to be efficacious in two Phase III trials, while VX-509, a JAK3 inhibitor, showed promising results in a Phase II trial. Fostamatinib and tofacitinib were associated with increased rates of infection, elevation of liver enzymes, and neutropenia. Moreover, fostamatinib caused elevations of blood pressure and diarrhea, while tofacitinib was associated with an increase in creatinine and elevation of lipid levels.

**Keywords:** rheumatoid arthritis, kinase inhibitors, mitogen-activated phosphokinase p38, spleen tyrosine kinase, Janus kinases

## Current treatment paradigm in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by infiltration of the synovium, a structure that lines the joints, with inflammatory cells. The thickened synovium forms a lesion called pannus that slowly destroys the cartilage and the bone adjacent to the joint. Both the small joints of the hands and feet and the larger joints such as the knees and wrists become damaged in RA, ultimately leading to severe functional impairment. More aggressive forms of RA also involve extra-articular tissues, causing lung inflammation, splenomegaly with cytopenia, skin nodules, and vasculitis. Therefore, treatment of RA aims at stopping the inflammatory response before permanent damage occurs.

The natural history of RA has changed dramatically since the 1980s with the introduction of methotrexate, a potent drug with a good safety profile.<sup>1</sup> Methotrexate, as compared with anti-inflammatory drugs that merely alleviate temporarily the symptoms of joint inflammation, changed the course of the disease, retarding or even preventing the development of bone erosions, thus becoming the penultimate disease-modifying antirheumatic drug (DMARD).

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In the 1990s, significant work on the pathophysiology of RA led to the development of specific DMARDs using monoclonal antibodies and receptor decoys. The extracellular cytokines, tumor necrosis factor- $\alpha$ <sup>2</sup> and interleukin-1,<sup>3</sup> were the first cytokines to be successfully targeted, followed by interleukin-6.<sup>4</sup> Additionally, T cell activation was targeted using a hybrid molecule, CTLA4-Ig,<sup>5</sup> that prevents the interaction between T cells and antigen-presenting cells. Finally, elimination of B cells using an antibody that targets the surface molecule CD20 was proven very effective in alleviating the disease.<sup>6</sup> The efficacy and side effect profiles of the biologic treatments made them a mainstay of treatment alongside or without methotrexate.

However, these biologic treatments need to be injected subcutaneously or intravenously, are expensive, and have significant side effects, such as infection<sup>7</sup> and immunologic reactions against the compound itself.<sup>8</sup> Moreover, a significant proportion of the patients treated with biologics and/or methotrexate do not respond or lose their response to the treatment. Therefore, oral, relatively cheap, small molecules targeting specific pathways could represent a valuable addition to the current DMARD armamentarium.

## Efficacy measures in clinical trials

In the 1990s, the European League Against Rheumatism and the American College of Rheumatology (ACR) developed disease outcome measures, of which the ACR 20% response (ACR20)<sup>9</sup> is widely used in most large randomized, placebo-controlled trials in RA. For a patient to be regarded as a responder based on the ACR20 response criterion, he or she must have at least 20% improvement in both swollen and tender joint counts and three out of the following five variables: patient and evaluator global disease activity, pain assessment, functional disability, and acute-phase reactants (sedimentation rate or C-reactive protein).

It has to be stated though that patients with 20% improvement in their disease activity may still have significant disease burden and are likely not in remission. Therefore, the ACR50 and ACR70 responses, which represent 50% and 70%, respectively, improvement over baseline, are routinely reported in RA trials and may be more important in assessing the effectiveness of antirheumatic treatments.

## Novel targets in RA: kinase inhibitors

More recently, a new category of drugs targeting cytoplasmic kinases has been developed and shown to be helpful in the treatment of immune diseases and cancer. As stated above, RA is characterized by activation of several different types

of immune cells that infiltrate the joints, ultimately leading to joint destruction. Successful activation of immune cells requires integration of external stimuli through their surface receptors. Once the receptor attaches to its ligand, such as a proinflammatory cytokine, (self)-antigen, or immune complex, conformational changes lead to activation of intracellular kinases attached to the receptor. These enzymes phosphorylate downstream molecules, propagating a cascade that leads to transcription of genes coding effector molecules. In the case of RA, kinases play a central role in the aberrant immune system activation and hence have been targeted using small molecule inhibitors. Mitogen-activated phosphokinase p38 (MAPK), spleen tyrosine kinase (Syk), and Janus kinases (JAKs) have been studied extensively in clinical trials in RA (summarized in Table 1) and are the focus of this review.

## p38 MAPK

One of the first kinases to be targeted in RA was MAPK. p38 MAPK is a serine-threonine kinase that is activated via phosphorylation by MAPK kinase.<sup>10</sup> Activation of MAPK is induced by various extracellular stimuli and can result in the production of tumor necrosis factor- $\alpha$  and interleukin-1 by monocytes, as well as interleukin-6.<sup>11,12</sup> Given the importance of these cytokines in the pathophysiology of RA, it is not surprising that MAPK was upregulated in rheumatoid synovium<sup>13</sup> and that inhibition of MAPK led to amelioration of the disease in experimental arthritis in rats.<sup>14</sup>

Following the promising *in vitro* and animal data, several small molecules specifically targeting p38 MAPK were developed. However, the results from clinical trials in humans were largely negative. Pamapimod<sup>15,16</sup> and VX-702<sup>17</sup> were studied in conjunction with methotrexate. The effect of these drugs was not statistically superior to placebo. More recently, the results of a Phase II clinical trial of SCIO-469 did not show an effect either.<sup>18</sup> Interestingly, these studies showed a biologic effect of MAPK inhibition, which was a decrease in the inflammatory index C-reactive protein in the first few weeks of treatment. Unfortunately, this decrease in C-reactive protein was not followed by a clinical response, and the C-reactive protein levels gradually climbed back up. Several factors have been blamed for the ineffectiveness of p38 inhibitors, including inadequate dosing due to side effects or induction of other kinases that can take over the role of p38 in cell activation.

## Syk

Unlike MAPK, Syk is a tyrosine kinase that associates directly with surface receptors, including the B cell receptor and Fc $\gamma$  receptor, on macrophages, mast cells, and neutrophils.<sup>19</sup>

**Table I** Summary of published studies of kinase inhibitors in patients with rheumatoid arthritis

Target	Compound	Phase (duration)	Trial design	ACR20 active compound	ACR20 control
p38 MAPK	Pamapimod	II (12 weeks)	Pamapimod + methotrexate versus methotrexate <sup>15</sup>	31%–43%	34%
		II (12 weeks)	Pamapimod versus methotrexate <sup>16</sup>	18%–31%	45%
	VX-702	II (12 weeks)	VX-702 versus placebo <sup>17</sup>	36%–40%	28%
		II (12 weeks)	VX-702 + methotrexate versus methotrexate <sup>17</sup>	40%–44%	22%
Syk	SCIO-469	II (12 weeks)	SCIO-469 versus placebo <sup>18</sup>	23.1%–32.9%	24%
		II (12 weeks)	Fostamatinib versus placebo <sup>21</sup>	65%–72% (100 and 150 mg)	38%
	Fostamatinib (R406, R788)	II (24 weeks)	Fostamatinib versus placebo <sup>22</sup>	57%–67%	35%
		II (patients who failed biologics)	Fostamatinib versus placebo <sup>23</sup>	38%	37%
JAK	Tofacitinib (CP-690,550)	Ila (6 week)	Tofacitinib versus placebo <sup>25</sup>	70.5%–81.2%	29.2%
		Ilb (24 weeks)	Tofacitinib + methotrexate versus methotrexate <sup>26</sup>	52.9%	33.3%
	II (12 weeks)	Tofacitinib versus adalimumab versus placebo <sup>27</sup>	39.2%–71.9%	35.9% (adalimumab) 22% (placebo)	
	III (6 months, endpoint at 3 months)	Tofacitinib versus placebo	59.8% (5 mg group), 65.7% (10 mg group)	26.7%	
	III (12 months, endpoint at 6 months)	Tofacitinib + methotrexate versus adalimumab + methotrexate versus methotrexate	51.5% (5 mg group), 52.6% (10 mg group)	47.2% (adalimumab) 28.3% (placebo)	

**Abbreviation:** ACR, American College of Rheumatology.

Myeloid-derived cells, such as osteoclasts, also express Syk, which makes this molecule an attractive targeting candidate in RA because its inhibition could theoretically target both inflammation and bone erosion. Indeed, the small molecule, R406, that blocks Syk, as well as its orally available prodrug R788, inhibited the development of experimental arthritis in rats without significantly affecting antibody production.<sup>20</sup>

In a randomized, placebo-controlled Phase II trial, R788 (renamed fostamatinib) when added to background methotrexate at a stable dose was effective in meeting the primary outcome of ACR20 response at 12 weeks.<sup>21</sup> Patients taking fostamatinib at a dose of 100 mg twice a day or 150 mg twice a day achieved ACR20 responses of 65% and 72%, respectively, as opposed to 38% in the placebo group. ACR50 and ACR70 responses were also significantly better than placebo. The lower dose of 50 mg twice a day did not improve the outcome as compared with placebo. Side effects included diarrhea, neutropenia, alanine transferase elevation, and increased blood pressure. Most side effects were associated with the higher doses of fostamatinib. A larger study for 24 weeks reported similar efficacy for the 100 mg and 150 mg twice-daily doses, although a dose effect was not seen with these doses.<sup>22</sup> Side effects were similar to those seen in the first study, with diarrhea, neutropenia, and abdominal pain being significantly more common in the two treatment groups

than in the placebo group, while upper respiratory infections were more common in the high-dose group as compared with placebo. The issue of the unexplained effect of fostamatinib on blood pressure was addressed thoroughly in this study. As in the previous smaller trial, there was an increase in mean blood pressure in the fostamatinib group by 5 mmHg one month following initiation of treatment. Some of the patients needed new antihypertensive agents or adjustment of the dose of their established antihypertensive medications.

Fostamatinib was also evaluated in patients who had failed treatment with biologics. This group of patients is generally the most difficult to treat, and their treatment remains an unmet need. Fostamatinib did not improve the ACR20 outcome significantly over placebo,<sup>23</sup> although some secondary outcomes showed that fostamatinib might have a minor effect, especially in patients with higher C-reactive protein at baseline. A Phase III clinical trial of fostamatinib is under way evaluating its efficacy in reducing inflammation and inhibiting erosions in patients who have a suboptimal response to methotrexate.

Overall, fostamatinib is a novel DMARD that is efficacious in reducing inflammation and improving clinical activity in patients with RA. Important side effects include neutropenia, elevation of liver enzymes, diarrhea, infections, and elevation of blood pressure.

## JAK inhibitors

The JAK family of tyrosine kinases was first recognized 20 years ago as essential in interferon-dependent signaling. Later, these kinases were found to be associated with a variety of cytokine receptors, such as those for interleukin-2, interleukin-12, and interleukin-6, as well as the receptor for erythropoietin. Upon ligation of these receptors with their ligand cytokine, JAKs become activated, phosphorylate their receptors, and recruit the signal transducers and activators of transcription proteins, leading to activation of the relevant genes. Because cytokine receptors are expressed on most immune cells, including T cells, B cells, monocytes, and granulocytes, JAK-mediated signaling is pivotal in immune activation. To date, four members of this family are known, ie, JAK1, JAK2, JAK3, and TYK2.

The best studied JAK inhibitor in RA is tofacitinib (also known as CP-690,550), a molecule that primarily inhibits JAK1 and JAK3 and, to a lesser extent, JAK2. This is thought to be advantageous in terms of potential hematologic toxicity, because hematopoietic cytokine receptors, such as the erythropoietin receptor, associate with JAK2 homodimers. Tofacitinib was shown to be effective in preventing cartilage damage in mouse and rat models of experimental arthritis.<sup>24</sup> After small proof-of-concept trials in humans, Kremer et al conducted a six-week Phase IIa study<sup>25</sup> that evaluated patients who either could not tolerate or did not respond to methotrexate and/or one tumor necrosis factor- $\alpha$  inhibitor. The patients were randomized to CP-690,550 5 mg twice a day, 15 mg twice a day, 30 mg twice a day, or placebo. The investigators described a rapid (within 1–2 weeks) response to the drug, with ACR20 responses of 70.5%, 81.2%, and 76.4% in the 5 mg, 15 mg, and 30 mg dose groups, as opposed to 29.2% in the placebo group.

In a Phase IIb study, tofacitinib at various doses (20 mg once a day or 1 mg, 3 mg, 5 mg, 10 mg, and 15 mg twice daily) or placebo was added onto stable background methotrexate.<sup>26</sup> The patients enrolled in the study had active disease despite methotrexate at a mean dose of 16–17 mg per week. Treatment with 3 mg twice daily or more of tofacitinib resulted in higher response rates than for placebo starting as early as week 2 and sustained through to week 24 of treatment. In particular, the ACR20 response rate was 52.9% for the 3 mg twice-daily group compared with 33.3% for the placebo group. Adverse events that seemed to be associated with tofacitinib included: infections (five serious, with one death); a decrease in neutrophil count, with one patient developing moderate neutropenia but no patient developing severe neutropenia; and small increases in creatinine

levels, transaminases, and lipid levels. Interestingly, patients receiving lower doses of tofacitinib had mild improvement in their hemoglobin possibly associated with better disease control, while patients on higher doses had a mild decrease in their hemoglobin levels, possibly reflecting JAK2 inhibition.

In a related study, Fleischmann et al<sup>27</sup> compared tofacitinib with adalimumab, a tumor necrosis factor- $\alpha$  inhibitor, in patients with active RA. Impressively, tofacitinib monotherapy resulted in a dose-dependent response that was better than both adalimumab or placebo. At week 12, the ACR20 responses were between 39.2% for the 3 mg twice-daily dose and 71.9% for the 15 mg twice-daily dose. This compared with 22% for placebo and 35.9% for adalimumab. Similarly, half the patients on the high dose of tofacitinib reached the ACR50 response mark and a quarter of them reached ACR70. The rate and severity of adverse events was comparable with that in the study by Kremer et al.<sup>25</sup>

Following on from these trials, several pivotal Phase III trials of tofacitinib in RA were recently published. Patients who failed at least one biologic or conventional DMARD were randomized to receive placebo or tofacitinib 5 mg twice a day (low dose) or 10 mg twice a day (high dose) for 6 months. Patients on the placebo arm were switched to active medication at three months. The primary endpoint of ACR20 was met in the study, with the two tofacitinib groups reaching ACR20 responses of 59.8% (low dose) and 65.7% (high dose) versus 26.7% for the placebo group.<sup>28</sup> The side effect profile of tofacitinib appeared similar to that in the Phase II trials, ie, infections, lipid level elevation, and hematologic effects (neutropenia). Neutropenia (mild in general) developed in 3.1% and 3.7% of patients in the two tofacitinib groups (5 mg and 10 mg, respectively) versus <1% in the placebo group. Seven serious infections were observed during the trial, four in the high-dose group (bronchitis, tuberculous pleural effusion, pyelonephritis, and liver abscess) and three cases of cellulitis in two patients, one in the low-dose group and one in the placebo group. Increased creatinine was observed, but this was mild, with only three patients having an increase of more than 50% from baseline and still within normal limits.

In a parallel 12-month study, patients on methotrexate were assigned to the same two doses of tofacitinib as above, adalimumab 40 mg every other week, or placebo. The patients on placebo who did not achieve an improvement of at least 20% by three months were switched to tofacitinib. At month 6, tofacitinib was found to be equivalent to

adalimumab,<sup>29</sup> with ACR20 responses of 51.5%, 52.6%, and 47.2% for low-dose tofacitinib, high-dose tofacitinib, and adalimumab, respectively. This was in contrast with a 28.3% ACR20 response rate in the placebo group. The side effects observed were similar to the monotherapy study, albeit with increased rates of infection and two cases of pulmonary tuberculosis in the high-dose group. A very mild decrease in hemoglobin was observed in patients receiving tofacitinib 10 mg twice daily with methotrexate.

Data from the clinical trials and long-term extension trials representing 5651 patient-years showed that the incidence of malignancy (excluding nonmelanoma skin cancer) was 0.89 per 1000 patient-years.<sup>30</sup> These malignancies mainly included lung cancer, breast cancer, and lymphomas, and their overall incidence did not significantly differ from the observed rate in patients with severe RA taking DMARDs. Similarly, cardiovascular events over 2098.2 patient-years seemed to be similar to those seen in patients with RA.<sup>31</sup> However, the follow-up period was probably inadequate to exclude small increases in malignancies and cardiovascular events convincingly.

Interim analysis of a related study at 12 months showed that tofacitinib 5 mg and 10 mg twice daily was superior to placebo in reducing the progression of structural damage, ie, bony erosions.<sup>32</sup>

Several other JAK inhibitors are currently in various stages of development. VX-509, a selective JAK3 inhibitor, was evaluated in a Phase II dose-finding trial as monotherapy for patients with active RA who had failed nonbiologic DMARDs.<sup>33</sup> VX-509 showed a dose-dependent increase in ACR20 versus placebo (ACR20 66%, 65%, 61%, 39% and 29% in 150 mg, 100 mg, 50 mg, 25 mg twice a day, or placebo groups, respectively). Again, mild elevations of low-density and high-density lipoprotein levels were observed, but with no effects on hemoglobin, neutrophils, or creatinine. Given the short period of the trial (12 weeks) and the low number of patients (40–41 per group), no firm conclusion regarding side effects can be determined. GLPG0634, a JAK1 inhibitor and INCB028050, a JAK1/2 inhibitor, are also being evaluated for their effectiveness in RA.

JAK inhibitors are efficacious oral medications in RA and can be used as monotherapy or with background methotrexate treatment. Dose-related side effects include infections, increased lipid levels, anemia, neutropenia, elevation of transaminases, and possibly changes in renal function.

## Conclusion

The use of biologics over the last 10 years has improved the outcomes for RA patients, building on the previous success

of methotrexate as a potent DMARD. Challenges remain, because a significant percentage of patients either cannot tolerate or obtain incomplete relief from these medications. Additionally, the cost of therapy remains very high, and the patients have to undergo either intravenous or subcutaneous injections.

The small molecules that target kinases are very potent in alleviating symptoms and seem to prevent structural damage, according to preliminary data. In particular, Syk and JAK inhibitors are in line to be approved as therapies for RA. These medications may represent a major shift in the treatment of RA. Given their cost and ease of administration, one could argue that they should be the first drugs to add in patients with RA who are intolerant or do not respond to methotrexate. Their precise role will need to be defined in real-world clinical practice.

As these drugs move towards approval, their long-term safety will need to be addressed as well. Aside from their expected side effects, such as suppression of the immune system, kinase inhibitors show class-specific adverse events that possibly represent off-target effects. Fostamatinib was associated with increased blood pressure whereas JAK inhibitors caused elevation of lipid levels. These side effects may increase the risk of cardiovascular disease, a known complication of RA. Therefore, the effects of fostamatinib and tofacitinib on cardiovascular risk factors will need to be investigated thoroughly during the pivotal Phase III trials, in Phase IV extension trials, and post-marketing surveillance.

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## References

- Weinblatt ME, Trentham DE, Fraser PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1988;31:167–175.
- Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med.* 1999;340:253–259.
- Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum.* 1998;41:2196–2204.
- Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 2006;54:2817–2829.

5. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med*. 2003;349:1907–1915.
6. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med*. 2004;350:2572–2581.
7. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum*. 2009;60:1884–1894.
8. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601–608.
9. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 1995;38:727–735.
10. Cuadrado A, Nebreda AR. Mechanisms and functions of p38 MAPK signalling. *Biochem J*. 2010;429:403–417.
11. Lee JC, Laydon JT, McDonnell PC, et al. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. *Nature*. 1994;372:739–746.
12. Beyaert R, Cuenda A, Vanden Berghe W, et al. The p38/RK mitogen-activated protein kinase pathway regulates interleukin-6 synthesis response to tumor necrosis factor. *EMBO J*. 1996;15:1914–1923.
13. Schett G, Tohidast-Akrad M, Smolen JS, et al. Activation, differential localization, and regulation of the stress-activated protein kinases, extracellular signal-regulated kinase, c-JUN N-terminal kinase, and p38 mitogen-activated protein kinase, in synovial tissue and cells in rheumatoid arthritis. *Arthritis Rheum*. 2000;43:2501–2512.
14. Nishikawa M, Myoui A, Tomita T, Takahi K, Nampei A, Yoshikawa H. Prevention of the onset and progression of collagen-induced arthritis in rats by the potent p38 mitogen-activated protein kinase inhibitor FR167653. *Arthritis Rheum*. 2003;48:2670–2681.
15. Alten RE, Zerbin C, Jeka S, et al. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. *Ann Rheum Dis*. 2010;69:364–367.
16. Cohen SB, Cheng TT, Chindalore V, et al. 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.
17. 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.
18. Genovese MC, Cohen SB, Wofsy D, et al. A 24-week, randomized, double-blind, placebo-controlled, parallel group study of the efficacy of oral SCIO-469, a p38 mitogen-activated protein kinase inhibitor, in patients with active rheumatoid arthritis. *J Rheumatol*. 2011;38:846–854.
19. Riccaboni M, Bianchi I, Petrillo P. Spleen tyrosine kinases: biology, therapeutic targets and drugs. *Drug Discov Today*. 2010;15:517–530.
20. Pine PR, Chang B, Schoettler N, et al. Inflammation and bone erosion are suppressed in models of rheumatoid arthritis following treatment with a novel Syk inhibitor. *Clin Immunol*. 2007;124:244–257.
21. Weinblatt ME, Kavanaugh A, Burgos-Vargas R, et al. Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial. *Arthritis Rheum*. 2008;58:3309–3318.
22. Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N Engl J Med*. 2010;363:1303–1312.
23. Genovese MC, Kavanaugh A, Weinblatt ME, et al. 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.
24. Milici AJ, Kudlacz EM, Audoly L, Zwillich S, Changelian P. Cartilage preservation by inhibition of Janus kinase 3 in two rodent models of rheumatoid arthritis. *Arthritis Res Ther*. 2008;10:R14.
25. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum*. 2009;60:1895–1905.
26. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum*. 2012;64:970–981.
27. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum*. 2012;64:617–629.
28. Mariette X, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495–507.
29. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508–519.
30. Mariette X, Curtis JR, Lee EB, et al. Tofacitinib (CP-690,550), an oral janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical programme. Presented at the Annual European Congress of Rheumatology. Berlin, Germany, June 6–9, 2012.
31. Charles-Schoeman C, Wicker P, Sechtem U, et al. Cardiovascular safety findings in rheumatoid arthritis patients treated with tofacitinib. Presented at the Annual European Congress of Rheumatology. Berlin, Germany, June 6–9, 2012.
32. van Vollenhoven RF, Fleischmann R, Cohen SB, et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, or adalimumab versus placebo in patients with rheumatoid arthritis on background methotrexate: a Phase 3 study. Presented at the American College of Rheumatology Annual Meeting. Chicago, IL, November 4–9, 2011.
33. Fleischmann R, Spencer-Green GT, Fan F, et al. Dose ranging study of VX-509, an oral selective JAK3 inhibitor, as monotherapy in patients with active rheumatoid arthritis (RA). Presented at the American College of Rheumatology Annual Meeting. Chicago, IL, November 4–9, 2011.

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