Review

New drugs beyond biologics in rheumatoid arthritis: the kinase inhibitors

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Abstract

Orally available small molecule compounds have recently been developed for the treatment of RA, and inhibitors of signalling cascades, specifically inhibitors of kinases, have reached advanced stages of clinical development. The p38 mitogen-activated protein kinase blockers have shown poor clinical response despite encouraging preclinical data. In contrast, inhibitors of the non-receptor tyrosine kinases, spleen tyrosine kinase and janus kinase 3, have demonstrated a significant clinical efficacy together with an acceptable safety profile. We herein present a review on published preclinical and clinical data on these new drugs.

Key words: Rheumatoid arthritis, Treatment, Small molecule, Signalling, kinases, fostamatinib, tocitakinib.

Introduction

RA is a chronic and debilitating condition that requires long-term treatment. Biological agents have proved to be very effective in treating RA and can significantly decrease disability, increase the quality of life and prevent structural damage. Approximately 30–50% of patients, however, do not have an appropriate clinical response to these drugs [1].

Newer anti-inflammatory therapies involve chemical compounds with a molecular weight of <1kDa, which are known as small molecules. These compounds are administered orally, and their manufacturing costs are below those of biologics [2]. Small molecule drugs that have been tested in RA patients include inhibitors of intracellular signalling pathways, inhibitors of cytokines and chemokines and inhibitors of cell surface markers [2].

Intracellular signalling pathways mediate cell responses to environmental stimuli, transmit and amplify the signals initiated by a ligand binding to its receptor on the cell membrane and drive the information through the cytoplasm to the nucleus to regulate gene expression [3]. Blocking signalling networks could significantly reduce the production of cytokines and other inflammatory mediators.

MAPK inhibitors

MAPks phosphorylate serine, threonine or tyrosine residues on intracellular proteins thereby regulating cell survival, proliferation, cytokine synthesis and the production of metalloproteases. There are three subfamilies of MAPks, each comprising several interactive kinase cascades: c-Jun N-terminal kinase (JNK), extracellular signal-related kinase (ERK) and p38 MAPk. In turn, each subfamily comprises several isoforms: JNK (JNK1, JNK2 and JNK3), ERK (ERK1 and ERK2) and p38 MAPk (α, β, γ and δ) [3]. The activity of MAPks is regulated through phosphorylation by MAPK kinases (MAPKKs), which in turn are regulated by MAPKK kinases (MAPKKKs). Protein phosphatases eliminate the phosphate residue, thereby de-activating the cell. MAPks play a role in inflammation and the destruction of tissue during RA and other rheumatic diseases. In addition, p38, JNK and ERK are constitutively activated in the synovium of RA patients [4], and their expression phosphorylation status is increased in RA synovial tissue compared with OA synovial tissue. Furthermore, JNK, p38 and ERK are detected in cultured synoviocytes and become readily activated by the
pro-inflammatory molecules present in the RA joint, such as IL-1 and TNF-α [3].

**p38 MAPK**

The p38 pathway is a potential therapeutic target in RA because it functions as a regulator of pro-inflammatory cytokine production both *in vitro* and *in vivo*. Cytokines regulated by the p38 pathway include IL-1, TNF-α and IL-6, and the α isofrom of p38 seems to be the most relevant isoform for macrophage cytokine synthesis. Macrophage inhibition factor (MIF) and p38 MAPK are up-regulated in RA synovium compared with OA synovium [5]. In addition, p38 is regulated by two kinases, MKK3 and MKK6, that are also activated in RA synovium and form stable complexes with p38 in RA fibroblast-like synoviocytes. Moreover, the phosphatase MAPK phosphatase 1 (MKP-1) negatively regulates p38 activity and is a therapeutic target of anti-inflammatory glucocorticoids, which have been described to up-regulate MKP-1 expression [6].

**p38 inhibitors**

Selective inhibition of p38 is effective in TNF-mediated arthritis. Blockade of p38 reduces both synovial inflammation and the destruction of bone and cartilage. Bone erosion is inhibited in part by the suppression of osteoclast activation through decreased expression of RANK ligand (RANKL) [7]. Interestingly, FR167653, a potent inhibitor of p38 MAPK, prevented the development of rat CIA and delayed articular destruction when treatment was started after the onset of the disease [8]. Furthermore, FR167653 decreased serum levels of TNF-α and IL-1 and blocked the osteoclast differentiation induced by synovial fibroblasts [8]. The synthetic p38 MAPK inhibitor, RWJ 67657, which is specific for α and β isoforms, induced a 90% decrease in TNFα, IL-6 and IL-8 production when the maximum dose was administered to healthy volunteers [9].

In 2002, Weisman *et al.* [10] presented the first results concerning the use of an oral p38 inhibitor, VX-745, in RA patients. The study included 59 patients, 44 of whom received the active drug at a dose of 250 mg twice a day (bid). After 12 weeks, the area under the curve of the ACR 20% improvement criteria (ACR20) for patients treated with VX-745 was significantly greater than for patients receiving placebo. In addition, no neurological adverse events (AEs) were seen. However, further development of this drug was discontinued due to adverse neurological effects observed in long-term animal studies [10].
A new oral p38 MAPK inhibitor, SCIO-469, was found to be ineffective in patients with active RA. The mean duration of the disease was 9 years and 80% were women. Demographics were similar among the four randomized groups, i.e. placebo or three different doses of SCIO-469. Primary endpoint was ACR20 at 12 weeks. At this time point, the three groups receiving the drug did not achieve a better ACR20 response than patients on placebo. A decrease in CRP levels was seen at Week 2, but this effect did not persist. In addition, dose-dependent AEs, especially cutaneous rashes, were common [11].

A selective inhibitor of α isoform of p38 MAPK, pamapimod, was also studied in RA patients. A total of 204 patients were assigned to four treatment groups. One group received MTX up to a maximum of 20 mg/week, and the other three groups received pamapimod monotherapy at once daily (qd) doses of 50, 150 or 300 mg. At 12 weeks, the primary endpoint (ACR20 response) showed a significantly better response for patients receiving MTX than those treated with pamapimod, although the upper limit of CI for the 300 mg was close to 0. The ACR50 response was also increased with MTX (Table 1). In addition, CRP levels were reduced during the first week in patients receiving the 300 mg dose, but these levels normalized after the second week of the trial. The most common AEs were skin infections, dizziness and elevated liver function tests. Indeed, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were observed in the first week, but these parameters returned to baseline levels after 4 weeks. The overall AEs were similar in both studies involving VX-702, although severe infections were more frequent in patients receiving VX-702 than in the placebo group in the veRA study (2.4 vs 0%) [14].

BMS-582949 is a new dual p38 inhibitor. It reverses p38 activation of cells previously activated by lipopolysaccharide (LPS) and inhibits p38 activation in cells [15]. A recent study was conducted on 121 RA patients who were receiving MTX as background therapy. At 12 weeks, this proof of concept study showed a significant improvement in patients treated with 300 mg of the drug compared with placebo (i.e. an ACR20 response of 53 vs 33%, P < 0.05, for BMS-582949 vs placebo). A DAS of 28 joints (DAS-28) decrease was also seen in patients receiving the p38 inhibitor (−0.83, 95% CI −1.29, −0.36). No major issues concerning safety were found [16].

There is no clear explanation for the lack of efficacy of p38 inhibitors in RA; however, inadequate dosing limited by toxicity is a likely possibility [17]. The redundancy of cytokine signalling pathways may also be an important contributor, and the success of therapy with blockers of upstream kinases, such as JAKs and Syk, supports this theory. In addition, p38 mediates the action of anti-inflammatory cytokines such as IL-10, but the balance of pro-inflammatory vs anti-inflammatory actions of p38 in humans is not known.

### JNK and ERK inhibitors

Limited data are available to support a role for JNK and ERK inhibitors in the treatment of RA, which may be due to a lack of efficient pharmacological inhibitors.

### Non-receptor tyrosine kinase inhibitors

**Syk**

Syk is a cytoplasmic tyrosine kinase involved in signalling through immunoreceptors such as the B-cell receptor (BCR) and the activating Fcγ receptors of macrophages, neutrophils and mast cells. Syk activates downstream MAPKs, especially JNK [18], leading to up-regulation of TNF-α, IL-6 and MMP synthesis. In addition, Syk plays a role in osteoclast differentiation [19]. Compared with OA synovial tissue, studies have observed increased expression of phosphorylated Syk in RA synovial tissue, and

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**Table 1** Responders at Week 12 with pamapimod

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACR20, %</th>
<th>ACR50, %</th>
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<tr>
<td>Pamapimod vs MTX [12]</td>
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<tr>
<td>MTX 7.5–20 mg/week</td>
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<td>23</td>
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<tr>
<td>50 mg pamapimod qd</td>
<td>23</td>
<td>12</td>
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<tr>
<td>150 mg pamapimod qd</td>
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<td>6</td>
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<tr>
<td>300 mg pamapimod qd</td>
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<tr>
<td>Pamapimod + MTX vs placebo + MTX</td>
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<tr>
<td>Placebo + MTX</td>
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<td></td>
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<td>25 mg pamapimod bid + MTX</td>
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<tr>
<td>75 mg pamapimod bid + MTX</td>
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<tr>
<td>50 mg pamapimod qd + MTX</td>
<td>42</td>
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<tr>
<td>150 mg pamapimod qd + MTX</td>
<td>31</td>
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<tr>
<td>300 mg pamapimod qd + MTX</td>
<td>43</td>
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*Coefran-Mantel-Haenszel analysis for ACR20, MTX vs pamapimod: −0.22 (95% CI −0.40, −0.05) for 50 mg dose; −0.28 (95% CI −0.45, −0.12) for 150 mg dose; −0.14 (95% CI −0.32, 0.04) for 300 mg dose. Comparisons for 50 and 150 mg favour MTX. No significance was found for all comparisons of pamapimod + MTX against placebo + MTX. Table has been adapted from references [12, 13].
mice deficient in Syk are protected from autoantibody-induced arthritis [20].

**Syk inhibitors**

R788 (fostamatinib disodium; Fig. 2), is an oral prodrug that is rapidly converted to R406 after oral administration. R406 is a potent selective inhibitor of Syk kinase [21]. Previous studies of R788 and R406 in rodent CIA models demonstrated a significant reduction in inflammation and bone erosion [22]. Cell culture studies of human synoviocytes have suggested a potent anti-inflammatory activity for this Syk inhibitor, which indicates that it may be useful for treating RA [18]. The efficacy of fostamatinib in patients with RA was tested in a 3-month, double-blind, ascending dose, placebo-controlled trial. Patients with an inadequate response to MTX were treated with three different doses of fostamatinib plus MTX (50, 100 and 150 mg bid, or placebo with MTX). The primary endpoint, ACR20 at 3 months, was significantly superior in patients treated with the 100 and 150 mg doses (Table 2). At 12 weeks, the ACR50 and ACR70 responses were also significant when compared with placebo (Table 2). A rapid response in the ACR20 was seen only 1 week after treatment initiation. Furthermore, significant decreases in IL-6 and MMP-3 were seen at 12 weeks in patients receiving the two higher doses; interestingly, the decrease started after the first week of treatment. The main AEs were dose related: diarrhoea appeared in 45% of patients treated with 150 mg bid, and neutropenia (<1500 mm$^3$) was seen in 10 and 30% of patients treated with 100 and 150 mg, respectively [23].

Another study assessed the clinical efficacy of fostamatinib and its effects on structural damage in RA patients who had not responded to biological therapy [24]. This trial was a randomized, double-blind, 3-month study that included 219 patients. The patients were given either 100 mg of fostamatinib bid or placebo. Although there was a significant ACR20 response when fostamatinib was compared with placebo at 6 weeks (41 vs 21%, $P=0.003$), the primary endpoint (ACR20 at 3 months) did not reach statistical significance (38 vs 37%, fostamatinib vs placebo). In addition, a significant decrease in ESR and CRP level was observed at all time points in the group receiving fostamatinib R788. Structural damage was evaluated by MRI using the amended OMERACT RA MRI scoring system (RAMRIS) score. The assessment demonstrated significant differences in osteitis score ($-0.19$ vs $1.17$ in the fostamatinib and placebo groups; $P=0.058$) and synovitis score ($-0.52$ vs $0.35$ in the R788 and placebo groups; $P=0.038$) [24]. As stated by the authors [24], baseline characteristics of both groups were different. Patients treated with fostamatinib had failed to more biologics and more were receiving:

<table>
<thead>
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<th>Table 2 Responders at Weeks 12 and 24 with fostamatinib</th>
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<tr>
<td><strong>ACR20, %</strong></td>
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<tr>
<td>Placebo + MTX</td>
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<td>FT 50 mg bid + MTX</td>
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<tr>
<td>FT 100 mg bid + MTX</td>
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<td>FT 150 mg bid + MTX</td>
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<tr>
<td>Placebo + MTX</td>
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<tr>
<td>FT 100 mg bid + MTX</td>
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<tr>
<td>FT 150 mg qd + MTX</td>
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Table has been adapted from [23, 25]. *$P<0.001$; **$P=0.002$, ***$P=0.008$, ****$P=0.036$, *****$P=0.003$, ******$P=0.007$ (all $P$-values FT compared with placebo arm). FT: fostamatinib.

**Fig. 2** Chemical structure of tofacitinib and fostamatinib disodium.
preinduced prednisone (42 vs 31%). Furthermore, the group receiving the Syk kinase inhibitor also had more synovitis, osteitis and erosion score on MRI. In conclusion, patients on fostamatinib had a more severe disease that might explain in part the failure to achieve the primary efficacy endpoint (ACR20).

A 6-month, phase II, double-blind, placebo-controlled study that included 457 RA patients with insufficient responses to MTX at doses of 7.5–25 mg/week for a minimum of 3 months was recently published [25]. Approximately 15% of patients had previously received biological treatment. Patients were randomly assigned to four groups to receive MTX plus placebo qd or bid, MTX plus 150 mg fostamatinib qd or 100 mg R788 bid. The primary endpoint was the 6-month ACR20 response. Secondary endpoints included the ACR50, ACR70 and DAS-28 remission scores (DAS-28 < 2.6). Both doses significantly increased the number of patients achieving the primary endpoint (Table 2). The ACR50 and ACR70 responses were also significantly greater with 100 mg bid. The ACR70, however, was not significant at the 150 mg qd dose (Table 2). At 6 months, the remission rates measured by DAS-28 were also significantly greater in both groups of patients receiving fostamatinib (Table 2). AEs included diarrhea, upper respiratory tract infections, neutropenia and abdominal pain. A significant increase in both systolic and diastolic blood pressure was also noted in both groups treated with the Syk inhibitor. The number of patients requiring anti-hypertensive treatment was superior in both fostamatinib arms when compared with placebo (18 vs 7%, \( P = 0.005 \) for 150 mg qd vs placebo and 23 vs 7%, \( P < 0.001 \), for the 100 mg bid vs placebo) [25].

JAK inhibitors

CP-690,550 (tofacitinib; Fig. 2) is an orally available, potent selective inhibitor of JAK that is in development for the treatment of RA and other autoimmune disorders, such as IBD, AS, psoriasis, PsA, and the prevention of transplant rejection [30]. In cell-based assays, tofacitinib potently inhibited JAK-1/3 over JAK2 [31]. Over 1000 patients with RA have been treated with tofacitinib in Phase II studies [32], and \(~4000\) are presently enrolled in clinical trials ([30], www.clinicaltrials.gov).

A proof of concept study was conducted by Kremer et al. [31]. A 6-week study with an additional 6 weeks of follow-up was carried out in 264 RA patients who had failed to respond to MTX, TNF blockers or other biologics. Tofacitinib was administered at doses of 5, 15 or 30 mg bid and was compared with placebo. At Week 6, the ACR20 response rate was 70.5, 81.2, 76.8 and 29.2% for 5, 15, 30 mg and placebo, respectively (\( P < 0.001 \) for all treatment groups). Patients receiving tofacitinib showed a rapid response, and an ACR20 improvement was observed from the first week across all groups receiving tofacitinib. The ACR50 and ACR70 responses were statistically significant at Week 2 in the 30 mg group and from Week 4 in all treatment groups (\( P < 0.05 \)). All doses showed a significant improvement in pain, disability [HAQ-disability index (HAQ-DI)] and health domains [short-form 36 health survey (SF-36)] when compared with placebo [33].

Kremer et al. [34] performed a 6-month, Phase IIIb, double-blind, placebo-controlled study that included 509 RA patients with an inadequate response to MTX. Tofacitinib with MTX was administered at six different doses (1, 3, 5, 10 and 15 mg bid or 20 mg qd; placebo was used for comparison). The primary endpoint was the ACR20 response at Week 12. The non-responder imputation (NRI) analysis at Week 12 of any dose \( \geq 3 \) mg bid achieved an ACR20 response that was statistically superior to placebo (Table 3). Most of the doses \( \geq 3 \) mg also showed significantly higher ACR50 and ACR70 responses when compared with placebo at Week 12 (Table 3). The percentage of patients achieving DAS28-3(CRP) remission (DAS < 2.6) at Week 12 was statistically superior to placebo (8.8%) in patients receiving 3 (32.1%), 10 (30.2%), 15 (37.7%) and 20 mg (24.6%) of tofacitinib (Table 3). Furthermore, all groups showed a statistically significant improvement in the HAQ-DI (\( P < 0.05 \)) [34]. A posterior NRI analysis of efficacy data at 24 weeks demonstrated that doses \( \geq 5 \) mg showed a sustained...
Table 3 Responders at Week 12 with tofacitinib

<table>
<thead>
<tr>
<th>Phase ll: tofacitinib + MTX vs placebo + MTX [34]</th>
<th>ACR20, %</th>
<th>ACR50, %</th>
<th>ACR70, %</th>
<th>DAS-28 remission, %</th>
</tr>
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<tbody>
<tr>
<td>Placebo + MTX</td>
<td>38</td>
<td>17</td>
<td>6</td>
<td>9</td>
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<tr>
<td>TF 1 mg bid + MTX</td>
<td>50</td>
<td>24</td>
<td>7</td>
<td>7</td>
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<tr>
<td>TF 3 mg bid + MTX</td>
<td>59**</td>
<td>31</td>
<td>22**</td>
<td>32**</td>
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<tr>
<td>TF 5 mg bid + MTX</td>
<td>61**</td>
<td>37**</td>
<td>18**</td>
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<td>TF 10 mg bid + MTX</td>
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<td>TF 15 mg bid + MTX</td>
<td>59**</td>
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<td>TF 20 mg qd + MTX</td>
<td>60**</td>
<td>36**</td>
<td>24**</td>
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</tbody>
</table>

The table has been adapted from Refs [34, 36, 39].

* P < 0.0001, ** P < 0.05, *** P < 0.01, **** P < 0.0001, ***** P < 0.001 (P-value TF compared with placebo arm).

TF: tofacitinib, ADA: adalimumab, eow: every other week, NA: not available.

Improvement in ACR20, ACR50, and ACR70 compared with placebo [35].

A Phase IIb, 6-month, double-blind, placebo-controlled study conducted in 384 RA patients with inadequate responses to DMARDs was carried out by treating these patients with tofacitinib monotherapy. Patients received five different doses of tofacitinib (1, 3, 5, 10, and 15 mg) administered bid or placebo. A seventh arm included patients treated with adalimumab at conventional doses for 12 weeks before receiving tofacitinib (5 and 10 mg bid) [36]. The primary endpoint was the NRI ACR response rate at Week 12. At 12 weeks, all active arms receiving tofacitinib at doses ≥3 mg had an ACR20 response that was significantly greater than placebo (Table 3). When the ACR20, ACR50, and ACR70 scores were assessed, the 6-month analysis confirmed the superiority of doses ≥5 mg bid. The adalimumab response at 12 weeks reached statistical significance for the ACR20 when compared with placebo (47.2 vs 28.8, P < 0.05); however, the ACR50 and ACR70 responses did not achieve statistical significance (Table 3). The design of the study, the low number of patients per arm and the characteristics of the RA population, might have influenced the poor results with adalimumab. Nonetheless, this response was surprisingly low for a TNF blocker, and we do not have a convincing explanation of this finding.

A 12-week, Phase IIb study conducted in Japan with four doses of tofacitinib (1, 3, 5 or 10 mg bid) in RA patients receiving MTX showed a significantly greater ACR20 response compared with placebo at all doses studied [37]. Further analysis of this study showed a decrease in disease activity measured by the DAS-28 (CRP) at Week 12 [38].

The results of the first Phase III study have recently been presented. This randomized, double-blind, placebo-controlled trial aimed to compare the efficacy, safety, and tolerability of two different doses of tofacitinib (5 and 10 mg bid) [39]. The primary endpoints at 3 months included the NRI ACR20 response, changes from baseline in HAQ-DI and remission using the DAS-28 (ESR; < 2.6). The results showed a significantly better response in the ACR20 score (Table 3) and a significant improvement in the HAQ-DI score compared with placebo. A slight increase in the number of patients with a DAS-28 < 2.6 was seen in patients treated with tofacitinib compared with placebo; however, the difference was not statistically significant. The high DAS-28 at baseline (mean = 6.67) could explain the failure to achieve significance at this endpoint.

The AEs that were most commonly associated with the use of tofacitinib were headache, diarrhea, nausea, upper respiratory infections and urinary infections. Indeed, an increase in infection rates and elevated liver enzymes has been described in clinical trials. Increases in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, as well as a slight increase in serum creatinine levels, have also been noted. Other data collected from tofacitinib studies included a dose-dependent decrease in haemoglobin, which was occasionally > 2 g/dl [31], and a dose-dependent decrease in the absolute neutrophil count in all four of the controlled Phase II studies [32]. Interestingly, no patient had severe neutropenia, defined by an absolute neutrophil count of < 1000/mm³ [32]. Two cases of tuberculosis were reported in the Phase III study. One case was a disseminated tuberculosis and the second case occurred 2 months after discontinuing tofacitinib (http://www.drugs.com/clinical_trials/first-phase-3-trial-tasocitinib-cp-690-550-oral-jak-inhibitor-administered-monotherapy-reduces-10563.html).

The 24-month follow-up of an open-label extension study from previous Phase II/III randomized trials was recently presented by Connell et al. [40]. Patients from Phase II started treatment with 5 mg bid and those from Phase III were initially treated with 10 mg bid. In total 1070 patients were treated for a total duration of 1295.7 patient-years; however, 6.3% of patients discontinued treatment due to AEs. Out of 188 serious AEs, 34 (18.1%) were infections. Increase in creatinine and lipid mean total levels, and decrease in mean absolute neutrophil count, which had shown changes in the randomized phase of the trial, did not progress in this extension study. Importantly, this open-label study showed that the clinical response was maintained across the 24-month follow-up.

Bruton tyrosine kinase

Bruton tyrosine kinase (Btk) is a non-receptor tyrosine kinase belonging to the Tec kinase family. It mediates BCR signalling and is upstream of nuclear factor κB (NF-κB) and MAPK pathways [41]. In human, Btk mutations result in X-linked agammaglobulinemia, a severe

www.rheumatology.oxfordjournals.org
immunodeficiency characterized by the absence of peripheral B cells and low concentrations of serum immunoglobulins [42]. Small molecule inhibitors of Btk have demonstrated therapeutic efficacy in animal models of lupus and arthritis [43], but to our knowledge no data on patients with RA are available.

NF-κB

The transcription factor NF-κB plays a key role in inflammation and autoimmunity. In mammals, the NF-κB family comprises five proteins: NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), c-Rel, RelB and RelA (p65) [44]. These proteins dimerize to form functional NF-κB complexes that are kept in the cytoplasm in an inactive form by interacting with specific inhibitory factors known as IκB. NF-κB is activated by the upstream IκB kinase (IKK) complex, which phosphorylates and degrades IκB. This process releases free NF-κB, which is able to migrate to the nucleus and activate the transcription of cytokines, chemokines, adhesion molecules and other pro-inflammatory factors. To our knowledge IKK inhibitors have not been tested in RA.

Kinase inhibitors in RA—what is their future?

The kinase inhibitors, fostamatinib and tofacitinib, are novel small molecules designed to be administered orally to patients with RA which may represent an advantage compared with the s.c. or i.v. administration of biologics. Furthermore, the lower manufacturing cost of these drugs compared with those of biologics should also represent a benefit. Concerning efficacy, no data from head to head comparisons with biologics are available so far. The only data are from the tofacitinib study in which adalimumab was administered in the first period of the trial. However, as mentioned before, the design of the study does not allow to conclude a superiority of tofacitinib vs adalimumab. Assuming that these kinase inhibitors might attain an efficacy comparable with that of biologics, which would position them as good therapeutic competitors, several aspects must be taken into account. Whereas all biologics are very effective at blocking structural damage [45–50], only fostamatinib has shown an impact on bone damage, as assessed by MRI. Concerning tofacitinib, several trials directed at evaluating structural damage are now under way, but no data are currently available.

In addition, kinase inhibitors are non-selective cytokine inhibitors. Several cytokines, including IL-2, TNF and IL-6, can be suppressed when using these drugs, which may cause unwanted AEs. In addition, profound immunosuppression may lead to severe side effects that have not yet been detected. We should not forget that some of the most important AEs of TNF blockers, such as tuberculosis, were mainly observed after the follow-up of patients in national registries [51]. Therefore, researchers must closely monitor the safety of these kinase inhibitors before they can be approved.

The failure of p38 blockers and the success of the upstream Syk and JAK inhibitors indicate that targeting molecules at the vertex of signalling cascades, such as Rho proteins, may be effective in RA. Recently, a Rac1 inhibitory peptide was shown to be effective in suppressing antibody production and paw swelling in CIA [52]. A potential drawback of trying upstream inhibition, however, may be increased toxicity.

In summary, if kinase inhibitors are to challenge biologics, these drugs must demonstrate an acceptable safety profile together with an inhibition of articular damage that is as effective as those shown by biologics. Furthermore, if approved, their place in the global treatment of RA would depend on the indications of the label. Other aspects, such as pricing, will also be crucial in an area where economic impact is growing year by year.

Rheumatology key messages

- Blocking intracellular signalling cascades is a promising therapeutic target in RA.
- Orally available inhibitors of Syk and JAK kinases have proven clinical efficacy in RA trials.

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