New molecules for the treatment of rheumatoid arthritis

Small molecules targeting JAKs—a new approach in the treatment of rheumatoid arthritis

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Abstract

Advances in the treatment of RA in the past decade have been achieved mainly by using combinations of different conventional and biologic DMARDs. However, until now no final victory has been achieved over this organ damaging and potentially life-threatening systemic autoimmune disease. Few patients, notably those with established disease, stay in remission permanently, even using advanced treatment concepts. Thus novel approaches, especially for patients resistant to biologics, are urgently needed. Pro-inflammatory signalling pathways beyond the level of cytokines and receptors have been intensively elaborated and provide such potential targets. This review focuses on the development of new small molecule inhibitors of Janus kinases in clinical trials in RA.

Key words: rheumatoid arthritis, tofacitinib, fostamatinib, janus kinase.

JAK inhibitors with focus on tofacitinib

Janus kinase (JAK) inhibitors of different affinity to their targeted enzymes are under clinical development for the treatment of RA [1, 2]. Currently, the most advanced compound is a small molecule named tofacitinib (development code CP-690,550, previously known as tasocitinib) [3–5] (Fig. 1). The drug interferes with the activity of JAK1, JAK2, JAK3 and to a lesser extent Tyk2 as a reversible, competitive inhibitor at the ATP binding site and is therefore a non-selective inhibitor of their signalling pathways [6]. The rank order of inhibitory potency of tofacitinib was found to be JAK3 over JAK1 and JAK2 over Tyk2 [7]. In cellular settings where JAKs signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. In fact, multiple cytokine-activated JAK/STAT signalling pathways were inhibited with IC₅₀ values below 200 nM [7].

Tofacitinib is administered as an oral compound with a half-life of approximately 3.5 h. After administration, the drug rapidly disappears from circulation and therefore no relevant plasma concentrations are measurable after 24 h. Tofacitinib is mainly eliminated via the hepatic CYP3A4 and CYP2C19 metabolism (approximately 70%), without a major active metabolite. The remaining clearance of the drug is provided by renal excretion [8].

Tofacitinib has been studied for the treatment of moderate-to-severe active RA in adults in a large Phase II–III programme. The successful clinical trial programme included six Phase II studies and six Phase III studies investigating the safety and efficacy of tofacitinib in adults with RA. In this context, tofacitinib was administered as monotherapy as well as in combination with different non-biologic DMARDS, mainly MTX. The targeted RA cohorts included MTX-naïve patients as well as patients after treatment failure to non-biologic and biologic DMARDs (Table 1). Approximately 5000 RA patients at more than 350 sites have been treated with tofacitinib in the RA development programme in 45 countries worldwide. Of note, a substantial proportion of patients were recruited from participating sites from North America, South America, Asia and Europe. In addition, patients from the Phase II and Phase III studies could be enrolled in ongoing long-term, open-label, extension (LTE) studies that will provide us with further data regarding the safety and efficacy of tofacitinib. Of note, the Phase III clinical trials are named under the acronym ORAL, which stands
for Oral Rheumatoid Arthritis Phase III Trials, as seen in Table 1.

**Efficacy data for tofacitinib in patients with RA with failure to DMARDs including TNF inhibitors**

The Phase III development programme of tofacitinib in RA has so far been successful with respect to the investigated outcome parameters, including ACR and EULAR response criteria as well as patient reported outcome (PRO) measures. In fact, all primary outcome criteria have been reached with the exception of DAS28-defined remission in ORAL Solo [9]. In addition, importantly, evidence has been provided for the inhibition of radiological progression of disease and the primary endpoint relating to structure [mean change from baseline in modified Total Sharp Score (mTSS)] was significant for the 10 mg twice-daily dose in the ORAL Scan study.

For interpretation of the efficacy results, it is important to note that certain response rates were calculated by using the non-responder imputation method. Furthermore, an advancement penalty was defined for ACR response and DAS28 remission (<2.6) rates. In detail, in the studies of longer duration (>6 months), patients with predefined non-response at month 3 were considered as treatment failures for the remainder of the trial, even if they subsequently achieved response after month 3 when compared with placebo. These very stringent approaches provide us with statistically more conservative results avoiding overestimation of treatment effects, but making a comparison with published trials more difficult. Furthermore, a step-down analysis method with sequential assessment of the primary efficacy endpoints was employed to minimize Type 1 error. In this context in the ORAL Solo, Standard, Sync and Step studies, achievement of a significant difference in the ACR20 response rate was a precondition for evaluation of change.
from baseline in the HAQ-disability index (DI) score, and subsequently, a significant improvement from baseline in the HAQ-DI score was a precondition for evaluation of the percentage of patients with a DAS28-4(ESR) <2.6 [9, 10]. In the ORAL Scan study, after evaluation of the ACR20 response rate, an additional primary endpoint defined by change from baseline in mTSS at 6 months was implemented in the statistical analyses.

**Tofacitinib in non-biologic or biologic DMARD-IR patients (ORAL Solo and Sync)**

The protocols of the different randomized, controlled trials have a comparison of two different dosages of tofacitinib (5 or 10 mg bd) with two placebo groups in common. In the ORAL Solo study over a period of 6 months, patients were randomized in a 4:4:1:1 ratio to two different dosages of tofacitinib (5 or 10 mg bd) as monotherapy or two placebo groups, respectively. At month 3, all placebo patients advanced blindly as specified at randomization to tofacitinib, either 5 or 10 mg monotherapy.

In the ORAL Sync trial over a period of 12 months, patients were randomized in a 4:4:1:1 ratio to tofacitinib 5 or 10 mg bd or two placebo groups, respectively. Different traditional DMARDs were allowed as stable background therapy. At month 3, patients under placebo were able to switch to a prespecified active treatment if no improvement of at least 20% of tender and swollen joint counts was reached. At month 6, all remaining patients from the placebo groups advanced in a blinded manner to active treatment with tofacitinib at one of the two different doses.

To summarize the results of the studies in non-biologic or biologic DMARD-IR patients with RA, all primary endpoints except the DAS remission rate in ORAL Solo were reached [9]. Rapid and significant improvement of ACR20, 50 and 70 response rates as well as EULAR outcome measures (DAS low disease activity and DAS remission) was shown for both tofacitinib dosages compared with placebo except for the DAS remission in ORAL Solo. For DAS remission (<2.6), stronger effects were observed in the higher dosage group of tofacitinib 10 mg bd compared with 5 mg bd. Furthermore, PROs were also significantly improved under tofacitinib compared with placebo. Patients who advanced to active treatment with tofacitinib also showed a rapid improvement in outcome measures including disease activity and reached a comparable level of response as the patients initially treated with the study drug.

**Tofacitinib in MTX-IR patients (ORAL Standard and ORAL Scan)**

The ORAL Standard trial (duration of 12 months) was special with respect to a fifth different treatment arm [10]. According to protocol, patients were randomized in a 4:4:4:1:1 ratio to tofacitinib 5 or 10 mg bd, adalimumab 40 mg s.c. every other week or two placebo groups, respectively. All patients were on a stable background therapy with MTX. To reduce bias, a previous therapy with adalimumab was an exclusion criterion and other previous TNF inhibitors (TNFis) were also excluded in case of treatment failure due to lack of efficacy or related adverse event (some were included if anti-TNF treatment had been stopped, for instance, for insurance reasons). At month 3, an early escape was possible for patients under placebo if no improvement of at least 20% of tender and swollen joint counts was reached. At month 6, all patients from the placebo groups advanced in a blinded manner to active treatment with tofacitinib in two different dosages. The trial was not designed for a non-inferiority or superiority comparison between tofacitinib and adalimumab. Therefore adalimumab cannot be addressed as a competitor, but rather as an active control in this setting.

In ORAL Standard, the level and onset of improvement of all outcome measures including PRO parameters was numerically similar between the tofacitinib and the adalimumab groups and for both groups superior to placebo [11].

The effects of tofacitinib on radiologic progression were investigated in the ORAL Scan trial. This 24-month, double-blind, Phase 3 study compared efficacy, including the reduction of structural damage progression, and safety of tofacitinib with placebo in patients with active RA with an inadequate response to MTX. Patients were randomized in a 4:4:1:1 manner to two different dosages of tofacitinib (5 or 10 mg bd) and two placebo groups in co-medication with background MTX therapy. Patients on placebo advanced to tofacitinib at 6 months, or at 3 months if non-responsive (<20% reduction from baseline in swollen/tender joint counts).

The primary outcome measure with respect to radiologic progression was the mean change from baseline in mTSS at month 6. As a result, the increase in mTSS was higher in the placebo group compared with both dosages of tofacitinib. However, the difference of radiographic changes was only statistically significant for the higher tofacitinib dosage of 10 mg bd compared with placebo. According to protocol, all placebo patients advanced in a blinded manner to treatment with tofacitinib at either month 3 or month 6, and therefore the radiology results for month 12 were extrapolated from the time of advancement (month 3 or 6) for the placebo group. The changes remained statistically significant for the higher dosage group of 10 mg tofacitinib bd. The percentage of patients with no detectable radiological progression at month 6 were 78% for placebo, 88.8% for tofacitinib 5 mg bd and 86.9% for tofacitinib 10 mg bd. Importantly, due to the predefined statistical evaluation procedures, statistical significance was not declared with 5 mg bd for HAQ-DI and DAS28-4(ESR) <2.6 responses in this trial. Due to the non-significant differences for the 5 mg bd group in the mTSS at month 6, a further step-down sequential assessment of the primary efficacy endpoints was not applicable.

**Tofacitinib in TNFi inadequate responders (ORAL Step study)**

Treatment of RA patients with failure to TNFi is always a challenge, and since it is likely that this cohort might
represent the main target for initial tofacitinib treatment in the future, the efficacy data from the ORAL Step trial will be shown in more detail. This randomized, controlled, Phase III study of 6 months’ duration recruited adult patients with moderate-to-severe RA and intolerance or inadequate response to TNFi [12]. Patients received blindly two different dosages of tofacitinib (5 or 10 mg bd) vs placebo in a randomization ratio of 2:2:1:1 for the first 3 months. Thereafter, all patients under placebo advanced in a blinded manner to active treatment with tofacitinib in two different dosages. Altogether, 400 patients with mean disease duration of RA of 12 years were included. From these difficult-to-treat patients, 27% had already been treated with two different TNFis and 48% with three TNFis. At baseline, patients with highly active RA entered the study with a mean number of tender joints of 27 and swollen joints of 16. Furthermore, the patients were already significantly disabled due to RA with a mean HAQ-DI of 1.6 [12].

With respect to the primary endpoint, after a treatment period of 3 months, both dosages of tofacitinib were significantly superior to placebo in achieving ACR20 response (48% for tofacitinib 10 mg bd, 42% for tofacitinib 5 mg bd compared with 24% for placebo, \( P < 0.0001 \) and \( P < 0.05 \), respectively) [12]. Significant improvement was also documented for ACR50 response (28% for tofacitinib 10 mg bd, 27% for tofacitinib 5 mg bd compared with 8% for placebo, \( P < 0.0001 \)). The remission rates according to EULAR DAS28-4 (ESR) \(<2.6\) responses were 11% and 7% for tofacitinib 5 and 10 mg, respectively, compared with 2% for placebo \( (P < 0.05) \). During the short evaluation period of 3 months, a significant improvement of disability (as measured by the mean change in HAQ-DI scores from baseline) was obvious for both tofacitinib dosages \((-0.46%\) for tofacitinib 10 mg bd, \(-0.43%\) for tofacitinib 5 mg bd compared with \(-0.18\) for placebo, \( P < 0.0001 \)). After the switch to active treatment, patients from the placebo group reached response rates comparable to those of patients on tofacitinib (e.g. ACR20 55–52%, ACR50 37–30%, ACR70 \(-16\)%) [12].

Safety data from Phase II–III development programme and long-term extension studies of tofacitinib

For the evaluation of the safety profile of tofacitinib in RA patients, data from the clinical development programme are available, where the drug was used as monotherapy in non-biologic or biologic DMARD-inadequate responders (DMARD-IR) patients (ORAL Solo), after MTX failure in combination with MTX (ORAL Standard and ORAL Scan) or with other DMARDs in non-biologic or biologic DMARD-IR patients (ORAL Sync) as well as from trials where tofacitinib was investigated after TNFi inadequate response (ORAL Step). As of September 2011, approximately 4800 patients with RA were treated with tofacitinib in the RA development programme, of which a high percentage are still on treatment in the long-term extension phase. The data available so far are based on approximately 5700 patient-years (PY) of exposure. The study programme was performed worldwide, including North and South America as well as Asia and Europe, with a considerably high percentage of patients from participating centres in Europe. The baseline characteristics showed that the study populations were representative for typical RA cohorts with respect to gender ratio and age distribution. Of note, approximately 15% of patients were 65 years of age or older. Furthermore, the cohorts included patients with different relevant comorbidities such as diabetes mellitus, hypertension, cardiovascular disease and hypercholesterolaemia [8].

As of September 2011, across the Phase III clinical programme, the incidence of serious adverse events (SAEs) was stable over time, with approximately 10 events per 100 PY and 12 events per 100 PY for tofacitinib 10 and 5 mg, respectively. The mortality rate was low and comparable to a typical RA cohort with 0.35 events per 100 PY across the entire clinical development programme (Phase II, III and LTE). Of special interest, the event rate for serious infections was higher under tofacitinib (3/100 PY) compared with the placebo group (1.5/100 PY) as well as to the active control, adalimumab (1.7/100 PY), across the clinical programme. However, this event rate as such would be in the same range as known for infection rates from other trials with biologics including TNFi. Even though the rate was higher in the 10 mg dose group compared with 5 mg in the LTE studies, again keeping in mind the differences between those populations (greater extent and length of exposure to 5 mg than 10 mg in LTE), there was no increase in infection rate over time under prolonged exposure to tofacitinib by assessing serious infection incidence rates over 6-month intervals. Nevertheless, opportunistic infections as well as several cases of tuberculosis (TB) were reported from the trials. Remarkably, TB has occurred in 12 reported cases so far despite appropriate screening procedures. With respect to geographical distribution, it is of note that only one case was reported from the USA and none from Europe. As another sign of relevant immunosuppression under tofacitinib, the event rate of herpes zoster in the pooled Phase III studies was relatively high, with approximately 4.4 events per 100 PY compared with placebo (1.5 events per 100 PY). An indirect comparison to other trials in RA with biologics and to RA registries also suggests an increased risk for herpes zoster reactivation under tofacitinib.

With respect to blood cell counts, cases of anaemia and neutropenia have been observed. However, the low grade of reduction of both cell lines was in most cases of no clinical relevance. The background of these potential side effects has not been clarified in total, but, as known from in vitro studies, inhibition of JAK function can reduce the expression of GM-CSF and erythropoietin. Therefore, under treatment with tofacitinib, close monitoring of blood cell counts appears to be appropriate. Of note, the observed anaemia and neutropenia were stable over time after prolonged exposure to tofacitinib, and there was no increased risk of infections in association with neutropenia.
Other changes in laboratory parameters under treatment with tofacitinib include a weak mean increase in creatine phosphokinase levels as well as serum creatinine levels. However, both parameters were stable over the time of exposure and no influence of tofacitinib on renal plasma flow or on creatinine clearance has been observed during the clinical development programme in healthy volunteers. As another frequent adverse event, a dose-related increase in lipid levels (low-density lipoprotein as well as high-density lipoprotein) has been observed. Of note, the atherogenic index was not changed and there was neither an increase in mean blood pressure levels nor a signal for an overall increased risk for cardiovascular events.

Few cases of gastrointestinal perforations occurred in the clinical trials with tofacitinib. The incidence was higher than expected in a comparable RA cohort, but similar to the published rates of TNFi and somewhat lower than the rates with tocilizumab. Therefore, the background for this potential side effect could be a reduction of IL-6 production as a result of effective JAK inhibition by tofacitinib.

As known from clinical trials and daily practice, RA patients with treatment failure to biologics represent not only a challenge for future therapies but also have a considerably higher safety risk. Therefore it is important to note that no additional or new safety signals emerged from tofacitinib trials in patients with non-response to TNFi. In this cohort, the overall incidence of AE was in fact comparable to other studies in such cohorts. Consistent with the known safety profile, infections and infestations were the most frequent reported AEs mostly of mild intensity. Remarkably, the incidence of SAEs was lower under exposure to tofacitinib compared with placebo during months 0–3 (1.5% and 4.5%, respectively). However, the rate of drug discontinuation due to adverse events was higher in the tofacitinib group compared with placebo (9% vs 3%, respectively, over the course of the 6-month study). One death was reported in a 51-year-old woman due to recurrent pulmonary artery embolism. However, according to the judgement of the investigator and an independent safety group, this event was not related to the treatment with tofacitinib, but more likely to concomitant HRT [12].

**Summary for tofacitinib**

In summary, the oral JAK inhibitor tofacitinib was found to significantly ameliorate signs and symptoms as well as disease activity and physical function in difficult-to-treat patients with RA. The onset of effects was rapid and the achieved improvement over time was more comparable to a biologic than to a classical DMARD response [12]. Thus the beneficial profile of the drug makes it a promising candidate for future treatment options of RA, especially for patients with failure to TNF inhibitors and other biologics. In fact, the validation process by the European Medicines Agency (EMA, Europe) as well as the Food and Drug Administration (FDA, USA) will establish the position of this drug in the near future. In May 2012 the FDA Arthritis Advisory Committee voted by the majority in favour of recommending approval of tofacitinib. In November 2012, the FDA approved tofacitinib 5 mg twice daily for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to MTX. Tofacitinib may be used as monotherapy or in combination with MTX or other non-biologic DMARDs. Tofacitinib should not be used in combination with biologic DMARDs or with potent immunosuppressive, such as azathioprine and ciclosporin (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203214s000lbl.pdf). In fact, tofacitinib is now the first-in-class compound on the market in the USA for the treatment of RA, since drugs like tofacitinib can neither be categorized as a classical DMARD due to their highly specific mode of action, nor do they belong to biologics, due to their synthetic structure. Other JAK inhibitors, including compounds with higher selectivity for distinctive JAK enzymes, are also in clinical development. However, the available data from early Phase II–III do not yet allow a comprehensive review.

**Other JAK inhibitors**

Another oral JAK inhibitor (VX-509, Vertex) with selectivity for JAK3 was investigated in a dose-finding, controlled Phase II study as monotherapy in 204 patients with moderate-to-severe RA [13]. Patients were biologic naive but refractory to the treatment of at least one DMARD. During the evaluation period of 12 weeks, significant improvements over placebo were achieved by dosages of VX-509 ≥ 50 mg bd and ≥ 100 mg bd with respect to ACR20 response ($P \leq 0.007$). Improvement in DAS28-CRP levels was also significant for dosages of VX-509 ≥ 50 mg bd ($P \leq 0.001$). With respect to safety evaluation, the frequency of AEs (7.9% vs 4.8%), infections (12.25% vs 17%) as well as SAEs (4.9% vs 2.4%) leading to withdrawal was higher with VX-509 compared with placebo. In summary, the use of VX-509 provides further evidence that the mode of action of selective JAK inhibitors seems to represent a promising approach for the treatment of RA. For baricitinib (or LY3009104, Eli Lilly & Incyte), a kinase inhibitor with selectivity for JAK1 and JAK2, data were presented from a study in 301 MTX-inadequate responders. For dose finding, patients with RA received baricitinib 1, 2, 4 or 8 mg qd for 12 weeks on a stable MTX background. The primary endpoint was defined as the combined proportion of patients in the 4 and 8 mg groups achieving an ACR20 response at 12 weeks compared with placebo. As a result, the primary endpoint was reached in 76% of patients in the active treatment arms compared with 41% in the placebo group [14].

Finally, data from a proof-of-concept trial were presented for GLPG0634 (Galapagos), a compound with selectivity for JAK1. In total, 36 patients with insufficient response to MTX were exposed to 100 mg bd or 200 mg qd over 4 weeks with continued background MTX or other low-dose anti-inflammatory drugs. In fact, this study also met the primary endpoint of ACR20 at week 4 with a pooled result for both treatment groups of 83% ACR20.
Rheumatology key messages

- The safety and efficacy of JAK inhibitors seems to be comparable to biologics in RA.
- Tofacitinib is the first JAK inhibitor approved for treatment of RA by the FDA.

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References