Baricitinib in rheumatoid arthritis: evidence-to-date and clinical potential

Bindee Kuriya, Marc D. Cohen and Ed Keystone

Ther Adv Musculoskel Dis
2017, Vol. 9(2) 37–44
DOI: 10.1177/1759720X16687481

***Abstract*:** Biologics have changed expectation and outcomes for rheumatoid arthritis (RA). However, the optimal duration and sequence of therapy for this disease has yet to be determined. Also, a significant number of patients do not satisfactorily respond to currently available therapies. The Janus kinase (JAK) inhibitors represent a new class of therapies for RA. These drugs work uniquely by inhibiting intracellular pathways thought to be important in the pathogenesis of RA. They are available as oral agents, which is also different from the currently available biologics. Baricitinib has now been evaluated in four phase III clinical trials, and although safety concerns cannot fully be answered until the drug is studied over longer periods of time, the data to date suggest that this drug with its once daily dosing, rapid onset of action and efficacy as monotherapy represents an important addition to the RA therapeutic armamentarium. Further study and experience will better define how baricitinib will be used and by which patients.

Keywords: baricitinib, Janus kinase inhibitors, rheumatoid arthritis

Received: 8 December 2015; revised manuscript accepted: 29 November 2016.

Correspondence to:
Ed Keystone
The Rebecca MacDonald Centre For Arthritis Mount Sinai Hospital, 60 Murray Street, Room 2-006, Box 4 Toronto, Ontario M5T 3L9, Canada
ed.keystone@sinaihealthsystem.ca

Bindee Kuriya
Rebecca MacDonald Centre for Arthritis and Autoimmune Diseases, Sinai Health System, Toronto, Canada

Marc D. Cohen
Division of Rheumatology, Mayo Clinic, Rochester, USA

Background

Biologic disease modifying antirheumatic drugs (biologics) have substantially changed the landscape of therapy for rheumatoid arthritis (RA). While they have significantly improved outcomes in patients with RA who are DMARD incomplete responders (IR), they require administration by the subcutaneous or intravenous routes. Biologics inhibit circulating or membrane-bound cytokines (e.g. tumor necrosis factor alpha (TNF) and interleukin 6) or cellular targets (B and T cells). Recently, a new class of targeted, synthetic, small molecules has been developed which interfere with intracellular signal transduction by inhibiting Janus kinase (JAK) enzymes.

JAK enzymes are part of the family of tyrosine kinases that constitutively bind to the intracellular domains of cytokine receptors.[1] When extracellular cytokines and growth factors bind to these receptors, JAKs are phosphorylated, leading to activation of signal transducers and activators of transcription. The result is modulation of a variety of signaling cascades involved in cytokine and chemokine transcription, hematopoiesis and innate and acquired immunity; many of which are critically involved in the pathogenesis of RA.[1,2]

There at least four JAK enzymes – JAK 1, 2, 3, and Tyk2. These are associated with a number of paired receptors.[1–3] JAK1 is expressed in lymphoid cells, but also more widely in other systems, including the central nervous system. It is associated with the beta chain of the interleukin 2 (IL-2) family of receptors as well as with other cytokine receptors including interferon-gamma (IFN-γ), IL-6, 10, 12, and IL-23.[1] JAK2 is expressed on a wide variety of cells and inhibits signaling by erythropoetin and growth hormones, and is important in controlling the production of blood cells from hematopoetic stem cells. JAK2 mutations are associated with myeloproliferative syndromes. JAK3 is expressed mostly in lymphoid cells and binds primarily with the gamma chain of the IL-2 family of receptors, including IL-2, 4, 7, 9, 15 and IL-21.[2] Tyk2 also has a somewhat ubiquitous expression and is a component of alpha- and beta-IFN signaling as well as IL-6, 10, 12, and IL-23 transduction.[1,2] Stimulation by IL-6, a key mediator in RA pathogenesis, also results in the activation of JAK1, JAK2 and Tyk2 kinases.[3] In summary, specific JAK kinases, either alone or in combination, are preferentially activated, depending on the type of the cytokine or growth factor receptor that is being engaged.

Tofacitinib *versus* baricitinib

Tofacitinib was the first JAK inhibitor approved by the U.S. Food and Drug Administration (FDA) in 2012[4] for adults with moderate-to-severe RA, with an inadequate response to or intolerant of methotrexate (MTX). Tofacitinib primarily inhibits JAK1 and JAK3.[3] The recommended dose is 5 mg orally twice daily or 11 mg extended release once daily.[3] In contrast, baricitinib selectively and reversibly inhibits JAK1 and JAK2. It is administered orally, once daily. Baricitinib is not yet available but was submitted in early 2016 to the FDA for approval as an oral, daily treatment for moderately-to-severely active RA.[5]

Immunologic activity and pharmacokinetics of baricitinib

Baricitinib potently inhibits JAK1 and JAK2 (approximately 100-fold) compared with JAK3, through the binding of intracellular mechanisms, similar to those described for tofacitinib.[3] As a result, generation of cytokines such as IL-2, IL-6, 12, 23, as well as granulocyte-macrophage colony stimulating factor and IFN-γ are inhibited. In animal models of inflammatory arthritis, baricitinib was shown to have significant anti-inflammatory effects, but also led to preservation of cartilage and bone, with no detectable suppression of humoral immunity or adverse hematologic effects.[6]

Following oral administration in healthy human volunteers, baricitinib attained a peak plasma concentration within 1.5 h, and demonstrated dose linear and time invariant pharmacodynamics, with low oral dose clearance of approximately 17 l/hr and minimal systemic accumulation following repeat oral dosing.[7] Mean renal clearance was approximately 2 l/hr.[5] The pharmacokinetics correlated well with plasma concentrations.[7]

Phase II clinical trials

A preliminary report of a phase II clinical trial in patients with active RA despite DMARD therapy was reported by Greenwald and colleagues.[8] In this study, 127 longstanding, biologic-naive RA patients were randomized to placebo, or 4 mg, 7 mg, or 10 mg of baricitinib in combination with DMARDs. The American College of Rheumatology (ACR) response rate for ACR 20 was 32% for the placebo group *versus* 52%, 59%, and 53% for the 4 mg, 7 mg, and 10 mg baricitinib groups respectively. The percentage of patients achieving a Disease Activity Score 28 Joints (DAS28) of <2.6 was 16% for the placebo group compared with 23% for the 4 mg, 25% the 7 mg and 17% for the 10 mg baricitinib group. Treatment emergent adverse events (TEAEs) were fairly similar across groups, with headache and diarrhea reported most commonly. There were two cases of herpes zoster. Increases in high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were observed.

In a phase IIb trial by Keystone and colleagues, 301 RA patients with active RA despite MTX were randomized 2:1:1:1:1 to receive placebo or 1 mg, 2 mg, 4 mg, or 8 mg of baricitinib once daily for 12 weeks while continuing their background DMARDs.[9] After 12 weeks, patients receiving placebo or 1 mg of baricitinib were changed to baricitinib 2 mg or 4 mg daily, and all patients were followed for an additional 12 weeks. The primary endpoint (ACR20 response rate at 12 weeks) was significantly higher in the combined baricitinib 4 mg and 8 mg groups compared with placebo (76% *versus* 41%; $p < 0.01$). Also at week 12, significant differences between these groups were observed for ACR50/70 response rates, DAS28 < 2.6 rates, clinical disease activity index (CDAI) and simplified disease activity index (SDAI) response rates. Patients in the 2 mg, 4 mg, and 8 mg groups maintained or improved all measures through 24 weeks. Adverse events were similar across groups. A total of three serious respiratory infections were observed (one each of bronchitis and pneumonia in the baricitinib 2 mg group, and one pneumonia in the 8 mg group). There were no cases of herpes zoster or opportunistic infections. Mild decreases in hemoglobin and neutrophil counts were seen and appeared to be dose dependent. Increases in HDL and LDL cholesterol, transaminases and creatinine levels also occurred.[9]

Phase III clinical trials

Preliminary data from three phase III clinical trials have been recently published.[10–12] In one, the RA-BUILD study, 684 RA patients with active disease despite conventional DMARD treatment were randomized 1:1:1 to placebo or baricitinib 2 mg or 4 mg once daily for 24 weeks.[10] Placebo-treated patients were switched to active treatment at 16 weeks. Significantly higher ACR 20 response rates compared with placebo were observed in both baricitinib groups: 40% *versus* 66% and 62% respectively ($p < 0.001$ for both, Table 1). Significant improvements in both baricitinib groups compared with placebo were also seen in

Table 1. Summary of phase II and III clinical trials of baricitinib in RA.

Study (reference)	Population	Baricitinib (bari)	Comparator	Primary endpoint comparing bari at various doses *versus* placebo (at week 12)	*p*-value	Key secondary endpoints comparing bari at various doses *versus* placebo (at week 12)	*p*-value
Phase II							
Greenwald[8]	MTX-IR	4, 7 or 10 mg once daily	Background MTX	ACR 20 (%) 4 mg *versus* placebo: 52% *versus* 32% 7 mg *versus* placebo: 59% *versus* 32% 10 mg *versus* placebo: 53% *versus* 32%	Abstract form (not available)		
Keystone[9,18]	MTX-IR	1, 2, 4 or 8 mg once daily	Background MTX	ACR 20 (%) 4 mg + 8 mg combined group *versus* placebo: 76% *versus* 41%	$p < 0.001$	ACR 50 and 70 1 mg *versus* placebo: ACR 50 31% *versus* 10% ACR 70 12% *versus* 2% 2 mg *versus* placebo: ACR 50 17% *versus* 10% ACR 70 8% *versus* 2% 4 mg *versus* placebo: ACR 50 35% *versus* 10% ACR 70 23% *versus* 2% 8 mg *versus* placebo: ACR 50 40% *versus* 10% ACR 70 20% *versus* 2% DAS28 < 2.6 1 mg *versus* placebo: 14% *versus* 4% 2 mg *versus* placebo: 15% *versus* 4% 4 mg *versus* placebo: 37% *versus* 4% 8 mg *versus* placebo: 22% *versus* 4%	<0.05 <0.05 NS NS <0.05 <0.05 <0.05 <0.05 <0.05 <0.05 <0.05 <0.05

(Continued)

Table 1. (Continued)

Study (reference)	Population	Baricitinib (bari)	Comparator	Primary endpoint comparing bari at various doses *versus* placebo (at week 12)	*p*-value	Key secondary endpoints comparing bari at various doses *versus* placebo (at week 12)	*p*-value
Phase III							
RA-BUILD[10]	MTX-IR	2 mg or 4 mg once daily	Background MTX	ACR 20 (%) 2 mg *versus* placebo: 66% *versus* 39% 4 mg *versus* placebo: 62% *versus* 39%	<0.001 <0.001	ACR 50 and 70 (%) 2 mg *versus* placebo: ACR 50 34% *versus* 13%; ACR 70 18% *versus* 3% 4 mg *versus* placebo: ACR 50 33% *versus* 13%; ACR 70 18% *versus* 3% DAS28<2.6 (%) 2 mg *versus* placebo: 11% *versus* 2% 4 mg *versus* placebo: 9% *versus* 2%	<0.001 <0.001 <0.001 <0.001 <0.001 <0.001
RA-BEACON[12]	TNF-IR	2 mg or 4 mg once daily	Background MTX	ACR 20 (%) 2 mg *versus* placebo: 49% *versus* 27% 4 mg *versus* placebo: 55% *versus* 27%	<0.001 <0.001	ACR 50 and 70 (%) 2 mg *versus* placebo: ACR 50 20% *versus* 8% ACR 70 13% *versus* 2% 4 mg *versus* placebo: ACR 50 28% *versus* 8% ACR 70 11% *versus* 2% DAS28 < 2.6 (%) 2 mg *versus* placebo: 6% *versus* 1% 4 mg *versus* placebo: 6% *versus* 1%	<0.01 <0.001 <0.001 <0.01 <0.01 <0.05
RA-BEGIN[14]	Minimal or no DMARD exposure	4 mg once daily (monotherapy) *versus* 4 mg once daily + MTX (combo therapy)	MTX monotherapy	ACR 20% 4 mg monotherapy *versus* MTX: 77% *versus* 62%	<0.01	Monotherapy 4 mg *versus* MTX ACR 50 60% *versus* 43% ACR 70 42% *versus* 21% DAS28-CRP < 2.6 (%) 40% *versus* 24% *Combination Therapy* 4 mg + MTX *versus* MTX ACR 50 63% *versus* 43% ACR 70 40% *versus* 21% DAS28-CRP<2.6 (%) 40% *versus* 24%	<0.05 <0.05 <0.05 <0.05 <0.05 <0.05

Table 1. (Continued)

Study (reference)	Population	Baricitinib (bari)	Comparator	Primary endpoint comparing bari at various doses *versus* placebo (at week 12)	*p*-value	Key secondary endpoints comparing bari at various doses *versus* placebo (at week 12)	*p*-value
RA-BEAM[15]	MTX-IR	4 mg once daily	MTX or ADA	ACR 20 (%) 4 mg *versus* placebo: 70% *versus* 40%	<0.001	ACR 20 (%) Bari *versus* ADA: 70% *versus* 60% ACR 50 (%) Bari *versus* ADA: 45% *versus* 35% ACR 70 (%) Bari *versus* ADA: 19% *versus* 13% Mean change in DAS28-CRP Bari *versus* ADA: −2.2 *versus* −1.9 CDAI ⩽ 10 (%) Bari *versus* ADA: 40% *versus* 33% SDAI ⩽ 11 (%) Bari *versus* ADA: 42% *versus* 35%	 ⩽0.05 <0.01 <0.05 <0.01 <0.05 <0.05
RA-BEYOND[16]	DMARD-naïve, DMARD-IR, Biologic-IR	4 mg once daily (continued dose)	Step down bari to 2 mg once daily	CDAI LDA (%) 4 mg *versus* 2 mg: 93% *versus* 84% CDAI REM (%) 4 mg *versus* 2 mg: 39% *versus* 37%	<0.05 NS	Change in DAS28-CRP 4 mg *versus* 2 mg: 0.70 *versus* 0.77	<0.05

ACR 20/50/70, American College of Rheumatology 20%, 50% or 70% response; ADA, adalimumab; Biologic-IR, biologic inadequate response; CDAI, clinical disease activity index; DAS28, disease activity score 28 joints; DAS28-CRP, disease activity score 28 joints using C-reactive protein; DMARD-IR, disease modifying antirheumatic drug inadequate response; LDA, low disease activity; MTX, methotrexate; MTX-IR, methotrexate inadequate response; NS, non-significant; REM, remission; SDAI, simplified disease activity index; TNF-IR, tumor necrosis factor alpha antagonist inadequate response.

ACR 50 and ACR 70 response rates, DAS28 < 2.6 (Table 1) as well as health assessment questionnaire disability index (HAQ-DI), CDAI and SDAI responses rates which were sustained through week 24. Slowing of radiographic progression was also observed at week 24, with changes in the mean modified total Sharp score (mTSS) of 0.33 and 0.15 in the baricitinib 2 mg and 4 mg group respectively, compared with mTSS of 0.70 in the placebo group.[10] Weekly assessments early in this trial, demonstrated rapid improvements in many patients, some as early as week 1. TEAEs were similar across groups. There were no serious infections and laboratory abnormalities were similar to those seen in the phase II studies.[10] Recent data from RA-BUILD demonstrated that the baricitinib-treated patients also exhibited significant improvement in patient-reported outcomes across different domains including pain, functional ability, and fatigue.[11]

Results from another phase III trial, the RA-BEACON study, have recently been published.[12] In this study, 527 RA patients with an inadequate response to one or more TNF-inhibitors were randomized 1:1:1 to placebo or baricitinib 2 mg or 4 mg once daily in addition to background non-biologic DMARDs for 24 weeks. Significantly higher ACR 20 response rates compared with placebo were observed in both baricitinib groups: 27% for placebo *versus* 49% and 55% for the baricitinib groups respectively ($p < 0.001$ for both). Improvements, often but not always statistically significant, were observed in the baricitinib groups for ACR 50 and ACR 70 response rates, a proportion achieving DAS28 < 2.6, mean HAQ-DI, CDAI and SDAI response rates (Table 1). Treatment benefit was sustained at 24 weeks in the 4 mg dose only. More TEAEs were seen in the baricitinib groups, including infections, but serious adverse events were similar across groups. There were no opportunistic infections and laboratory abnormalities were similar to those seen in prior phase II studies.

Preliminary data demonstrated that in both RA-BUILD and RA-BEACON a lack of early clinical response, as indicated by a failure to achieve a decrease in DAS28 > 0.6 or CDAI > 6 after 4 weeks of treatment, was associated with lower attainment of low disease activity or remission at 12 or 24 weeks.[13] In fact, larger decreases in DAS28 or CDAI at week 4 were associated with improved clinical responses. This potential ability to identify patients very early who are not likely to achieve significant clinical targets might be useful in tailoring therapy to individual patients.

In a novel phase III trial (RA-BEGIN), baricitinib was administered as monotherapy or in combination with MTX to patients with early, active RA who had limited or no prior treatment with conventional DMARDs.[14] In this study, 584 active RA patients with no prior DMARD treatment or fewer than three doses of MTX were randomized 4:3:4 to MTX monotherapy (increased from 10 mg to 20 mg once weekly over 8 weeks), baricitinib 4 mg once daily, or baricitinib 4 mg once daily plus MTX (increased as described) for up to 52 weeks. The primary outcome evaluated non-inferiority of baricitinib 4 mg monotherapy compared with MTX monotherapy for ACR 20 response at week 24 (using a 12% margin). A total of 87% percent of the patients treated with MTX monotherapy, 89% of the patients treated with baricitinib monotherapy and 91% of the patients treated with baricitinib plus MTX completed 24 weeks of the study. The ACR 20 response rate at week 24 was higher in the baricitinib monotherapy group compared with MTX monotherapy (77% *versus* 62%, $p < 0.01$). Compared with MTX alone, baricitinib monotherapy produced significantly greater improvements in secondary measures of disease activity, including ACR 50 and ACR 70 response rates, remission and low disease states according to the DAS28, CDAI and SDAI as well as HAQ-DI and Functional Assessment of Chronic Illness Therapy scores; many seen as early as week one (for all $p < 0.05$). Interestingly, MTX in combination with baricitinib did not appear to increase the benefit observed with baricitinib monotherapy in terms of response rates. However, it is notable that the combination of baricitinib with MTX demonstrated a greater reduction in radiographic progression compared with either monotherapy alone. TEAEs and SAEs were similar across groups, with more infections and one death noted in the MTX monotherapy group compared with the baricitinib monotherapy group. Through 24 weeks, 2 (1.0%), 6 (3.8%) and 14 (6.5%) patients discontinued the study because of an adverse event in the MTX, baricitinib 4 mg and baricitinib 4 mg + MTX groups respectively. Anemia, lymphopenia, and transaminitis were generally less frequent in the baricitinib monotherapy group compared with the other two groups.[14]

The RA-BEAM trial compared the efficacy of baricitinib to adalimumab and placebo among patients who were MTX-IR.[15] Patients were

randomized 3:3:2 to placebo, baricitinib 4 mg once daily or adalimumab 40 mg bi-weekly with background MTX. Nonresponders were rescued from week 16 and patients on placebo were switched to baricitinib 4 mg at week 24. The primary endpoint was ACR 20 response at week 12 for baricitinib compared with placebo. Major secondary endpoints included comparisons of baricitinib *versus* adalimumab for ACR 20 rates and change in DAS28-CRP at week 12 as well as response rates at week 24 comparing baricitinib or adalimumab to placebo (Table 1). Of the 1305 randomized patients, 89%, 94% and 93% completed week 24 in the placebo, baricitinib and adalimumab groups, respectively. An ACR 20 response was achieved at 12 weeks by 40% of patients in the placebo group, 61% in the adalimumab arm and by 70% in the baricitinib group ($p < 0.001$ for comparisons *versus* placebo). At week 12 and 24, significant improvements in ACR 20/50/70, HAQ-DI response rates, and low disease activity and remission rates (according to DAS28, CDAI, and SDAI) were seen for baricitinib *versus* placebo (all $p < 0.001$).[15] Significantly more patients in the baricitinib plus MTX arm achieved low disease activity, compared with placebo or with adalimumab plus MTX (Table 1). Furthermore, inhibition of structural damage at week 52 (defined as van der Heijde mTSS $\leqslant 0.5$), was significantly higher for both the baricitinib (85.2%) and adalimumab group (86.5%) compared with placebo (70.4%, $p < 0.001$).

Baricitinib also demonstrated significantly higher ACR 20/50/70 responses compared with adalimumab at 12 weeks and higher ACR 20 and ACR 70 responses at week 24. Rates of TEAE were higher for the active treatment groups *versus* placebo: 47.3% for placebo, 52.8% for baricitinib and 50.9% for adalimumab. Specifically, infection rates during weeks 0–12 were 17.8%, 21.8% and 20% respectively. There were four malignancies and two deaths reported in the baricitinib group and none in the adalimumab group in weeks 0–24.

Patients who completed RA-BUILD, RA-BEGIN or RA-BEAM were eligible to complete a long-term extension study called RA-BEYOND.[16] In this study, those who received baricitinib 4 mg once daily for at least 15 months and who achieved sustained low disease activity or remission (defined by CDAI score at two consecutive visits at least 3 months apart) were rerandomized in a double blind manner to continue receiving baricitinib 4 mg once daily or to step down to a 2 mg daily dose. Disease activity was assessed at 12 weeks. The majority of patients were able to sustain a state of low disease or remission in both the continued 4 mg and reduced 2 mg groups (Table 1). However, compared with the 4 mg group, the reduction to 2 mg at week 12 was associated with statistically significant increases in tender and swollen joint counts, physician global assessments, DAS28-CRP, CDAI and SDAI scores (all p-values < 0.05). Consistent with other phase III studies, these data indicate that 4 mg once daily is the most efficacious dose of baricitinib.

Safety

An integrated analysis presented this year reviewed safety of baricitinib across all phase I to phase III studies and the RA-BEYOND study.[17] Among 3464 patients (4214 patient-years) exposed to baricitinib, there have been no increases in deaths, malignancies, serious infections, opportunistic infections or adverse events leading to drug discontinuation. A statistically higher rate of herpes zoster (4.3% in the first 24 weeks) in the baricitinib 4 mg group has been reported compared with placebo. Baricitinib treatment has been associated with changes in hemoglobin, lymphocytes, transaminases, creatine kinase and creatinine levels, but fewer than 1% have discontinued due to abnormal lab results. Furthermore, there does not appear to be an increased risk over time for adverse events with longer exposure.

Conclusion

JAK inhibitors are a new class of targeted small molecules that inhibit intracellular transduction and represent an important addition to the treatment of moderate-to-severe RA. Formal results and publication of phase III trials and long-term extension studies to assess the full efficacy and safety profile of baricitinib are eagerly awaited. For now, the early data suggest that baricitinib, particularly with its once-daily oral dosing and early-onset of efficacy, may be another important treatment option in a competitive marketplace.

Acknowledgements

We would like to thank Dr Shelly Chandran for her assistance with manuscript preparation.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Dr Kuriya: The Arthritis Society/Canadian Rheumatology Association Clinician Investigator Award; Advisory Board Member for F. Hoffman La Roche Inc, Abbott laboratories, Sanofi-Aventis Inc.

Dr Keystone: Sources of funding for research, consulting agreements/advisory boards, speaker honoraria agreements: Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, F. Hoffman La Roche Inc., Janssen Inc, Lilly Pharmaceuticals, Lilly Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Aventis Inc.

References

1. **O'Shea J., Holland S. and Staudt L. JAKs and STATs in immunity, immunodeficiency, and cancer. *N Eng J Med* 368: 161–170. This is a clear and concise review of this complicated subject.
2. Tanaka Y. and Yamaoka K. JAK inhibitor for treating rheumatoid arthritis: from basic to clinical. *Mod Rheumatol* 23: 415–424.
3. **Scott L. Tofacitinib: a review of its use in adult patients with rheumatoid arthritis. *Drugs* 73: 857–874. This is an inclusive review which includes preclinical observations and presentation of the important aspects of the tofacitinib clinical trials.
4. U.S. Food and Drug Administration. *FDA approves Xeljanz for rheumatoid arthritis*, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm (accessed 11 October 2016).
5. Eli Lilly and Company. Lily and Incyte announce submission of new drug application to FDA for oral once-daily baricitinib for treatment of moderate-to-severe rheumatoid arthritis, https://investor.lilly.com/releasedetail.cfm?ReleaseID=950678 (accessed 15 October 2016).
6. Fridman J., Scherle P., Collins R., *et al.* Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol* 184: 5298–5307.
7. Shi J., Chen X., Lee, F., *et al.* The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol* 2014; 54: 1354–1361.
8. Greenwald M., Fidelus-Gort R., Levy R., *et al.* A randomized dose-ranging, placebo-controlled study of INCN028050, a selective JAK1 and JAK2 inhibitor in subjects with active rheumatoid arthritis. *Arthritis Rheum* 62(Suppl. 10): 2172.
9. Keystone E., Taylor P., Drescher E., *et al.* Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis* 74: 333–340.
10. Dougados M., van der Heijde D., Chen Y., *et al.* Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. Epub ahead of print, 2 November 2016.
11. Emery P., Gaich C., DeLozier A., *et al.* Patient-reported outcomes from a phase III study of baricitinib in patients with rheumatoid arthritis with inadequate –response to conventional synthetic disease-modifying antirheumatic drugs. *Ann Rheum Dis*. Epub ahead of print, 31 October 2016.
12. Genovese M., Kremer J., Zamani O., *et al.* Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 374: 1243–1252.
13. Kremer J., Dougados M., Genovese M., *et al.* Response to baricitinib at 4 weeks predicts response at 12 and 24 weeks in patients with rheumatoid arthritis: results from two phase 3 studies. *Arthritis Rheumatol* 67(Suppl. 10): 1368–1370.
14. Fleischmann R., Schiff M., van der Heijde D., *et al.* Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. Epub ahead of print, 9 October 2016.
15. Taylor P., Keystone E., van der Heijde D., *et al.* Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis and an inadequate response to background methotrexate therapy: results of a phase 3 study. *Arthritis Rheumatol* 67(Suppl. 10): 3927–3931.
16. Takeuchi T., Genovese M., Xie L., *et al.* Baricitinib dose stepdown following disease control in patients with rheumatoid arthritis. *Ann Rheum Dis* 75(Suppl. 2): 144.
17. Smolen J., Genovese M., Takeuchi T., *et al.* Safety profile of baricitinib in patients with active RA: an integrated analysis. *Ann Rheum Dis* 75(Suppl. 2): 243–244.
18. Genovese M., Keystone E., Taylor P., *et al.* 24-week results of a blinded phase 2b dose-ranging study of baricitinib, an oral janus kinase 1/januse kinase 2 inhibitor, in combination with traditional disease modifying antirheumatic drugs in patients with rheumatoid arthritis. *Arthritis Rheum* 64 (Suppl. 10): S1049–S1050.