Review

The effect of JAK1/JAK2 inhibition in rheumatoid arthritis: efficacy and safety of baricitinib

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ABSTRACT

Numerous cytokines have been implicated in the pathogenesis of inflammatory diseases, and their dysregulation is a main feature of rheumatoid arthritis (RA). Cytokines stimulate signal transduction through several intracellular pathways, including Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathways, leading to changes in cell activation, proliferation and survival. Consequently, agents that selectively target elements of the JAK/STAT pathways have received significant attention in recent years as potential new treatments for the disease. Baricitinib, an oral selective inhibitor of JAK1 and JAK2, offers an effective treatment for RA in a wide range of patients. The in vitro selectivity of different JAK inhibitors is an important consideration given that key cytokines, growth factors and hormone receptors involved in the pathogenesis of RA signal through specific JAKs. However, it is complex and far from understood how the in vitro effects of JAK inhibitors extrapolate into in vivo and clinical effects in individual patients. This narrative review focuses on the clinical efficacy and safety of baricitinib, but also provides an overview of its mechanism of action in relation to JAK1/JAK2 signalling and discusses the possible clinical implications in patients with RA.

Introduction

Janus kinases (JAKs) play an essential role in the intracellular signalling pathways of various cytokines, colony-stimulating factors and hormones involved in the pathogenesis of immune-related diseases, including rheumatoid arthritis (RA) (1-3). Thus, agents that selectively inhibit JAKs have received significant attention in recent years as potential new treatments for the disease. This narrative review focuses on the clinical efficacy and safety of the selective JAK1 and JAK2 inhibitor baricitinib (4, 5) and provides an overview of its mechanism of action and the possible clinical implications in patients with RA. The review was written by experts in the field and reflects their experience and perspective. It was developed with the aid of references identified through non-systematic searches of the internet, including PubMed and Google Scholar, using the search terms 'rheumatoid arthritis' and 'baricitinib' for the time period January 2005 to July 2018.

The role of cytokines in inflammation and their potential as extracellular therapeutic targets in RA

In RA, a dysregulated systemic immune response causes the infiltration of immune cells into the joint synovium (6), resulting in the overproduction of pro-inflammatory cytokines (Table I) (7). These attract further inflammatory and immune cells, stimulating the release of additional cytokines, chemokines and matrix metalloproteinases, which cause joint destruction (12). The inhibition of pro-inflammatory cytokines or their receptors therefore provides a therapeutic opportunity for patients with RA (7), as already demonstrated by the development of inhibitors of tumour necrosis factor (TNF)-α and interleukin (IL)-6. More recently, RA research has focused on intracellular pathways rather than on the extracellular milieu as potential targets for immune m odulation (13).

JAK/STAT intracellular signalling pathways in RA

Attempts to develop therapies that target major intracellular signal transduction

Table I. Cytokines involved in the pathogenesis of rheumatoid arthritis[¥] (7–11).

Net pro-inflammatory	Net anti-inflammatory
• IL-1, IL-6, IL-7, IL-8, IL-12, IL-15, IL-17, IL-18, IL-21, IL-22, IL-23	• IL-10, IL-25, IL-27, IL-35
• TNF-α	• IL-1 Ra, IL-1 RII, soluble IL-1 RI, soluble IL-1 R II
• IFNα, -β and -γ	• Soluble gp130
• Lymphotoxin	• IL-13 Rα
• MMIF	• IL-18 binding protein, IL-22 binding protein
• Resistin	• TNF-RI, TNF-RII
• GM-CSF, G-CSF, M-CSF	• TGFβ
• Fibroblast growth factor-2	• $CXCL^{ELR-}$
• VEGF	• Duffy antigen receptor for chemokines
• $CXCL^{ELR+}$	• Osteoprotegerin
• CCL2, CCL3, CCL21, CCL25	• 7ND
• CXCL8 and 13	• Chemerin 15
• Chemerin 9	

[¥]Adiponectin has both anti- and pro-inflammatory effects (7,11).
7ND: N-terminal natural deletion variant of monocytes chemotactic protein-1/CCL2; CCL: C-C motif chemokine ligand; CXCL: chemokine (C-X-C motif) ligand; $CXCL^{ELR+/-}$: CXCL with/without glutamic acid-leucine-arginine motif; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; gp130: glycoprotein 130; IFN: interferon; IL: interleukin; IL-1 Ra: interleukin-1 receptor antagonist; IL-1 RI: IL-1 receptor I; IL-1 RII: IL-1 receptor II; IL-13 Rα: IL-13 receptor α; M-CSF: macrophage colony-stimulating factor; MMIF: macrophage migration inhibitory factor; TGFβ: transforming growth factor β; TNF-RI: TNF-receptor I; TNF-RII: TNF-receptor II; TNF-α: tumour necrosis factor α; VEGF: vascular endothelial growth factor.

pathways for inflammatory cytokines in RA, such as the p38 mitogen-activated protein kinase (MAPK) and spleen tyrosine kinase (SYK) pathways, have either proved unsuccessful because of safety concerns or moderate efficacy, or have yet to be proven effective (1, 14-16). By contrast, agents that target JAK/signal transducers and activators of transcription (STAT) signalling pathways have shown much greater promise as RA therapies. The JAK family of cytoplasmic protein tyrosine kinases comprises JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2). JAKs bind to type I and type II cytokine receptors and transmit extracellular cytokine signals to STATs (2, 17). The STATs become activated and translocate to the nucleus, where they modulate the transcription of effector genes important for cell proliferation, differentiation, survival and death (2, 18). JAKs work in pairs (hetero- or homodimers), and different cytokines use different JAK pairs for signalling (Fig. 1). Figure 2 illustrates the seven key steps to cytokine signalling via JAK/STAT pathways.

JAK1 and JAK2 are expressed ubiquitously (3, 18, 21) and mediate the signalling of several key cytokines in RA, including IL-6, IL-23, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferons (IFNs) and erythropoietin (1). By contrast, JAK3 is confined to haematopoietic cells, such as myeloid and lymphoid cells, and is primarily involved in T-cell and natural killer (NK) cell signalling, maturation and immune function (3, 21, 22). Despite its ubiquitous distribution, functional deficits related to JAK2 signalling in knockout mice have a severe impact on haematopoietic, erythroid and thrombopoietic cells (23, 24), whereas deletions of JAK3 in mice and humans principally cause lymphopoietic defects that manifest as severe combined immunodeficiency (3, 18, 21, 22).

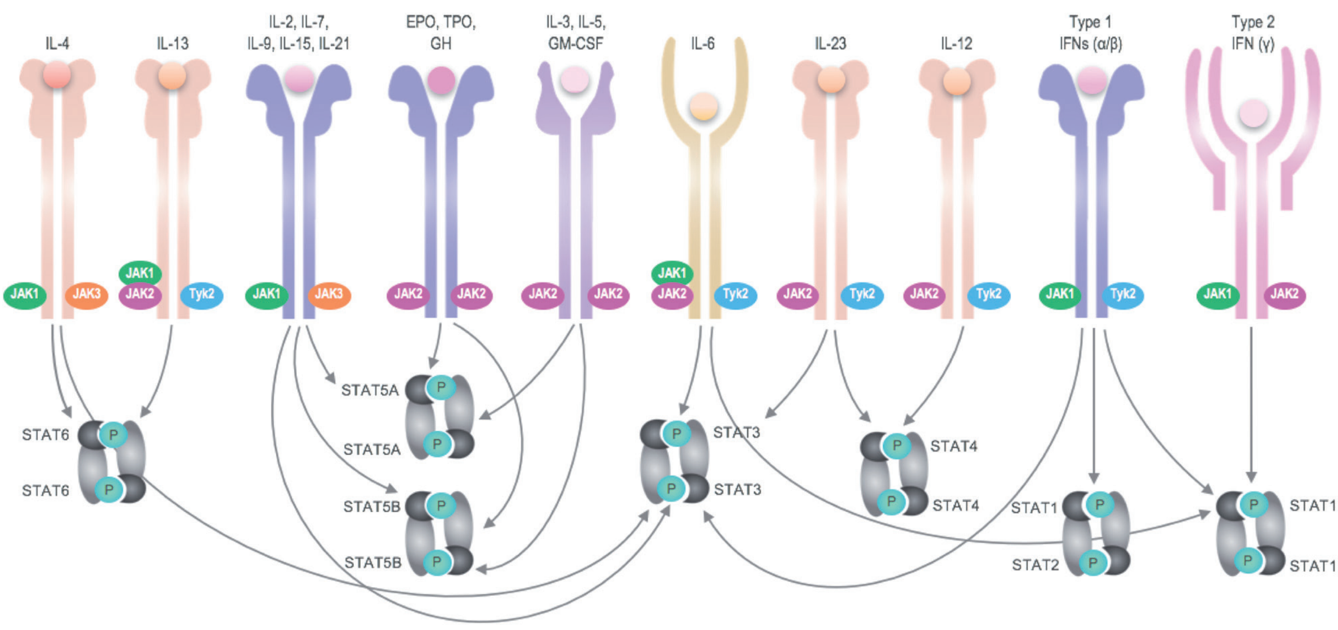

Fig. 1. The dependence of different cytokines on different JAKs (2,19,20) (adapted from O'Shea *et al.* (2)).
EPO: erythropoietin; GH: growth hormone; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; IL: interleukin; JAK: Janus kinase; P: phosphorylation; STAT: signal transducers and activators of transcription protein; TPO: thrombopoietin; Tyk2: tyrosine kinase 2.

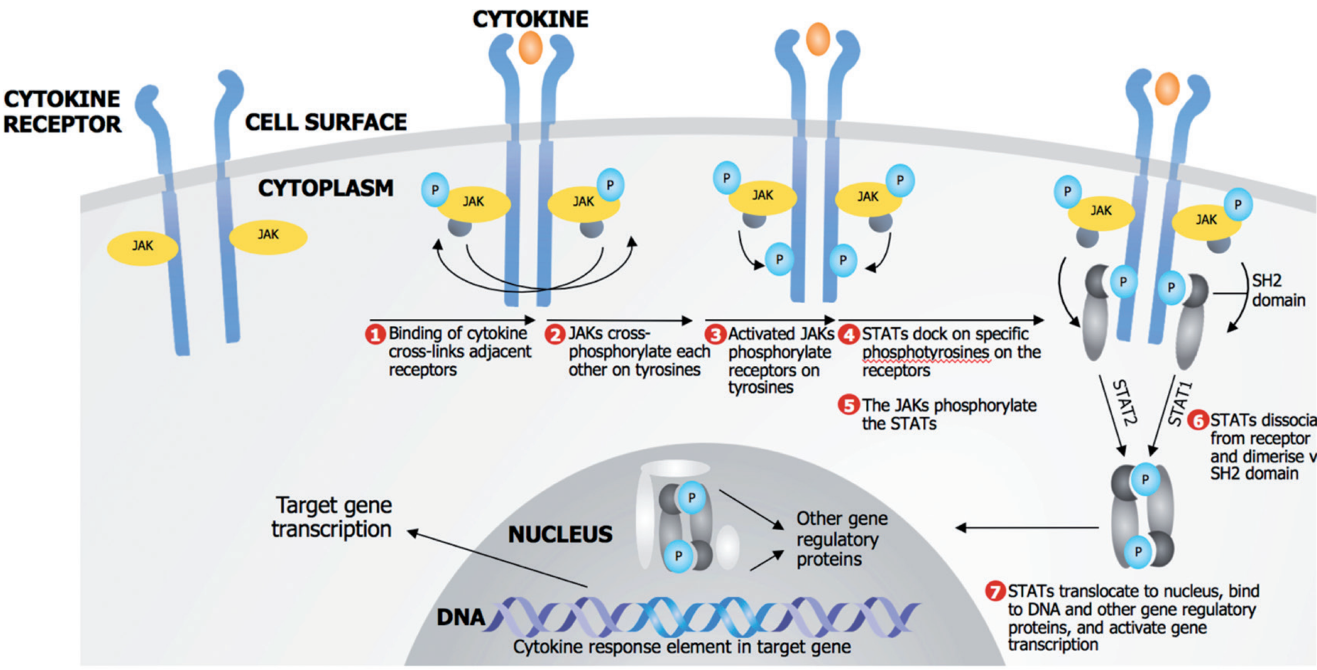

Fig. 2. Seven steps of the JAK/STAT cytokine signalling pathway (adapted from O'Shea *et al*. (2)).
JAK: Janus kinase; P: phosphate group; SH2: Src homology 2 protein domain; STAT: signal transducers and activators of transcription.

Introduction to baricitinib

Pharmacodynamics

Baricitinib is an oral selective inhibitor of JAK1 and JAK2, with half maximum inhibitory concentration (IC_{50}) values of 5.9±0.9 nM for JAK1, 5.7±1.7 nM for JAK2, ≈560 nM for JAK3 and 53 nM for Tyk2 (4, 25). Baricitinib is a competitive adenosine triphosphate (ATP) kinase inhibitor, and blocks the signalling of certain cytokines by preventing the transfer of phosphate from ATP to JAKs and hence JAK activation (4, 26). *In vitro* assays using human peripheral blood mononuclear cells showed that baricitinib inhibited the signalling of several JAK1/JAK2-dependent cytokines, including IL-6 signalling in cluster of differentiation (CD)-4$^+$ T cells and monocytes (5, 27, 28), and IFN (JAK1/JAK2, JAK1/Tyk2) signalling in CD4$^+$ T cells, NK cells and monocytes (27, 28). Baricitinib also inhibited the signalling of a number of JAK2-dependent cytokines and hormones, including IL-23 (JAK2/Tyk2) signalling in CD4$^+$ T cells, G-CSF (JAK2/Tyk2) and GM-CSF (JAK2/JAK2) signalling in monocytes (5, 28), and erythropoietin signalling in CD34$^+$ T cells (JAK2/JAK2). However, it was less active against JAK3-dependent cytokines, such as IL-21 (JAK1/JAK3) and IL-15 (JAK1/JAK3) (5).

Pharmacokinetics

Baricitinib is rapidly absorbed after oral administration, attaining peak plasma concentrations within 1.5 hours of dosing (29). It has a terminal half-life of approximately 14 hours, which supports once-daily dosing (30, 31). Food does not affect the extent of absorption (29). Baricitinib is excreted in the urine largely unchanged (64.1%) (29) without significant hepatic metabolism (32). However, dose adjustment is required when creatinine clearance is between 30 and 60 mL/minute, and it is not recommended for use if creatinine clearance is <30 mL/minute (32). In the USA, baricitinib is not recommended in patients with an estimated glomerular filtration rate of <60 mL/minute/1.73m^2 (33).

Potential drug interactions

Baricitinib acts as a substrate for numerous renal transporter proteins, such as organic anion transporter (OAT)-3 and P-glycoprotein (P-gp). Theoretically, strong OAT3 inhibitors, such as probenecid, and the less potent OAT3 inhibitors ibuprofen, diclofenac and leflunomide, could affect the plasma exposure of baricitinib. However, physiologically based pharmacokinetic modelling predicted no increase in baricitinib exposure with diclofenac and only a small increase in exposure with ibuprofen (34). Conversely, coadministration with probenecid doubled baricitinib exposure (34, 35); thus, a maximum dose of baricitinib 2 mg once daily is recommended when coadministered with probenecid. Dedicated interaction studies between leflunomide and baricitinib have not been conducted, thus caution should be used when these drugs are given concomitantly (32). The pharmacokinetics of baricitinib were unaffected by coadministration with methotrexate (MTX) and vice versa (35).

Baricitinib in RA: from development to clinical practice

Pre-clinical studies

• *Effect of baricitinib on joints at the cellular level*

Cytokine signalling via JAKs plays an important role in osteoclast formation, a process regulated by osteoblasts through the cytokines IL-6, IL-11, leukaemia inhibitory factor (LIF) and receptor activator of nuclear factor κ-light-chain-enhancer of activated B cells ligand (RANKL) (36). *In vitro* studies using murine osteoclasts and osteoblasts showed that baricitinib has a minimal direct effect on osteoclasts but inhibits their formation by suppressing 1,25-dihydroxyvitamin D_3 and prostaglandin

E_2-induced secretion of IL-6, IL-11 and LIF and expression of RANKL from osteoblasts via the gp130/JAK signalling pathway, which is dependent on JAK1 and JAK2 (36).
Fibroblast-like synoviocytes have been implicated in the pathogenesis of RA, and biochemical studies have shown that baricitinib inhibits IFNγ-induced activation of focal adhesion kinase (FAK-Y925), an enzyme involved in the migration of these cells (37). The inhibitory action of baricitinib on osteoblast RANKL expression and fibroblast-like synoviocyte migration may, in part, explain its efficacy in preventing inflammation and joint damage (36, 37).

• *Effect of baricitinib on joints in vivo*
In a rat model of adjuvant-induced arthritis, treatment with baricitinib 10 mg/kg for 14 days significantly reduced disease severity, as early as day 2, as well as joint inflammation, ankle width and bone resorption in a dose-dependent manner compared with vehicle-treated animals. Microcomputed tomography imaging showed that baricitinib treatment prevented the joint destruction seen in vehicle-treated animals in the ankles and tarsals. Results were similar in a mouse model of collagen-induced arthritis (4).

Clinical studies: efficacy and safety
The efficacy and safety of baricitinib in RA have been extensively evaluated in a clinical study programme including 19 clinical pharmacology studies, three phase II studies (38-40), four phase III studies (RA-BEGIN (41), RA-BEAM (42), RA-BUILD (43), RA-BEACON (44)) and one ongoing long-term extension study (RA-BEYOND; NCT01885078).

• *Efficacy*
Results from the phase III study RA-BEGIN (41) showed that baricitinib 4 mg once daily was superior to MTX in patients with early active RA who were biologic disease-modifying anti-rheumatic drug (bDMARD)-naïve and had no or limited exposure to conventional synthetic DMARDs (csDMARDs). In RA-BEAM (42), baricitinib 4 mg with background MTX also proved superior to adalimumab 40 mg biweekly in patients with an inadequate response to MTX for specific predefined efficacy outcomes (Table II). In addition, baricitinib 4 mg in combination with MTX significantly reduced radiographic joint damage progression compared with placebo in patients with an inadequate response to MTX (42) and compared with MTX in bDMARD-naïve patients with limited or no exposure to csDMARDs (41). Both baricitinib 2 mg and 4 mg produced statistically significant improvements in efficacy outcomes compared with placebo in patients with an inadequate response, intolerance or a contraindication to csDMARDs or TNF inhibitors (43, 44). Higher doses of baricitinib (7, 8 and 10 mg) did not provide additional clinical benefit (38, 39).
In RA-BEYOND, response rates at 96 weeks were similar to or greater than those observed at weeks 12 and 24 in the original phase III studies, demonstrating a durable response (45). In RA-BEYOND, patients receiving baricitinib 4 mg once daily for ≥15 months who had achieved sustained low disease activity or remission (Clinical Disease Activity Index [CDAI] score ≤10 in RA-BEYOND, ≤2.8 in RA-BEGIN) for ≥3 months without prior rescue were blindly re-randomised to continue with baricitinib 4 mg once daily (n=281) or to step down to baricitinib 2 mg once daily (n=278). At 48 weeks after randomisation to taper, double-blind dose reduction to 2 mg once daily was associated with modest but statistically significant increases in disease activity across a number of measures compared with patients who continued with baricitinib 4 mg. However, most patients (in both the continued 4-mg and step-down 2-mg groups) retained a state of low disease activity or remission, or recaptured disease control with return to baricitinib 4 mg (46).

• *Safety*
The safety of baricitinib was evaluated during up to 5.5 years of treatment in an integrated safety analysis (data cut-off 1 September 2016) of 3,492 patients with RA with 6,637 patient-years of exposure (PYE). The analysis was based on nine studies, including four phase III studies, three phase II studies, one phase Ib study and RA-BEYOND. Among the 3,492 patients who received a dose of baricitinib (All-Bari-RA analysis set), the incidence rate (IR) of serious adverse events (including death) was 9.0/100 PYE, and the mortality IR was 0.33/100 PYE (47, 48). The IR for serious infections was similar between placebo and baricitinib 4 mg (Table III). The most common serious infections were pneumonia (IR 0.5/100 PYE), herpes zoster (IR 0.4/100 PYE), urinary tract infections (IR 0.3/100 PYE) and cellulitis (IR 0.1/100 PYE) (48). Herpes zoster infection was significantly more frequent with baricitinib 4 mg than with placebo in the first 24 weeks. Ten cases of tuberculosis (TB) were reported, all of which occurred in TB endemic areas (50).
The IRs of major adverse cardiovascular events (MACE) were similar between placebo and baricitinib 4 mg and there was no evidence of exacerbation of congestive heart failure (51). In the placebo-baricitinib 4-mg analysis set, there were five cases of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), all in the baricitinib 4-mg group (IR of 1.2/100 PYE, n=997) compared with no cases in the placebo group (n=1,070) through week 24 (51). After the 1 September 2016 data cut-off, an additional DVT event was identified in the baricitinib 4 mg group during the placebo-controlled period, giving six cases of DVT and/or PE in this group (IR 1.4/100 patient-years) (49, 51). All patients who experienced DVT and/or PE during the placebo-controlled period had multiple risk factors for these events, such as prior DVT, family history of PE, hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, peripheral oedema and varicose veins. The IR of DVT and/or PE in the extended dataset was comparable between the 2- and 4-mg doses of baricitinib (IR 0.5 and 0.6/100 PYE, respectively). At data cut-off, a total of 31 patients (IR 0.5/100 PYE) had reported DVT and/or PE in the All-Bari-RA analysis set (51), which was comparable to the published rates in patients with RA (0.3–0.7/100 PYE in patients with RA in general, 0.4–0.8/100

Table II. Efficacy of baricitinib in the treatment of moderate-to-severe rheumatoid arthritis in four phase III clinical trials (32).

Study population Study duration	RA-BEGIN DMARD-naïve patients¥ 52 weeks (NCT01711359 (41))			RA-BEAM Patients with inadequate response to MTX‡ 52 weeks (NCT01710358 (42))			RA-BUILD Patients with inadequate response to csDMARDs¶ 24 weeks (NCT01721057 (43))			RA-BEACON Patients with inadequate response to bDMARDs$ 24 weeks (NCT01721044 (44))		
Treatment group	MTX	BARI 4 mg	BARI 4 mg+MTX	PBO	BARI 4 mg	ADA 40 mg Q2W	PBO	BARI 2 mg	BARI 4 mg	PBO	BARI 2 mg	BARI 4 mg
N	210	159	215	488	487	330	228	229	227	176	174	177
Response rates												
ACR20												
Week 12	59%	79%***	77%***	40%	70%***†	61%***	39%	66%***	62%***	27%	49%***	55%***
Week 24	62%	77%**	78%***	37%	74%***†	66%***	42%	61%***	65%***	27%	45%***	46%***
Week 52	56%	73%***	73%***		71%††	62%						
ACR50												
Week 12	33%	55%***	60%***	17%	45%***††	35%***	13%	33%***	34%***	8%	20%**	28%***
Week 24	43%	60%**	63%***	19%	51%***	45%***	21%	41%***	44%***	13%	23%*	29%***
Week 52	38%	57%***	62%***		56%†	47%						
ACR70												
Week 12	16%	31%***	34%***	5%	19%***†	13%***	3%	18%***	18%***	2%	13%***	11%**
Week 24	21%	42%***	40%***	8%	30%***†	22%***	8%	25%***	24%***	3%	13%***	17%***
Week 52	25%	42%***	46%***		37%	31%						
LDA rates												
DAS28-hsCRP ≤3.2												
Week 12	30%	47%***	56%***	14%	44%***††	35%***	17%	36%***	39%***	9%	24%***	32%***
Week 24	38%	57%***	60%***	19%	52%***	48%***	24%	46%***	52%***	11%	20%*	33%***
Week 52	38%	57%***	63%***		56%†	48%						
DAS28-ESR ≤3.2												
Week 12	15%	21%	34%***	7%	24%***	21%***	7%	21%***	22%***	4%	13%**	12%**
Week 24	23%	36%**	39%***	10%	32%***	34%***	10%	29%***	32%***	7%	11%	17%**
Week 52	27%	36%	45%***		39%	36%						
Remission rates												
SDAI ≤3.3												
Week 12	6%	14%*	20%***	2%	8%***	7%***	1%	9%***	9%***	2%	2%	5%
Week 24	10%	22%**	23%***	3%	16%***	14%***	4%	17%***	15%***	2%	5%	9%**
Week 52	13%	25%**	30%***		23%	18%						
CDAI ≤2.8												
Week 12	7%	14%*	19%***	2%	8%***	7%**	2%	10%***	9%***	2%	3%	6%
Week 24	11%	21%**	22%**	4%	16%***	12%***	4%	15%***	15%***	3%	5%	9%*
Week 52	16%	25%*	28%**		22%	18%						
Changes in physical function												
HAQ-DI minimum clinically important difference (decrease in HAQ-DI score of ≥0.30)												
Week 12	60%	81%***	77%***	46%	68%***	64%***	44%	60%***	56%**	35%	48%*	54%***
Week 24	66%	77%*	74%	37%	67%***†	60%***	37%	58%***	55%***	24%	41%***	44%***
Week 52	53%	65%*	67%**		61%	55%						

¥Patients had received limited or no prior treatment with MTX and were treatment naïve to bDMARDs and other csDMARDs.
‡Patients remained on background MTX throughout the study. All patients were bDMARD naïve.
¶Patients showed an inadequate response or were intolerant to at least one previous csDMARD but had not received a bDMARD and continued with stable doses of any current csDMARD throughout the study.
$Patients showed an inadequate response to at least one TNF inhibitor or other bDMARD and continued to receive csDMARDs throughout the study.
§Proportions of responders at each time point based on those initially randomised to treatment (N). Patients who discontinued or received rescue therapy were considered as non-responders thereafter.
*$p \le 0.05$, **$p<0.01$, ***$p<0.001$ *vs*. PBO (MTX for RA-BEGIN). †$p \le 0.05$, ††$p<0.01$ vs. ADA.
ACR20, ACR50, ACR70: ≥20%, ≥50% and ≥70% improvement in symptoms according to American College of Rheumatology criteria; ADA: adalimumab; BARI: baricitinib; bDMARD: biologic DMARD; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic DMARD; DAS28-ESR: Disease Activity Score for 28-joint count with erythrocyte sedimentation rate; DAS28-hsCRP: Disease Activity Score for 28-joint count with high-sensitivity C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; HAQ-DI: Health Assessment Questionnaire-Disability Index; LDA: low disease activity; MTX: methotrexate; PBO: placebo; Q2W: once every 2 weeks; SDAI: Simplified Disease Activity Index; TNF: tumour necrosis factor.

Table III. Incidence (per 100 patient-years) of safety measures of special interest in an integrated safety analysis involving up to 5.5 years of exposure to baricitinib (48).

Safety measure	Data analysis set				
	Placebo-4 mg¥ (6 studies to Week 24)		2 mg-4 mg-extended‡ (4 studies + LTE)		All-bari-RA¶
	Placebo	Bari 4 mg	Bari 2 mg	Bari 4 mg	
Exposure					
No. of patients	1,070	997	479	479	3,492
Patient-years of exposure	394	409	555	604	6,637
Median, days	166	169	257	342	760 (2.1 years)
Longest exposure, days	235	211	1,276	1,991	2,019 (5.5 years)
Permanent discontinuation due to AE, n (EAIR)	35 (8.9)	47 (11.5)	37 (6.6)	55 (8.9)	393 (5.8)
Mortality, n (IR), [95% CI]	2 (0.5) [0.1, 1.8]	3 (0.7) [0.1, 2.1]	1 (0.2) [0.0, 1.0]	3 (0.5) [0.1, 1.4]	22 (0.3) [0.2, 0.5]
Infections, n (IR), [95% CI]					
Serious infection	17 (4.2) [2.5, 6.8]	16 (3.8) [2.2, 6.2]	18 (3.3) [1.9, 5.2]	29 (4.8) [3.2, 6.9]	194 (2.9) [2.5, 3.4]
Herpes zoster	4 (1.0) [0.3, 2.5]	18 (4.3)* [2.6, 6.8]	15 (2.7) [1.5, 4.5]	23 (3.8) [2.4, 5.7]	212 (3.2) [2.8, 3.7]
TB	0	1 (0.2) [0.01, 1.3]	0	6 (0.6) [0.2, 1.2]	10 (0.2) [0.1, 0.3]
Malignancy, n (IR), [95% CI]					
Malignancy excluding NMSC					
As treated analysis set$	2 (0.5) [0.1, 1.8]	2 (0.5) [0.1, 1.7]	3 (0.5) [0.1, 1.6]	8 (1.3) [0.6, 2.6]	52 (0.8) [0.6, 1.0]
As randomised analysis set§	No data	No data	7 (0.7) [0.3, 1.4]	9 (0.9) [0.4, 1.6]	No data
Lymphoma	0	0	0	1 (0.1) [0.002, 0.5]	6 (0.1) [0.03, 0.2]
NMSC	1 (0.2) [0.0, 1.4]	3 (0.7) [0.1, 2.1]	2 (0.4) [0.04, 1.3]	6 (1.0) [0.4, 2.2]	24 (0.4) [0.2, 0.5]
CV outcomes, n (IR), [95% CI]					
MACE£	2 (0.6) [0.1, 2.0]	3 (0.8) [0.2, 2.2]	1 (0.2) [0.0, 1.1]	2 (0.4) [0.05, 1.4]	31 (0.5) [0.4, 0.7]
DVT/PE£,#,†	0	5 (1.2) [0.4, 2.8]	3 (0.5) [0.1, 1.6]	4 (0.6) [0.2, 1.7]	31 (0.5) [0.3, 0.7]
GI perforation, n (IR), [95% CI]	0	0	0	1 (0.2) [0.0, 0.9]	3 (0.1) [0.01, 0.1]

*$p<0.05$ for bari 4 mg *vs.* placebo.

¥Placebo *vs.* baricitinib 4 mg through 24 weeks of treatment, with data up to rescue/treatment switch or the end of the placebo-controlled period ('as treated' analysis). The six studies comprised three phase II studies (38-40) and three phase III studies: RA-BEAM (42), RA-BUILD (43) and RA-BEACON (44).

‡Data from patients receiving baricitinib 2 or 4 mg, including data from placebo- and non-placebo-controlled periods and the LTE study with data cut-off on 1 September 2016. All analyses based on 'as-treated' method (data censored at rescue or dose change) unless otherwise specified. This maximises the information for a randomised dose comparison. The studies comprised two phase II studies (39,40), two phase III studies (RA-BUILD (43) and RA-BEACON (44)), and the LTE study RA-BEYOND (NCT01885078).

¶All patients who received at least one dose of baricitinib, with data cut-off on 1 September 2016. Data were not censored at dose change or rescue.

$In the 'as treated' analysis, data were censored at rescue or at any dose change. This maximises the information for a randomised dose comparison.

§In the 'as randomised' analysis, evaluation was conducted without censoring for rescue or dose change because of the long latency period of malignancy (excluding NMSC).

£Potential CV adverse events from the phase III and LTE trials identified by investigators or according to a predefined list of event terms were adjudicated by an independent, external Clinical Endpoint Committee, which remained blinded to treatment assignments.

#MedDRA preferred terms of 'deep vein thrombosis'/'pulmonary embolism' were analysed without adjudication.

†After the 1 September 2016 data cut-off, an additional DVT event was identified in the baricitinib 4 mg group during the placebo-controlled period, giving six cases of DVT and/or PE in this group (IR 1.4/100 patient-years, 95% CI: 0.5, 3.1) and an overall DVT and/or PE incidence rate in the All-bari-RA analysis set of 0.5/100 patient-years (95% CI: 0.4, 0.7) (49).

AE: adverse event; bari: baricitinib; CI: confidence interval; CV: cardiovascular; DVT: deep vein thrombosis; EAIR: exposure-adjusted incidence rates events/100 patient-years (patient exposure not censored at event); GI: gastrointestinal; IR: incidence rate/100 patient-years (patient exposure censored at event); LTE: long-term extension study; MACE: major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients in the specified category; NMSC: non-melanoma skin cancer; PE: pulmonary embolism; TB: tuberculosis.

PYE in DMARD-treated patients with RA (52)). Baricitinib should therefore be used with caution in patients with risk factors for DVT and/or PE, such as older age, obesity, a medical history of DVT and/or PE, or surgery and immobilisation (32, 51).

In the integrated safety analysis, the IR of malignancy (excluding non-melanoma skin cancer) was similar between placebo and baricitinib 4 mg and did not increase with prolonged exposure (48). Three cases of gastrointestinal perforation were reported in the All-Bari-RA analysis set. These comprised a perforated appendix, a perforated diverticulum and a proximal intestinal perforation after knee surgery. All three patients were on background MTX and taking non-steroidal anti-inflammatory drugs; two were also taking prednisone (48).

Cellular effects and other laboratory changes with baricitinib

Neutrophils

In RA, the abnormal migration of neutrophils into the joint synovium leads to further inflammation and joint damage (53). *In vitro* and *ex vivo* studies of the effect of baricitinib on neutrophils from patients with RA showed that it significantly prevented neutrophil chemotaxis towards IL-8 (known to activate JAK2/STAT3 in hepatocellular carcinoma cell lines (54)) but had no effect on other aspects of neutrophil function, such as secretion of degradation enzymes (specifically reactive oxygen species) or apoptosis (55). This would appear paradoxical, in that the neutrophil count would be expected to increase rather than decrease (see below) with baricitinib treatment. However, no phosphorylation of STAT1 or STAT3 was observed in neutrophils in response to IL-8 in the *in vitro* or *ex vivo* studies (55). Thus, uncertainty remains as to the mechanism of this phenomenon.

An analysis by Kremer *et al*. (56) of pooled data from six phase II and III studies, including RA-BEYOND, in patients with RA treated with baricitinib for up to 52 weeks showed that mean absolute neutrophil count decreased within the first month of treatment but stabilised thereafter and returned to baseline counts after treatment discontinuation. The occurrence of neutropenia (<1000 cells/mm^3) was uncommon (<1% of patients) and was not associated with a higher risk of overall or serious infections. Only two patients (0.1%) discontinued treatment due to neutropenia (56). There was no evidence that changes in absolute neutrophil count were a consequence of myelosuppression (29).

Platelets

Since JAK2 is essential for thrombopoietin signalling (18), platelet counts during up to 52 weeks of baricitinib treatment were evaluated in the pooled analysis by Kremer *et al*. (56). In contrast to the decrease in platelet levels that might be expected mechanistically, mean platelet counts increased in the first 2 weeks of baricitinib treatment then returned towards baseline and stabilised over time. Two patients (0.1%) discontinued baricitinib treatment permanently due to thrombocytosis. There was no evident association between increased platelet counts and the occurrence of DVT/PE (56).

Erythrocytes

Since erythropoietin stimulates erythrocyte production via the JAK2 signalling pathway (57, 58), the effect of baricitinib treatment on erythropoietin, haemoglobin and related parameters was assessed in a 52-week pooled analysis of six phase II and III studies. Initial decreases in haemoglobin concentrations were accompanied by a decrease in reticulocyte counts but increases in erythropoietin concentrations and iron utilisation measures, suggesting that the homeostasis of haemoglobin and related parameters is maintained during baricitinib treatment. Haemoglobin levels decreased transiently before returning to levels slightly higher than baseline at week 52. Permanent discontinuations due to anaemia or decreased haemoglobin levels occurred infrequently (0.2% of patients). Haemoglobin levels <8 g/dL were reported in <1% of patients (59).

Lymphocytes

All four members of the JAK family play a role in the signalling of cytokines involved in lymphocyte functioning (26). In phase III baricitinib studies (RA-BUILD, RA-BEACON, RA-BEAM), levels of T and B cells increased by week 4, but the levels of T cells subsequently decreased in weeks 12–24, whereas levels of B cells remained increased. Changes in T-cell subset counts showed no consistent pattern and were within the normal reference range in the majority of patients (60, 61). The Kremer *et al*. (56) pooled analysis showed that the mean absolute lymphocyte count increased in the first month of treatment but returned to baseline with longer treatment. For most patients, changes in lymphocyte count were within the normal reference range. Lymphopenia was associated with a slightly higher overall infection rate (overall infection rate at week 24: 29.1% with placebo, 43.7% with baricitinib 4 mg for those with common terminology criteria for adverse events [CTCAE] grade 2 lymphopenia; 23.1% and 50.0%, respectively, for those with CTCAE grade 3 lymphopenia), but there was no increase in the rate of serious infections. Two patients (0.1%) discontinued treatment because of lymphopenia, and one (0.1%) discontinued because of lymphocytosis.

Natural killer cells

The heterodimer JAK1/JAK3 is required for the functioning of lymphocytes, including NK cells. These cells are critical for antiviral defence, and their depletion may lead to an increased risk of viral infection (26). Lymphocyte NK cell subsets are not routinely measured in clinical practice. However, in the phase III baricitinib studies, changes in NK cell subsets over time were measured at baseline and at weeks 4, 12 and 24 (61). The mean NK cell count increased in the first 4 weeks after starting baricitinib treatment but had decreased compared with baseline (but was still within the normal range) by weeks 12 and 24. In RA-BEACON, the incidence of a treatment-emergent abnormality in NK cell count at any time during treatment up to the time of rescue was similar for baricitinib 4 mg and placebo (16% for both (61)), but in RA-BUILD and RA-BEAM, the incidence was greater for baricitinib than for placebo (22% *vs*. 10%, respectively [RA-BUILD (61)] and 22% *vs*. 8%, respectively [RA-BEAM (60)]). The rates of serious infections and herpes zoster infection in the small subset of patients with a low NK cell count at any time were similar to those observed in patients receiving placebo (60).

Other laboratory parameters

• *Lipids*

Treatment with baricitinib was associated with a dose-dependent significant increase in lipid parameters, including low-density lipoprotein cholesterol (LDL-C; mean increase of 9.5 mg/dL [4-mg dose]), high-density lipoprotein cholesterol (HDL-C; mean increase of 7.3 mg/dL [4 mg]) and triglycerides (mean increase of 8.5 mg/dL [4 mg]). These changes plateaued at week 12 (62) and stabilised thereafter (47). There was no meaningful change in the LDL-C/HDL-C ratio (62). The change in lipid parameters was largely confined to an increase in the number of large LDL particles, whereas the number of small and very small LDL particles (considered to be the most atherogenic) significantly decreased (62). Initiation of statins post baseline led to a decrease in the levels of total cholesterol, LDL-C and triglycerides to pre-statin values, but HDL-C levels remained elevated (63).

• *Creatine phosphokinase*

In the baricitinib studies, elevated creatine phosphokinase (CPK) levels were observed at week 4 and remained stable at a higher level than baseline thereafter and throughout RA-BEYOND. However, abnormally high CPK values at baseline were common. A significant increase (≥5 × the upper limit of normal [ULN]) in CPK levels occurred in 0.8% of patients treated with the drug for up to 16 weeks, compared with 0.3% of patients receiving placebo. The likelihood of increased CPK levels to ≥5 × ULN was dose dependent (0.8% [2 mg] and 1.5% [4 mg] of patients at 16 weeks *vs*. 0.6% of placebo patients). Most cases of elevated CPK levels were transient and did not require treatment discontinuation. There were no confirmed cases of rhabdomyolysis (32).

• *Serum creatinine*

An increase in mean serum creatinine level was observed with baricitinib after 2 weeks of treatment. This was a mean of 3.8 μmol/L greater than that occurring with placebo and remained stable during up to 104 weeks of treatment. The increase in serum creatinine with baricitinib may be due to an inhibitory effect of the drug on creatinine secretion by the renal tubules. Thus, estimates for glomerular filtration rate based on serum creatinine may be slightly reduced during baricitinib treatment without loss of renal function or the occurrence of renal adverse events (32).

• *Alanine transaminase and aspartate transaminase*

Increases in alanine transaminase (ALT) and aspartate transaminase (AST) to ≥3 × ULN occurred in 1.4% and 0.8%, respectively, of patients treated with baricitinib for up to 16 weeks. Corresponding figures for placebo were 1.0% and 0.8%, respectively. Increased levels to ≥5 and ≥10 × ULN occurred in <1% of patients. Most cases of elevated hepatic transaminases were transient and asymptomatic. In treatment-naïve patients, a combination of baricitinib and MTX for up to 52 weeks increased the frequency of ALT and AST elevations to ≥3 × ULN to a greater extent (7.5% and 3.8% of patients, respectively) than baricitinib monotherapy (1.9% and 1.3% of patients, respectively) or MTX monotherapy (2.9% and 0.5% of patients, respectively). In RA-BEYOND, the pattern and incidence of elevated transaminase levels remained stable (32).

Discussion

The JAK1/JAK2 inhibitor baricitinib offers an effective treatment for RA, providing statistically significant improvements in a number of clinical endpoints compared with current standard-of-care drugs (41, 42). It has been approved in more than 40 countries, including European countries (2 and 4 mg once daily), Japan (2 and 4 mg once daily) and, recently, the USA (2 mg once daily), as monotherapy or in combination with MTX in adults with moderate to severe RA who do not respond adequately (or are intolerant) to one (or more) csDMARDs or bDMARDs (25, 32, 33). Reflecting this, baricitinib 4 mg is recommended for the treatment of RA in patients with an inadequate response to MTX according to guidelines from the European League Against Rheumatism (64). A dose of 2 mg once daily is recommended for patients ≥75 years of age (32).

Mechanistically, the effects of approved doses of baricitinib on different cell types and hormones/growth factors might not extrapolate into specific clinical effects. For example, the low-grade decrease in haemoglobin levels observed in some patients during treatment with baricitinib was accompanied by an increase in erythropoietin levels, suggesting that haemoglobin homeostasis was maintained (59). This was supported by very few reports of anaemia during long-term baricitinib treatment (4/3,822 patients (25)). In addition, no association between increased platelet counts and the occurrence of thromboembolic events, such as DVT or PE, was observed with baricitinib (56). However, further studies on platelet function are required. The IR of MACE was also low, comparable across treatment arms and analysis sets, and did not increase with prolonged exposure (48).

In relation to the potential cellular effects of baricitinib, neutropenia was uncommon (<1% of patients) and was not associated with a higher risk of overall or serious infections (56). Any changes in absolute lymphocyte count were generally within the normal range (60, 61). Although the presence of lymphopenia was associated with a slightly higher overall infection rate, there was no increase in the rate of serious infections (56). Similarly, despite the reduction in NK cell numbers observed in some patients, there was no evident association between low NK cell count and the incidence of infections (61). However, the effect of baricitinib on the function of all of these cell types has yet to be investigated.

Finally, the IRs for death, serious infections and malignancy with baricitinib in the clinical trial programme (0.3, 2.9 and 0.8/100 patient-years, respectively, in all patients treated with baricitinib,

Table IV. Guidance for monitoring of laboratory parameters during treatment with baricitinib (32).

Laboratory parameter	Action	Monitoring guidance
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia
Absolute neutrophil count (ANC)	Treatment should be interrupted if ANC is $<1 \times 10^9$ cells/L and may be restarted once the ANC is above this value	Before treatment initiation and thereafter according to routine patient management
Absolute lymphocyte count (ALC)	Treatment should be interrupted if ALC is $<0.5 \times 10^9$ cells/L and may be restarted once the ALC is above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb is <8 g/dL and may be restarted once the Hb level is above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

n=3,492 (48)) are similar to those observed with biologic drugs (65-72).

As the number of patients using baricitinib in the long term increases and more data are collected through large registries, the risk/benefit profile of the drug should become clearer. Indeed, an integrated safety analysis with data cut-off of 1 April 2017 has recently been disclosed that reports data from 7,860 PYE and >2 years of treatment for >50% of patients (49). Nevertheless, the risk of many potential side effects can be mitigated by appropriate screening (32). Such pre-treatment screening should include testing for tuberculosis (TB) and other infections, appropriate prophylaxis (anti-TB treatment should be considered in patients with previously untreated latent TB) and vaccination (see international treatment guidelines on vaccination in RA (73, 74)). Laboratory parameters, including lipids, absolute neutrophil count, absolute lymphocyte count, haemoglobin and hepatic transaminases, should also be monitored (Table IV (32)). In the event of side effects or abnormal laboratory results, treatment should be interrupted and restarted once the issue has been resolved (32). Interrupted treatment is associated with only a modest increase in symptoms and does not affect overall response rates (75).

In view of the impact of baricitinib on a wide variety of cytokines (such as IFNs, IL-6, IL-12, IL-23 and GM-CSF), hormones (such as erythropoietin and thrombopoietin) and growth factors that are involved in other inflammatory conditions besides RA, research into further indications for the drug is underway (2, 76, 77). Additional research is needed to better understand how the mechanism of action of baricitinib extrapolates into clinical effects. Data from patients exposed to the drug over a prolonged period are also required to inform long-term safety on topics currently included in the warnings/precautions section of the approved labels across the global arena, such as the risk of infections, haematological abnormalities, viral reactivation, malignancy, venous thromboembolism and abnormal laboratory measures.

Limitations of a narrative review such as this one include the possibility of subjective selection bias and reliance on authors' clinical experience. In addition, data extraction for this review was not protocol based. In this review, we did not compare baricitinib with the JAK1/JAK 3 inhibitor tofacitinib, due to their differing mechanisms of action and the absence of head-to-head trials. Numerous reviews on tofacitinib are available in the literature (*e.g.* 78, 79).

Conclusions

The pathogenesis of RA involves dysregulated cytokine production and cytokine-mediated intracellular signal transduction. A number of pro-inflammatory cytokines, growth factors and hormones use JAK/STAT signalling pathways, and inhibition of these pathways provides a therapeutic option in RA. However, it is complex and far from understood how the *in vitro* effects of JAK inhibitors extrapolate into *in vivo* and clinical effects in individual patients. Once-daily dosing with baricitinib, an oral selective inhibitor of JAK1 and JAK2, has proved an effective treatment for adults with moderately to severely active RA, and further indications for the drug are being explored. Currently, patients most likely to benefit from treatment with baricitinib are adults with moderately to severely active RA who have responded inadequately to, or are intolerant to, one or more csDMARDs or bDMARDs, and have no contraindications to the drug.

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