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ADIS DRUG EVALUATION

Baricitinib: A Review in Rheumatoid Arthritis

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Abstract Baricitinib (Olumiant®) is an oral, targeted synthetic DMARD that inhibits JAK1 and JAK2, which are implicated in the pathogenesis of rheumatoid arthritis (RA). This novel, small molecule is approved for use as monotherapy, or in combination with methotrexate, for the treatment of adults with moderate to severe active RA who responded inadequately to or were intolerant of ≥ 1 DMARD. In pivotal multinational trials, once-daily baricitinib 4 mg, with/without methotrexate (± another csDMARD), improved the signs and symptoms of RA, disease activity and physical function in DMARD-naive patients and in patients with an inadequate response to methotrexate, csDMARDs or TNF inhibitors; baricitinib treatment also slowed structural joint damage in DMARD-naive patients and in those with an inadequate response to methotrexate and csDMARDs. Baricitinib plus methotrexate was more effective than adalimumab plus methotrexate in patients with an inadequate response to methotrexate. The onset of these benefits was generally rapid and sustained over time. Baricitinib was generally well tolerated during up to 5.5 years' treatment; the most commonly reported adverse drug reactions were upper respiratory tract infections, increased LDL cholesterol, nausea and thrombocytosis. Thus, once-daily baricitinib, as monotherapy or in combination with methotrexate, is an effective and generally well tolerated emerging treatment for patients with moderate to severe active RA who have responded inadequately to or are intolerant of ≥ 1 DMARD, and extends the options available for this population.

Baricitinib: clinical considerations in RA
A selective, reversible JAK1 and JAK2 inhibitor, which interferes with intracellular signal transduction
Convenient once-daily oral formulation
As monotherapy or combination therapy, provides rapid and sustained improvements in RA signs and symptoms, disease activity and physical function, and slows progression of structural joint damage
Generally well tolerated during up to 5.5 years' treatment

1 Introduction

Traditionally, patients with rheumatoid arthritis (RA) have been treated with conventional therapies including NSAIDs, corticosteroids and DMARDs [1]; methotrexate remains the anchor drug for patients with RA (monotherapy and combination therapy) [2]. The advent of bDMARDs (i.e. TNF-α inhibitors, IL-6 inhibitors, B- and

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T-cell targeted therapies) has revolutionized the landscape of therapy for RA, particularly in patients who do not completely respond to csDMARD therapy, but challenges remain, such as inconvenient administration (i.e. subcutaneous or intravenous) [3] and the potential for diminishing efficacy over time in some patients [4]. Moreover, challenges associated with limiting toxicities of current therapeutic options, the complex aetiology of RA [5] and the lack of options that are effective in all patients necessitate the development of newer agents with novel mechanisms of action that target new pathways. In recent years, there have been significant advances in the understanding of pathogenic processes involved in RA, including the importance of JAKs in physiological signaling pathways of various cytokines, growth factors and hormones, and thus, their pathogenic role in RA [6].

The oral, targeted synthetic DMARD (tsDMARD) [7], JAK1 and JAK2 inhibitor baricitinib (Olumiant®) is a novel small molecule [1] that is approved in the EU [8] and Japan [9] for the treatment of adults with RA (moderate or severe active [8]), who responded inadequately to (other treatments [9]) or who were intolerant of ≥ 1 DMARD [8]. This article provides an overview of the pharmacological properties of baricitinib and reviews the clinical data relevant to its use in these indications.

2 Pharmacodynamic Properties

Baricitinib is an ATP competitive kinase inhibitor that selectively, potently and reversibly inhibits JAK1 and JAK2, with IC_{50} values of 5.9 and 5.7 nmol/L [5]. Baricitinib also inhibited the effects of JAK3, TyK2, c-MET and Chk2 kinases (respective IC_{50} values of ≈ 560, 53, > 10,000, > 1000 nmol/L) [5]. The role of JAKs in the pathogenesis of RA has been established, as they transduce intracellular signals for various cytokines and growth factors involved in inflammation, haematopoiesis, and immune function [5, 10]. In the signaling pathway, signal transducers and activators of transcription (STATs) are phosphorylated and activated by JAKs, thereby activating gene expression within the cell [10]. Baricitinib modulates these intracellular signaling pathways, reducing the phosphorylation and activation of STATs by partially inhibiting JAK1 and JAK2. Baricitinib demonstrated dose-dependent efficacy in patients with moderate to severe RA for up to 24 weeks [11]. Results of population pharmacokinetic/pharmacodynamic models demonstrated that the optimum benefit-risk balance was offered by the 4 mg once daily dosage; an acceptable benefit-risk profile was also evident with the lower dosage of baricitinib (i.e. 2 mg once daily) [11].

Sustained neutropenia and increased rates of infection have been reported in clinical trials and in patients receiving JAK inhibitors (Sect. 5) [12]; there is no clear association between reductions in neutrophil counts and the occurrence of serious infections [8]. Neutrophils are implicated in the pathophysiology of RA and orally-active JAK inhibitors affect apoptosis, chemotaxis and the production of reactive oxygen species; these key aspects of neutrophil function are crucial for response to infection and are involved in unwanted activation during inflammatory disease [12]. Dose-dependent inhibition of anti-apoptotic effects of granulocyte–macrophage-colony stimulating factor and IFN-γ was evident following incubation of RA and healthy control neutrophils with baricitinib. In RA neutrophils, baricitinib increased the turnover of active, phosphorylated STAT1 and STAT3, and prevented chemotaxis towards IL-8 [12].

In cell-based assays, the intracellular signaling of various proinflammatory cytokines, including IL-6 and IL-23, was inhibited by baricitinib at concentrations of < 50 nmol/L [5]. In a molecular analysis of drained lymph nodes of rat adjuvant-induced arthritis, oral baricitinib (10 mg/kg once daily) reduced the expression of the pathogenic Th1 (IL-12, IFN-γ) and Th17 (IL-17, IL-22) cytokines by 55 to ≈ 80%. Baricitinib was also effective in multiple murine models of arthritis [e.g. marked reductions in pannus formation and bone damage ($p < 0.05$)], with no evidence of humoral immunity suppression or adverse haematological effects [5].

Time- and dose-dependent inhibition of cytokine (IL-6 or thrombopoietin)-induced STAT3 phosphorylation was evident following administration of baricitinib (healthy volunteers); maximal inhibition was observed 1–2 h postdose and levels returned to baseline by 16–24 h [1]. By week 12 after initiating treatment with baricitinib in RA patients, mean serum values of immunoglobulin (Ig)G, IgM and IgA had decreased and remained stable below baseline values thereafter through ≥ 104 weeks [8]. Mean absolute lymphocyte counts (ALCs) increased by week 1, returned to baseline counts by week 24, and thereafter remained stable through ≥ 104 weeks. For most patients, the changes in mean serum Ig levels or ALCs occurred within the normal reference ranges. Decreases in C-reactive protein (CRP) levels were evident at week 1 after baricitinib treatment initiation in RA patients, with reduced levels maintained throughout treatment [8].

After 2 weeks of treatment, baricitinib induced a mean increase in serum creatinine levels of 3.8 μmol/L, which remained stable for ≤ 104 weeks of treatment; this could be due to the inhibition of creatinine secretion by baricitinib in the renal tubules [8]. Therefore, estimates of glomerular filtration rates (GFR) based on serum creatinine may be slightly reduced, despite the absence of renal adverse events (AEs) or the actual loss of renal function [8].

3 Pharmacokinetic Properties

Oral baricitinib exhibits dose-linear and time-independent pharmacokinetics [1]. Following oral administration, the maximum plasma concentration (C_{max}) of baricitinib is reached in a median time of ≈ 1 h and the absolute bioavailability is 79%, with food having no clinically relevant effects on its pharmacokinetics [8]. In patients with RA, steady-state C_{max} and area under the concentration-time curve (AUC) values were 1.4- and 2-fold higher than in healthy volunteers. Baricitinib is ≈ 50% bound to plasma proteins, and has a mean volume of distribution of ≈ 76 L following an intravenous infusion [8].

Metabolism of baricitinib is mediated by CYP3A4, but with <10% of the administered dose undergoing biotransformation [8]. Baricitinib is predominantly eliminated via the renal route, with ≈ 75 and 20% of the administered dose eliminated in the urine and faeces. In patients with RA, the mean apparent clearance was 9.42 L/h and the half-life was 12.5 h. In patients with mild or moderate renal impairment, baricitinib exposure is increased compared with patients with normal function [8]. A reduced dosage of baricitinib 2 mg once daily is recommended in patients with creatinine clearance (CL_{CR}) of 30–60 mL/min (moderate renal impairment [9]) and the use of baricitinib is not recommended in patients with CL_{CR} of <30 mL/min (severe renal impairment [9]) [8].

Baricitinib is a substrate for CYP3A4, OAT3, P-gp, BCRP and MATE2-K, in vitro [13]. Following co-administration of baricitinib with probenecid (a strong OAT3 inhibitor), a twofold increase in AUC_{∞} of baricitinib was evident [13]; a dosage reduction to 2 mg once daily is recommended in patients concomitantly receiving strong OAT3 inhibitors [8, 9]. Given the potential increase in baricitinib exposure, caution is recommended when leflunomide (prodrug) or its active form, teriflunomide (a weak OAT3 inhibitor), are co-administered with baricitinib [8].

4 Therapeutic Efficacy

The efficacy of once-daily oral baricitinib as monotherapy or combination therapy in adults with moderate to severe active RA was assessed in randomized, double-blind, multinational phase 3 trials of 24 (RA-BUILD [14] and RA-BEACON [15]) or 52 (RA-BEGIN [16] and RA-BEAM [17]) weeks' duration. In dose-finding studies [18–21] and model-based simulations (Sect. 2), there were no additional benefits with baricitinib doses of >4 mg.

Eligible patients were csDMARD-naive (or had received ≤3 doses of methotrexate) [RA-BEGIN] [16], or had an inadequate response to methotrexate (RA-BEAM) [17], an inadequate response to or intolerance of ≥1 csDMARD (RA-BUILD) [14], or an inadequate response to or intolerance of ≥1 TNF inhibitor and/or other bDMARD (RA-BEACON) [15]. Three trials excluded patients who had previously received bDMARD therapy [14, 16, 17]. All patients had active RA (i.e. ≥6/68 tender and ≥6/66 swollen joints) with serum high-sensitivity CRP (hsCRP) levels of ≥3 [15], ≥3.6 [14, 16] or ≥6 [17] mg/mL. Patients were excluded from the trials if they had a current or recent clinically significant comorbidity, including infection [14–17]; however, patients with latent tuberculosis could be included if appropriate treatment was commenced ≥4 weeks before randomization. Patients with an estimated GFR (eGFR) of <40 mL/min/1.73 m^2 and selected abnormal laboratory test results were excluded [14–17]; in each of the phase 3 trials, patients with an eGFR of ≥40 to <60 mL/min/1.73 m^2 received 2 mg once daily [14–17]. Rescue treatment with baricitinib 4 mg (+ methotrexate [16]) was assigned at week 16 [14, 15, 17] or week 24 [16] to patients whose tender and swollen joint counts were reduced by <20% from baseline at both week 14 and 16 [14, 15, 17], or 24 [16], with investigators assigning rescue treatment on the basis of joint counts thereafter [14, 15, 17].

The primary endpoint was the proportion of patients meeting ACR criteria for a 20% improvement (ACR20) at the primary timepoint of week 12 [14, 15, 17] or 24 [16], assessed in the modified intent-to-treat analyses. Endpoints were tested in a hierarchical manner [14–17]. In RA-BEGIN [16] (Sect. 4.1) and RA-BEAM [17] (Sect. 4.2), to control for type 1 errors for primary and major secondary endpoints, a prespecified, closed, sequentially rejective, weighted Bonferroni multiple-testing procedure was used [16, 17]; endpoints tested outside the closed testing procedure were not controlled for multiplicity [16, 17]. To control for type 1 error in RA-BUILD [14] (Sect. 4.3), the primary endpoint was analyzed followed by hierarchical testing of three secondary endpoint families [14]. In RA-BEACON [15] (Sect. 4.4), control for multiplicity testing was utilized for the ACR20 response and for changes from baseline in DAS28-CRP and HAQ-DI scores.

Patients who completed these trials [14–17] or a phase 2 exploratory trial [10] were eligible to enter the ongoing long-term extension (LTE) study (Sect. 4.6).

4.1 Treatment-Naive Patients

In RA-BEGIN in patients with early-stage disease (median disease duration 0.2 years), >91% of patients were naive to DMARDs and 8% had received up to three once-weekly doses of methotrexate [16].

Baricitinib, alone or in combination with methotrexate, was more effective than methotrexate alone at improving clinical outcomes [16]. At week 24, having established the noninferiority of baricitinib monotherapy (4 mg/day) to

methotrexate monotherapy in terms of ACR20 response rates (Table 1), superiority ($p \leq 0.01$) was demonstrated (secondary endpoint). ACR20 response rates were also significantly higher with baricitinib combination therapy than with methotrexate alone at 24 weeks (Table 1). ACR20 response rates favoured ($p \leq 0.01$) baricitinib monotherapy or combination therapy over methotrexate alone from week 1 to week 52. Outside closed testing, ACR50 and ACR70 response rates were also significantly higher in baricitinib monotherapy and combination therapy than methotrexate groups at week 24 (Table 1) [16].

At week 24, baricitinib monotherapy and combination therapy were associated with significant improvements in disease activity (DAS28-CRP scores) and physical function (HAQ-DI scores) versus methotrexate monotherapy (Table 1); these significant improvements in baricitinib groups occurred rapidly (week 1) and were continued throughout the study [16]. Outside closed testing, significantly ($p \leq 0.05$) more baricitinib (monotherapy and combination therapy) than methotrexate monotherapy recipients achieved a HAQ-DI minimum clinically important difference (MCID) [i.e. score improvements of ≥ 0.22 and ≥ 0.3] at week 24 and 52. In both baricitinib groups, SDAI remission (closed testing) and low disease activity (LDA) [outside closed testing] rates were significantly higher than in the methotrexate group (Table 2), with significant between-group differences (BGDs) maintained at week 52 [16]. Remission and LDA, as defined by different disease activity scores (CDAI, DAS28-CRP, DAS28-ESR and Boolean remission), were achieved by significantly ($p \leq 0.05$) more baricitinib monotherapy and combination therapy than methotrexate recipients at week 24, with these BGDs generally maintained at week 52 [10].

At week 24, least-squares mean (LSM) changes from baseline in mTSS, erosion and joint space narrowing (JSN) scores were significantly smaller (i.e. less structural joint damage progression) in the baricitinib combination than in the methotrexate group, with significant BGDs maintained at week 52 (Table 2). At 24 and 52 weeks, significantly ($p \leq 0.01$) more baricitinib combination therapy than methotrexate recipients had no evidence of radiographic progression (i.e. mTSS change of ≤ 0) [16].

For the majority of prespecified patient-reported outcomes (PROs), LSM improvements from baseline were significantly ($p \leq 0.01$) better at weeks 24 and 52 with baricitinib monotherapy and combination therapy than with methotrexate, including Patient's Global Assessment of Disease Activity (PtGA), patient's assessment of pain, fatigue (FACIT-F scores), SF-36 physical component score (PCS), worst joint pain, worst tiredness and EQ-5D health-state profile [22]. At 52 weeks, patients in both baricitinib groups had significant ($p \leq 0.01$) improvements in SF-36

Table 1 Efficacy of oral once-daily baricitinib, as monotherapy or combination therapy, in patients with moderate to severe active rheumatoid arthritis in phase III trials. Results at the primary timepoint of 12 [14, 15, 17] or 24 [16] weeks

Trial	Treatment (no. of randomized pts)	ACR20[a] (% pts)	ACR50 (% pts)	ACR70 (% pts)	LSM change in HAQ-DI (mean BL)	LSM change in DAS28-CRP (mean BL)
In treatment-naive pts						
RA-BEGIN [16]	BAR 4 (159)	77**[b]	60**	42***	− 1.04*** (1.6)	− 2.85*** (5.9)
	BAR 4 + MTX (215)	78***	63***	40***	− 1.03*** (1.6)	− 3.06*** (5.9)
	MTX (210)	62	43	21	− 0.74 (1.7)	− 2.16 (5.9)
In treatment-experienced pts (all pts received MTX [17] and/or other csDMARDs as background therapy [14, 15])						
RA-BEACON [15, 25]	BAR 4 (177)	55***	28***	11**	− 0.41*** (1.7)	− 1.85***[c] (5.9)
	BAR 2 (174)	49***	20**	13***	− 0.37*** (1.7)	− 1.45***[c] (6.0)
	PL (176)	27	8	2	− 0.17 (1.8)	− 0.85[c] (5.9)
RA-BEAM [17]	BAR 4 (487)	70***[†b]	45***[††]	19***[†]	− 0.66***[†] (1.6)	− 2.24***[†] (5.8)
	ADA 40 (330)	61***	35***	13***	− 0.56*** (1.6)	− 1.95*** (5.8)
	PL (488)	40	17	5	− 0.34 (1.6)	− 0.98 (5.7)
RA-BUILD [14, 24]	BAR 4 (227)	62***	33***	18***	− 0.56*** (1.6)	− 2.0***[c] (5.6)
	BAR 2 (229)	66***	34***	18***	− 0.57*** (1.5)	− 1.92***[c] (5.6)
	PL (228)	39	13	3	− 0.36 (1.5)	− 1.16[c] (5.5)

ACR20, 50 and 70 $\geq 20\%$, $\geq 50\%$ and $\geq 70\%$ improvement in ACR criteria; *ADA* subcutaneous adalimumab 40 mg every 2 weeks; *BAR* baricitinib 2 or 4 mg once daily; *BL* baseline; *DAS28-CRP* Disease Activity Score for 28 joints based on high-sensitivity C-reactive protein level; *HAQ-DI* Health Assessment Questionnaire-Disability Index; *LSM* least-squares mean; *MTX* methotrexate; *PL* placebo; *pts* patients

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ vs. MTX or PL, †$p \leq 0.05$, ††$p \leq 0.01$ vs. ADA

[a]Primary endpoint

[b]BAR was noninferior to MTX at week 24 (primary analysis) [16] or ADA at week 12 (key secondary analysis) [17]

[c]Values estimated from graphs

Table 2 Efficacy of oral once-daily baricitinib in patients with moderate to severe active rheumatoid arthritis in phase III trials

Trial	Treatment (no. of randomized pts)	Remission[a] (% pts)	LDA[a] (% pts)	LSM change in mTSS (mean BL)		LSM change in ES (mean BL)		LSM change in JSN (mean BL)	
				Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
In treatment-naive pts									
RA-BEGIN [16]	BAR 4 (159)	22**	62***	0.39 (13.3)	0.80	0.33 (8.7)	0.55	0.06 (4.6)	0.25
	BAR 4 + MTX (215)	23***	61***	0.29* (11.4)	0.40**	0.26* (7.5)	0.34**	0.03 (4.0)	0.06
	MTX (210)	10	40	0.61 (11.8)	1.02	0.47 (7.9)	0.81	0.14 (3.9)	0.21
In treatment-experienced pts (all pts received MTX [17] and/or other csDMARDs as background therapy [14, 15])									
RA-BEACON [15]	BAR 4 (177)	5	28***						
	BAR 2 (174)	2	22***						
	PL (176)	2	9						
RA-BEAM [17]	BAR 4 (487)	8***	42***†	0.41*** (43)	0.71***	0.29*** (25)	0.51***	0.12** (17)	0.21***
	ADA 40 (330)	7***	35***	0.33*** (44)	0.60***	0.24*** (26)	0.42***	0.10** (18)	0.19**
	PL (488)	2	16	0.90 (45)	1.80	0.61 (27)	1.23	0.29 (18)	0.58
RA-BUILD [14]	BAR 4 (227)	9***	35***	0.15** (24)		0.11** (15)		0.04* (9)	
	BAR 2 (229)	9***	33**	0.33* (26)		0.30 (16)		0.03* (10)	
	PL (228)	1	20	0.70 (19)		0.47 (12)		0.23 (7)	

ADA subcutaneous adalimumab 40 mg every 2 weeks, *BAR* baricitinib 2 or 4 mg once daily, *BL* baseline, *ES* erosion score, *JSN* joint-space narrowing score, *LDA* low disease activity, *LSM* least-squares mean, *mTSS* van der Heijde modified Total Sharp Score, *MTX* methotrexate, *PL* placebo, *pts* patients, *SDAI* Simplified Disease Activity Index

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ vs. MTX or PL, †$p \leq 0.05$ vs. ADA

[a]Remission defined as SDAI score of ≤ 3.3 (key secondary endpoint) and LDA as SDAI score of ≤ 11, assessed at week 12 [14, 15, 17] or 24 [16]

mental component scores (MCS), versus methotrexate recipients. For the Work Productivity and Activity Impairment-RA (WPAI-RA) assessment, significant ($p \leq 0.05$) LSM improvements from baseline in daily activity were evident for baricitinib monotherapy and combination therapy versus methotrexate at weeks 24 and 52, and in work productivity, presenteeism and absenteeism in employed patients at week 24, but not at week 52 (except for work productivity scores in the baricitinib combination therapy group; $p \leq 0.05$ vs. methotrexate). Recipients of baricitinib combination therapy, but not baricitinib monotherapy, had significantly ($p \leq 0.01$) greater improvements from baseline in median morning joint stiffness (MJS) duration than methotrexate recipients at 24 and 52 weeks [22].

4.2 Inadequate Response to Methotrexate

In the 52 week RA-BEAM trial, most patients (> 99%) received background methotrexate therapy, with patients who were initially randomized to placebo switched to baricitinib 4 mg once daily from week 24 until week 52 [17]; the mean disease duration at baseline was 10 years.

4.2.1 Versus Placebo

In combination with methotrexate, baricitinib was associated with significantly higher ACR20, ACR50 and ACR70 response rates (outside closed testing) than add-on placebo at week 12 (Table 1), and significantly greater improvements in disease activity (DAS28-CRP scores) and physical function (HAQ-DI scores) measures (Table 1) [17]. Outside closed testing, MCIDs in HAQ-DI were evident in significantly ($p \leq 0.001$) more baricitinib than placebo recipients at weeks 12 and 24. The onset of significant ($p \leq 0.001$) BGDs for ACR20 response rates, and LSM changes from baseline in DAS28-CRP and HAQ-DI scores was rapid (week 1) and sustained (up to week 24) [17].

SDAI remission (closed testing) and LDA (outside closed testing) were achieved by significantly more baricitinib than placebo recipients at week 12 (Table 2), with significant ($p \leq 0.001$) BGDs in SDAI remission rates also favouring baricitinib at week 24 [17]. Rates of remission and LDA, as defined by other outcome scores (including Boolean remission [10]) were significantly ($p \leq 0.01$) higher in the baricitinib than placebo group at week 12 [17].

Add-on baricitinib was associated with significantly less radiographic progression of structural joint damage than add-on placebo at weeks 24 and 52, with significant BGDs in erosion and JSN scores (Table 2) [17]. Significantly ($p \leq 0.01$) more baricitinib than placebo recipients had no radiographic progression at weeks 24 and 52 [17].

At 12 weeks, add-on baricitinib was associated with significantly ($p \leq 0.05$) greater improvements in median MJS duration and LSM scores of MJS severity, worst tiredness

and worst joint pain than add-on placebo, with BGDs in these PROs favouring baricitinib from 1 week (within 1–3 days for mean MJS duration and LSM scores of the other PROs [23]) onwards [17]. Baricitinib combination therapy also significantly improved ($p \leq 0.05$) most other PROs compared with placebo, including PtGA, patient's assessment of pain, FACIT-F, SF-36 PCS (but not MCS), EQ-5D index and VAS scores, and WPAI-RA daily activity score [23]. In patients who were employed at baseline, improvements in all WPAI-RA measures favoured ($p \leq 0.05$) baricitinib 4 mg combination therapy over add-on placebo at week 12.

4.2.2 Versus Adalimumab

Having established the noninferiority and subsequent superiority of add-on baricitinib versus add-on placebo (Sect. 4.2.1), the noninferiority and subsequent superiority of add-on baricitinib to add-on adalimumab for the ACR20 response at week 12 were demonstrated [17]. ACR50 and 70 response rates (outside closed testing) were also significantly higher with add-on baricitinib than add-on adalimumab treatment (Table 1). At week 12, the superiority of baricitinib to adalimumab was also demonstrated for disease activity (DAS28-CRP scores) [Table 1]. In supportive analyses (without control for multiplicity), baricitinib recipients experienced greater improvements in physical function (HAQ-DI scores) than adalimumab recipients (Table 1), with significantly ($p \leq 0.05$) more baricitinib than adalimumab recipients achieving MCIDs in HAQ-DI of ≥ 0.22 and ≥ 0.3 at week 24, and ≥ 0.22 at week 52 [17]. There was no BGD in the SDAI remission rate at week 12, whereas significantly more baricitinib than adalimumab recipients achieved SDAI LDA (Table 2). LDA, as defined by other measures (e.g. DAS28-CRP ≤ 3.2, CDAI ≤ 10), was generally achieved by significantly ($p \leq 0.05$) more baricitinib than adalimumab recipients at weeks 12 and 52, but not at week 24. There were no significant BGDs for inhibition of radiographic progression at weeks 24 and 52 (Table 2).

Compared with add-on adalimumab, add-on baricitinib was associated with significant ($p \leq 0.05$) improvements in PROs of duration and severity of MJS, worst tiredness and worst joint pain [17, 23]. Add-on baricitinib was also associated with significantly ($p \leq 0.05$) greater improvements in most other PROs, including physical functioning (assessed by HAQ-DI and SF36 scores), patient's assessment of pain and EQ-5D VAS score (but not EQ-5D Index score), than add-on adalimumab at week 12, with these effects generally maintained at week 52 [23].

4.3 Inadequate Response to csDMARDs

In RA-BUILD, in addition to randomized study drug, patients were permitted to, but not required to, use ≤ 2 csDMARDs if they had been used for ≥ 12 weeks, with ≥ 8 weeks of stable dosages [14]. At baseline, the majority of patients were receiving background methotrexate, alone (49%) or with another csDMARD (23%); the mean duration of disease was $\approx$ 8 years.

At 12 weeks, ACR20 response rates and improvements from baseline in disease activity (DAS28-CRP scores) and physical function (HAQ-DI scores) were significantly higher in the baricitinib 4 mg/day than placebo group (family 1) [Table 1]. The onset of significant ($p \leq 0.05$) BGDs for these outcome measures was rapid (week 1) and sustained through to week 24 [14]. The SDAI remission rate and median duration of MJS were significantly ($p \leq 0.001$) better in baricitinib 4 mg than placebo recipients at week 12 (Table 2) [subfamily 2a], with the beneficial effects of baricitinib on SDAI remission rates continuing at week 24 (15 vs. 4%; $p \leq 0.001$). In the baricitinib 4 mg group, significant ($p \leq 0.05$) LSM improvements from baseline in MJS severity, worst tiredness and worst joint pain scores were also significantly ($p \leq 0.05$) greater in the baricitinib 4 mg than placebo group at week 12 (family 3), with baricitinib recipients having significantly ($p \leq 0.05$ vs. placebo) greater improvements in these outcomes from 1–4 weeks onwards [14].

Similarly, with the lower dosage of baricitinib 2 mg/day, ACR20 response rates, and improvements in HAQ-DI and DAS28-CRP scores were significantly higher than with placebo at week 12 (subfamily 2b) [Table 1], with significant ($p \leq 0.05$) BGDs in favour of baricitinib observed from week 1 (ACR20 responses and DAS28-CRP scores) or 8 (HAQ-DI scores) until week 24 [14]. Significantly more baricitinib 2 mg than placebo recipients achieved SDAI remission at week 12 (family 3) [Table 2], with differences sustained at 24 weeks (17 vs. 4%; $p \leq 0.001$). At 12 weeks, improvements in the duration of MJS and scores for severity of MJS, worst tiredness and worst joint pain were significantly ($p \leq 0.05$) greater in the baricitinib 2 mg than placebo group, albeit these BGDs (vs. placebo) were generally numerically smaller in the baricitinib 2 mg than 4 mg group [14].

Radiographic outcomes also favoured baricitinib treatment at 24 weeks, with significantly less progression of structural joint damage based on mTSS and JSN scores in the baricitinib 2 and 4 mg groups than placebo group, with numerically greater benefits versus placebo in the baricitinib 4 mg than 2 mg group (Table 2). In the baricitinib 4 mg group, but not the 2 mg group, LSM change in erosion score at 24 weeks was significantly lower than in the placebo group (Table 2). Significantly ($p \leq 0.01$) more baricitinib 4 mg than placebo recipients had a change from baseline in mTSS of ≤ 0.5 or the smallest detectable change of 1.2 units, although there was no significant difference in this outcome between the baricitinib 2 mg and placebo groups and no significant BGD for the proportion of patients with no radiographic progression [14].

Results for other secondary endpoints at week 12 also favoured baricitinib (both dosages) over placebo, including ACR50 and ACR70 response rates (Table 1), SDAI LDA (Table 2), and remission and LDA as defined by different activity scores (including Boolean remission [10]) [all $p \leq 0.01$] [14]. MCIDs in HAQ-DI scores were achieved by significantly ($p \leq 0.05$) more baricitinib (2 and 4 mg) than placebo recipients at weeks 12 and 24 [14]. Improvements in most other prespecified PROs were also significantly ($p \leq 0.05$) greater in the baricitinib 2 and 4 mg than placebo group at weeks 12 and 24 (all $p \leq 0.05$), including scores for severity of MJS, SF-36 PCS (but not MCS), PtGA and patient's assessment of pain [24].

4.4 Inadequate Response to bDMARDs

At study entry, eligible patients had to have been receiving ≥ 1 csDMARD for ≥ 12 weeks at stable dosages for ≥ 8 weeks; bDMARDs had to be discontinued ≥ 4 weeks prior to randomization (or ≥ 6 months if previously receiving rituximab) [15]. At baseline, the mean duration of disease was 14 years.

At week 12, ACR20 response rates were significantly higher and improvements in HAQ-DI and DAS28-CRP scores significantly greater in baricitinib 4 mg than placebo recipients, as were ACR50 and ACR70 response rates (Table 1). Significant ($p \leq 0.01$) improvements versus placebo in ACR20 response rates and HAQ-DI and DAS28-CRP scores were evident at week 1 and sustained up to week 24 [15]. MCIDs in HAQ-DI were achieved by significantly ($p \leq 0.001$) more baricitinib than placebo recipients at 12 and 24 weeks. There was no significant difference between the baricitinib 4 mg and placebo groups for the proportion of patients achieving SDAI remission (Table 2); therefore, based on hierarchical testing, analyses stopped and comparisons of baricitinib 2 mg with placebo were considered to be supportive analyses [15]. In supportive analyses, significantly ($p \leq 0.05$) more baricitinib 4 mg than placebo recipients achieved SDAI remission at weeks 14, 16, 20 and 24 [10].

In supportive analyses, ACR20, ACR50 and ACR70 response rates were higher and improvements in HAQ-DI and DAS28-CRP scores were greater in the baricitinib 2 mg than placebo group (Table 1), as was the SDAI LDA rate (Table 2) [15]. Significantly ($p \leq 0.05$) more patients in the baricitinib 2 mg than placebo group achieved MCIDs in HAQ-DI at weeks 12 and 24.

In the baricitinib 2 and 4 mg groups at week 12, remission as defined by DAS28-CRP or DAS28-ESR scores was achieved by significantly ($p \leq 0.05$) more patients than in the placebo group [15]. LDA, as defined by different scores [including SDAI (Table 2)], was also achieved by significantly more recipients in the baricitinib 2 and 4 mg than placebo groups at week 12. At week 24, remission and LDA as defined by different measures were achieved by significantly ($p \leq 0.05$) more baricitinib 4 mg than placebo recipients. In the baricitinib 2 mg group, significant BGDs (vs. placebo) at 24 weeks were only evident for DAS28-CRP LDA and SDAI LDA rates [15].

At 24 weeks, baricitinib (both 2 and 4 mg/day) recipients experienced significantly ($p \leq 0.05$) greater improvements in most PROs than placebo recipients, including for SF-36 PCS, EQ-5D 5L components, FACIT-F, PtGA and pain scores [25]. At weeks 12 and 24, activity impairment due to RA was significantly ($p \leq 0.05$) reduced in baricitinib versus placebo recipients, as was the median duration of MJS [25].

4.5 In Pooled Analyses

Based on post hoc pooled analyses of RA-BEAM (Sect. 4.2) and RA-BUILD (Sect. 4.3), baricitinib 4 mg/day provided better efficacy than placebo at 12 weeks, irrespective of the number of concomitant csDMARDs or concomitant use of corticosteroids [26], and was effective irrespective of baseline characteristics such as age (including in the elderly [27]), ethnicity (including in the US/Puerto Rico and 'the rest of the world' subpopulations [28]) [29–31], rheumatoid factor/anti-citrullinated peptide antibodies serology or disease activity [32] or BMI tertile [33].

In individual phase 3 trials, baseline characteristics in the Japanese patients reflected the expected genetic and clinical differences compared with the overall populations [34]. Based on pooled and/or individual data from the four pivotal phase 3 trials, the efficacy of baricitinib 4 mg/day in Japanese patients was generally consistent with that in the overall population, including for improvements in disease activity (DAS28-CRP scores), physical functioning (HAQ-DI scores) and radiographic disease progression measures [34].

4.6 Long-Term Efficacy

In the LTE study, patients who completed the phase 3 trials continued to receive the same baricitinib dose they were assigned [35]. At 52 weeks (LTE entry), patients from RA-BEGIN who had received baricitinib 4 mg/day combination therapy or methotrexate alone were switched to baricitinib 4 mg/day monotherapy, and patients from RA-BEAM who had received adalimumab were switched to baricitinib 4 mg on background methotrexate; patients from RA-BEAM who had received placebo were switched to baricitinib 4 mg on background methotrexate at week 24. Patients from RA-BUILD who had received placebo were switched to baricitinib 4 mg/day on a background of csDMARDs at 24 weeks (LTE entry) [35]. Progression of

structural joint damage over ≈ 2 years was significantly ($p \leq 0.05$) slower (based on lower LSM changes in mTSS) in patients receiving baricitinib 4 mg/day throughout this period than in patients who had initially received methotrexate (RA-BEGIN) or placebo (RA-BUILD) [35].

Progression of structural joint damage was generally similar in patients receiving baricitinib 4 mg/day throughout the ≈ 2-year period (RA-BEAM and LTE) to that in patients who initially received adalimumab in RA-BEAM and was significantly ($p \leq 0.01$) lower than that in placebo recipients from who were switched to baricitinib [35].

In the LTE study, most responders (i.e. LDA based on SDAI ≤ 11 or MCID of HAQ-DI improvement of ≥ 0.22) at study entry maintained their response during an additional 96 weeks' baricitinib therapy, with > 25% of SDAI or HAQ-DI nonresponders at study entry achieving a response during the LTE [36].

In the LTE study, a subset of patients who received baricitinib 4 mg/day for ≥ 15 months and achieved sustained CDAI LDA or remission (CDAI ≤ 10 or ≤ 2.8, respectively) at two consecutive visits ≥ 3 months apart were re-randomized to continue with baricitinib 4 mg or step down to 2 mg/day [37]. Consistent with results of the pivotal trials, continuing baricitinib 4 mg/day was significantly ($p \leq 0.01$) more effective than step-down baricitinib 2 mg/day in terms of CDAI LDA and remission rates at weeks 12, 24 and 48 [37]. The majority of patients in both treatment groups maintained CDAI LDA or remission during the study.

5 Tolerability of Baricitinib

Oral baricitinib, as monotherapy or in combination with csDMARDs, was generally well tolerated in patients with moderate to severe active RA. Discussion focuses on earlier integrated data [8, 10] and an updated integrated analysis (data cut-off of 1 Sep 2016), which included 3492 RA patients treated with baricitinib, as monotherapy or in combination with csDMARDs, in nine clinical trials (including an ongoing LTE trial), representing 6637 patient-years (PYs) of exposure (all baricitinib RA dataset), with a maximum exposure of 5.5 years [38]. In the updated integrated analysis, 11.3% (393/3492) of patients permanently discontinued treatment due to an AE, corresponding to an exposure-adjusted incidence rate (EAIR)/100 PYs of 5.8. Comparisons of baricitinib 4 mg plus csDMARDs (n = 997) with placebo plus csDMARDs (n = 1070) included data (≤ 24 weeks' treatment) from six placebo-controlled trials, with censoring at rescue or treatment switch. Dose-response evaluations of baricitinib 2 and 4 mg plus csDMARDs (n = 479/group) versus placebo plus csDMARDs (n = 551 [10]) were based on four trials (censored at rescue or dose change), including data from the LTE study (baricitinib 2 and 4 mg extended dataset) [38].

In placebo-controlled trials up to 24 weeks (i.e. pre-rescue or dose change; earlier integrated analysis), ≥ 1 treatment-emergent AE (TEAE) occurred in 69.7 and 61.6% of patients in the baricitinib 4 mg and placebo groups [10]. In this analysis, the most commonly reported (≥ 2% incidence) adverse drug reactions (ADRs) with baricitinib were increased levels of LDL cholesterol (33.6 vs. 10.3% of placebo patients), upper respiratory tract infections (URTIs) [14.7 vs. 11.7%], nausea (2.8 vs. 1.6%) and thrombocytosis (2.0 vs. 1.1%) [8, 10]. The incidence of serious AEs (SAEs) was generally similar in baricitinib 4 mg and placebo recipients at 24 weeks (i.e. data up to rescue; earlier integrated analysis), with rates of 5.3 and 4.7% reported in these patients [10]. At the time of the updated integrated safety analysis, 4.7 and 3.3% of baricitinib and placebo recipients had permanently discontinued treatment due to an AE (EAIR/100 PYs' exposure 11.5 and 8.9) [38].

In dose-response evaluations, ADRs occurring in ≥ 2% of patients in any group were LDL cholesterol elevations (28.5, 20.2 vs. 11.6% of patients receiving baricitinib 4 mg or 2 mg vs. placebo), URTIs (17.3, 16.3 vs. 11.4%) nausea (2.9, 2.7 vs. 2.0%) and thrombocytosis (2.3, 1.1 vs. 1.3%) [10]. Permanent discontinuation due to an AE was reported in 11.5 and 7.7% (EAIR/100 PYs of 8.9 and 6.6) of patients in the baricitinib 4 and 2 mg groups in the updated integrated analysis [38].

The overall tolerability profile of baricitinib was generally similar to that of methotrexate in RA-BEGIN [16] and to that of adalimumab in RA-BEAM [17]. After 52 weeks' treatment in RA-BEGIN, TEAEs were reported by 71, 78 and 72% of patients in the baricitinib 4 mg monotherapy, baricitinib 4 mg combination therapy and methotrexate monotherapy groups, respectively, with AEs leading to permanent discontinuation of treatment in 6, 11 and 5% of patients and SAEs occurring in 8, 8 and 10% of patients [16]. In RA-BEAM (≤ 52 weeks' treatment), AEs occurred in 79 and 77% of baricitinib 4 mg (includes patients who switched from placebo to baricitinib at week 24) and adalimumab recipients, leading to withdrawal in 7 and 4% of these patients; SAEs occurred in 8 and 4% of patients [17]. The most commonly reported AEs (i.e. incidence of ≥ 2% and occurring in more baricitinib than adalimumab recipients) in baricitinib and adalimumab recipients were urinary tract infections (UTIs; 7 and 5%), URTIs (6 and 5%), bronchitis (6 and 4%), influenza (5 and 2%), anaemia (4 and 1%), hypercholesterolemia (4 and 1%), increased blood creatine phosphokinase (CPK) [3 and 1%], gastroenteritis (3 and 2%), arthralgia (2 and 1%), cellulitis (2 and < 1%) and dizziness (2 and < 1%) [17].

Over 52 weeks, infections occurred in 43, 50 and 38% of patients receiving baricitinib monotherapy, baricitinib

combination therapy and methotrexate monotherapy, respectively, in RA-BEGIN [16], and in 48 and 44% of baricitinib 4 mg and adalimumab recipients in RA-BEAM [17]. Serious infections occurred in 4, 2 and 4% of patients in the baricitinib monotherapy, baricitinib combination therapy and methotrexate monotherapy groups, respectively, in RA-BEGIN [16], and in 2 and 2% of patients in the baricitinib 4 mg and adalimumab groups in RA-BEAM [17].

In the updated integrated safety analysis, rates of death were low (e.g. 0.6% in the all baricitinib RA dataset) in the baricitinib 4 mg and placebo groups, the baricitinib 2 and 4 mg extended and the all baricitinib RA datasets [38]. Across clinical trials, the causes of death were heterogeneous and were not considered to be treatment-related; deaths were rarely caused by infections or major adverse cardiovascular events (MACE) [10].

Tolerability and safety data in Japanese patients were generally consistent with those in the overall study populations in phase 3 clinical trials, with the exception of rates of herpes zoster (HZ) infections [34] (Sect. 5.1).

5.1 Adverse Events of Special Interest

Baricitinib treatment ($\leq$ 16 weeks) was associated with elevations in lipid levels in controlled studies, with more baricitinib than placebo recipients experiencing elevations in levels of total cholesterol (49.1 vs. 15.8%), HDL (42.7 vs. 13.8%; a beneficial impact on lipid profiles), LDL (33.6 vs. 10.3%) and triglycerides (0.4 vs. 0.5%) [8]. Increases were evident at week 12 and thereafter remained stable at higher than baseline levels; elevated LDL levels responded to statin therapy and returned to pre-treatment levels. A dose-relationship was observed for total cholesterol elevations in studies that included both baricitinib doses, with reported elevations in 48.8 and 34.7% of patients in the baricitinib 4 and 2 mg groups (vs. 17.8% of placebo recipients) [8]. Through 52 weeks of treatment, LSM increases in LDL and HDL levels were higher in baricitinib 4 mg recipients (as monotherapy or combination therapy) than methotrexate monotherapy recipients in RA-BEGIN (2.3- to 2.6-fold increase) [16], and adalimumab recipients in RA-BEAM (2.3-fold) [17]. Following initiation of baricitinib therapy, lipid parameters should be assessed (periodically [9]) at $\approx$ 12 weeks with subsequent management of hyperlipidaemia as appropriate [8].

In placebo-controlled trials ($\leq$ 24 weeks' of treatment, with data up to rescue), infections and infestations were reported in 36.3 and 27.9% of baricitinib 4 mg and placebo recipients (odds ratio 1.4; 95% CI 1.2–1.7; $p < 0.001$) [10]; the majority of infections were mild to moderate in severity at the time of the primary safety analysis at 16 weeks [8]. Besides URTIs (Sect. 5), other infection-related ADRs reported in baricitinib and placebo patients in these trials were UTIs (3.4 vs. 2.7%), herpes simplex (1.8 vs. 0.7%) and gastroenteritis (1.6 vs. 0.8%) [8]. Serious infection incidence rates (IRs) for the baricitinib 4 mg or placebo groups were 3.8 and 4.2/100 PYs' exposure [38]; HZ and cellulitis were the most commonly reported serious infections with baricitinib treatment [8]. In the baricitinib 2 and 4 mg dataset, infections occurred in 38.2 and 32.6% of patients in the baricitinib 4 and 2 mg groups until week 24, with respective incidences of 53.4 and 48.5% during up to 52 weeks' treatment [10]. In trials evaluating dose-responses, serious infections were reported by 6.1 and 3.8% of baricitinib 4 and 2 mg recipients (IRs/100 PYs' exposure 4.8 and 3.3), and by 5.6% of patients in the all baricitinib RA dataset (IR/100 PYs' exposure 2.9) [38]. The risk of additive immunosuppression cannot be excluded when immunosuppressive agents (e.g. azathioprine) are concomitantly used with JAK inhibitors; caution should be exercised when these agents are co-administered [8]. The combined use of baricitinib with other JAK inhibitors or bDMARDs is not recommended [8, 9].

Viral reactivation (e.g. herpes virus reactivation) has been reported in clinical trials [8]. In placebo-controlled studies in the updated integrated analysis, baricitinib 4 mg was associated with a significantly ($p < 0.05$) increased risk of HZ compared with placebo (1.8 vs. 0.4% of patients; IR/100 PYs' exposure 4.3 vs. 1.0) [38]; HZ events were reported by 4.8 and 3.1% of baricitinib 4 and 2 mg recipients (IR/100 PYs' exposure 23 and 15). In the all baricitinib RA dataset of the updated integrated safety analysis, treatment-emergent HZ was reported by 6.1% of patients (IR/100 PYs exposure 3.2) [38]; the majority (95%) of HZ events were of mild or moderate severity, with few cutaneous disseminated (none were visceral) or complicated events occurring by the data cut-off of 1 Jan 2016 [39]. Higher HZ rates were reported in Japan (including in Japanese participants in RA-BEGIN and RA-BEAM [34]) and in patients with advancing age, but not in patients who had previously received corticosteroids or had longer duration of RA [39]. HZ was also more commonly reported in patients who had previously been treated with $\geq$ 3 bDMARDs [15], both bDMARDs and csDMARDs and those aged $\geq$ 65 years [8]. Over 52 weeks, rates of HZ were generally similar between treatment groups in RA-BEGIN (1–3%) [16] and RA-BEAM (2% in each group) [17]. Baricitinib should be discontinued (temporarily until episode resolution [8]) if the patient develops HZ [8, 9].

In clinical trials, decreased haemoglobin levels, absolute neutrophil counts (ANCs) and ALCs occurred in $<$1% of patients, with elderly patients with RA being at an increased risk of lymphocytosis [8]. ALT and AST elevations of $\geq$ 3 $\times$ the upper limit of normal (ULN) occurred in $\leq$ 1.4% of baricitinib recipients and 0.8% of placebo recipients in clinical trials ($\leq$ 16 weeks); ALT and AST

increases of ≥ 5 and $\geq 10 \times$ ULN occurred in $<1\%$ of patients. The majority of transaminase elevations were asymptomatic and transient. In treatment-naive patients, ALT and AST elevations of $\geq 3 \times$ ULN occurred more frequently with baricitinib plus methotrexate therapy than with baricitinib or methotrexate monotherapy [8].

CPK elevations were observed at 4 weeks, most of which were transient and did not necessitate treatment discontinuation; no confirmed cases of rhabdomyolysis were reported [8]. Deep venous thrombosis and pulmonary embolism events have been reported in patients receiving baricitinib [8]; therefore, baricitinib should be administered with caution in patients with a high risk of these events [8, 9]. There was no association between increased platelet counts in controlled studies and AEs of a thrombotic nature [8]. Treatment discontinuation due to abnormal laboratory results was reported in $<1\%$ of patients in the updated integrated analysis [38].

Based on results of an updated integrated analysis [38], the safety profile of baricitinib after up to 5.5 years' exposure was generally similar to that previously reported, with no increase in risk with longer exposure. There were no differences between the baricitinib 2 and 4 mg groups or the baricitinib 4 mg and placebo groups for rates of malignancies, serious infections or MACE. In the all baricitinib dataset, IRs/100 PYs' exposure for lymphoma, GI perforations and tuberculosis were 0.09, 0.05 and 0.15, respectively [38].

6 Dosage and Administration of Baricitinib

In the EU [8] and Japan [9], oral baricitinib is approved (as monotherapy or in combination with methotrexate [8]) for the treatment of adults with (moderate to severe active [8]) RA who responded inadequately (to other treatments [9]) [8, 9], or who were intolerant of ≥ 1 DMARD [8]. The recommended dosage of baricitinib is 4 mg once daily; consideration may be given to a lower dosage of 2 mg once daily in patients who achieve sustained control of disease activity (with the higher dosage) and are eligible for dose tapering [8, 9]. The lower dosage is recommended for some patients, is appropriate for patients aged ≥ 75 years, and may also be appropriate for those with a history of chronic or recurrent infections [8]. In patients with mild or moderate hepatic impairment, no dose adjustments are required; the use of baricitinib is not recommended in patients with severe hepatic impairment [8].

Temporary or permanent discontinuation of baricitinib may be required for the management of AEs and laboratory abnormalities associated with baricitinib therapy [8, 9]. Local prescribing information should be consulted for further information, including contraindications, warnings, precautions, drug interactions and use in special patient populations.

7 Place of Baricitinib in the Management of Rheumatoid Arthritis

Despite the availability of several treatment options, challenges associated with their use and/or efficacy (Sect. 1) mean the development of newer agents targeting other pathways involved in the pathogenesis of RA is warranted. Current EULAR guidelines state that the goal of treatment should be sustained remission and at least LDA in every patient, with these individual targets particularly relevant in DMARD-naive patients and patients who fail previous therapies, respectively [2]. If treatment targets are not achieved with the first csDMARD strategy, and in the absence of poor prognostic factors (i.e. autoantibodies, high disease activity, early erosions, failure of two csDMARDs), consideration must be given to the use of other csDMARDs. However, in the presence of poor prognostic factors, addition of tsDMARDs (specifically the JAK inhibitors baricitinib and tofacitinib) or a bDMARD (current practice; e.g. TNF inhibitors, abatacept, rituximab, tocilizumab, including the respective EMA/FDA approved biosimilars) to the csDMARD is recommended; treatment with another tsDMARD or bDMARD should be considered if this strategy fails. The use of biosimilars is likely to become increasingly important in the management of RA, especially given the similar efficacy and safety as their respective bDMARDs and the potential for cost reductions [2].

Administration of tsDMARDs and bDMARDS should be in combination with csDMARDs; in patients who are unable to use csDMARDs as a comedication, the use of tsDMARDs or IL-6 pathway inhibitors (e.g. tocilizumab, sarilumab) may be advantageous versus other bDMARDs [2]. The efficacy of a JAK inhibitor in RA patients in whom another JAK inhibitor has failed is yet to be established. In general, the NICE guidance for the use of baricitinib in patients with moderate to severe active RA is in agreement with recent EULAR guidelines and recognizes the need for new treatment strategies [40]. In the NICE guidance, baricitinib was reported to be cost-effective under certain scenarios (e.g. for severe active RA after csDMARDs) [40]. Furthermore, less frequent oral administration of baricitinib (once daily) may be advantageous compared with other oral agents requiring more frequent administration (e.g. twice daily tofacitinib) [10]. Cost and convenience may be key factors in determining the choice of treatment.

In pivotal multinational trials (≤ 52 weeks' duration) in adults with moderate to severe active RA, baricitinib monotherapy or combination therapy (+ methotrexate ±

another csDMARD) provided rapid and sustained improvements in clinical and HR-QOL in both early-stage (no/very limited exposure to methotrexate) [Sect. 4.1] and established RA (inadequate response to or intolerant of prior csDMARD and/or bDMARD therapy) [Sects. 4.2, 4.3 and 4.4]; importantly, rapid and sustained improvements were also evident in radiographic outcomes. These beneficial effects were sustained during an additional up to 96 weeks' baricitinib treatment in the LTE study (Sect. 4.6). Baricitinib 4 mg/day, alone or in combination with methotrexate, was more effective than methotrexate alone in RA-BEGIN (Sect 4.1) and, in combination with methotrexate, was more effective than adalimumab plus methotrexate in RA-BEAM (Sect. 4.2). In phase 3 trials, the higher 4 mg/day dosage (usual recommended dosage; Sect. 6) generally provided more rapid and numerically greater improvements in clinical and radiographic outcomes than the lower recommended dosage of baricitinib 2 mg/day, with both baricitinib dosages providing better efficacy than add-on placebo (Sects. 4.3 and 4.4).

Further support for the short-term efficacy of baricitinib monotherapy or combination therapy comes from a Bayesian network meta-analysis of seven 12-week, randomized controlled trials, in which baricitinib 4 mg/day (+ DMARD) was associated with the highest ACR20 response rate, followed by baricitinib 4 mg/day monotherapy, baricitinib 2 mg/day (+ DMARD), adalimumab (+ methotrexate) and placebo (+ DMARD) [41]. Further long-term clinical experience with baricitinib will help to more definitively establish its position compared with other DMARDs for the treatment of RA.

Baricitinib was generally well tolerated in clinical trials and during up to 5.5 years' treatment (Sect. 5). The most commonly (≥ 2%) reported ADRs with baricitinib were lipid elevations, infections, nausea and thrombocytosis. There is a significant increase in the risk of HZ infections during baricitinib treatment compared with placebo, with these infections occurring more frequently in Japanese patients (Sect. 5.1). The majority of HZ cases were of mild to moderate severity (Sect. 5.1). Long-term safety evaluations are ongoing, with current integrated safety data indicating that there were no new safety concerns with long-term exposure (up to 5.5 years' exposure) [Sect. 5].

In conclusion, albeit further long-term experience will help to more definitively establish the position of baricitinib in RA management, once-daily baricitinib, as monotherapy or in combination with methotrexate, is an effective and generally well tolerated emerging treatment for patients with moderate to severe active RA who have responded inadequately to or are intolerant of ≥ 1 DMARD, thereby extending the options available for this population.

Data Selection Baricitinib: 199 records identified	
Duplicates removed	41
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication, preclinical study; reviews; case reports; nonrandomized trial)	79
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	38
Cited efficacy/tolerability articles	26
Cited articles not efficacy/tolerability	15
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Baricitinib, Olumiant, Rheumatoid Arthritis. Records were limited to those in English language. Searches last updated 10 April 2018	

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Compliance with Ethical Standards

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