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REVIEW

A Review of Safety Outcomes from Clinical Trials of Baricitinib in Rheumatology, Dermatology and COVID-19

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ABSTRACT

Baricitinib is an oral, selective inhibitor of Janus kinase (JAK)1/JAK2 that transiently and reversibly inhibits many proinflammatory cytokines. This mechanism is a key mediator in a number of chronic inflammatory diseases; accordingly, baricitinib has been studied and approved for the treatment of several rheumatological and dermatological disorders, as well as COVID-19. This narrative review summarises and discusses the safety profile of baricitinib across these diseases, with special focus on adverse events of special interest (AESI) for JAK inhibitors, using integrated safety data sets of clinical trial data, and puts findings into context with the underlying risk in the respective disease populations, using supporting literature. We show that rates of infection with baricitinib generally reflected the inherent risk of the disease populations being treated, with serious infections and herpes zoster being more frequent in rheumatic diseases than in dermatological disorders, and herpes simplex being reported particularly in atopic dermatitis. Similarly, rates of major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and malignancies were generally within or below the ranges reported for the respective disease populations, thereby reflecting the underlying risk; these events were therefore more frequent in patients with rheumatic diseases than in those with dermatological disorders, the latter of whom generally had low absolute risk. AESI were

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usually more common in patients with risk factors specific for each event. When a population similar to that of ORAL Surveillance was considered, the incidence rate of MACE with baricitinib was numerically lower than that reported with tofacitinib and similar to that of tumour necrosis factor inhibitors. No safety concerns were observed in hospitalised patients with COVID-19 who received baricitinib for up to 14 days. Identifying the patterns and likelihoods of AEs that occur during treatment in large groups of patients with different diseases can help the physician and patient better contextualise the benefit-to-risk ratio for the individual patient.

PLAIN LANGUAGE SUMMARY

The oral selective inhibitor of Janus kinase (JAK)1/JAK2 baricitinib transiently and reversibly inhibits elements of the inflammatory pathway, which are key mechanisms for several chronic, inflammatory rheumatological and dermatological diseases but, as with all drugs, it can be associated with unwanted effects. This narrative review summarises adverse events of special interest (AESI) for baricitinib, considered as such either because of characteristics of patients with the disease being treated (rheumatological and dermatological disorders and COVID-19) or the mechanism of action of the drug. The risk of these events is considered in light of the inherent risk of each event in populations with the respective diseases. We show that serious infections and herpes zoster during baricitinib therapy were most common in patients with rheumatological disorders, and herpes simplex was reported particularly in patients with atopic dermatitis, likely because of disease-related risk factors. MACE, VTE and malignancies generally occurred in baricitinib-treated patients with a frequency within or below the ranges reported for the respective disease populations. Rates generally reflected the underlying risk of the disease populations, being higher in patients with rheumatological diseases than in those with dermatological disorders, and mostly occurring in patients with underlying risk factors for the AESI. No safety concerns were observed in hospitalised patients with COVID-19 who received baricitinib for up to 14 days. Characterising patterns and likelihoods of unwanted events that occur during treatment in large groups of patients with different diseases can help put the actual risk to an individual patient into perspective.

Keywords: Baricitinib; Rheumatoid arthritis; Atopic dermatitis; Alopecia areata; Systemic lupus erythematosus; Safety; COVID-19

Key Summary Points

Learnings across specialities assist our understanding of the impact of the underlying disease, patient characteristics and differences in the spectrum of comorbidities for different indications on safety outcomes and can help assess the benefit-to-risk ratio in individual patients.

Rates of adverse events of special interest with baricitinib generally reflected the underlying risk of the disease populations and were highest in patients with underlying risk factors for the specific event.

Rates of serious infections and herpes zoster were higher in patients with rheumatological diseases than in those with dermatological disorders; herpes simplex was predominantly reported in patients with atopic dermatitis, likely because of disease-related risk factors.

Incidence rates of major adverse cardiovascular events, venous thromboembolism and malignancies with baricitinib in each disease population were usually below or within the ranges reported in the literature for the respective disease population, being higher in patients with rheumatological diseases than in those with dermatological disorders.

No safety concerns were observed in hospitalised patients with COVID-19 who received baricitinib for up to 14 days in combination with standard of care.

INTRODUCTION

Baricitinib is an oral, selective inhibitor of Janus kinase (JAK)1 and JAK2 [1, 2] that transiently and reversibly inhibits many proinflammatory cytokines via the JAK-signal transducer and activator of transcription (STAT) intracellular signalling pathway. These cytokines have been identified as key players in the pathogenesis of chronic inflammatory diseases, including, but not limited to, rheumatoid arthritis (RA), atopic dermatitis (AD) and alopecia areata (AA) [3–5].

Baricitinib is approved in many countries around the world, firstly as a treatment for adults with moderate-to-severe active RA, since 2020, as the first oral JAK inhibitor (JAKi) for the treatment of adults with moderate-to-severe AD, and most recently it has received approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of severe AA in adults [6, 7] and was approved by the US FDA for the treatment of COVID-19 in hospitalised adults with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [8]. Identification of baricitinib as a possible treatment for COVID-19 was based on its anti-cytokine effects and its inhibition of host cell viral propagation [9]. Baricitinib is currently under investigation as a treatment for moderate-to-severe AD in paediatric patients [10] and juvenile idiopathic arthritis [11], and is available via an expanded access programme to patients with autoinflammatory interferonopathies, such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) [12] and Aicardi–Goutières syndrome [13]. Additional studies have been conducted to assess the efficacy and safety of baricitinib in other autoimmune, chronic inflammatory diseases, including systemic lupus erythematosus (SLE) [14, 15], psoriasis [16] and diabetic kidney disease (DKD) [17]; however, investigations in these indications have been halted because of insufficient efficacy.

Safety analyses in clinical trials largely involve identifying adverse events (AEs), whether or not considered drug related [18]. Treatment-emergent AEs (TEAEs) are events reported as first occurring or worsening in severity after the start of treatment and can be influenced by several factors, including the mechanism of action of the drug, patient characteristics, e.g. sex, age, the presence of comorbid conditions and concomitant medications, or other factors unrelated to therapy. Clinical trials of available JAKis in rheumatologic disease have identified the risk of herpes virus infections, serious infections, malignancy, cardiovascular (CV) events, including major adverse CV events (MACE), and venous thromboembolism (VTE) as events of concern or of potential relevance to this class of drug, i.e. AEs of special interest [19]. Importantly, pathophysiology, intrinsic factors and related comorbidities may play a role in determining the likelihood of specific TEAEs and the frequency of certain AEs can be related to the disease being treated (Table 1).

This review summarises the adverse events of special interest for baricitinib, as reported in clinical trials, across the diseases for which it is approved and has been investigated, and puts these events into context regarding the risk of these events in the population with the disease. The results of this review will contextualise the safety profile of baricitinib within the framework of the specific disease for which it is being administered.

METHODS

This is a narrative review based on published integrated safety reports of randomised controlled clinical trials of baricitinib up to June 2022 for diseases in which baricitinib has been investigated, with a focus on RA, AD, AA, SLE and COVID-19. Clinical trial data pertaining to the additional investigated diseases comprising autoinflammatory interferonopathies, including CANDLE, psoriasis and DKD are also summarised, as applicable.

Included studies and integrated safety data sets are summarised in Table 2. This review focuses on data from the most recently published integrated safety data sets, supplemented

Table 1 Characteristics of populations with selected autoimmune disorders

Predominant features	Rheumatoid arthritis	Atopic dermatitis	Alopecia areata	Systemic lupus erythematosus
Sex	Female 69–81% [20, 21]	Female 38–62% [22–25]	Female 51–67% [26–29]	Female 91% [30]
Age	Age at onset ≈ 46–56 years [20, 21]	Age at onset 12 years [22]	Age at onset 33–37 years [27–29]	Age at onset 43 years [30]
Common comorbidities	May include CVD (affects 6% [20]); RR 1.48–1.66 [31, 32],[a] metabolic disorders [20],[b] diabetes mellitus (14%) [20], depression (15%) [20], asthma (7%) [20], COPD (4%) [20]	May include allergic and other immune-mediated disorders [22, 33–35],[c] anxiety OR 1.44–2.81 [36, 37], depression OR 1.64–3.27 [36, 37], obesity OR 1.46–3.92 [33],[d] hypertension OR 1.48–3.68 [33],[e] CVD OR 1.20–2.59 [33][f]	May include atopic disorders [27, 38] (38%) [26], depression/anxiety [38] (25.5%) [26], overweight/obese (51%) [28], thyroid disease (3–15%) [26, 27]	May include CVD (affects 21%), thyroid (46%) and metabolic disorders[b] [30] osteoporosis (22%), allergic disorders (21%), anxiety (11%), depression (27%) [30], GI disease (19%), atherosclerosis[g] [39–41]
Common treatments	NSAIDs, systemic GCs, csDMARDs, including MTX, bDMARDs, tsDMARDs [42]	Topical GCs, TCI, systemic GCs, immunosuppressants (e.g. CyA), dupilumab [22, 24, 25]	Topical or systemic GCs [43]	Hydroxychloroquine, systemic GCs, immunosuppressants, belimumab, rituximab [44]
Risk of infection	Increased [45]; IR[h] of 19.64/100 PY and 32.05/100 PY [46]	Increased [33, 51]; OR 1.93 [52][j]	Uncertain [55][l]	Increased [56][m]
	Serious infection IR of 1.5–87.7/100 PY [46–48][i]	Serious infection: increased [51, 53, 54][k]		Severe infection risk ratio 2.96 [56]
	HZ risk ratio 1.51 [49]	HZ HR 1.3–1.6		HZ risk ratio 2.08–2.50 [49, 56]
	Serious HZ IR of 0.06/100 PY [50]	HS HR 1.5 [53]		
Risk of MACE	Increased [32]; IR of 0.27–3/2/100 PY [57–60]	Moderately increased [33]; IR 0.15–0.63/100 PY [61][n]	No increase [27, 62, 63]	Increased; IR 0.93–0.99/100 PY [64, 65]
Risk of VTE	Increased; IR of 0.33–0.79/100 PY [66–74]	Possibly increased [75–77];[o] IR 0.18–0.24/100 PY [76, 77]	No increase; IR 0.09/100 PY [77]	Increased; IR 0.52–1.85/100 PY [74, 78–80]
Risk of malignancy	Increased [81–83]; by 10% overall versus general population [81] (lymphoma SIR 2.46, lung SIR 1.64, melanoma SIR 1.3) [81]	No increase, except lymphoma [33, 51][p]	Uncertain [84–86]	Increased, SIR of 1.14 overall, including lymphoma [87, 88]
	Reduced for colorectal cancer (SIR 0.77) [81] and some hormone-dependent cancers			

Table 1 continued

Predominant features	Rheumatoid arthritis	Atopic dermatitis	Alopecia areata	Systemic lupus erythematosus
Risk of GI perforation	Increased; IR 0.17/100 PY (IR 0.14/100 PY for the lower GI tract) [89, 90]	No[l]	No[l]	No[l]

bDMARD biologic DMARD, *csDMARD* conventional synthetic DMARD, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *CyA* cyclosporine, *DMARD* disease-modifying antirheumatic drug, *GC* glucocorticoids, *GI* gastrointestinal, *HR* hazard ratio, *HZ* herpes zoster, *IR* incidence rate, *MACE* major adverse cardiovascular events, *MTX* methotrexate, *NSAID* nonsteroidal anti-inflammatory drug, *OR* odds ratio, *PY* person-years, *RR* relative risk, *SIR* standardised incidence ratio (observed/expected cases), *TCI* topical calcineurin inhibitors, *tsDMARD* targeted synthetic DMARD, *US* United States, *VTE* venous thromboembolism

[a]Depending on the definition of CVD in comparison with either nonrheumatic populations or the general population [31, 32]; the RR of cardiovascular mortality in patients with RA is 1.58 compared with nonrheumatic populations [31]

[b]Metabolic disorders include hypertension (in 40% of patients with RA and 25% of those with SLE), dyslipidaemia (in 32% of patients with RA and 33% of those with SLE), overweight/obese (in 31% of patients with RA and 35% of those with SLE) [20, 30]

[c]Risk ratio of 1.25–1.72 depending on the disorder (RA, inflammatory bowel disease); OR of 1.94 for risk of SLE [33]. Also includes food allergy (affects 40%), asthma (54%), allergic rhinitis (63%) [22] alopecia areata, vitiligo, SLE and chronic urticaria [22, 34]

[d]Definition of obesity varied across studies [33]

[e]Depending on the definition of hypertension [33]

[f]Depending on the definition of CVD: includes coronary artery disease, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease [33]

[g]The risk of atherosclerotic CVD is increased in patients with versus without SLE (OR 1.45) [41]

[h]Objectively confirmed infections and physician-documented infections, respectively in a US cohort study of adult patients with RA [46]

[i]Range for SIs (i.e. requiring hospitalisation or intravenous antibiotics) reported in RCTs and their long-term extension studies, and RWE from patient registries in patients with RA (IR 1.5–7/100 PY) [47], SIs (defined as infections requiring hospitalisation in a general RA population) (IR 9.57/100 PY) [46] and a retrospective cohort analysis of patients all treated with DMARDs (77.4 to 87.7/100 PY) [48]

[j]The odds of presenting to a US emergency department with a skin infection compared with those without AD [52]; risk is increased (extent not specified) [33, 51]

[k]OR of serious infection 1.2–2.2 for patients with AD versus controls [51, 54]; HR of 1.17–1.68 for patients with mild to severe AD versus controls [53]

[l]Data concerning the specific risk have not been identified

[m]Based on findings of meta-analyses. Additionally, the risk ratio was 2.58 for pneumonia and 6.11 for tuberculosis [56]

[n]Depending on severity of AD; higher in mild versus severe disease [61]

[o]Patients with AD may be at higher risk of VTE (OR, 1.22), DVT (1.28) and PE (1.08) than people without AD [75], but some have found the risk to be only slightly, non-significantly, elevated [77] while others found the association only in patients with moderate-to-severe AD who have an IR of 0.31/100 PY [76]

[p]RR 1.43; OR 1.83–3.72 depending on AD severity. No increased risk for other cancer types [33]

Table 2 Data sources for the safety of baricitinib in clinical trials

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
Rheumatoid arthritis							
Integrated clinical trial patient database [91]	1–15 mg for median 4.6 years (maximum 9.3 years)	3770 Mean age 53 years 79% female 79% receiving MTX 51% receiving GC	14,744: 80.5% with BARI 4 mg 18.1% with BARI 2 mg	I4V-MC-JADB[a] (1b)	*N* = 53 100% receiving MTX	NR	BARI 5 mg bid × 4 wks BARI 10 mg × 4 wks BARI 15 mg × 4 wks
				NCT00902486[a,b] (2)	*N* = 127 80% female Mean age 56 years	csDMARD or bDMARD	PBO × 12–24 wks BARI 4 mg × 24 wks BARI 7 mg × 12–24 wks BARI 10 mg × 12–24 wks
				NCT01185353 [92][a,b] (2)	*N* = 301 83% female Mean age 51 years 100% receiving MTX 49% receiving GC	MTX ± other csDMARD	PBO × 12 wks BARI 1 mg × 12 wks BARI 2 mg × 12–24 wks BARI 4 mg × 12–24 wks BARI 8 mg × 24 wks
				NCT01469013 [93][a,b,c] (2)	*N* = 145 (in Japan) 81% female Mean age ≈ 54 years 100% receiving MTX 59% receiving GC	MTX	PBO × 12 wks BARI 1 mg × 12 wks BARI 2 mg × 12 wks BARI 4 mg × 40–52 wks BARI 8 mg × 40–52 wks

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
				RA-BEAM [94][a,b,c] (3)	*N* = 1305 77% female Mean age 53 years > 99% receiving MTX 59% receiving GC	csDMARD	PBO × 24 wks BARI 4 mg × 28–52 wks ADA × 52 wks
				RA-BEACON [95][a,b,c] (3)	*N* = 527 82% female Mean age 56 years 82% receiving MTX 58% receiving GC	bDMARD (most commonly TNFi), csDMARD	PBO × 24 wks BARI 2 mg × 24 wks BARI 4 mg × 24 wks
				RA-BUILD [96][a,b,c,d] (3)	*N* = 684 82% female Mean age 52 years 93% receiving csDMARD 51% receiving GC	csDMARD	PBO × 24 wks BARI 2 mg × 24 wks BARI 4 mg × 24 wks
				RA-BEGIN [97][a,b,c] (3)	*N* = 584 73% female Mean age 50 years 35% receiving GC	DMARD naïve (> 91%) Limited MTX (8%)	MTX × 52 wks BARI 4 mg × 52 wks BARI 4 mg + MTX × 52 wks

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
				RA-BALANCE [98] (3)	*N* = 290 (≈ 80% in China) 80% female Mean age 49 years 100% receiving MTX 58% receiving GC	MTX	PBO × 12 wks BARI 4 mg × 40–52 wks
				RA-BEYOND[a,b,c,e] (3)	*N* = 2877 79% female	As per contributing studies	BARI 2 mg for up to 7 years[f] BARI 4 mg for up to 7 years[f]
Atopic dermatitis							
Integrated clinical trial patient database [99]	1 mg, 2 mg or 4 mg	2531[g] Mean age 36 years 39% female 89% receiving TCS 34% receiving CYC	2247	NCT02576938[d] (2)	*N* = 124 45% female Mean age 38 years 100% receiving TCS	NR	PBO × 16 wks BARI 2 mg × 16 wks BARI 4 mg × 16 wks
				BREEZE-AD1 [100] (3)	*N* = 624 37% female Mean age ≈ 36 years	Topical therapy ± systemic immunosuppressant	PBO × 16 wks BARI 1 mg × 16 wks BARI 2 mg × 16 wks BARI 4 mg × 16 wks
				BREEZE-AD2 [100] (3)	*N* = 615 38% female Mean age ≈ 35 years	Topical therapy ± systemic immunosuppressant	PBO × 16 wks BARI 1 mg × 16 wks BARI 2 mg × 16 wks BARI 4 mg × 16 wks

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
				BREEZE-AD4 (NCT03428100) [101] (3)	*N* = 463 34% female Mean age 38 years 100% receiving TCS	Topical therapy	PBO × 16 wks BARI 1 mg × 16 wks BARI 2 mg × 58–74 wks BARI 4 mg × 58– 74 wks
				BREEZE-AD5 [102] (3)	*N* = 440 49% female Mean age ≈ 40 years	Topical therapy ± systemic immunosuppressant	PBO × 16 wks BARI 1 mg × 16 wks BARI 2 mg × 16 wks
				BREEZE-AD7 [103] (3)	*N* = 329 34% female Mean age 34 years 100% receiving TCS[h]	Topical therapy ± systemic immunosuppressant (including biologics)	PBO × 16 wks BARI 2 mg × 16 wks BARI 4 mg × 16 wks
				BREEZE-AD3[d,i] (3)	*N* ≈ 1760 100% receiving TCS	As per contributing studies	BARI 2 mg × 105 wks[j] BARI 4 mg × 105 wks[j]
				BREEZE-AD6[k] (3)	*N* ≈ 380 100% receiving TCS	As per contributing studies	BARI 2 mg × 89 wks[j]
Alopecia areata							
Integrated clinical trial patient database [104]	2 mg or 4 mg for median 1.1 years	1244 Mean age 38 years 62% female	1362	BRAVE-AA1 [105] (2/3)	Part A: *N* = 110 75% female Mean age ≈ 41 years PART B: *N* = 654 59% female Mean age ≈ 37 years	NR	PBO × 12 wks BARI 1 mg × 12–36 wks BARI 2 mg × 12–36 wks BARI 4 mg × 12–36 wks
				BRAVE-AA2 [106] (3)	*N* = 546 63% female Mean age ≈ 38 years	NR	PBO × 36 wks BARI 2 mg × 36 wks BARI 4 mg × 36 wks

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
Systemic lupus erythematosus							
Pooled clinical trial patient database [107]	2 mg or 4 mg	1235	975.4	NCT02708095 [14] (2)	*N* = 314 94% female Mean age 44 years 73% receiving GC 71% receiving antimalarials 45% receiving immunosuppressants	Standard of care	PBO × 24 wks BARI 2 mg × 24 wks BARI 4 mg × 24 wks
				SLE-BRAVE-I [15][d] (3)	*N* = 760 Could receive GC	NR	PBO × 52 wks BARI 2 mg × 52 wks BARI 4 mg × 52 wks
				SLE-BRAVE-II [15][d] (3)	*N* = 775 Could receive GC	NR	PBO × 52 wks BARI 2 mg × 52 wks BARI 4 mg × 52 wks

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
COVID-19							
Individual clinical trials [108–110]	4 mg for ≤ 14 days[i]	750	NA	Marconi et al. 2021 [108] (3)	*N* = 1502 37% female Mean age 58 years 100% hospitalised with elevated inflammatory marker(s) 79% receiving GC 19% receiving remdesivir > 99% had comorbidities[m]	Standard of care	PBO × ≤14 days BARI 4 mg × ≤14 days
		507		Kalil et al. 2021 [109] (3)	*N* = 1016 37% female Mean age 55 years 100% hospitalised with elevated inflammatory marker(s) 100% receiving standard of care 84% had comorbidities[n]	Standard of care	Remdesivir BARI 4 mg + remdesivir × ≤14 days
		50	NA	Ely et al. 2022 [110] (exploratory)	*N* = 99 46% female Mean age ≈ 58 years 100% hospitalised with elevated inflammatory marker(s) 86% receiving GC 2% receiving remdesivir 100% had ≥ 1 comorbidities[o]	Standard of care	PBO × ≤14 days BARI 4 mg × ≤14 days

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	**Number of patients (characteristics)**	**PYE**	**Study (phase)**	**Study cohort**	**Prior treatment**	**Treatments (duration of available data)**
Other							
Psoriasis clinical trial [16]	2–10 mg for 12–24 wks	256	NA	Papp et al. 2016 [16] (2b)	*N* = 271 27% female Mean age ≈ 47 years	NR	PBO × 12–24 wks BARI 2 mg × 12–24 wks BARI 4 mg × 12–24 wks BARI 8 mg × 12–24 wks BARI 10 mg × 12–24 wks
Autoimmune interferonopathies clinical trial [12]	NA for median 2.8 years	18	NA	Montealegre Sanchez et al. 2018 [12] (NR)	*N* = 18 Female 37% Mean age 13 years	1–6 csDMARDs/bDMARDs 78% long-term GC	BARI 100 µg escalated to optimal dose

Table 2 continued

Main data source	Baricitinib exposure			Included studies			
	Regimen (administered od)	Number of patients (characteristics)	PYE	Study (phase)	Study cohort	Prior treatment	Treatments (duration of available data)
Diabetic kidney disease clinical trial [17]	0.75–4 mg for median 169 days	129	NA	Tuttle et al. 2018 [17] (2)	*N* = 129 Female 27% Mean age 63 years	ACE inhibitor or ARB	PBO × 24 wks BARI 0.75 mg × 24 wks BARI 0.75 mg bid × 24 wks BARI 1.5 mg × 24 wks BARI 4 mg × 24 wks

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *BARI* baricitinib, *bDMARD* biologic DMARD, *bid* twice daily, *csDMARD* conventional synthetic DMARD, *CYC* cyclosporine, *DMARD* disease-modifying antirheumatic drug, *eGFR* estimated glomerular filtration rate, *GC* glucocorticoid, *LTE* long-term extension, *MTX* methotrexate, *NA* not applicable, *NR* not reported, *od* once daily, *PBO* placebo, *PYE* patient-years exposure, *TCS* topical glucocorticoids, *TNFi* tumour necrosis factor inhibitor, *wks* weeks

In studies allowing patients with renal impairment (eGFR < 60 mL/min), affected patients randomised to BARI 4 mg received BARI 2 mg

[a]Study included in the integrated analysis of infection [111], cardiovascular events [112] and selected haematological parameters [113]; these studies included a total of 1070 placebo-treated, 479 baricitinib 2 mg-treated and 997 baricitinib 4 mg-treated patients in the placebo-controlled phases

[b]Study included in the integrated analysis of lipid profiles during baricitinib therapy [114]

[c]Study included in the East Asian-specific integrated analysis [115] (included patients from Japan [*n* = 514], Taiwan [92], Korea [84] and China [50])

[d]Limited details available in the public domain

[e]Studies contributing to LTE RA-BEYOND were phase 2 trial NCT01185353 and phase 3 trials RA-BALANCE, RA-BEAM, RA-BEACON, RA-BUILD and RA-BEGIN

[f]In addition to the original trial duration

[g]39% female; mean age 36 years; 89% received prior TCS; 55% received prior topical calcineurin inhibitor; 34% received prior cyclosporine

[h]Topical calcineurin inhibitors and/or crisaborole, in countries where approved, could be used in place of TCS

[i]Studies contributing to LTE BREEZE-AD3 were BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7; this study is ongoing

[j]Cumulative with the original study duration

[k]Study contributing to LTE BREEZE-AD6 was BREEZE-AD5

[l]Patients with baseline eGFR of 30 to < 60 mL/min per 1.73 m^2 received baricitinib 2 mg

[m]Comorbidities were those of interest and included obesity (33% of patients), type 1 or 2 diabetes mellitus (30%), chronic respiratory disease (5%) and/or hypertension (48%); in addition, 87% required some form of supplemental oxygen at study entry

[n]Comorbidities were those of interest and included obesity (56% of patients), type 1 or 2 diabetes mellitus (37%), chronic respiratory disease (7%), asthma (10%), congestive heart failure (6%), coronary artery disease (10%), hypertension (52%) and/or history of deep vein thrombosis (2%); in addition, 86% required some form of supplemental oxygen at study entry

[o]Comorbidities were those of interest and included obesity (56% of patients), type 1 or 2 diabetes mellitus (37%), chronic respiratory disease (3%) and/or hypertension (54%); in addition, 100% required some form of supplemental oxygen at study entry

with further analyses if these provided relevant additional safety information. Data from post-marketing surveillance were also included, where available, providing real-world supporting information. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Rheumatoid Arthritis

The review of baricitinib safety in patients with RA utilised the final RA integrated safety data set that included 3770 patients (All baricitinib data set), with 14,744 person-years of exposure (PYE) and maximum exposure of 3405 days (Table 2) [91]. In addition, specific subsets of patients were evaluated for selected adverse events: herpes zoster in Asian patients and MACE in patients with at least one CV risk factor [91]. An East Asian-specific analysis was also included [115], utilising data from 740 patients who received baricitinib for a total of 1294 PYE (All baricitinib data set) in any of six baricitinib trials (Table 2).

Three additional integrated analyses that utilised data specific to selected TEAEs from nine baricitinib trials (Table 2) were also reviewed: an integrated analysis of infection-related data from 3492 patients with RA who received baricitinib for a total of 7860.3 PYE [111], an integrated analysis of CV-related data from 3492 patients with RA who received baricitinib for a total of 7860.3 PYE (maximum 2230 days) [112] and an integrated analysis of changes in selected haematological parameters occurring during baricitinib therapy in 3492 patients with RA who received baricitinib for a total of up to 7993 PYE (Table 2) [113]. The final RA integrated analysis to be included utilised eight baricitinib trials (Table 2) and considered lipid profiles in 3492 patients (PYE not reported) [114].

Analyses reported the incidence rate (IR) of TEAEs either using total exposures (PYE; selected infections and laboratory findings) or person-years at risk (PYR, i.e. including follow-up and with exposure censored at first event; for selected infections, laboratory findings and all other TEAEs). The main data sets of interest were the 'All baricitinib' data set (data for all patients who received at least one dose of baricitinib using all available data after the first dose without censoring at rescue or dose change for the period under consideration by the integrated analysis) and the 'extended data set' that included patients within the All baricitinib data set who were randomised to either baricitinib 2 mg or 4 mg (data were censored at rescue or dose change).

Atopic Dermatitis

The review of baricitinib safety in patients with AD utilised the AD integrated safety data set that included 2531 patients, followed for 2247 PYE and with a maximum exposure of 736 days; data cut-off December 2019 (Table 2) [99]. Data sets reported included the placebo-controlled data set (placebo [n = 743], baricitinib 2 mg [n = 576] and baricitinib 4 mg [n = 489]), the 'extended data set' and 'All baricitinib' data set [99]. An additional integrated safety analysis of baricitinib 2 mg utilising data from 1598 patients with 1434.2 PYE to baricitinib 2 mg (maximum 869 days) was also included in this review [116].

Since the integrated AD safety analysis did not report 95% confidence intervals, unpublished data have been used to show these values. Analyses reported the IR of all TEAEs using PYR or percentages of patients affected.

Alopecia Areata

The review of baricitinib safety in patients with AA utilised the AA integrated safety data set that included 1244 patients, followed for 1362.2 PYE and with a maximum exposure of 903 days (Table 2) [104]. Data sets reported included the placebo-controlled data set (placebo [n = 371], baricitinib 2 mg [n = 365] and baricitinib 4 mg [n = 540]), the 'extended data set' and 'All baricitinib' data set. Since the integrated AA safety analysis did not report 95% confidence intervals, unpublished data have been used to show these values. Analyses reported the IR of

all TEAEs using PYR or percentages of patients affected.

Systemic Lupus Erythematosus

The review of baricitinib safety in patients with SLE was based on a pooled analysis of data from studies of the drug in SLE that included 1849 patients, with 1463.5 PYE (Table 2) [107]. Data sets reported included patients treated with placebo (n = 614), baricitinib 2 mg (n = 621) and baricitinib 4 mg (n = 614) and an All baricitinib data set. Additional laboratory findings were obtained from the phase 2 placebo-controlled clinical trial by Wallace and colleagues [14] in 314 patients with SLE (Table 2).

Analyses reported the IR of all TEAEs using PYR or percentages of patients affected.

COVID-19

Baricitinib safety in hospitalised patients with COVID-19, most of whom required oxygen supplementation, has been reported in three clinical trials, as the proportions of patients with TEAEs (Table 2) [108–110]. In Marconi et al.'s study [108], adults hospitalised with laboratory-confirmed SARS-CoV-2 infection, evidence of pneumonia or active and symptomatic COVID-19 and at least one elevated inflammatory marker received baricitinib or placebo (83% of whom received 14 days of treatment) in addition to standard of care. After a protocol amendment, baseline oxygen support (National Institute of Allergy and Infectious Disease Ordinal Scale [NIAID-OS] score 5 or 6) also became a requirement. Participants were excluded if, at study entry, they required invasive mechanical ventilation (IMV; NIAID-OS score 7), were receiving immunosuppressants or had ever received convalescent plasma or intravenous immunoglobulin for COVID-19 [108].

In Kalil et al.'s study [109], baricitinib or placebo, both in combination with remdesivir, were administered for 14 days or until hospital discharge (in 98% of patients) to adults with laboratory-confirmed SARS-CoV-2 infection and one of the following criteria suggestive of lower respiratory tract infection at the time of enrolment: radiographic infiltrates on imaging, peripheral oxygen saturation $\leq$ 94% on room air or requiring supplemental oxygen, mechanical ventilation or ECMO; 11% of patients had an NIAID-OS score 7 [109].

In Ely et al.'s study [110], adults hospitalised with laboratory-confirmed SARS-CoV-2 infection, using IMV or ECMO (3% of participants) at study entry and randomisation, evidence of pneumonia or clinical symptoms of COVID-19 and indicators of progression risk with at least one elevated inflammatory marker received either baricitinib or placebo, both with standard of care for a median of 11 and 12 days, respectively [110].

Data from the RECOVERY trial have not been included as safety data are yet to be disclosed [117].

Background Data

To put the baricitinib data into perspective, data from the disease populations of interest, where available, and in some instances from selected trials of other drugs with similar mechanisms of action used in the indications of interest, were also included.

ADVERSE EVENTS OF SPECIAL INTEREST: BARICITINIB CLINICAL EVIDENCE

Infections

Infections and JAK Inhibition

The JAK/STAT pathway is involved in immune regulation, thereby modulating defences against infection [118]. Increased risk of infection versus placebo has been reported with JAKis, with the risk of serious infections being comparable to that of biologics in rheumatologic diseases [118]. In common with all JAKis [119–122], baricitinib has been associated with upper respiratory tract infections, urinary tract infections, herpes zoster [91], and in patients with AD, herpes simplex [99]. Herpes zoster has

been the most recognised opportunistic infection associated with JAKis [47], which might be linked to the critical role of interferon (IFN) and also interleukin (IL)-15 [5]. This finding might be of particular concern for patients with SLE, AD or RA, who have an increased baseline risk of herpes zoster relative to the general population [5, 53, 123, 124].

Rheumatoid Arthritis

Disease-Specific Risk of Infections in RA

Patients with RA are susceptible to infections (Table 1), particularly bacterial infections, most commonly pulmonary, urinary, skin/soft tissue and joint infections, rather than viral or fungal infections [45–47, 83, 84]. This increased infectious risk has been attributed to RA itself, comorbid conditions and immunosuppressive therapies used to treat the disease [45, 46, 83, 118, 125–128]. Indeed, the risk of infection is increased in those with high RA activity, advanced age and male sex, in smokers and with the use of immunosuppressive treatment [45, 118, 125–127].

Risk of Infections in Baricitinib RA Clinical Trials

Serious Infections In the baricitinib RA integrated safety analysis, serious infections occurred at an IR of 2.58/100 PYE and did not increase with prolonged exposure (ranging from 3.48/100 PYE during weeks 0–48 to 1.57/100 PYE in the period after week 336) or show a dose relationship (2.13/100 PYE vs 2.62/100 PYE with baricitinib 2 mg vs 4 mg) [91]. The most common serious infections occurring in baricitinib-treated patients in the RA integrated analysis included pneumonia (IR 0.6/100 PYE), herpes zoster (IR 0.3/PYE), urinary tract infection (0.2/100 PYE) and cellulitis (0.2/100 PYE) [91]. Infections were more frequent in patients aged 65 years or older than in those aged less than 65 years (IR, 5.5/100 PYE vs 2.1/100 PYE) [91] and slightly more frequent in East Asian patients with RA treated with baricitinib (IR, 4.15/100 PYE) [115] than in the total baricitinib-treated population. The infection-related integrated safety analysis by Winthrop and colleagues [111] (Table 2) revealed that the risk of serious infection with baricitinib was similar to that with placebo (Table 3) and was increased in those with advancing age ($\geq$ 65 years), abnormal body mass index (BMI; $<$ 18 or $\geq$ 30 kg/m^2 vs 18–24 kg/m^2) and in those receiving concomitant glucocorticoid therapy [111].

Herpes Zoster Herpes zoster was reported at an IR of 3.0/100 PYR in the baricitinib integrated RA analysis, although cases were generally mild or moderate (94%) in severity and monodermatomal [91, 115], and were most frequent in Asia (IR 5.2/100 PYR) [91]. When specific Asian countries were considered, the IR was 6.49/100 PYR in Japan, 6.43/100 PYR in Taiwan, 6.75/100 PYR in Korea and 1.31/100 PYR in China [115]. In the placebo-controlled periods of baricitinib clinical trials [111], the IR of herpes zoster was higher with baricitinib 4 mg than with placebo ($p \leq 0.01$), with the IR with baricitinib 2 mg being between those of these groups (Table 3); importantly, there was no increase in the IR of herpes zoster with prolonged exposure [111]. Advancing age and Asian ethnicity were associated with an increased risk of herpes zoster [111].

Atopic Dermatitis

Disease-Specific Risk of Infections in AD

It is well established that patients with AD are at increased risk of bacterial, fungal and viral infections, particularly, but not limited to, skin infections (Table 1) [33, 51–54, 129]. The risk of serious infection and *Staphylococcus aureus*, herpes simplex, including eczema herpeticum (EH), and varicella zoster virus infections are all increased in patients with AD, particularly those with severe AD [52, 53, 130, 131]. Accordingly, the tendency to *S. aureus* or herpes simplex cutaneous infections was included as minor diagnostic criteria for AD more than 40 years ago [132]. Similarly, patients with AD are more likely to develop extracutaneous infections, including ear infection, streptococcal pharyngitis and urinary tract infection [133], with some studies also showing

increased rates of influenza/pneumonia or gastroenteritis [134].

The increased susceptibility to infections in AD might be linked to the defective skin barrier, alterations in bacterial colonisation and lower antimicrobial peptide expression, as well as to inherent immune dysregulation [33, 51, 54, 129, 131]. Serious infections are associated with increasing age and comorbid diabetes mellitus or obesity in patients with AD and are decreased in those of female sex [54].

Risk of Infections in Baricitinib AD Clinical Trials

Serious Infections In the baricitinib AD integrated analysis of safety data, the IR of serious infection with baricitinib was comparable to that of placebo in the 16-week placebo-controlled period of the trials (Table 3) [99]. Overall, serious infections had an IR of 2.1/100 PYR in patients with AD treated with baricitinib irrespective of dose; the IR was 1.5/100 PYR with baricitinib 2 mg and 3.0/100 PYR with baricitinib 4 mg in the extended data set [99]. The most common serious infections reported with baricitinib in patients with AD were EH (IR, 0.5/100 PYR), cellulitis (0.3/100 PYR) and pneumonia (0.1/100 PYR).

Herpes Zoster Herpes zoster was reported more frequently with baricitinib 2 mg than placebo and was not reported in the baricitinib 4 mg group during the placebo-controlled periods of AD clinical trials (Table 3). When extended exposure was considered, the number of herpes zoster events remained higher with baricitinib 2 mg (3.8/100 PYR) versus 4 mg (1.8/100 PYR) in the extended data set [99]. The IR of herpes zoster overall was 2.3/100 PYR, with no cases of serious herpes zoster [99].

Herpes Simplex Herpes simplex infections occurred more frequently with baricitinib 4 mg than with baricitinib 2 mg or placebo in the placebo-controlled phase of clinical trials (Table 3) [99]. IRs decreased with extended exposure, with an IR of 10. 3/100 PYR reported overall (Table 3). Most cases of treatment-emergent herpes simplex infections were rated by investigators as mild or moderate in severity (93%) and were most commonly oral herpes (IR 4.9/100 PYR), unspecified herpes simplex (4.0/100 PYR) and EH (including the preferred terms EH and Kaposi's varicelliform eruption; 1.9/100 PYR). Of note, EH events were linked to poor disease control prior to the event in the majority of patients, supporting the notion that EH is linked to more severe AD [99].

Skin Infections Requiring Antibiotic Treatment Skin infections requiring antibiotic treatment were reported with similar frequency in patients treated with baricitinib 2 mg (4.8%) or placebo (4.4%), but with lower frequency in patients treated with baricitinib 4 mg (3.4%) versus placebo, which might be linked to improved skin barrier integrity or improvement of the skin microbiome with baricitinib treatment [99].

Alopecia Areata

Disease-Specific Risk of Infections in AA

It has been postulated that several infections, such as *Helicobacter pylori*, Cytomegalovirus, Epstein–Barr virus, hepatitis B virus, hepatitis C virus and human immunodeficiency virus, may act as triggers for AA [55]. Patients with AA may therefore have an increased prevalence of these bacterial and viral infections (Table 1). However, it is also possible that the genetic predisposition for AA is caused by genetic factors that confer protection against common infections [55].

Risk of Infections in Baricitinib AA Clinical Trials

Serious Infections During the placebo-controlled periods, serious infections occurred with a similar IR in patients treated with placebo, baricitinib 2 mg and baricitinib 4 mg (Table 3), with few patients experiencing these events (none, two and one, respectively); the overall IR for baricitinib was 0.6/100 PYR [104].

Herpes Zoster Herpes zoster occurred infrequently and showed no baricitinib dose dependency (Table 3); the overall IR for baricitinib was 1.4/100 PYR [104].

Herpes Simplex The occurrence of herpes simplex infections was comparable in patients treated with baricitinib and placebo (Table 3), with an overall IR for baricitinib of 2.5/100 PYR [104].

Systemic Lupus Erythematosus

Disease-Specific Risk of Infections in SLE

Risk of infection is significantly increased in patients with SLE (Table 1) compared with the general population or healthy controls [56]. The risk of infection is not affected by gender or disease duration but is increased by glucocorticoid treatment. This increased risk may result from impaired immune function, comorbidities common in patients with SLE and the use of glucocorticoids and immunosuppressive drugs [135] and translates into infection being one of the leading causes of morbidity and mortality in patients with SLE [136].

Risk of Infections in Baricitinib SLE Clinical Trials

Serious Infections In the pooled analysis of data from clinical trials of baricitinib in SLE, the IRs for serious infections showed a dose-relationship (Table 3), with an overall IR for baricitinib of 5.2/100 PYR [107].

Herpes Zoster The IRs of herpes zoster were similar for placebo and baricitinib 2 mg but increased with baricitinib 4 mg (Table 3), with an overall IR for baricitinib of 4.8/100 PYR [107].

Other Autoimmune Disease

Clinical trials evaluating a range of doses of baricitinib in relatively small groups of patients with moderate-to-severe psoriasis [16], DKD [17] and autoimmune interferonopathies [12] (Table 2) revealed no new safety concerns with respect to infection risk.

COVID-19

Patients with SARS-CoV-2 infection can develop an intense hyperinflammatory state with cytokine storm, leading to multiple organ dysfunction and death. Baricitinib has anti-cytokine effects and inhibits host cell viral propagation, making it a useful treatment for severe COVID-19 [9].

Risk of Infections in Baricitinib COVID-19 Clinical Trials

Serious Infections In 1502 hospitalised patients with severe COVID-19 infection and multiple comorbidities (33% were obese, 30% had diabetes mellitus, almost half had hypertension and almost 90% required some form of supplemental oxygen at study entry; Table 2), the risk of non-COVID-19 serious infections was comparable for patients who received baricitinib 4 mg (8.5%) and those who received placebo (9.8%) in addition to standard of care (including systemic glucocorticoids and, in some instances, remdesivir). Of note, 91% and 85% of patients who had a serious infection during baricitinib therapy or whilst receiving placebo, respectively, were also receiving glucocorticoids [108]. In 99 patients with more severe COVID-19 infection (using IMV or ECMO at baseline) and a similar prevalence of comorbidities (Table 2), serious infections were reported in 44% of baricitinib and 53% of placebo recipients [110].

Specific serious infections occurred less frequently in patients treated with baricitinib plus remdesivir than with placebo plus remdesivir (septic shock, 0.8% vs 1.6%; pneumonia, 0.4% vs 1.6%; sepsis, 0.2% vs 1.0%) in another trial in 1033 hospitalised patients with COVID-19; glucocorticoid use was once again associated with a greater risk of infection [109].

Herpes Infections Herpes simplex and zoster infections were reported in one patient (0.1%) each in the baricitinib-treated group and in four patients (0.5%) each in the placebo-treated group in the study by Marconi et al. [108]; similarly, herpes simplex was reported in a single patient receiving baricitinib (2%) in the study by Ely et al. [110].

Conclusions on Risk of Infections with Baricitinib Based on Evidence Across Indications

Patients with RA, AD and SLE have an increased risk for infections compared with those without the disease or the general population, with the risk likely greatest in those with SLE or RA (Table 1). Patients with AD are at particular risk of skin infection, especially *S. aureus* and herpes simplex infections.

When serious infections were considered, as expected, the IR with baricitinib was highest in clinical trials in patients with SLE, who were receiving numerous other medications that can affect the risk of infection (Table 2). Patients with RA had a higher risk of serious infection than those with AD or AA during treatment with baricitinib, possibly because 79% and 51% of these former patients were also receiving methotrexate or glucocorticoids, respectively, [91] and they tended to be, on average, older than patients receiving the drug for dermatological diseases (Table 2). Increased vulnerability to serious infection with age is well established [118] and this was further shown in the baricitinib safety data [111]. Winthrop et al. [111] also showed that the risk in baricitinib-treated patients was increased in those with abnormal BMI and in those receiving concomitant glucocorticoid therapy. Short-term findings indicated that the risk of serious infections was similar in patients with AD or AA treated with baricitinib compared with placebo, and data for up to 14 days of treatment from very ill patients with COVID-19 support the acceptable risk of infection during treatment with baricitinib in these patients. Findings from a Japanese post-marketing study of baricitinib in clinical use support the results of the integrated analyses revealing that, during the first 24 weeks of treatment in 3445 patients with RA, serious infections were reported in 1.5% of patients (IR, 3.8/100 PY) [137].

When herpes zoster was considered, patients with SLE appeared most likely to experience this event. In patients with RA, but not AD or AA, the risk appeared to be dose-dependent. Advancing age was an independent risk factor for increased risk of herpes zoster [111]. The risk of herpes zoster during baricitinib therapy also appeared to be greater in patients of Asian descent than in non-Asian patients, a finding also observed with tofacitinib [138]. Indeed, in a Japanese post-marketing study of baricitinib in clinical use, herpes zoster was a major reported AE (in 2.9%; IR, 7.4/100 PY), with 0.3% of patients experiencing serious infection [137].

The IR of herpes simplex infections was increased with baricitinib compared with placebo in patients with AD but not AA in clinical trials. This might be linked to the well-known susceptibility of AD patients to experience herpes simplex infections, most probably as a result of their impaired skin barrier, along with alterations in the microbiome, antimicrobial peptides and aberrant inflammation. In addition, more severe AD is associated with increased risk of most infections; thus, patients enrolled in AD studies of baricitinib may have been particularly susceptible to herpes simplex because of their moderate-to-severe AD. The contribution of a defective skin barrier and poor control of skin lesions on cutaneous infections in patients with AD was also shown by the findings that cases of EH were linked to poor disease control and that fewer skin infections requiring antibiotic therapy were seen in patients treated with baricitinib 4 mg (which generally provides better control of skin disease than the 2 mg dose [100]). EH, a skin infection which is caused by the herpes simplex virus, affects about 3% of patients with AD and can be life-threatening [129]. It is more likely to affect an adult patient with versus without AD (odds ratio of 24.82) [52], particularly those with severe disease [53, 130]. Risk of this infection may be increased by an impaired IFNγ immune response in some patients with AD [139] and EH lesions are generally only found in skin regions previously affected by the underlying AD [140]. For these reasons, EH was included as an event of special interest specifically in AD trials.

Major Adverse Cardiovascular Events

Definitions of the composite outcome MACE can vary but usually include myocardial infarction (MI), cerebrovascular accident (CVA)/

Table 3 Incidence rate (95% confidence interval) of infections in patients treated with baricitinib in the placebo-controlled periods of clinical trials and the All baricitinib data set (integrated safety database results [91, 99, 104, 107]) by disease being treated

	Rheumatoid arthritis (/100 PYE)				Atopic dermatitis (/100 PYR)[b]				Alopecia areata (/100 PYR)[b]				Systemic lupus erythematosus (/100 PYR)			
	Placebo	Bari 2 mg	Bari 4 mg	All Bari[a]	Placebo	Bari 2 mg	Bari 4 mg	All Bari[a]	Placebo	Bari 2 mg	Bari 4 mg	All Bari[a]	Placebo	Bari 2 mg	Bari 4 mg	All Bari[a]
PYE	393.8	185.8	409.4	14,744.4	211.8	169.1	147.1	2247.4	243.2	240.6	363.4	1362.2	488.1	494.0	481.4	1463.5
Serious infections	4.2 (2.5, 6.8)	4.2 (1.8, 8.2)	3.8 (2.2, 6.2)	2.58 (2.33, 2.86)	2.1 (0.7, 5.3)	1.0 (0.4, 5.0)	1.9 (0.4, 5.8)	2.1 (1.5, 2.8)	0 (–, 1.5)	0.8 (0.1, 3.0)	0.3 (0.0, 1.5)	0.6 (0.3, 1.2)	2.5 (1.3, 4.3)	4.5 (2.8, 6.8)	5.9 (3.9, 8.6)	5.2 (3.9, 6.9)
Herpes zoster	1.0 (0.3, 2.5)	3.1 (1.1, 6.8)	4.3 (2.6, 6.8)	3.0 (2.70, 3.28)	1.0 (0.3, 4.0)	2.7 (1.3, 7.5)	0 (–, 2.4)	2.3 (1.7, 3.0)	0.8 (0.1, 3.0)	2.1 (0.7, 4.8)	1.4 (0.4, 3.2)	1.4 (0.9, 2.2)	3.7 (2.2, 5.9)	3.5 (2.0, 5.6)	6.2 (4.1, 8.9)	4.8 (3.5, 6.4)
Herpes simplex	NR	NR	NR	NR	9.4 (6.3, 15.3)	12.4 (9.5, 21.7)	21.3 (16.8, 33.4)	10.3 (9.0, 11.8)	5.0 (2.6, 8.7)	3.8 (1.7, 7.2)	1.9 (0.8, 4.0)	2.5 (1.7, 3.5)	NR	NR	NR	NR

Bari baricitinib, *NA* IR not identified in the literature, *NR* not reported, *PYE* patient-years of exposure, *PYR* patient-years at risk, *SI* serious infection

[a]All patients who received at least one dose of baricitinib using all available data after the first dose without censoring for rescue or dose change

[b]95% confidence intervals were not reported in the integrated safety analysis for atopic dermatitis or alopecia areata; values were therefore provided by Eli Lilly and Company data on file

stroke and CV death. In studies that evaluated baricitinib (Table 2), MACE was defined as MI, stroke and CV death; adjudication was performed only in the phase 3 studies.

Rheumatoid Arthritis

Disease-Specific Risk of MACE in RA

The risk of CV disease (CVD) in RA is estimated to be higher than in the general population (Table 1), by 48% in a meta-analysis of observational study data [32], and higher than that of patients with diabetes mellitus [60]. CVD symptoms present earlier in patients with RA, and CVD is a leading cause of morbidity and mortality in this population [31, 32, 83]. Endothelial damage occurs early in the course of RA, and is linked to poorer clinical outcomes [141, 142]. The greatest subclinical changes in carotid arteries occur in the first 6 years of RA and further deterioration is seen as RA disease duration increases [143, 144]. A link between inflammation and symptomatic CVD is observed in patients with high-grade chronic inflammation in RA, with increased atherogenic progression in patients with long-lasting RA ($\geq$ 20 years) compared with RA of shorter duration ($\leq$ 7 years), which suggests that atherosclerosis acceleration occurs with disease severity and duration [145]. Apart from premature atherosclerosis, CVD is also linked to the increased incidence of traditional CV risk factors in patients with RA compared with people without RA, such as hypertension, diabetes mellitus, older age, higher BMI, history of smoking and family history of coronary artery disease [58, 83]. In addition, increased CVD risk in RA is determined by several factors including genetic background, metabolic status, systemic inflammation, the extent of disease control (number and duration of disease exacerbations) and possibly changes in the gut microbiome, such that about 30% of CV events in patients with RA have been attributed directly to the characteristics of RA [141]. In patients with active RA, high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol levels have been described, similar to findings for other inflammatory conditions, such as sepsis, cancer, trauma or the postoperative period, with cytokine-induced activation of the reticuloendothelial system being a potential explanation for these changes. Treatment of RA, especially with agents blocking IL-6, results in cessation of inflammation and leads to increases in HDL- and LDL-cholesterol levels and triglyceride levels described as the lipid paradox in RA [145]. Therefore, changes in lipid profiles during anti-inflammatory treatment are expected and may not represent increased CV risk [145]. Finally, treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and systemic glucocorticoids increase CVD risk, while methotrexate, and tumour necrosis factor inhibitors (TNFis), may potentially reduce CVD risk [146, 147].

Risk of MACE in Baricitinib RA Clinical Trials

In the RA integrated report of baricitinib safety data, the IR of positively adjudicated MACE was 0.5/100 PYR (Fig. 1) and was not affected by duration of baricitinib therapy [91]. Patients in this analysis had a mean age at baseline of 53 years and 79% were female. Of the 1780 patients (54.8% of the study population) with at least one CV risk factor, the IR of MACE was 0.70/100 PYR and among those aged 50 years or older with at least one additional CV risk factor (n = 1325), the IR of MACE was 0.77/100 PYR. IRs for stroke, MI and CV death were 0.3/100 PYR, 0.2/100 PYR and 0.1/100 PYR, respectively, in the All baricitinib data set [91].

In the integrated analysis of CV-related data, the IR of arterial thromboembolism with baricitinib was 0.4/100 PYE and remained stable over time [112].

In an integrated analysis of data from 597 patients from East Asia treated with any dose of baricitinib, the IR of positively adjudicated MACE was 0.26/100 PYR (three patients had an MI or stroke, no patient had CV death) [115]. This lower IR compared with the overall baricitinib population might be caused by ethnic differences, such as a potentially lower prevalence of CV risk factors and the lower baseline mean body weight of patients from East Asia (58.4 kg vs 73.0 kg) than the overall study population [112, 115].

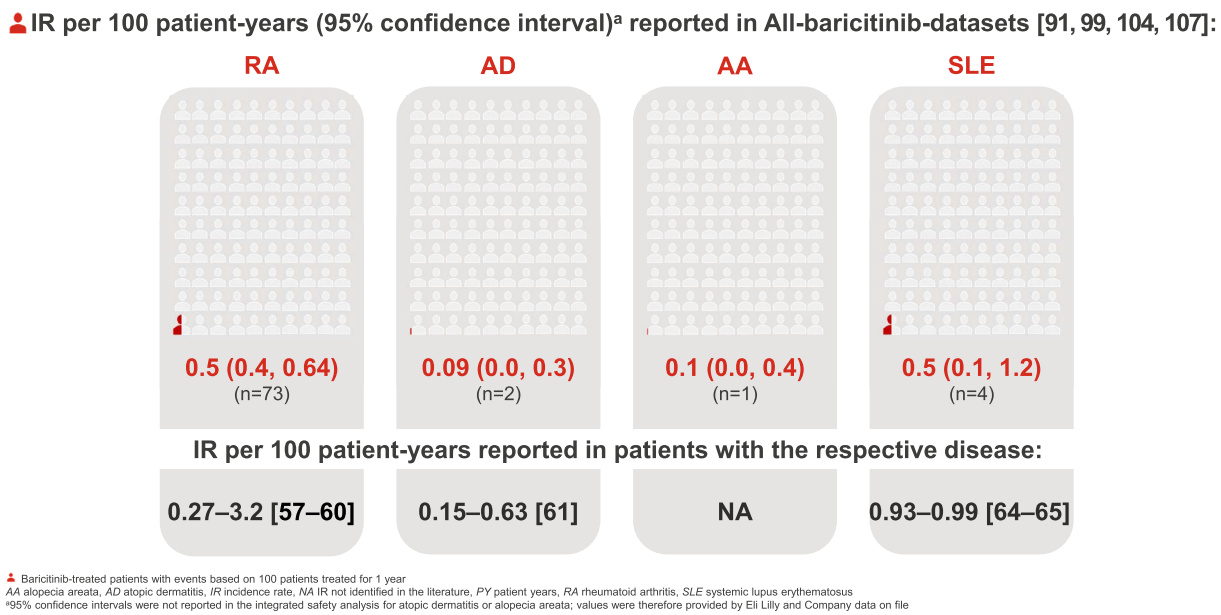

Fig. 1 Incidence rate of MACE in patients treated with baricitinib by disease and rates in the general disease populations[a]

No association was identified between LDL-cholesterol increases and the incidence of MACE [112, 115]. Lipid changes with baricitinib are discussed in a later section of this review.

Atopic Dermatitis

Disease-Specific Risk of MACE in AD

A Danish cohort study identified a reduced incidence of CVD, including MI, stroke and CV death, in patients with mild AD [61]. However, a greater weight of data suggest an increased risk of these outcomes compared with the general population or those without AD (Fig. 1; Table 1), especially in those with more severe and active disease [33, 51, 61, 148–151]. Nevertheless, the absolute risk for MACE in patients with AD seems low [152]. The association could be at least partially explained by an increased presence of comorbidities, such as hypertension, diabetes and cardiac dysrhythmias, but was also linked to detrimental lifestyle behaviours, such as smoking, sleep deprivation and a sedentary lifestyle, especially in the population with severe AD [61], and may be increased by the need for systemic therapies, which were used as a surrogate to define severe disease in a number of these studies [148–150]. AD, particularly severe disease, has been shown to be associated with an increased incidence of hypertension, angina pectoris and peripheral arterial disease [149, 150, 153], which may increase MACE occurrence. Moderate-to-severe AD, particularly severe disease, was also linked to vascular inflammation and to subclinical atherosclerosis [154]. Paradoxically, lipid levels, traditional risk factors for CVD, are reduced in patients with AD [155].

Risk of MACE in Baricitinib AD Clinical Trials

In the AD integrated analysis of baricitinib safety data, the IR of positively adjudicated MACE was 0.09/100 PYR (Fig. 1) and based on two patients with adjudicated MACE [99]. One was a patient receiving baricitinib 2 mg who had several risk factors, including age, history of smoking, hypertension, obesity, cholesterolemia and concomitant RA, who experienced MI, and the second was a patient treated with baricitinib 2 mg who had a ruptured cerebral aneurysm that was positively adjudicated as haemorrhagic stroke. No further MACE were identified during the extended follow-up of patients receiving baricitinib 2 mg for up to 2.4 years. One patient with a history of

peripheral arterial occlusive disease had an arterial bypass occlusion (IR, 0.07/100 PYE) [116].

Alopecia Areata

Disease-Specific Risk of MACE in AA

The risk of heart disease (heart failure, angina pectoris, acute or chronic MI) does not appear to be increased in patients with AA [62], although conflicting findings reporting small increases or decreases in risk have been reported (Fig. 1; Table 1). One study showed a possible reduced risk of stroke and acute MI in patients with AA compared with matched controls [63], whereas another study showed a possible increased risk of coronary artery disease and stroke [156].

Risk of MACE in Baricitinib AA Clinical Trials

In the AA integrated safety analysis, MACE was identified in only one patient with multiple risk factors who had an MI while receiving baricitinib 2 mg [104].

Systemic Lupus Erythematosus

Disease-Specific Risk of MACE in SLE

The risk of atherosclerotic CVD is increased in patients with SLE (Fig. 1; Table 1). Similar to RA, subclinical changes begin to accumulate early in the course of SLE and progress with disease duration [40], suggesting that chronic immune dysregulation in SLE promotes atherosclerosis. Unlike patients with RA, those with SLE do not present with proinflammatory activity, which might indicate that triggers accelerating atherosclerosis in SLE, RA and the general population differ [157]. MIs occur in patients with SLE at a younger age than that seen in the general population [39, 41, 158]. This increased CV risk in patients with SLE is multifactorial, comprising both an increased incidence of many traditional CV risk factors and SLE-specific factors, such as disease activity and duration, and therapy [39, 157].

Risk of MACE in Baricitinib SLE Clinical Trials

In the pooled analysis of phase 3 SLE data, the IR of positively adjudicated MACE was numerically higher with baricitinib 2 mg (0.2/100 PYR) and baricitinib 4 mg (0.7/100 PYR) than with placebo (0/100 PYR); however, the IR for the total baricitinib group was 0.5/100 PYR [104] (Fig. 1).

Other Autoimmune Disease

No relevant data were reported in trials conducted in patients with other autoimmune disease.

COVID-19

COVID-19 infection might be associated with an increased risk of MACE [159]. The incidences of positively adjudicated MACE (1.1% vs 1.2%), CV death (0.1% vs 0.4%), MI (0.5% vs 0.5%) and stroke (0.5% vs 0.5%) were similar or the same in 1502 hospitalised patients with COVID-19 treated with baricitinib versus placebo [108]. Among 99 hospitalised patients with severe COVID-19 infection, one CV death and one stroke were reported in baricitinib recipients; no such events were reported with placebo [110].

Conclusions on Risk of MACE with Baricitinib Based on Evidence Across Indications

Across the indications in which baricitinib has been studied, the risk of MACE was dependent on the underlying disease, with the prevalence of risk factors in the different study populations, being of particular concern. Therefore, patients with AA do not appear to have an increased risk of CVD (no IR identified in the literature) and patients with AD have a low absolute risk for MACE, with reported IRs of 0.05–0.21 for MI, 0.07–0.28 for stroke and 0.08–0.44 for CV death [61, 149]. In contrast, in patients with RA, who are generally older, and more frequently experience multiple comorbidities and receive concomitant NSAID or low-dose systemic glucocorticoid therapy, the adjusted relative risk of CVD in patients with RA was 1.66 in one meta-analysis [31]. Indeed, CVD is a leading

cause of morbidity and mortality in this population. It has therefore been suggested that all patients with RA may benefit from additional screening for CV risk factors and more intensive CVD prevention strategies [91, 141]. In support of this strategy, patients with RA who developed MACE during baricitinib therapy were more likely to have CV risk factors than those who did not [91]. Patients with SLE, although younger than those with RA, receive higher doses of glucocorticoids and are also at increased risk of MACE. Finally, patients with COVID-19 might be at increased risk of MACE.

The risk of MACE in patients treated with baricitinib needs to be considered with respect to findings from the IL-6 inhibitor tocilizumab and other JAKis. In the ENTRACTE trial, tocilizumab increased lipid levels after initiation of therapy but did not lead to an increased risk of MACE relative to the TNFi etanercept over a mean follow-up of 3.2 years [160]. To date, JAKis have shown no association with a significant increase in the risk of overall CV events or MACE (MI, CVA or CV death) compared with placebo in patients with RA enrolled in predominantly short-term clinical trials [161]. Preliminary data suggested that the JAKi tofacitinib might reduce atherosclerotic changes by reducing carotid intima-media thickness, atherosclerotic plaque formation, pro-inflammatory M1 macrophages and foam cell formation, and increasing anti-inflammatory M2 macrophages [162, 163], and have an effect on CV outcomes, including MACE (non-fatal CV outcomes or CV death) similar to that seen with TNFis [164]. However, non-inferiority of tofacitinib compared to TNFi therapy (either adalimumab or etanercept) for the risk of MACE (nonfatal MI, nonfatal stroke or CV death) over a median follow-up of 4 years in patients with RA was not demonstrated in ORAL Surveillance, but the hazard ratio (HR) did not show significant increase (3.4% vs 2.5%; HR [95% confidence interval], 1.33 [0.91, 1.94]) [165]. Patients enrolled in ORAL Surveillance were aged 50 years or older and had at least one additional CV risk factor; most MACE in this trial occurred in patients who were at least 65 years of age, those with a history of smoking and those from North America [19, 165]. This last finding may have reflected the higher prevalence of CV risk factors among patients from North America compared with the rest of the world [165]. On the basis of these findings from ORAL Surveillance, which was conducted in patients with RA and risk factors for CVD, MACE has been identified as requiring a warning and precaution for tofacitinib [165–168]. The recent real-world STAR-RA study with the same inclusion criteria as ORAL Surveillance revealed that tofacitinib was not associated with an increased risk of CV outcomes overall when compared with TNFi therapy, but a numerically increased risk of CV outcomes was observed in patients with a history of CV disease [169].

In the baricitinib clinical trial programme, patients with RA, AD or SLE treated with baricitinib had IRs for MACE that appeared similar compared with IRs reported historically for patients with the respective disease, with low rates in patients with AD or AA. As expected, MACE occurred infrequently in patients with AA treated with baricitinib, being reported in only one patient who also had multiple risk factors. In patients with RA aged 50 years or older with at least one additional CV risk factor treated with baricitinib, the IR of MACE (0.77/100 PYR) was lower than the IR of MACE for tofacitinib and similar to that of MACE for TNFis as reported in ORAL Surveillance (0.98/100 PY and 0.73/100 PY, respectively) [165]. However, while these findings suggest that baricitinib has not increased the risk of MACE (Fig. 1) long-term direct data comparing baricitinib with TNFi are presently not available. Two studies are currently ongoing that are considering the risk of MACE in patients with RA receiving baricitinib compared with adalimumab or etanercept (RA-BRANCH [NCT04086745] and RA-BRIDGE [NCT03915964]). Current data from patients with RA, for whom the longest follow-up is available, indicate that the risk of MACE is not affected by the duration of baricitinib therapy [91]. MACE was also infrequent in a Japanese post-marketing study—reported in 0.1% of 3445 patients over the first 24 weeks of therapy (IR of 0.37/100 PY; 0.69 with baricitinib 2 mg and 0.22 with baricitinib 4 mg) [137]. Participants in this study had a mean age of 63.5 years,

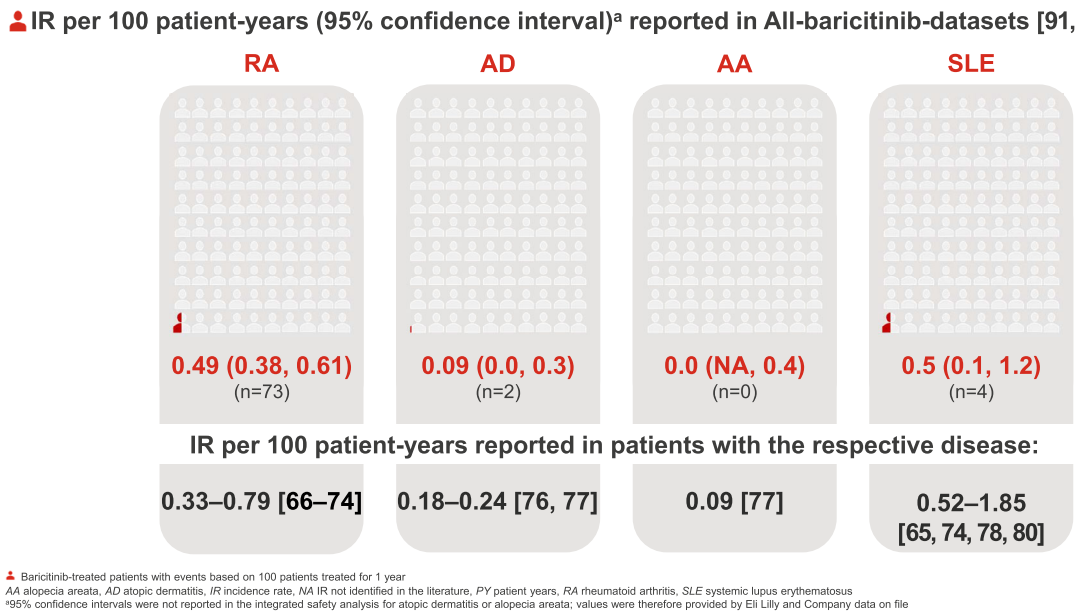

Fig. 2 Incidence rate of VTE in patients treated with baricitinib by disease and rates in the general disease populations

with 54% aged 65 years or older, and a mean BMI of 22.7 kg/m^2, which is within the normal range for Asian patients [137].

Venous Thromboembolism

Rheumatoid Arthritis

Disease-Specific Risk of VTE in RA

The chronic proinflammatory state in RA results in endothelial injury and hypercoagulability leading to VTE [170]. Thus, the risk of VTE is increased in patients with RA compared with age- and sex-matched controls (Fig. 2; Table 1) [68, 71–74, 171]. For example, the risk of VTE is increased up to twofold in patients with RA when compared with the general population and appears to be independent of traditional VTE risk factors [66, 170]. Factors associated with RA, such as old age, smoking, obesity, prolonged immobility, postoperative conditions, and cancer, may be present and increase the risk of VTE [73, 170]. The risk of VTE is highest during the first year after RA diagnosis and decreases over time [170]. The risk of VTE may also depend on the type of treatment and is increased after introduction of biologic disease-modifying antirheumatic drugs (DMARDs), compared with conventional synthetic DMARDs and methotrexate, particularly within 6 months of follow-up [172]. It can be at least partially explained by more severe disease or poorly controlled RA in those who switch [173]. Cyclooxygenase (COX)-2 inhibitors and NSAIDs also increase the risk of VTE by around twofold [174].

Risk of VTE in Baricitinib RA Clinical Trials

In the RA integrated report of baricitinib safety data, the IR of VTE (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) was 0.49/100 PYR [91] (Fig. 2) and was not affected by baricitinib dose, (0.49/100 PYR for baricitinib 2 mg and 0.51/100 PYR for baricitinib 4 mg). Cases of VTE were not externally adjudicated in the clinical trials of baricitinib in RA.

When the placebo-controlled periods of clinical trials evaluating baricitinib in patients with RA were considered in the integrated CV safety analysis, an imbalance in the numbers of patients experiencing VTE (DVT and/or PE) was observed (n = 6 in patients treated with baricitinib 4 mg and 0 in those who received placebo) [112]. All six affected patients had conventional

risk factors for VTE. The incidence of VTE did not increase over time with continued exposure to baricitinib [112]. Of more than 25 risk factors considered, encompassing patient demographics, baricitinib dose, previous and concomitant medications, medical history and RA-related factors, only increased age, increased BMI, a previous history of VTE and selective COX-2 inhibitor use at baseline were associated with VTE occurrence in multivariable analyses. Oral contraceptive/selective oestrogen receptor modulator use was not associated with risk of VTE [112].

When DVT and PE were considered separately in the RA integrated analysis of baricitinib safety data, the IRs were 0.35/100 PYR and 0.26/100 PYR, respectively, and remained stable over time [91]. Among the patients from East Asia treated with baricitinib in clinical trials (mean age 53 years at baseline), there were no cases of PE and four cases of DVT (IR 0.3/100 PYR), all reported in Japan [115].

Atopic Dermatitis

Disease-Specific Risk of VTE in AD

Two US claims database analyses found an association between increased risk of VTE and AD in patients with moderate-to-severe AD [75] or only a slightly, non-significantly, elevated risk of VTE in patients with AD [76], with the absolute risk being low (Fig. 2; Table 1). The increased risk of VTE in patients with moderate-to-severe AD or any AD was linked to an increased prevalence of comorbidities in these patients [76, 77]. In hospitalised patients, patients with AD appeared to be at higher risk of VTE, DVT and PE than people without AD, with an AD diagnosis also being associated with a prolonged duration of VTE-related hospitalisation and greater inpatient mortality [75].

Risk of VTE in Baricitinib AD Clinical Trials

In the AD integrated analysis of baricitinib safety data, the IR of adjudicated VTE (DVT and/or PE) was 0.09/100 PYR [99] (Fig. 2). This IR was based on reports of PE in two patients who received baricitinib 4 mg, one of whom had risk factors for VTE (oral contraceptive use, ex-smoker) and the other of whom was a 61-year-old man with no risk factors other than age.

Alopecia Areata

Disease-Specific Risk of VTE in AA

Data concerning the risk of VTE in patients with AA are limited. In a real-world claims database analysis, the risk of VTE was not increased in patients with AA compared with people without chronic inflammatory skin diseases (Fig. 2; Table 1). Instead, results of this analysis suggested that patients with AA may have a lower risk that is lost when concomitant risk factors for VTE are considered [77].

Risk of VTE in Baricitinib AA Clinical Trials

No cases of VTE were reported in patients with a median of 393.5 days of exposure to baricitinib in the AA integrated analysis of safety data from ongoing trials [104].

Systemic Lupus Erythematosus

Disease-Specific Risk of VTE in SLE

The risks of VTE, PE and DVT are increased in patients with SLE (Fig. 2; Table 1) [74, 80, 81, 171, 175, 176], and higher than that in patients with RA in database analyses [74, 175, 177]. The increased risk of VTE in patients with SLE is also maintained after controlling for risk factors for VTE [79] and persists during follow-up, remaining elevated compared with control groups without SLE [74, 79]. Thrombosis is among the most common causes of death among patients with SLE [136]. The increased risk of VTE in patients with SLE is associated with inflammation, acquired protein S deficiency, comorbidities, traditional risk factors and, most importantly, the presence of antiphospholipid antibodies [79, 178].

Risk of VTE in Baricitinib SLE Clinical Trials

In the pooled analysis of SLE data, excluding the phase 2 study data that was not adjudicated, the IRs of VTE (DVT and/or PE) were highest for placebo (1.4/100 PYR), with lower rates for baricitinib 2 mg and baricitinib 4 mg (0.7/100 PYR and 0.2/100 PYR, respectively) [107].

The IR for the overall baricitinib population was 0.5/100 PYR, at the lower end of the range previously reported for the SLE disease population (Fig. 2).

Other Autoimmune Disease

No relevant data were reported in trials conducted in patients with other autoimmune disease.

COVID-19

Disease-Specific Risk of Thrombosis in COVID-19

COVID-19 is considered a risk factor for thrombosis, with an increased risk of VTE despite anticoagulation prophylaxis in hospitalised patients with COVID-19 [159, 179], in whom endothelial activation, glycocalyx damage and severe capillary impairment have been observed [180]. The pro-inflammatory cytokine storm in COVID-19 can directly act on the endothelium and cause acute cellular dysfunction, loss of endothelial barrier function and increased vascular leakage [181, 182]. Together, these factors increase the risk for microvascular thrombosis and the development of disseminated intravascular coagulopathy (DIC) [182], which increases risk of morbidity and mortality [183]. Over 71% of patients who died from COVID-19 met criteria for overt DIC [184]. In contrast, DVT associated with COVID-19 is thought to occur via activation of tissue factor following endothelial and subendothelial damage and development of fibrin clots [182].

Risk of Thrombosis in Baricitinib COVID-19 Clinical Trials

VTE was reported in only 3% of hospitalised patients with COVID-19 treated with baricitinib and 3% treated with placebo [108]; whereas patients receiving remdesivir and baricitinib experienced a slightly higher incidence of serious PE than those in the remdesivir plus placebo group (1.0% vs 0.4%) [109]. In both trials, VTE prophylaxis was recommended or required for all patients without a major contraindication. In 99 hospitalised patients with severe COVID-19 infection, positively adjudicated VTE was reported in 6% of both baricitinib- and placebo-treated patients in the 28-day assessment period, although an additional baricitinib recipient experienced VTE in the period 28–60 days post enrolment [110].

No other non-VTE thrombotic outcomes were reported in either baricitinib versus placebo study [108, 110], and potential events were reported with numerically lower frequency with baricitinib plus remdesivir when compared with placebo plus remdesivir in the combination therapy study [109]. Serious acute respiratory distress syndrome was reported in 0.8% compared with 2% of placebo recipients, while grade 3 or 4 multiple organ dysfunction syndrome was reported in 0.4% and 0.8% of patients, respectively, grade 3 or 4 acute respiratory distress syndrome was reported in 1.0% and 1.2% of patients, respectively, and grade 3 or 4 dry gangrene was reported in 0 and 0.2% of patients, respectively [109].

Conclusions on Risk of VTE with Baricitinib Based on Evidence Across Indications

Although not quantified, patients with COVID-19 have a very high risk of VTE as a result of the inflammatory changes and endotheliopathy that occur during SARS-CoV-2 infection. These patients are also at risk of disseminated microvascular thrombosis. Patients with SLE have an increased risk of VTE, more so than patients with RA, as shown in Fig. 2. The increased risk of VTE in patients with SLE is associated with greater disease duration and activity, presence of lupus nephritis, hypertension and, most importantly, antiphospholipid antibodies, and is maintained after controlling for traditional risk factors for VTE. Patients with RA also have numerous risk factors for VTE, most importantly history of previous VTE and major surgery (including hip/knee replacement) or trauma. Patients with immune-mediated skin disorders are at a lesser risk for VTE than those with SLE or RA, although some evidence suggests that moderate-to-severe AD, but not AA, increases the risk of VTE, DVT and PE, possibly

as a result of associated comorbidities. Nevertheless, the absolute risk of VTE in patients with AD is low, being lower than that of patients with SLE or RA [177].

In keeping with this disease-specific risk, patients with RA or SLE treated with baricitinib had a higher IR of VTE than patients with the other immune-mediated disorders being considered (Fig. 2), although data were limited for some indications. Most patients who experienced VTE during baricitinib therapy had conventional risk factors for this event. The factors associated with VTE in these patients were increased age, increased BMI, a previous history of DVT and/or PE and selective COX-2 inhibitor use [112]. IRs for VTE during treatment with baricitinib for each indication were similar to those reported for the respective disease population (Fig. 2) and in patients with AD, within the range reported for the general population (any age 0.07–0.18/100 PY) [185, 186]. To help clarify the risk of VTE in patients receiving baricitinib, two studies are currently ongoing in patients with RA and a history of VTE receiving baricitinib compared with adalimumab or etanercept (RA-BRANCH [NCT04086745] and RA-BRIDGE [NCT03915964]).

Short-term treatment with baricitinib did not appear to increase the risk of VTE in hospitalised patients with COVID-19. In a Japanese post-marketing study, in which 80% of participants were female and mean age was 63.5 years, VTE was reported in 0.1% of 3445 patients with RA for an overall IR of 0.22/100 PY [137].

Malignancy

Rheumatoid Arthritis

Disease-Specific Risk of Malignancy in RA

RA is associated with a small increased overall risk of malignancy compared with the general population (Table 1). The probability of both solid and haematological malignancies is increased by persistent, chronic inflammation [187]. When specific cancers are considered, RA increases the risk of lymphoma, lung cancer and melanoma [81–83]. Continuous B cell activation producing autoantibodies may lead to the development of malignant lymphoproliferative disease in some patients, whereas solid tumours develop more frequently in target tissues affected by inflammation [187]. In particular, patients with RA have 12-fold increase in the incidence of lymphoproliferative diseases compared with the general population [187], possibly because the same inflammatory processes that drive RA also contribute to the development of lymphoma [83]. Diffuse large B cell lymphoma is the most common subtype, although both non-Hodgkin's lymphoma and Hodgkin's lymphoma have an increased incidence in RA [83]. A higher risk for lymphoma in RA has been also reported in Japan compared to other countries [188]. The risk of lung cancer also appears to be increased twofold in patients with RA compared with the general population [81]; again, chronic inflammatory processes—activation of bronchial-associated lymphoid tissue (BALT) and smoking—may contribute to this increased risk [187]. Although RA does not seem to increase the risk of breast, prostate, gastric or liver cancers [82], the prognosis of these cancers is worse than in the general population, and the progression of an abnormal pap smear to pre-cancerous lesions is accelerated in people with RA compared to the general population [82].

Chronic intake of NSAIDs may lower the risk for colorectal and gastric cancers [187], and the risk of colorectal cancer is decreased in patients with RA [81]. However, other treatments (DMARDs) used in RA may contribute to increased malignancy risk, although it may be difficult to distinguish whether the underlying disease or the treatment has the dominating influence [187] and recent data demonstrate that the risk of malignancy is similar in biologic DMARD-treated and DMARD-naïve patients [189].

The risk of non-melanoma skin cancer (NMSC) has been reported to be both increased and decreased in patients with RA, and the prognosis for squamous cell carcinoma may be worse [82]. Treatments may affect the risk of malignancy in patients with RA; however, it is uncertain to what extent drug- or disease-related factors are contributing, as some drugs are reserved for the treatment of more severe

disease [82]. In one analysis, use of TNFis and prednisone was associated with an increased risk of NMSC [190].

Risk of Malignancies Excluding NMSC in Baricitinib RA Clinical Trials

In the RA integrated report of baricitinib safety data, the IR of malignancy excluding NMSC was 0.6/100 PYR at 48 weeks and remained

Fig. 3 **a** Incidence rate of malignancy (excluding NMSC) in patients treated with baricitinib by disease and rates in the disease populations including populations receiving immunosuppressant therapy. **b** Incidence rate of NMSC in patients treated with baricitinib by disease and rates in the general disease populations or tocilizumab-treated patients

stable thereafter; the IR over the entire analysis period was 0.9/100 PYR (Fig. 3a) and this IR was similar to that seen in the general US population [91]. The most commonly reported malignancies with baricitinib were respiratory and mediastinal, breast and gastrointestinal malignancies; the IR of lymphoma was 0.06/100 PYR, with diffuse large B cell lymphoma being the most common subtype. In East Asian patients with RA treated with baricitinib, the IR of malignancy excluding NMSC was 0.99/100 PYR, the most commonly reported being breast cancer (n = 2) and lymphoma (n = 2); B cell lymphoma and lymphoproliferative disorder were reported in one patient each [115].

Risk of NMSC in Baricitinib RA Clinical Trials

The IR of NMSC was 0.3/100 PYR and did not increase over time in the RA integrated report of baricitinib safety data (Fig. 3b) [91]. Among East Asian patients, only one case of NMSC was reported [115].

Atopic Dermatitis

Disease-Specific Risk of Malignancy in AD

Reviews attempting to determine the association between AD and cancer risk have found inconsistent and unclear evidence, including information available to support an increased, decreased or unchanged risk for many cancer types (Table 1) [10, 33, 197–199]. However, severe, long-term AD does seem to increase the risk of lymphomas in adults [10, 33, 199] although a protective effect of AD against malignancy overall has also been concluded [33]. AD appears to be associated with a reduced risk of melanoma, but an increased risk of NMSCs, specifically basal cell carcinoma and, more so, squamous cell carcinoma [200, 201]. It is difficult to assess whether AD is an independent risk factor for skin cancers because of the confounding effects of factors such as sun exposure or treatment, including systemic immunosuppressive agents such as cyclosporine and azathioprine, and phototherapy [33, 34].

Risk of Malignancies Excluding NMSC in Baricitinib AD Clinical Trials

There were no malignancies excluding NMSC reported in either of the baricitinib 2 mg or 4 mg groups in the placebo-controlled period of AD trials, with two malignancies excluding NMSC reported in the placebo group (IR, 0.66/100 PYR), one breast cancer and one papillary thyroid cancer [99]. In the AD integrated analysis of safety, five malignancies excluding NMSC were reported (IR, 0.22/100 PYR) (Fig. 3a), one patient treated with baricitinib 4 mg had anaplastic large cell lymphoma T cell and null-cell types, and one patient each treated with baricitinib 2 mg had B cell lymphoma (symptoms began while on placebo), diffuse large B cell lymphoma, prostate cancer and rectal cancer [99].

Risk for NMSC in Baricitinib AD Clinical Trials

NMSC was reported in six patients (IR 0.26/100 PYR) in the AD integrated baricitinib data set (Fig. 3b): basal cell carcinoma (n = 3 patients treated with baricitinib 2 mg), Bowen's disease (n = 2 patients treated with baricitinib 4 mg) and keratoacanthoma (n = 1 patient treated with baricitinib 4 mg) [99].

Alopecia Areata

Disease-Specific Risk for Malignancy in AA

AA may increase the risk of certain malignancies, but the overall effect on cancer risk is uncertain (Table 1) [84, 85]. In one analysis, overall cancer risk was found to be slightly higher in patients with AA than in patients without alopecia (HR 1.043) [85]. In contrast, the risk of overall cancer in patients with AA was almost as expected based on an analysis of insurance claims data covering 99% of the population in Taiwan [84]. With regard to skin cancer, AA was associated with a reduced risk of NMSC, and a neutral or reduced risk of melanoma [84, 86].

Risk for Malignancies Excluding NMSC and for NMSC in Baricitinib AA Clinical Trials

In the AA integrated analysis of baricitinib safety data, two malignancies were reported during the placebo-controlled period (prostate cancer in one placebo recipient [IR 0.4/100 PYR] and B cell lymphoma in a patient treated with baricitinib 4 mg [IR 0.3/100 PYR]) [104]. During the longer-term phases of the trials, breast cancer was identified in one patient treated with baricitinib 4 mg, leading to an IR of 0.1/100 PYR for malignancy excluding NMSC in the total baricitinib AA safety population (Fig. 3a) [104]. NMSC was found in one patient treated with baricitinib 2 mg during the longer-term phases of the trials, giving an IR of 0.1/100 PYR for NMSC in the total baricitinib AA safety population (Fig. 3b) [107].

Systemic Lupus Erythematosus

Disease-Specific Risk for Malignancy in SLE

The overall risk of malignancy appears to be increased in patients with SLE (Table 1), as is the risk of certain cancer types [87, 88]. Recent reviews and meta-analyses have confirmed increased rates of all haematological malignancies (particularly non-Hodgkin's lymphoma) and lung, hepatobiliary (particularly liver), vulvar/vaginal, laryngeal, otopharyngeal, oesophageal, anal, bladder, thyroid, and brain and nervous system malignancies, as well as cervical dysplasia/cancer. Various mechanisms may increase the risk of malignancy in patients with SLE; these include chronic immune stimulation as a result of disease activity; persistent viral infections, such as Epstein–Barr virus, viral hepatitis or human papilloma virus; oxidative stress; or risk factors similar to those seen in the general population, such as smoking and inflammatory processes [202, 203]. Immunosuppressive treatments used in SLE, such as cyclophosphamide, may also increase the risk of malignancy, either directly via immunosuppression and cytotoxicity or indirectly by promoting oncogenic virus emergence [87].

Decreased rates of breast, uterine, melanoma and prostate cancer in SLE have also been shown [87, 88]. The risk of hormone-sensitive cancers such as breast, uterine and prostate malignancies may be lower as a result of autoantibody profiles [203, 204], and for the last two malignancies, earlier menopause, and/or avoidance of oral contraceptives or hormone-replacement therapy that arises from concerns over adverse outcomes [203].

Risk for Malignancies Excluding NMSC and for NMSC in Baricitinib SLE Clinical Trials

In the pooled analysis of baricitinib data in patients with SLE, the IR of malignancy excluding NMSC was similar across treatment groups, being 0.4, 0.6 and 0.4/100 PYR with placebo, baricitinib 2 mg and baricitinib 4 mg, respectively; the IR for the overall baricitinib population was 0.5/100 PYR (Fig. 3a) [107]. The IR of NMSC in this analysis was 0.4/100 PYR for placebo and zero for baricitinib (both doses and overall) (Fig. 3b) [107].

Other Autoimmune Disease

No relevant data were reported in trials conducted in patients with other autoimmune disease.

COVID-19

No relevant data were reported in trials conducted in patients with COVID-19.

Conclusions on Risk of Malignancy with Baricitinib Based on Evidence Across Indications

The risk of malignancy overall or of specific cancer types appears to be increased in RA and SLE, while evidence is less conclusive in AD and AA. In clinical trials of baricitinib, the risk of malignancy excluding NMSC was as expected for the patient populations and did not increase with longer exposure to baricitinib. Similarly, the IRs reported for baricitinib in patients with RA or AD (Fig. 3) were comparable to IRs reported for other JAKis or tocilizumab in the respective patient populations [119–122, 205].

For example, in patients with RA newly initiated on tocilizumab or TNFis from claims database records, IRs were between 0.83/100 PYR and 2.32/100 PYR [206], and IRs of 1.13/100 PY and 0.77/100 PY were reported for tofacitinib and TNFis, respectively, in ORAL Surveillance, which included patients aged 50 years or older with risk factors [165]. The IRs for NMSC with baricitinib in patients with RA and AD were also similar to those reported for other JAKis in RA and AD clinical trials [120, 121, 205, 206].

In real-world baricitinib data from a Japanese post-marketing study, malignancy was reported in 0.3% of 3445 patients (mean age 63.5 years; 54% of whom were aged $\geq$ 65 years) with RA, resulting in an IR of 0.81/100 PY [137].

The lack of long-term follow-up with a randomised control arm for some of the diseases discussed in this review may prevent the accurate ascertainment of the risk of malignancy with baricitinib, but the observation period of up to 9.3 years in patients with RA (Table 2) provides some reassurance of no increased risk. In addition, two studies are currently ongoing that are considering the risk of malignancy excluding NMSC in patients with RA receiving baricitinib compared with adalimumab or etanercept (RA-BRANCH [NCT04086745] and RA-BRIDGE [NCT03915964]).

Gastrointestinal (GI) Perforation

As the IL-6 inhibitor tocilizumab has been associated with GI perforation [90], it was hypothesized that JAKi therapy might also increase the risk of GI perforation as a result of IL-6 inhibition [5]. This event has been reported with JAKis, albeit less frequently than with tocilizumab [5].

Rheumatoid Arthritis

Disease-Specific Risk of GI Perforation in RA

One of the main underlying causes of mortality in patients with RA before the introduction of DMARDs, with an excess relative to the general population, was GI disease [207]. With progress in RA treatments, GI perforation is rare, with perforations most frequently occurring in the lower GI tract (83% of all cases) [89, 207]. The use of NSAIDs and glucocorticoids remains the most likely underlying mechanism [89, 207, 208]. Decreased incidence of NSAID-related upper GI complications in recent years can be attributed to the protective role of a proton pump inhibitor, but only in the upper bowel. As a consequence, this may have led to increased reporting of lower GI events [207].

Risk of GI Perforation in Baricitinib RA Clinical Trials

In the RA integrated analysis of baricitinib safety data (IR 0.06/100 PYR) of the nine GI perforations reported, seven (IR 0.05/100 PYE) were lower GI perforations [91]. Twenty-three treatment-emergent events of diverticulitis were reported (IR 0.15/100 PYR); these occurred in patients with risk factors including pre-existing diverticulosis, older age, overweight/obese and chronic glucocorticoid or NSAID treatment [91]. Among patients from East Asia in the clinical trials of baricitinib in RA, two cases of GI perforation were reported in the baricitinib-treated cohort (a perforated diverticulum and a perforated appendix), both in patients concomitantly receiving prednisolone plus NSAIDs [115].

Other Indications

Confirmed cases of GI perforation have not been reported in patients with AD [99] or AA [104] receiving baricitinib, or patients with COVID-19 treated with baricitinib or placebo, both with the standard of care [108]. Information relating to the GI tolerability or risk of GI perforation in patients with SLE receiving baricitinib has not been reported [14, 107].

Conclusions on Risk of GI Perforations with Baricitinib Based on Evidence Across Indications

RA is rarely associated with GI perforation, and only small numbers of patients with RA treated with baricitinib have experienced this event, such that the IR of GI perforation was lower

among patients treated with baricitinib in clinical trials than was previously reported for patients with RA. The pattern of GI perforation in patients with RA receiving baricitinib was similar to that of the general RA population (i.e. mainly lower GI perforation). There are no reports of any patient receiving baricitinib for an investigated disease other than RA experiencing GI perforation, suggesting that reports in patients with RA could be related more to the disease or patient characteristic than its treatment. In contrast, use of the IL-6 inhibitor tocilizumab is a risk factor for lower intestinal perforation (IR, 0.27/100 PY) and is associated with a higher risk than conventional synthetic or biologic DMARDs (IR, 0.02–0.06/100 PY) [90].

Laboratory Findings of Interest

JAK Inhibition and Changes in Blood Cell Count, Haemoglobin and Lipids

JAK2 signalling is essential for erythropoietin signalling, which stimulates erythrocyte production, and GM-CSF-induced signal transduction, crucial for leucocyte production [113, 209]. Therefore, sustained JAK2 inhibition was expected to cause cytopenias. However, baricitinib is a reversible JAK1/2 inhibitor that does not inhibit cytokine signalling for the full 24-h dosing period [2]. IL-6 signalling through JAK2 is implicated in the regulation of thrombopoietin [210] and inhibition of this cytokine might reduce platelet levels, while activated JAK2 directly phosphorylates the thrombopoietin receptor, suggesting JAK inhibition can result in thrombocytopenia [211]. Since IL-6 promotes insulin resistance and redistribution of fatty acids from the blood to peripheral tissues, resulting in reductions in serum lipids, changes in lipid levels induced by treatments that affect IL-6 may or may not correlate with incidence rates of CV disease [212].

Rheumatoid Arthritis

Anaemia

Anaemia occurs in 30–70% of patients with RA, and usually presents as anaemia of chronic disease [213, 214]. Anaemia of chronic disease is generally mild and nonprogressive, with haemoglobin levels rarely less than 70% of normal [214]. Other causes of anaemia in RA are iron-deficiency anaemia, folate deficiency anaemia, vitamin B_{12} deficiency anaemia, haemolytic anaemia or induced by DMARDs [213–215]. Although often mild (with a median minimum haemoglobin level of 6.8 mmol/L in one study) resolving and first occurring early in the course of RA, repeated bouts of anaemia are not uncommon [213].

In the analysis of haematological changes occurring during baricitinib therapy by Kay and colleagues [113], small decreases from baseline in mean haemoglobin levels occurred soon after initiation of baricitinib and were followed by increases in levels toward baseline that correlated with reductions in inflammation, as measured by high-sensitivity C-reactive protein levels [113]. The early reductions in haemoglobin levels were seldom considered to be clinically relevant and resulted in discontinuation of baricitinib in 0.5% of patients. In the RA integrated report of baricitinib safety data, the IR of laboratory-related anaemia with baricitinib (all doses) was 1.74/100 PYR, and the IR of categorical haemoglobin change to below 8 mg/dL was 0.3/100 PYE [91].

Leucopenia

Neutropenia in patients RA is usually acquired, often secondary to DMARD use [216]. The IR for baricitinib (all doses) for laboratory-related treatment-emergent neutropenia was 0.4/100 PYR and laboratory-related lymphopenia was 1.04/100 PYR in the integrated RA safety analysis [91]. In the analysis by Kay and colleagues [113], the initial decrease in neutrophils was similar to those reported in studies of other JAKis for RA, and both neutropenia and lymphopenia infrequently resulted in discontinuation (0.2% of patients, each) or temporary interruption of baricitinib [113].

Platelets

Thrombocytosis was observed with baricitinib with an IR of 0.3/100 PYR in the integrated RA safety analysis [91] and infrequently resulted in discontinuation (0.2% of patients) or temporary interruption of baricitinib in the analysis by Kay and colleagues [113]. Thrombocytosis (platelet counts $> 400 \times 10^9$/L) occurred in similar proportions of baricitinib-treated patients with versus without VTE (35.7% vs 37.2%), although very high platelet counts ($\geq 600 \times 10^9$/L) were reported in 7.1% vs 3.6% [113]. This low overall incidence limited interpretation of the finding. Thrombocytosis was not associated with MACE in the integrated RA safety report [91]. A potential explanation for the observed transient increase in platelet count with baricitinib, which occurs in tandem with a transient decrease in mean platelet volume, is that the primary cause is reduced platelet clearance and a transient increase in older, smaller platelets in the circulation [217]. Older, smaller platelets may contain fewer granules, express fewer adhesion molecules on their surface, activate more slowly, and would therefore be expected to cause fewer VTE than larger platelets [218]; in one study increased mean platelet volume but not platelet count was identified as a predictor of VTE [219].

Lipids

Active RA is associated with a lipid paradox as described above [145, 220]. In the RA integrated report of baricitinib safety data, the IRs for change to LDL-cholesterol at least 160 mg/dL and change to HDL-cholesterol below 40 mg/dL were 7.2/100 PYE and 2.4/100 PYE, respectively, being reported in 39.6% and 11.4% of patients, respectively [91]. A previous analysis of lipid data from phase 2 and 3 baricitinib clinical trials revealed that although early changes were observed in LDL- and HDL-cholesterol levels during baricitinib therapy, there was no change in the LDL to HDL-cholesterol ratio and levels remained stable from week 12 to 104 [114].

Atopic Dermatitis

Anaemia

There were no haemoglobin grade 3 (< 8 mg/dL) or higher changes with either baricitinib 2 mg or 4 mg at any time during the studies; overall, 0.9% of patients had a haemoglobin level below 10 mg/dL in the integrated AD analysis of safety data [99].

Leucopenia

Few patients overall treated with baricitinib had a change in lymphocyte counts to below 500 cells/mm^3 (0.5%) or in neutrophil counts to below 1000 cells/mm^3 (0.2%) in the integrated AD analysis of safety data [99]. Decreases of neutrophils to below 1000 cells/mm^3 were not associated with serious infections and did not lead to study drug discontinuation.

Platelets

Although increases in platelets to greater than 600×10^9/L were reported in more patients in the baricitinib 2 mg (1.2%) and 4 mg (0.6%) groups than the placebo group (0%) and in 1.0% of the overall baricitinib population, changes were not associated with AEs in the integrated AD analysis of safety data [99].

Lipids

AD is associated with reduced triglycerides, LDL-cholesterol and total cholesterol, but not altered HDL-cholesterol [155]. In the AD integrated analysis of safety data, a higher proportion of patients in the baricitinib 2 mg and 4 mg groups than the placebo group had categorical increases in LDL-cholesterol of 130 mg/dL or more (12.0% and 13.2%, respectively, vs 6.3%) and in HDL-cholesterol of 60 mg or more (19.4% and 25.3%, respectively, vs 14.7%); 21.8% and 29.5% of all baricitinib-treated patients, respectively, had these changes in lipid levels. Given the low occurrence of MACE or CV events, these data did not indicate an increased risk of these events [99].

Alopecia Areata

Anaemia

In all baricitinib-treated patients, the IR of haemoglobin below 8 mg/dL was 0.1/100 PYE in the integrated AA analysis of safety data [104].

Leucopenia

In the integrated AA analysis of safety data, the IR of neutrophil count below 1.0×10^9 cells/L was 1.2 /100 PYE and of lymphocyte count below 0.5×10^9/L was 0.2/100 PYE in all baricitinib-treated patients; no patients treated with placebo reported these laboratory changes [104].

Platelets

In the integrated AA analysis of safety data, the IR of platelets greater than 600×10^9/L was 0.5/100 PYE in all baricitinib-treated patients; no patients treated with placebo reported this laboratory change [104]. No patient with a platelet increase greater than 600×10^9/L reported a thromboembolic event or CVD.

Lipids

In the AA integrated analysis of safety data, a higher proportion of patients in the baricitinib 2 mg and 4 mg groups than in the placebo group had categorical increases in LDL-cholesterol to 4.14 mmol/L or more (9.8% and 12.2%, respectively, vs 3.4%) and in HDL-cholesterol to 1.55 mmol/L or more (38.8% and 42.4%, respectively, vs 11.9%); the IRs for these changes in lipid levels in all baricitinib-treated patients were 11.2/100 PYE and 21.1/100 PYE, respectively [104].

Systemic Lupus Erythematosus

SLE is characterised by multi-organ involvement including haematological manifestations such as haemolytic anaemia, leukopenia, lymphopenia and immune-mediated thrombocytopenia [221]. Dyslipidaemia in SLE is multifactorial, with autoantibodies, cytokines, lupus nephritis presence and treatment with glucocorticoids and cyclosporine A all playing a role in its development [222]. Data concerning changes in laboratory parameters during baricitinib treatment are available only from a phase 2, 24-week placebo-controlled trial [14].

Anaemia

There were modest dose-associated decreases in haemoglobin levels, with no baricitinib recipient experiencing grade 3 or 4 anaemia [14].

Leucopenia

There were early increases in lymphocyte counts with baricitinib treatment, but lymphocytes returned to baseline levels by week 24 and no patient had grade 4 lymphocytopenia (< 200 cells/mm^3) in any group at this time; about 6% of patients treated with baricitinib 2 mg or 4 mg and 12% of those who received placebo had grade 3 lymphocytopenia (≥ 200 to < 500 cells/mm^3) at week 24. There were modest dose-associated decreases in neutrophil levels, with 1.0% and 3.8% of baricitinib 2 mg or 4 mg recipients experiencing grade 3 neutropenia versus 1.9% of placebo recipients (no patient had grade 4 neutropenia) [14].

Platelets

Platelet counts increased during baricitinib treatment and 4.8% of patients treated with either baricitinib 2 mg or 4 mg had abnormally high levels to 60 days post-treatment, compared with 1% of placebo-treated patients [14].

Lipids

After 12 weeks of baricitinib treatment, there were statistically significant dose-associated increases in HDL-cholesterol and total cholesterol, dose-independent increases in LDL-cholesterol and modest dose-associated increases in triglyceride levels among 314 patients with SLE treated with baricitinib 2 mg or 4 mg, or placebo [14]. At week 24, abnormally high (not further defined) HDL-, total and LDL-cholesterol, and triglyceride levels were reported in 16.2%, 4.5%, 2.3% and 2.3% of patients, respectively, treated with baricitinib 4 mg and 10.5%, 1.2%, 0% and 0%, respectively, of those treated with baricitinib 2 mg [14].

Other Autoimmune Disease

Anaemia

In patients with psoriasis, baricitinib, at doses of 2–10 mg daily, was associated with small dose-related decreases in haemoglobin level at week 12 [16].

Leucopenia

In patients with psoriasis, baricitinib, at doses of 2–10 mg daily, was associated with small dose-related decreases in neutrophil count at week 12; lymphocyte counts initially increased, but then returned to baseline levels [16].

Platelets

In patients with psoriasis, baricitinib, at doses of 2–10 mg daily, was associated with small increases in LDL- and HDL-cholesterol [16]. Baricitinib was also associated with modest increases in LDL- and HDL-cholesterol by week 24 that returned to baseline levels at the 4-week washout visit in patients with DKD [17].

COVID-19

No relevant data were reported in trials conducted in patients with COVID-19.

Conclusions on Laboratory Changes in Blood Cell Count, Haemoglobin and Lipids with Baricitinib Based on Evidence Across Indications

Although continuous JAK2 inhibition might be expected to result in anaemia and reduced leucocyte and platelet counts, with baricitinib, which reversibly inhibits JAK2 signalling for only part of a dosing cycle at approved doses, changes in haematological parameters were generally small to moderate in magnitude and were often transient [113]. Nevertheless, product information recommends that absolute neutrophil and lymphocyte counts and haemoglobin levels be monitored before initiation of baricitinib and thereafter according to routine patient management and treatment not be initiated/interrupted in patients with low counts [6].

The observed increases in lipid profiles, particularly cholesterol and triglycerides, during baricitinib treatment may not represent an increased CV risk as is accepted in individuals with elevated lipid level and without significant inflammation but may represent a predictable response to attenuation of inflammation [145]. In patients receiving baricitinib, lipid parameters should be monitored 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia, and that patients be managed according to those guidelines [6]. In the Japanese post-marketing study, anaemia and hyperlipidaemia were each reported infrequently (1% of 3445 patients with RA) [137].

CLINICAL PERSPECTIVE

What Patient Factors Should be Considered When Initiating a Systemic Treatment in a Patient with RA, AD or AA?

Important factors to consider when initiating treatment for a patient with active RA, AD or AA are the age of the patient, the associated comorbidities and any comedications they might be receiving. Disease activity and duration of RA, AD or AA are important safety considerations together with previous treatment tolerance. Factors specific to each disease, such as skin barrier defects in AD and extraarticular manifestations in RA, and uncontrolled disease can also increase the risk of specific adverse events such as infections. Critical for treatment success and compliance is shared decision-making, which enables an understanding of the patient's expectations and preferences.

All three diseases are characterised by systemic and chronic inflammation with risk of irreversible damage if not treated in a timely and long-term manner. The high impact of these diseases on the quality of life of patients (as a result of pain and mobility impairment for RA, itch for AD, and stigmatisation for AA) needs to be the foremost consideration.

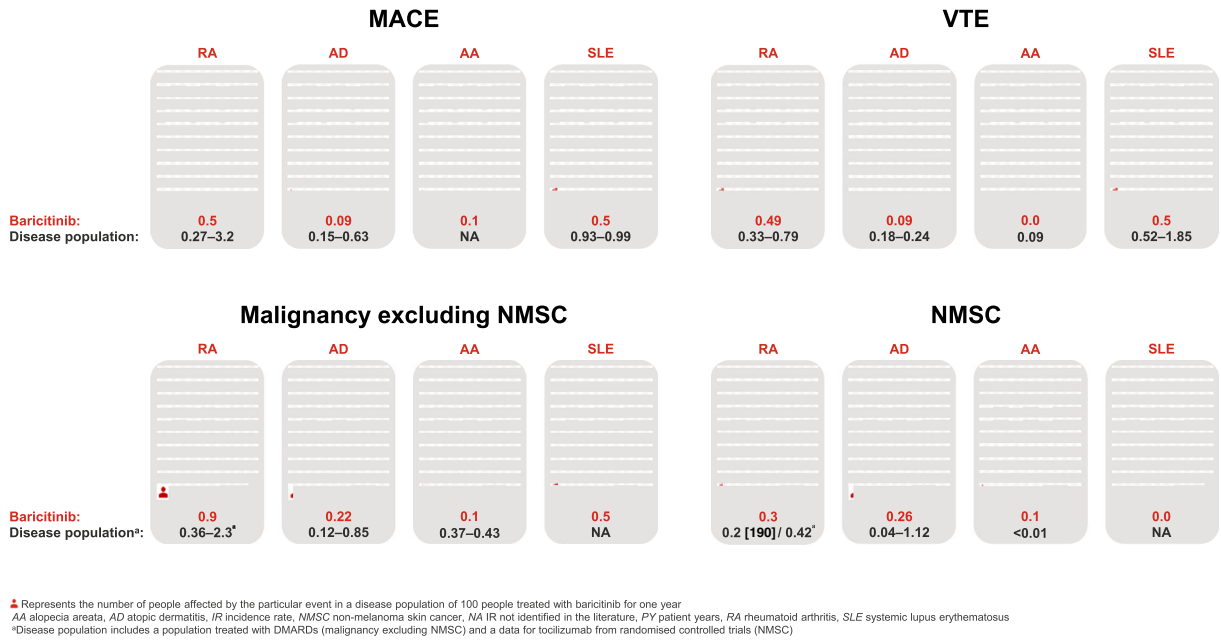

Fig. 4 Incidence rates of adverse events of interest in patients treated with baricitinib by disease and rates in the general disease populations

What Guidance Would You Give to Rheumatologists/Dermatologists When Initiating Baricitinib in Patients with RA, AD or AA?

For every systemic immunosuppressive therapy being considered for a patient with immune-mediated inflammatory disease, a basic assessment to screen for any as yet uncontrolled or unknown infectious or CV condition is essential. It is important to evaluate the risks in each patient to allow an individualised benefit–risk balance. Important infectious conditions to consider include latent tuberculosis, human immunodeficiency virus or viral hepatitis positivity. Screening of malignancy during annual or regular check-ups is also recommended. The findings of these assessments can be used to guide the appropriate management strategy for the patient and assist in the decision as to the best treatment option. This assessment also provides an opportunity for close collaboration with other specialities to improve patient care. This general guidance holds for initiation of baricitinib. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. A satisfactory immunoglobulin G immune response to pneumococcal or tetanus vaccination was achieved in patients with RA receiving baricitinib in a vaccine study. Vaccination with live, attenuated vaccines during or immediately prior to baricitinib therapy is not recommended [6].

A general rule is to treat early to prevent damage and, utilising shared decision-making, determine an individualised assessment of benefit and risk aligned with the patient's expectations.

What are Learnings from the Baricitinib Safety Information in Indications Outside of Your Speciality?

Learnings across specialities help our understanding of the impact of the underlying disease, patient characteristics and differences in the spectrum of comorbidities for different indications on safety outcomes. Both RA and AD are characterised by a flaring, relapsing and remitting nature, but there are differences across specialities in the use of systemic

therapies that provide insights into the impact of the varying strategies on likely safety outcomes with baricitinib. For example, there is also variability in the approach to symptom management and use of systemic combination therapy versus monotherapy. In rheumatology, adoption of a treat-to-target approach was a breakthrough in halting disease progression and maintaining physical function. In AD, a stepwise approach to therapy is often mandated by third party payers; and traditional immunosuppressants must often be tried before advanced therapies can be initiated.

Data from different diseases can also help to support the use of baricitinib—skin diseases are not limited to the skin, and RA is not only a joint disease, so a holistic approach to therapy is beneficial. It is possible that some insights from different specialities can be applied to a patient with a specific disease, as some aspects or complications of the inflammatory condition may be common to multiple diseases.

It can also be helpful to see the patterns and likelihoods of AEs that occur during treatment in large groups of patients with different diseases. This can help both the physician and patient to better contextualise the perception of benefit-to-risk ratio in the process of a shared decision-making approach when considering the use of baricitinib and in ensuring that risk mitigation approaches are appropriately communicated and actioned.

Although the IRs reported for baricitinib in clinical trials do not appear to be different from the risks of unexposed patients (Fig. 4), the current exposure data may not be sufficient to detect small incremental risks, even in patients with RA. To better characterise the risk of events of special interest in patients receiving baricitinib, two large post-marketing studies are currently underway to compare the safety of baricitinib compared with adalimumab or etanercept, primarily with respect to VTEs, in patients with RA and a history of VTE in the USA (RA-BRANCH [NCT04086745]) and worldwide (RA-BRIDGE [NCT03915964]). These studies are also considering the risk of MACE, malignancy excluding NMSC, and opportunistic and serious infection with baricitinib in these patients.

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