Baricitinib for systemic lupus erythematosus: not enough, or not enough evidence?

Sirs,

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disorder, characterised by significant heterogeneity in clinical presentation, disease severity and treatment response (1). Treatment targets remain long-term patients' survival, prevention of disease flares and target organ damage, along with improvement in patients' quality of life (2). Current treatment guidelines include hydroxychloroquine, glucocorticoids, immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide) and biological agents, including belimumab and rituximab (3). The Janus kinase/signal transduction and activator of transcription (JAK-STAT) signalling pathway has been implicated into SLE pathogenesis, rationalising the use of JAK inhibitors in patients with SLE (4). Baricitinib is an oral JAK 1/2 inhibitors, which has been investigated in subjects with SLE in recent, relevant randomised controlled trials (RCTs). Therefore, we sought to determine whether baricitinib treatment is associated with increase in SLE treatment response, according to data from published RCTs.

A detailed search in two major databases, namely PubMed and Cochrane Library, was performed on 13th March 2023, utilising the following search strategy: (((baricitinib) OR (olumiant)) OR (LY3009104)) OR (INCB028050) AND (systemic lupus erythematosus) OR (SLE), in order to identify all relevant RCTs assessing the safety and efficacy of baricitinib in subjects with SLE. We did not impose any filter regarding study setting, sample size or treatment duration. In addition, we did not impose any filter regarding publication language.

We set as primary efficacy outcome the odds for achieving a Systemic Lupus Erythematosus Responder Index 4 (SRI-4) response. We also set as secondary efficacy outcome the odds for achieving a Lupus Low Disease Activity State (LLDAS).

As we assessed only dichotomous variables, differences were calculated with the use of odds ratios (OR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel (M-H) random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.

Our search retrieved one phase 2 RCT (5) and two phase 3 RCTs (6, 7). All eligible RCTs compared two doses of once-daily administered baricitinib, 2 mg and 4 mg, with placebo. Regarding the primary efficacy outcome, baricitinib 2 mg was not superior

Fig. 1A. Effect of baricitinib 2 mg versus placebo on the odds for SRI-4 response.

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	Baricitinib	2 mg	Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Phase 2 trials							
Wallace 2018	54	105	50	105	17.1%	1.16 [0.68, 2.00]	
Subtotal (95% CI)		105		105	17.1%	1.16 [0.68, 2.00]	
Total events	54		50				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.55 (P	= 0.58)					
1.1.2 Phase 3 trials							
Morand 2023	127	255	116	253	41.2%	1.17 [0.83, 1.66]	
Petri 2023	121	261	117	256	41.8%	1.03 [0.73, 1.45]	
Subtotal (95% CI)		516		509	82.9%	1.10 [0.86, 1.40]	
Total events	248		233				
Heterogeneity: Tau ² =	= 0.00; Chi ² =	0.28, dt	f=1 (P=	0.60); I	²= 0%		
Test for overall effect	Z = 0.73 (P	= 0.46)					
Total (95% CI)		621		614	100.0%	1.11 [0.89, 1.39]	-
Total events	302		283				
Heterogeneity: Tau ² =	= 0.00; Chi ² =	0.32, dt	= 2 (P =	0.85);1	² =0%		0.2 0.5 1 2 5
Test for overall effect	Z = 0.90 (P	= 0.37)					Favours placebo Favours baricitinib 2 mg
Test for subgroup dif	ferences: Ch	i ² = 0.04	, df = 1 (F	P = 0.84	I), I ² = 0%		r avours praceso - r avours banciumb 2 mg

B: Effect of baricitinib 4 mg versus placebo on the odds for SRI-4 response.

	Baricitinib	4 mg	Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.2.1 Phase 2 trials							
Wallace 2018	67	104	50	105	23.7%	1.99 [1.14, 3.47]	
Subtotal (95% CI)		104		105	23.7%	1.99 [1.14, 3.47]	
Total events	67		50				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 2.43 (P	= 0.01)					
1.2.2 Phase 3 trials							
Morand 2023	143	252	116	253	38.0%	1.55 [1.09, 2.20]	
Petri 2023	122	258	117	256	38.4%	1.07 [0.75, 1.51]	e
Subtotal (95% CI)		510		509	76.3%	1.28 [0.89, 1.85]	
Total events	265		233				
Heterogeneity: Tau ² =	0.04; Chi ² =	2.21, df	= 1 (P =	0.14); F	²= 55%		
Test for overall effect:	Z=1.33 (P	= 0.18)					
Total (95% CI)		614		614	100.0%	1.42 [1.01, 2.00]	
Total events	332		283				
Heterogeneity: Tau ² =	0.05; Chi ² =	4.23, df	= 2 (P =	0.12); F	²= 53%		0.2 0.5 1 2 5
Test for overall effect:							0.2 0.5 1 2 5 Favours placebo Favours baricitinib 4 mg
Test for subgroup diff			. df = 1 (F	e = 0.20), $l^2 = 40$.	4%	Favours pracebo Favours bancitinio 4 mg

C: Effect of baricitinib 2 mg versus placebo on the odds for LLDAS response.

	Baricitinib		Place			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Phase 2 trials Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applicat	ole					
1.3.2 Phase 3 trials							
Morand 2023	66	255	66	253	51.2%	0.99 [0.67, 1.47]	
Petri 2023	63	261	59	256	48.8%	1.06 [0.71, 1.59]	
Subtotal (95% CI)		516		509	100.0%	1.02 [0.77, 1.36]	
Total events	129		125				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.06, df	= 1 (P =	0.81); F	² =0%		
Test for overall effect:	Z= 0.17 (P=	0.87)					
Total (95% CI)		516		509	100.0%	1.02 [0.77, 1.36]	-
Total events	129		125				
Heterogeneity: Tau ² =	0.00; Chi ² =	0.06, df	= 1 (P =	0.81); F	² =0%		0.2 0.5 1 2
Test for overall effect:	Z=0.17 (P=	0.87)					U.2 U.5 1 2 Favours placebo Favours baricitinib 2 mg
Test for subgroup diff	erences: No	t applica	ble				Favours placebo Favours banciunib 2 mg

D: Effect of baricitinib 4 mg versus placebo on the odds for LLDAS response.

	Baricitinib	4 mg	Place	bo		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Phase 2 trials							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applicab	le					
1.3.2 Phase 3 trials							
Morand 2023	66	258	66	253	50.1%	0.97 [0.66, 1.45]	
Petri 2023	75	252	59	256	49.9%	1.41 [0.95, 2.10]	
Subtotal (95% CI)		510		509	100.0%	1.17 [0.81, 1.69]	
Total events	141		125				
Heterogeneity: Tau ² =	0.03; Chi ² =	1.70, df	= 1 (P =	0.19); F	² = 41%		
Test for overall effect:	Z = 0.86 (P =	0.39)					
Total (95% CI)		510		509	100.0%	1.17 [0.81, 1.69]	
Total events	141		125				
Heterogeneity: Tau ² =	0.03; Chi ² =	1.70, df	= 1 (P =	0.19); F	² = 41%		0.2 0.5 1 2 5
Test for overall effect:	Z = 0.86 (P =	0.39)					0.2 0.5 1 2 5 Favours placebo Favours baricitinib 4 mg
Test for subaroup diff	erences: Not	applica	ble				Favours pracebo Favours banciumb 4 mg

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to placebo in increasing the odds for SRI-4 response (OR=1.11, 95% CI; 0.89-1.39, I² =0%, p=0.37), as shown in figure 1a. However, baricitinib 4 mg was associated with a significant increase in the odds for SRI-4 response, compared to placebo, by 42% $(OR=1.42, 95\% CI; 1.01-2.00, I^2 = 53\%)$ p=0.04), as shown in Figure 1B. Concerning the secondary efficacy outcome, neither baricitinib 2 mg (OR=1.02, 95% CI; 0.77 to 1.36, $I^2 = 0\%$, p=0.87), nor baricitinib 4 mg (OR=1.17, 95% CI; 0.81-1.69, I² =41%, p=0.39), were superior to placebo in increasing the odds for achievement of LLDAS, as depicted in Figures 1A and D, respectively. Overall, only baricitinib 4 mg was associated with a significant increase in the odds for SRI-4 response, compared to placebo; however, baricitinib, either at 2 mg or 4 mg dosing regimen, was not associated with a significant increase in the odds for achieving SRI-4 response and LLDAS response, compared to placebo. Therefore, it remains unclear whether this combined JAK 1/2 inhibitor can represent an effective treatment option for subjects with SLE, despite recent evidence suggesting a multitargeted mechanism of action, involving a network of genes in the JAK-STAT pathway, cytokines and type 1 interferons, all crucial in disease pathofenesis (8-10). Further RCTs are required to answer this interesting and important clinical question, which can open a new pathway in SLE therapeutics.

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