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
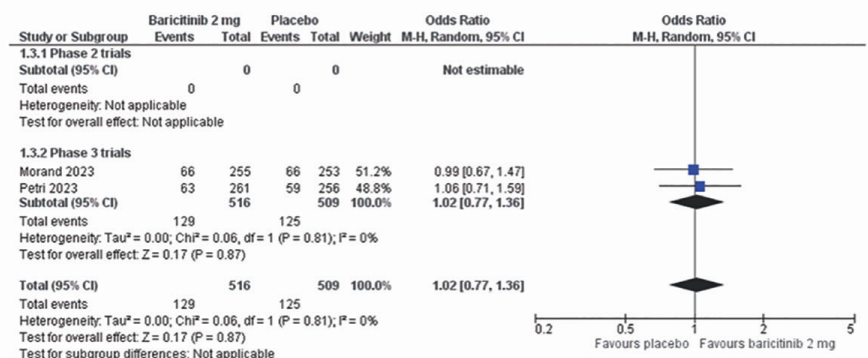

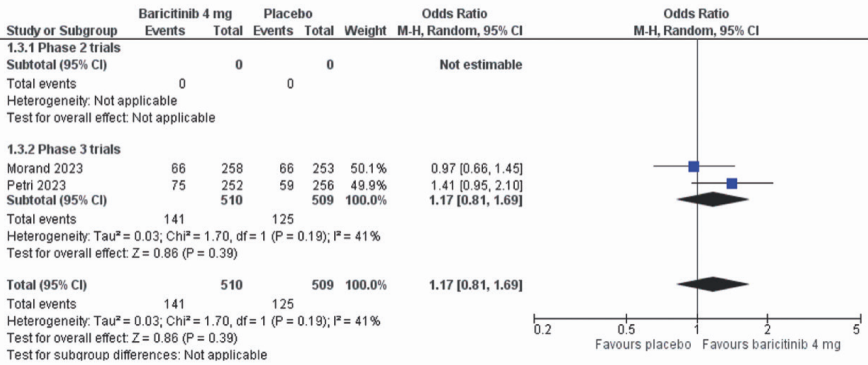Fig. 1A. Effect of baricitinib 2 mg *versus* placebo on the odds for SRI-4 response.
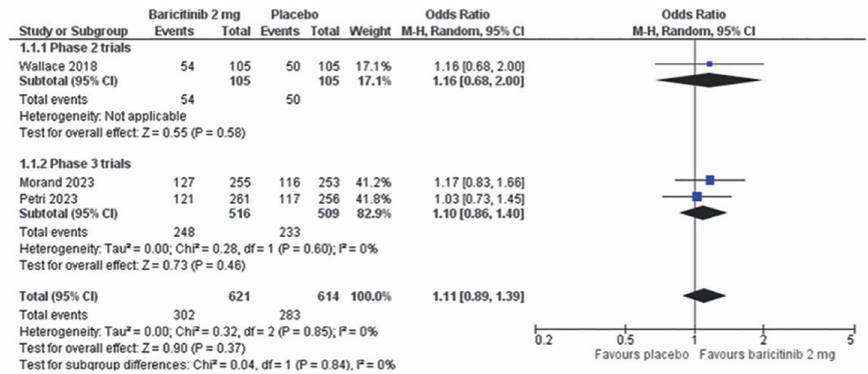
B: Effect of baricitinib 4 mg *versus* placebo on the odds for SRI-4 response.
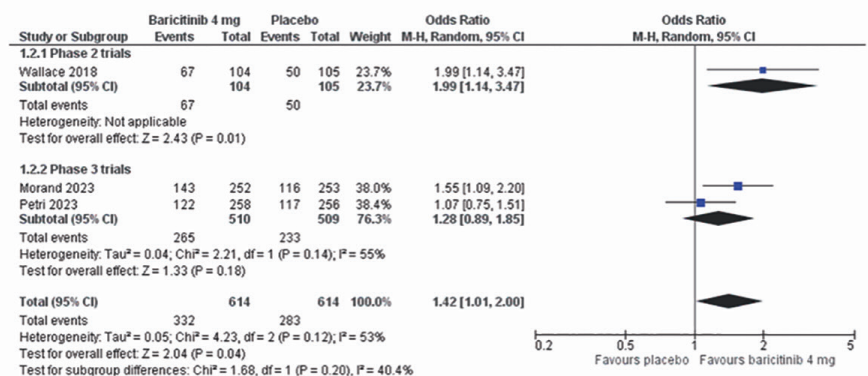
C: Effect of baricitinib 2 mg *versus* placebo on the odds for LLDAS response.

D: Effect of baricitinib 4 m*g versus* placebo on the odds for LLDAS response.

Letters to the Editors

to placebo in increasing the odds for SRI-4 response (OR=1.11, 95% CI; 0.89–1.39, I^2 =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, I^2 =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.

D. Patoulias[1], *MD, MSc, PhD*
A. Dimosiari[1], *MD, MSc*
T. Dimitroulas[2], *MD, MSc, PhD*

[1]*Second Department of Internal Medicine, European Interbalkan Medical Center, Thessaloniki, Greece;*
[2]*Fourth Department of Internal Medicine, Aristotle University of Thessaloniki, General Hospital Hippokration, Thessaloniki, Greece.*

Please address correspondence to:
Dimitrios Patoulias
Second Department of Internal Medicine,
European Interbalkan Medical Center,
Asklipiou 10,
57001 Thessaloniki, Greece.
E-mail: dipatoulias@gmail.com

Competing interests: none declared.

References

1. ARNAUL L, TEKTONIDOU MG: Long-term outcomes in systemic lupus erythematosus: trends over time and major contributors. *Rheumatology* (Oxford) 2020; 59(Suppl 5): v29-v38. https://doi:10.1093/rheumatology/keaa382
2. FANOURIAKIS A, TZIOLOS N, BERTSIAS G, BOUMPAS DT: Update on the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis* 2021; 80(1): 14-25. https://doi:10.1136/annrheumdis-2020-218272
3. FANOURAKIS A, KOSTOPOULOU M, ALUMNO A *et al.*: 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78(6): 736-45. https://doi:10.1136/annrheumdis-2019-215089
4. GOROPEVSEK A, HOLCAR M, PAHOR A, AVCIN T: STAT signaling as a marker of SLE disease severity and implications for clinical therapy. *Autoimmun Rev* 2019; 18(2): 144-54. https://doi:10.1016/j.autrev.2018.08.010
5. WALLACE DJ, FURIE RA, TANAKA Y *et al.*: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial [published correction appears in *Lancet* 2018; 392(10146): 476]. *Lancet* 2018; 392(10143): 222-31. https://doi:10.1016/S0140-6736(18)31363-1
6. MORAND EF, VITAL EM, PETRI M *et al.*: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). *Lancet* 2023; 401(10381): 1001-10. https://doi: 10.1016/S0140-6736(22)02607-1
7. PETRI M, BRUCE IN, DORNER T *et al.*: Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). *Lancet* 2023; 401(10381): 1011-19. https://doi: 10.1016/S0140-6736(22)02546-6
8. DORNER T, TANAKA Y, DOW ER *et al.*: Mechanism of action of baricitinib and identification of biomarkers and key immune pathways in patients with active systemic lupus erythematosus. *Ann Rheum Dis* 2022; 81(9): 1267-72. https://doi:10.1136/annrheumdis-2022-222335
9. DORNER T, TANAKA Y, PETRI MA *et al.*: Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial implicates a mechanism of action through multiple immune-related pathways. *Lupus Sci Med* 2020; 7(1): e000424. https://doi:10.1136/lupus-2020-000424
10. BERTSIAS G: Therapeutic targeting of JAKs: from hematology to rheumatology and from the first to the second generation of JAK inhibitors. *Mediterr J Rheumatol* 2020; 31(Suppl 1): 105-11. https://doi: 10.31138/mjr.31.1.105