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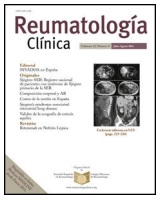

Review Article

Systematic review and network meta-analysis of interventions for articular involvement in patients with systemic lupus erythematosus

Revisión sistemática y metaanálisis en red de intervenciones para el compromiso articular en pacientes con lupus eritematoso sistémico

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ABSTRACT

Several immunosuppressive therapies beyond corticosteroids have demonstrated efficacy in controlling symptoms and reducing inflammation in lupus-related arthritis. The current standard of care (SOC) remains the combination of antimalarials and low-dose steroids, with the addition of other immunosuppressants in refractory cases. This study aimed to compare the efficacy of available biological and non-biological immunosuppressive therapies in controlling articular activity in patients with systemic lupus erythematosus (SLE). A systematic review and network meta-analysis were conducted following the PRISMA-NMA checklist (PROSPERO registration: CRD42024562392). Randomized controlled trials up to December 2023 evaluating biological and non-biological immunosuppressive treatments in lupus with articular involvement were included. Searches were performed in MEDLINE, EMBASE, LILACS, and SCIELO, including gray literature. Two reviewers independently selected studies, extracted data, and assessed risk of bias (RoB2). A fixed-effects frequentist model was applied using *netmeta*, estimating relative risks (RR), heterogeneity (I^2, τ^2), and efficacy *ranking* using *P-scores*. A total of 1635 records were identified, and five randomized controlled trials met inclusion criteria, comprising 1476 patients, 93.3% of whom were women, with a mean age of 40 years. Evaluated interventions included methotrexate, anifrolumab, and baricitinib, all compared to placebo. Three studies showed low risk of bias, while two presented some concerns in specific domains. The network meta-analysis revealed no significant heterogeneity (Q = 2.44; *P* = .29) or inconsistency between designs, though global inconsistency was detected by netsplitting analysis. No statistically significant differences in efficacy were observed among the evaluated treatments. In the exploratory *ranking* analysis, *P-scores* indicated that methotrexate (*P-score* = 1.0), baricitinib (*P-score* = .62), and anifrolumab (*P-score* = .37) were numerically positioned at the top of the *ranking*. Nevertheless, these estimates represent probabilistic rather than inferential measures and should therefore be interpreted with caution. Meta-regression did not identify a significant influence of risk of bias on the results (*P* = .42), although substantial residual heterogeneity was observed (I^2 = 98.8%), which limits the comparative interpretation of treatment efficacy.

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Palabras clave:
Lupus eritematoso sistémico
Manifestaciones musculoesqueléticas
Análisis en red de tratamientos

RESUMEN

Existen diversas terapias inmunosupresoras para el lupus articular más allá de los corticoides que han demostrado utilidad en el control de los síntomas y disminución de la respuesta inflamatoria; el «*standard of care*» (SOC) continúa siendo la combinación de antimaláricos más esteroides a bajas dosis y en caso

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de refractariedad a este SOC, la terapia combinada con otros inmunosupresores. Nuestro objetivo fue comparar la eficacia en el control de la actividad articular con las diferentes terapias inmunosupresoras biológicas y no biológicas disponibles en el tratamiento de LES. Se realizó una revisión sistemática y metaanálisis en red siguiendo la lista de chequeo *Preferred Reporting Ítems for Systematic Reviews and Meta-Analysis* (PRISMA) -NMA (PROSPERO: CRD42024562392). Se incluyeron ensayos clínicos hasta diciembre de 2023 que evaluaran tratamientos inmunosupresores biológicos y no biológicos en lupus con compromiso articular. La búsqueda se efectuó en Medline, EMBASE, LILACS y SciELO, incluyendo literatura gris. Dos revisores realizaron la selección, extracción y evaluación del riesgo de sesgo (RoB2). Se aplicó un modelo de efectos fijos con enfoque frecuentista mediante netmeta, estimando riesgos relativos (RR), heterogeneidad (I^2, τ^2) y *ranking* de eficacia por *P-score*. Se identificaron 1.635 estudios, de los cuales cinco fueron ensayos clínicos aleatorizados, incluyeron 1.476 pacientes, de los cuales el 93,3% fueron mujeres, con una media de edad 40 años. Las intervenciones evaluadas fueron: metotrexate (MTX), anifrolumab (Ani) y baricitinib, todas comparadas con placebo. En la evaluación del riesgo de sesgo, tres estudios presentaron bajo riesgo y dos mostraron alguna preocupación en dominios específicos. El metaanálisis en red no evidenció heterogeneidad individual significativa (Q = 2,44; *P* = ,29) ni inconsistencia entre diseños, pero si en la evaluación global por *netsplitting*. No se observaron diferencias estadísticamente significativas en la eficacia entre los tratamientos evaluados. En el análisis exploratorio de jerarquización, los *P-scores* mostraron que MTX (*P-score* = 1,0), baricitinib (*P-score* = ,62) y Ani (*P-score* = ,37) se posicionaron numéricamente en los primeros lugares del *ranking*; sin embargo, estas estimaciones representan una medida probabilística y no inferencial, por lo que deben interpretarse con cautela. La metarregresión no identificó una influencia significativa del riesgo de sesgo sobre los resultados (*P* = ,42), aunque se observó una heterogeneidad residual elevada (I^2 = 98,8%), lo que limita la interpretación comparativa de la eficacia entre tratamientos.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of variable severity, in which joint involvement occurs at least once in up to 48.1% of cases[1] in a cohort of European patients and up to 93.2% according to reports from the GLADEL cohort.[2] Joint manifestations in SLE can range from very mild forms such as arthralgia to more severe and deforming non-erosive arthropathies in 42% of cases.[3] Jaccoud's arthropathy is a type of non-erosive, deforming arthritis resulting from persistent synovitis and fibrotic retraction of the joint capsule, which produces reversible deformities. It has been described with a prevalence of 6% in patients with SLE,[4] with a tendency towards lower quality of life compared to patients without this arthropathy.[5] It has also been shown to behave as an independent variable associated with poorer quality of life in the physical and mental domains of the SF-36v2.[6]

Various immunosuppressive therapies beyond corticosteroids have proven useful in controlling symptoms and reducing the inflammatory response in the treatment of joint manifestations in SLE. The standard of care (SOC) in the treatment of musculoskeletal manifestations in SLE continues to be the combination of antimalarials (hydroxychloroquine [HCQ]) plus low-dose steroids (<7.5 mg of prednisolone or equivalents for a short period of time) and in case of refractoriness to this SOC, combination therapy with other immunosuppressants such as methotrexate (MTX), leflunomide (LFN), belimumab (Bel) or abatacept (Aba) are recommended.[7] Furthermore, the EULAR guidelines suggest that all patients with SLE should receive HCQ at a dose of 5 mg/kg/day unless contraindicated. For those who do not respond to monotherapy and cannot reduce their corticosteroid dose, the addition of other immunosuppressants such as MTX, azathioprine (AZA), mycophenolate (MMF), or biologic agents such as Bel or anifrolumab (Ani) should be considered.[8] However, these recommendations are specific to joint involvement.

There are few comparative studies among the different immunosuppressants available for managing joint manifestations, which would clarify the best treatment option for this type of involvement in SLE. However, MTX has shown good results in controlling morning stiffness and is as effective as HCQ in controlling arthritis in SLE.[9]

Biological therapies explored in the articular domain of the disease include Bel, a B-cell stimulatory factor (BlyS) inhibitor, which demonstrated efficacy in reducing joint activity as measured by DAS28 and SLEDAI 2K[10] scores. Aba, a fusion protein that selectively inhibits the co-stimulation of CD80/86 receptors with CD28, has been explored in a series of SLE patients overlapping with rheumatoid arthritis (rhupus), showing a significant decrease in activity scores and C-reactive protein (CRP) levels.[11] Ani, a monoclonal antibody that inhibits type I interferon subunit 1, has demonstrable efficacy in reducing musculoskeletal involvement versus placebo (56% vs. 44%) as well as reducing the number of swollen joints at week 52.[12]

Due to the limited information comparing the best pharmacological strategy for treating joint involvement in patients with SLE, this network meta-analysis was conducted to evaluate the direct and indirect evidence for the available biological and non-biological immunosuppressive therapies, with the aim of proposing a ranking based on clinical efficacy. Our objective was to compare the efficacy of the different biological and non-biological immunosuppressive therapies available for the treatment of SLE in controlling joint activity.

Methodology

- Protocol and registration: This protocol was designed using the checklist in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) – NMA guidelines, which include a review of network meta-analyses.[13] It was registered in PROSPERO with registration code: CRD42024562392.
- Eligibility criteria:
  - ○ Study types: Randomised controlled clinical trials and cohort studies were included up to December 2023, including grey literature, in English and Spanish.

○ Participant types: Patients diagnosed with SLE with joint involvement and/or musculoskeletal manifestations.

○ Intervention types: The following interventions were included in the network: non-biologic immunosuppressive treatments: HCQ, MTX, AZA, LFN, cyclosporine A; biologic immunosuppressive treatments: Bel, Aba, rituximab, Ani; and placebo. All were included in different nodes, except for studies comparing dose differences, which were incorporated into the same node corresponding to the intervention molecule.

○ Outcome type:

Primary: Proportion of patients achieving a reduction in the inflammatory response in the joint domain. Given the high heterogeneity in the determination of response across different studies, the joint domain was operationalised using clinical outcomes that explicitly included the improvement of musculoskeletal manifestations.

Secondary: Proportion of patients with adverse events and serious adverse events.

• Information sources

Study identification and data extraction were performed by searching the Medline Central (Cochrane Central Register of Controlled Trials), EMBASE, LILACS, and SciELO databases from January 1993 to December 2023. Filters were applied to select randomised controlled trials and cohort studies. The search strategy used the following MeSH terms as keywords: (((((((lupus erythematosus, systemic)) AND (joints)) AND (therapeutics)) AND (placebo)) AND (treatment outcome). The search was limited to studies published in English and Spanish, and included grey literature or literature not formally published in CADTH Gray Matter.[14]

• Data collection procedures

Information on the titles of potentially included studies was registered through the RAYYAN Intelligent Systematic Review platform.[15] These studies were subsequently assessed independently by at least two reviewers (CG, JT) based on eligibility criteria and following the CONSORT[16] guidelines for randomised controlled trials and the CARE guidelines for case reports.[17] Abstracts of selected articles were submitted for further independent review, and in case of disagreement, a third review (JM) was included. The following information was extracted from the full text of the articles chosen for the meta-analysis:

1 General information: reference number, author, year of publication, journal, and country.
2 Study information: study design and randomisation.
3 Patient information: age, disease duration, overlap with rheumatoid arthritis (rhupus), arthralgia, and Jaccoud's arthropathy (non-erosive/deforming).
4 Type of intervention: non-biologic immunosuppressants: HCQ, AZA, MTX, LFN, cyclosporine A; biologic immunosuppressants: Bel, Aba, rituximab, Ani, and placebo.
5 Outcomes: proportion (%) of patients achieving remission of the joint domain according to the criteria defined in each study; proportion of adverse events for each intervention.

• Network geometry

The "netmeta" package was used to identify the treatment network in order to visualise and analyse the connected comparison networks. Five studies were included: Wallace et al. (2018),[18] Furie et al. (2017, 2019),[19,20] Morand et al. (2020),[12] and Carneiro et al. (1999).[21] All trials presented paired comparisons and included three main treatments: baricitinib, Ani, and MTX.

Risk of bias assessment

The risk of bias was assessed for each study individually using the RoB2 tool for randomised controlled trials, considering the following domains: random sequence generation, allocation concealment, participant blinding, blinding of study assessors, incomplete outcome data, and selective reporting of results. These domains were assessed independently by two evaluators (CG, JT), and in case of disagreement, a third evaluator (JM) defined the level of bias. Assessments were reported as "low risk," "some concern," or "high risk." The assumption of transitivity between studies was assessed by evaluating the consistency of effect measures in comparisons.

Summary measures

Summary measures were included based on the effect measurement, taking the relative risk (RR) and estimating the standard error for each study. To estimate the direct and indirect effect measures between interventions in the network, a fixed-effects model was applied under a frequentist approach. Heterogeneity between studies was assessed using the Tau2 statistic and the Q statistic (heterogeneity test), considering heterogeneity with a *P*-value <.1. The proportion of heterogeneity was estimated using the I^2 index, interpreting values greater than 50% as indicative of significant heterogeneity. Cochran's Q value was obtained to estimate consistency within studies, between studies, and between designs, considering inconsistency with *P*-values greater than .05 for individual studies. To assess the proportion of direct and indirect evidence, minimum parallelism and mean path length were used. To evaluate the ranking of the best treatment in terms of efficacy, it was estimated using the *P*-score, with higher values considered as the best treatment in terms of efficacy.

• Statistical analysis

A frequentist model was estimated using fixed effects. The effect of direct and indirect interventions was estimated from the effects matrix. The results were expressed as relative risk (RR) with 95% confidence intervals (CI) and p-value estimates.

Comparisons were made using RR as the measure of effect. All estimates were analysed on a logarithmic scale (log-RR), which allowed for the estimation of standard errors, 95% CI, and statistical significance values. The results were subsequently transformed back to the original scale using the exponential function for presentation. A continuity correction of .5 was applied to cells with zero events.

• Consistency assessment:

Individual consistency within studies, between designs, and between studies was assessed using Cochrane's Q test.

Overall consistency was assessed using netsplitting and a forest plot. Inconsistency between direct and indirect evidence was defined as a *P*-value <.05.

Results

Qualitative analysis of the systematic review

A total of 1635 articles were identified through the systematic search, of which only five met the eligibility criteria (Fig. 1)

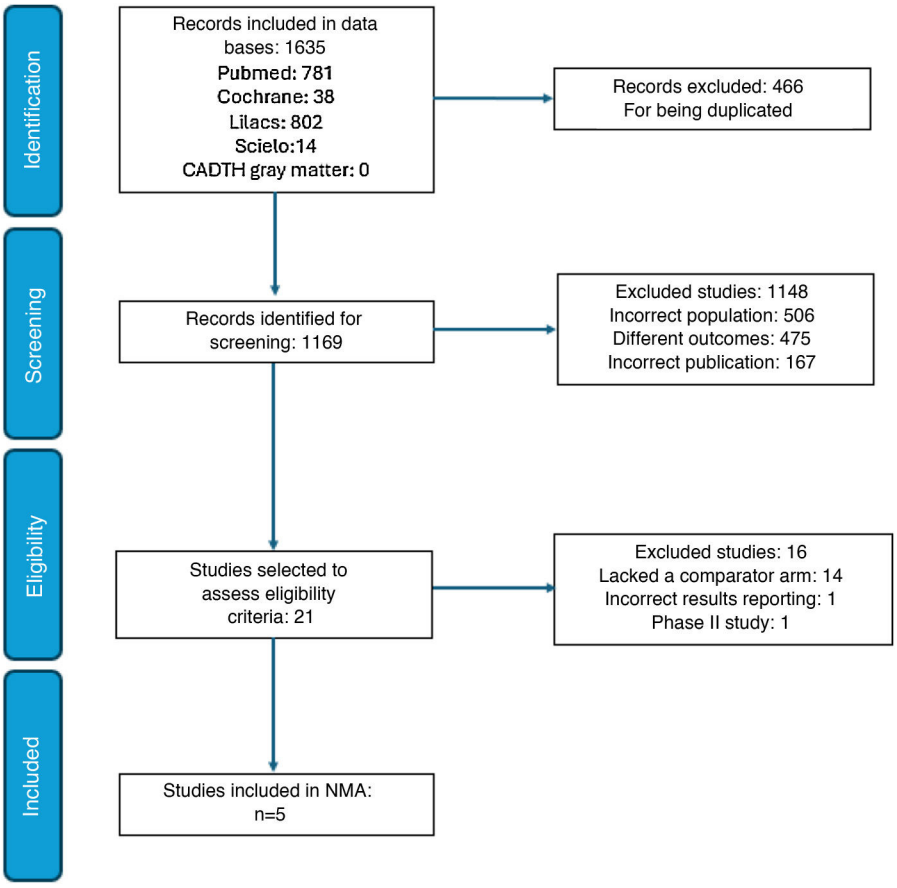

Fig. 1. Article selection process.

and were included in the network meta-analysis (NMA). A total of 1476 patients were analysed, of whom 1378 (93.3%) were women. The mean age was 40 years (SD: 5.25) and the median disease duration was 7.9 years (IQR: 3.82). All included studies were randomised controlled trials evaluating the following interventions: MTX (Carneiro et al., 1999),[21] Ani (Morand et al., 2020[12]; Furie et al., 2019[20]; Furie et al., 2017[19]), and baricitinib (Wallace et al., 2018)[18], with placebo as the comparator arm (Table 1). The inclusion of cohort studies had been considered, but when selecting studies according to eligibility criteria, these observational studies did not meet the selection criteria due to the heterogeneity in response outcomes.

To assess the transitivity assumption, the main clinical and methodological characteristics of the studies included in each node of the network were compared (Table 2). Overall, the studies showed clinically comparable populations in terms of age, sex, baseline disease activity, and concomitant use of standard treatment. Since the outcomes were assessed using heterogeneous composite instruments, the measurement of joint involvement was approached from a clinical perspective, specifically considering the musculoskeletal domain common to these instruments. This approach allowed for the evaluation of an equivalent clinical construct across the included studies, supporting the plausibility of the transitivity assumption.

In the risk of bias assessment, the studies by Wallace et al. (2018),[18] Furie et al. (2017)[18] and Carneiro et al. (1999)[21] were classified as "low risk." However, the latter presented "some concern" in domain 2: "deviations from planned interventions." On the other hand, the studies by Furie et al. (2019)[20] and Morand et al. (2020)[12] were rated as having "some concern" in domain 5: "selection of reported outcomes" (Fig. 2).

Quantitative analysis: network meta-analysis

- Heterogeneity and inconsistency

In the evaluation of heterogeneity and inconsistency of the network meta-analysis, no significant evidence of global heterogeneity was found (Q = 2.44, $P = .29$) nor inconsistency between the study designs (Q between = 0); thus, all heterogeneity was attributed to variations within designs (Q within-designs = 2.44; $P = .296$), likewise the variance between studies $\tau^2 = .0226$ ($\tau = .15$), the I^2 statistic was 17.9%, which suggests a reduced proportion of the variability attributable to real heterogeneity, although with a wide CI (.0%–91.5%), probably related to the limited number of studies included. These data showing low heterogeneity and inconsistency support the use of fixed-effects models in the network meta-analysis. A sensitivity analysis was also performed by replicating both the fixed and random models, and by excluding each study without observing significant changes in the effect size.

When assessing the individual impact of the studies included in the network meta-analysis, the study by Morand et al. (2020)[12] was found to have the greatest contribution to overall heterogeneity

Table 1
Summary of randomised controlled trials.

Year	Author	Country	Intervention	Control	Outcome	Result
1999	Carneiro et al.[21]	Brazil	Methotrexate	Placebo	Proportion of patients with cutaneous, renal, haematologic, and vascular joint manifestations at the end of 6 months of follow-up	Joint manifestations: 1/20 en methotrexate (5.5%) vs. 16/21 (84.2%) placebo $P < .001$* Cutaneous manifestations: 3/20 Methotrexate (16.6%) vs. 16/21 (84.2%) in placebo $P < .001$* Proteinuria: 1/20 Methotrexate (5.4%) and 4/21 (21%) in placebo $P = .18$ Haematuria: 1/20 Methotrexate (5,4%) y 4/21 (21%) en placebo $P = .18$
			n = 20	n = 21		
2017	Furie et al.[19]	USA	Anifrolumab 300 mg	Placebo	Proportion of patients reaching SRI-4 at week 24 and week 52	Week 24: Placebo 18/102 (17.6%) vs. Anifrolumab 300 mg 34/99 (34.3%) OR 2.38 95% CI (1.3- 4.2) $p = .014$*
			n = 99	n = 102		Placebo 18/102 (17.6%) vs. Anifrolumab 1.000 mg 30/104 (28.8%) OR 1,94 95% CI (1.08- 3.49) $P = .063$
			Anifrolumab100 mg			Week 52: Placebo 26/102 (25.5%) vs. Anifrolumab 300 mg 51/99 (51.5%) OR 3.08 95% CI (1.86- 5.09) $P < .0001$* Placebo 26/102 (25.5%) vs. Anifrolumab 1.000 mg 40/104 (38.5%) OR 1.84 95% CI (1.11- 3.404 $P = .048$*
			n = 104			
2018	Wallace et al.[18]	USA	Baricitinib 2 mg	Placebo	Proportion of patients with resolution of arthritis or rash through SLEDAI −2 K at week 24.	baricitinib 4 mg: Resolution in 70/104 (67%) vs. 56/105 of placebo (53%). OR 1.8 95% CI 1–3.3 $P = .0414$*
			n 105	n = 105	Proportion of patients responding to the SRI-4 index (Decrease of at least 4 points in SLEADI-SK, no deterioration in BILAG A/B)	baricitinib 2 mg: Resolution in 61/105 (58%) vs. 56/105 of placebo (53%). OR 1.3 95% CI .7–2.3; $P = .39$
			Baricitinib 4 mg		No increase in the Physician's Global Assessment of Disease Activity (PGA).	SRI-4 total (> SLEDAI + > BILAG + No impairment PGA): Placebo 50/105 (48%) vs. baricitinib 2 mg 54/105 (51%) OR 1.3 95% CI (.7–2.2) $P = .44$ Placebo 50/105 (48%) vs. baricitinib 4 mg 67/104 (64%) OR 2 95% CI (1.2 – 3.6) $P = .0151$*
			n 104			
2019	Furie et al.[20]	Germany	Anifrolumab 150 mg	Placebo	Proportion of patients achieving the SRI-4 response index at week 52.	Proportion of patients achieving the SRI-4 response index at week 52: Placebo 74/184 (40%) vs. Anifrolumab 150 mg 65/180 (36%) OR −4.2 95% CI −14.2 to 5.8 $P = .41.2$
			n = 93	n = 184	SRI-4 at week 52 in patients with high type I interferon genes	Placebo 79/184 (43%) vs. Anifrolumab 300 mg 84/180 (47%) OR 3.9 95% CI −6.3 to 14.1 $P = .45$
			Anifrolumab 300 mg		SRI-4 at week 24	SRI-4 at week 52 in patients with high type I interferon genes: Placebo 59/151 (39%) vs. Anifrolumab 150 mg 53/148 (36%) OR −3.4 95% CI −14.4 to 7.6 $P = .54$ Placebo 53/151 (42%) vs. Anifrolumab 300 mg 71/148 (48%) OR 6.4 95% CI −4.8 to 17.7 $P = .26$ SRI-4 at week 24: Placebo 75/184 (41%) vs. Anifrolumab 150 mg 74/180 (42%) OR .6 95% CI −9.4 to 10.6 $P = .905$ Placebo 79/184 (43%) vs. Anifrolumab 300 mg 83/180 (46%) OR 3.3 95% CI −6.7 to 13.4 $P = .515$ Steroid dose reduction at week 52: Placebo 33/102 (32%) vs. Anifrolumab 150 mg 42/103 (41%) OR 8.9 95% CI −4.4 to 21.9 $P = .,180$ Placebo 33/102 (32%) vs. Anifrolumab 300 mg 50/103 (49%) OR 16.7 95% CI 3.5–29.8 $P = .013$* Decrease > 50% in CLSI activity at week 12 from baseline: Placebo 14/54 (25%) vs. Anifrolumab 150 mg 24/58 (42%) OR 17 95% CI −.3 to 34,3 $P = .054$ Placebo 14/54 (25%) vs. Anifrolumab 300 mg 25/58 (44%) OR 18.7 95% CI 1.4–36 $P = .034$* Annual flare rate at week 52: Placebo .72 vs. Anifrolumab 150 mg .6 (OR .83) 95% CI .60–1.14 $P = .25$ Placebo .72 y Anifrolumab 300 mg .6 OR .83 .60–1.14 $P = .25$

Table 1
(*Continued*)

Year	Author	Country	Intervention	Control	Outcome	Result
			n = 180		Steroid dose reduction at week 52 Decrease > 50% in CLSI activity at week 12 compared to baseline Decrease> 50% in CLSI activity at week 12 compared to baseline	
2020	Morand et al.[12]	Australia	Anifrolumab 150 mg	Placebo	Response at week 52 with the use of BILAG and BICLA.	Response at week 52 using the BILAG, BICLA: Placebo 57/182 (31.5%) vs. Anifrolumab 86/180 (47.8%) OR 16.3 95% CI 6.3–26.6 *P* = .001*
			n = 180	n = 182	Decrease in steroid dose to target dose at weeks 40–52.	Decrease in steroid dose to target dose in weeks 40–52: Placebo: 46/151 (30.7%) vs. Anifrolumab 72/150 (48%) OR 17.3 CI 6.5–28.2 *P* = .002*
					Decrease in CLASI activity by more than ≥ 50% of baseline at week 12.	Decrease in CLASI activity by more than ≥ 50% of baseline at week 12: Placebo: 10/40 (25%) vs. Anifrolumab 24/49 (49%) OR 24 CI 4.3–43.6 *P* = .04*
					Decrease of more than 50% in joint inflammation and pain compared to baseline at week 52	Decrease of more than 50% in joint inflammation and pain from baseline at week 52: Placebo: 34/90 (37.5%) vs. Anifrolumab 30/71 (42.2%) OR 4.7 CI −10.6 to 20 *P* = .55
					Annual flare rate at week 52.	Annual flare rate at week 52: Placebo .64 vs. Anifrolumab .43 OR .67 CI −.4 to .94 *P* = .05

BILAG: British Isles Lupus Assessment Group; BICLA: BILAG-based composite lupus assessment; SRI-4: Systemic Lupus Erythematosus Response Index.
* Statistical significance. Odds ratios (ORs) were converted to risk ratios (RRs) for network meta-analysis. A continuity correction of .5 was applied to studies with cells containing zero events. Multi-arm trials were treated using standard network meta-analysis methods to avoid double counting of participants.

Table 2
Qualitative assessment of transitivity.

Comparison	Number of studies	Number of patients	Average age	Proportion of women	SLEDAI average	Follow-up time	Operationalisation of the outcome variable of joint improvement
Methotrexate vs. placebo	1	41	31,2	95%	8,7–9,4	330 weeks	Number of patients with joint manifestations SLEDAI (joint domain)
Anifrolumab vs. placebo	3	(Furie) 305 (Morand) 305	18–70 39	93%	11 11	52 weeks	SLEDAI (joint domain) BILAG (musculoskeletal domain)
		(Furie) 457	43		11		SRI-4 (joint domain) Number of tender and swollen joints
Baricitinib vs. placebo	1	314	44	94%	8,9	24 weeks	Proportion of patients who achieved resolution of arthritis Number of tender and swollen joints

(Q = .76), whilst the studies by Wallace et al. (2018)[18] and Carneiro et al. (1999)[21] showed the greatest influence on the model, with a leverage value of =1.00, indicating high sensitivity of the model to these studies (Fig. 3).

- Network meta-analysis structure

A network was constructed that included three designs and four treatments, in which the interventions with direct comparisons were Ani, baricitinib, and MTX, using placebo as the common comparator arm. Three direct comparisons were identified (Ani vs. placebo, baricitinib vs. placebo, and MTX vs. placebo), from which three indirect comparisons were derived: Ani vs. MTX, baricitinib vs. MTX, and Ani vs. baricitinib, all with placebo as the common connector (Fig. 4).

To identify the network structure, two metrics were evaluated: minimum parallelism and average path length. Minimum parallelism indicates the number of independent paths between treatments. In this analysis, all indirect comparisons showed a value of 1, reflecting a single connecting path. For its part, the average length of the paths represents the average number of steps needed to connect each pair of treatments: direct comparisons showed a length of 1, while indirect comparisons showed a length of 2, which shows a greater degree of structural separation in the network (Fig. 5).

- Efficacy outcome

When analysing the effect matrix between interventions (MTX, Ani, baricitinib) using a fixed-effects model and frequentist analy-

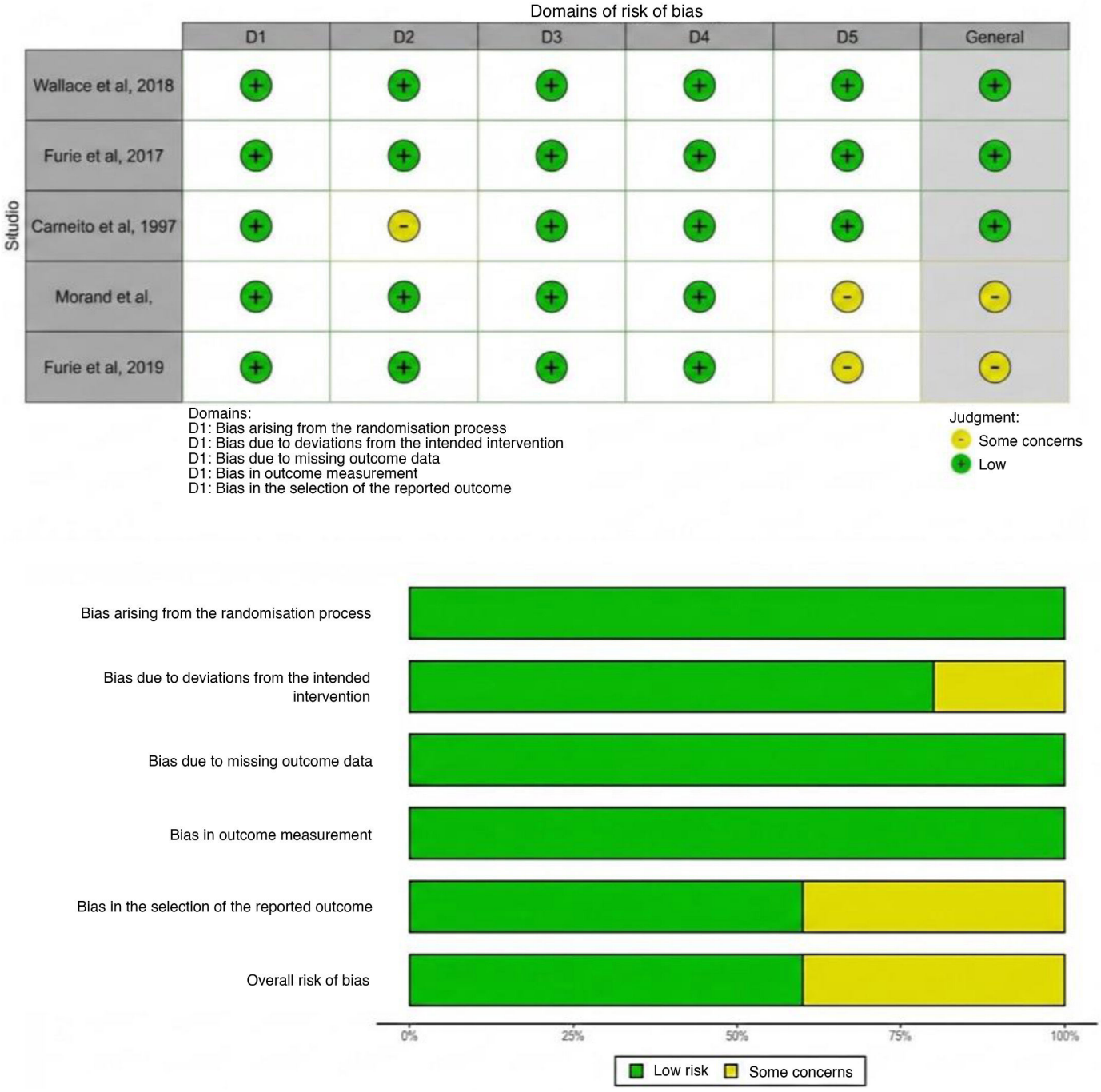

Fig. 2. Evaluation of bias risk (RoB 2.0).

sis, no statistically significant differences in efficacy were observed among the treatments evaluated. In the exploratory ranking analysis, the *P*-scores showed that MTX (*P*-score = 1.0), baricitinib (*P*-score = .62), and Ani (*P*-score = .37) ranked highest numerically. However, these estimates represent a probabilistic, not inferential, measure and should therefore be interpreted with caution. The meta-regression did not identify a significant influence of risk of bias on the results ($p = .42$), although high residual heterogeneity was observed ($I^2 = 98.8\%$), which limits the comparative interpretation of efficacy between treatments. No statistically significant differences were found to suggest the superiority of one intervention over the other (Table 3). The limited magnitude of the effect observed among the active comparisons may be related to the fact that they were all based on indirect evidence derived from a common comparator, which was the placebo. This increases uncertainty and could attenuate the effect, among other probable causes, such as the limited number of studies and the comparable efficacy of the interventions in managing the disease.

- Treatment ranking: *P*-score

For the exploratory evaluation of the treatment ranking in the control of the joint manifestations of SLE, P-scores were estimated using a fixed-effects model. In this analysis, MTX (P-score = 1.0) and baricitinib (P-score = .62) ranked highest. However, given that P-scores represent a probabilistic, not inferential, measure, and considering the presence of inconsistency in the network, these

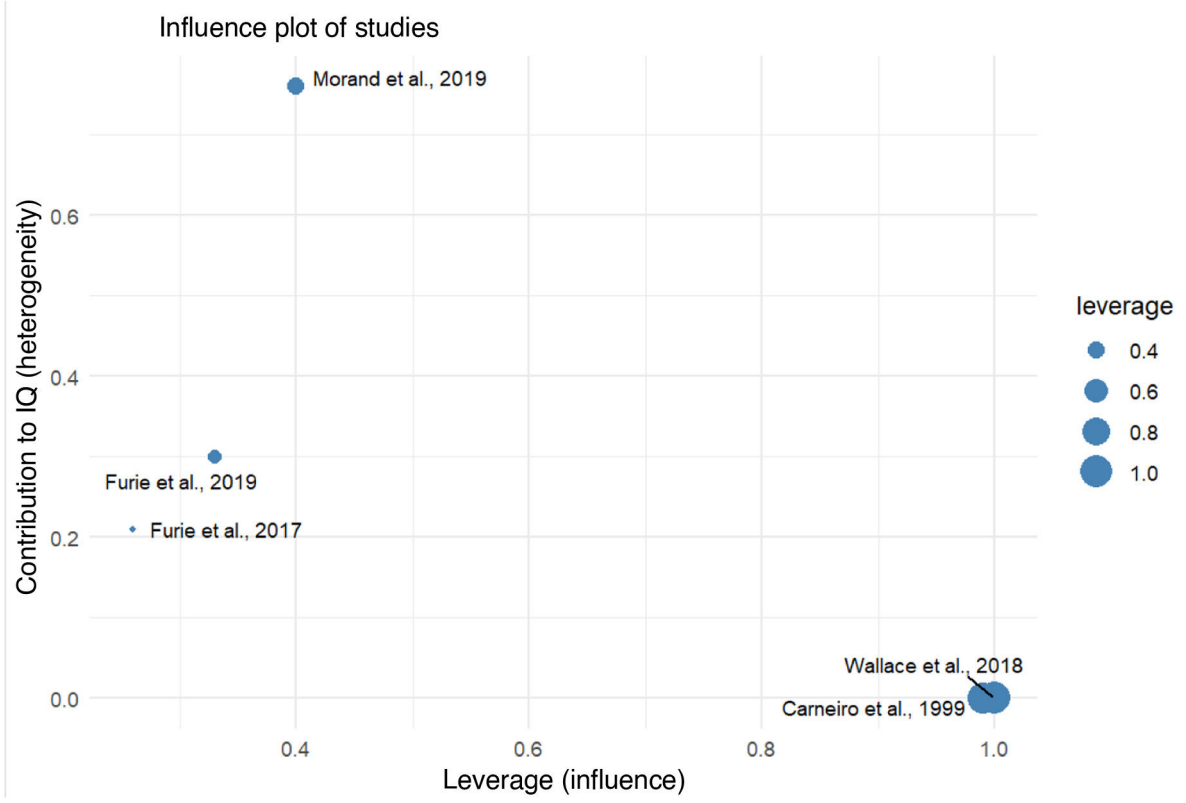

Fig. 3. Influence plot of studies on heterogeneity.

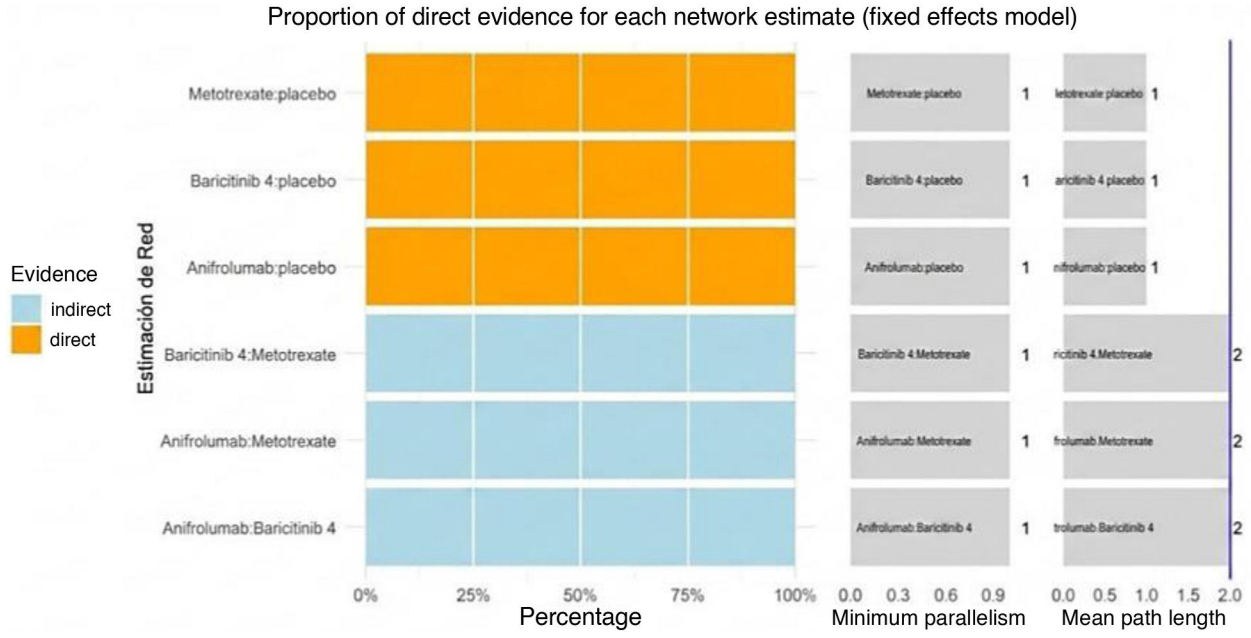

Fig. 5. Proportion of direct and indirect evidence in the fixed-effects model.

results should be interpreted with caution and only as a descriptive complement to the direct and indirect effect estimates (Table 4).

- Evaluation of inconsistency using netsplitting

The consistency between direct and indirect comparisons was evaluated using netsplitting. A significant inconsistency was found with p-values<.05 for five of the six comparisons, demonstrating relevant discrepancies between the effect measures estimated in the direct comparison trials and the indirect estimates obtained through the network. The only comparison that did not show inconsistency was that of baricitinib vs. Ani, indicating good agreement between the direct and indirect evidence for this comparison (Fig. 6). The inconsistency found in most of the comparisons assessed suggests that estimates derived from indirect evidence should be interpreted with caution, particularly in a network

Table 3
Intervention effect matrix.

	Anifrolumab RR (95% GIR)	baricitinib RR (95% CIR)	Methotrexate RR (95% CIR	Placebo RR (95% CIR)
Anifrolumab	1	.99	.95	1.01
RR		(.25–3.93)	(.46–1.92)	(.57–1.78)
(95% GIR)		*P* = .99	*P* = .89	*P* = .97
baricitinib	1.0	1	.95	1.01
RR	(.53–1.87)		(.24–3.75)	(.49–.04)
(95% CIR)	*P* = .99		*P* = .94)	*P* = .97
Methotrexate	1.04	1.04	1	1.05
RR	(.59–1.85)	(.55–1.96)		(.26–2.04)
(955 CIR)	*P* = .87	*P* = .88		*P* = .93
Placebo	.98	.98	.94	1
RR	(.48–2.0)	(.55–1.74)	(.50–1.76)	
(95% CIR)	*P* = .97	*P* = .96	*P* = .84	

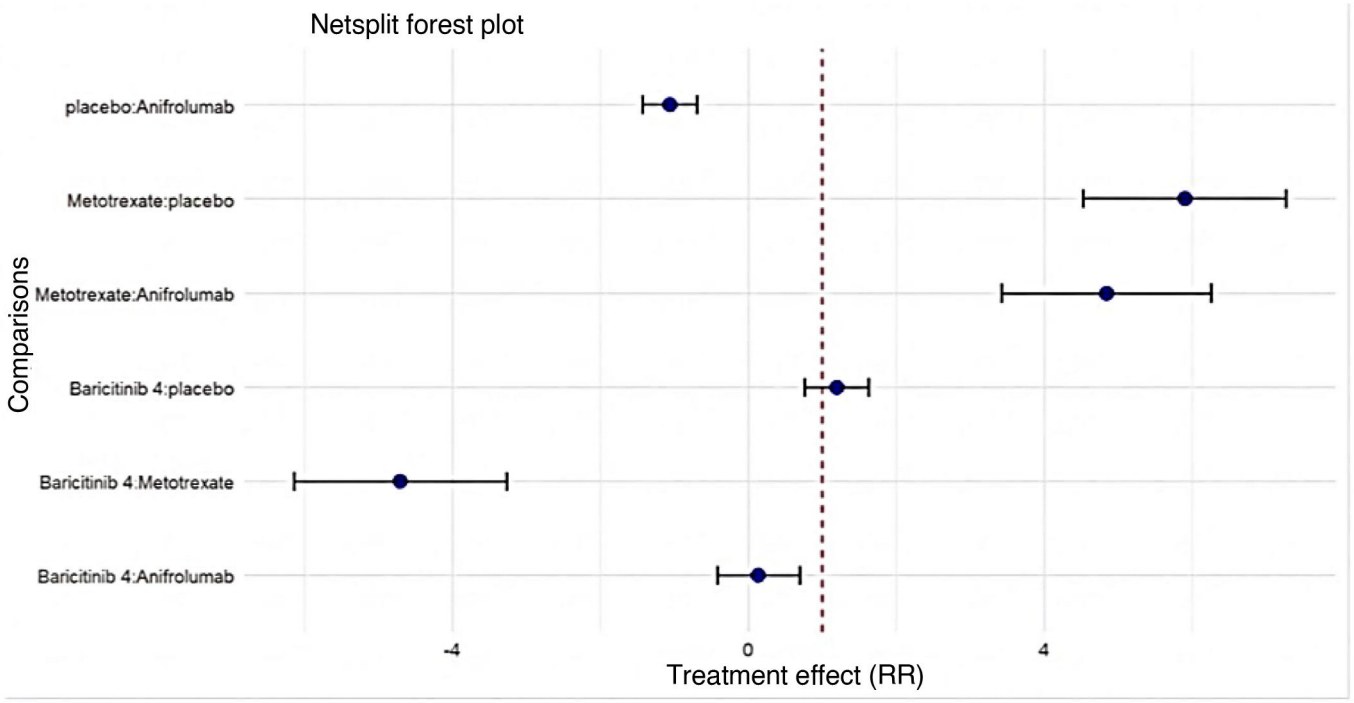

Fig. 6. Consistency assessment by netsplitting.

Table 4
Treatment ranking.

Intervention	*P*-score
Methotrexate	1.00
Baricitinib	.62
Anifrolumab	.37
Placebo	0

with limited connectivity and clinical heterogeneity among the included studies. These discrepancies may be related to differences in outcome definitions, trial design, concomitant use of standard treatment, and baseline disease activity—factors that could not be uniformly controlled due to limitations in the original reporting of the studies. In this context, netsplitting allowed for the identification of comparisons with greater uncertainty, reinforcing the need to consider the results of the network meta-analysis as exploratory and complementary to the available direct evidence, rather than as definitive estimates of superiority between interventions.

- Meta-regression

A meta-regression was performed to assess how the risk of bias modifies the effect size. This was done using a restricted maximum likelihood (REML) method in a mixed-effects model. Considerable residual heterogeneity was observed ($\tau^2 = 4.51$, $I^2 = 98.8\%$), which was statistically significant (QE[df = 3] = 45.10, $P < .0001$).

When assessing the moderating effect of the risk of bias, no statistically significant effect was found (QM[df = 1] = .64, $P = .42$). Although studies with a bias assessment of "some concern" could reduce the effect by −1.56 times, this estimate was not significant ($P = .42$).

The high heterogeneity observed ($I^2 = 98.8\%$) suggests significant variability among the studies, which cannot be attributed to chance. Despite assessing the risk of bias as a potential moderator, it did not significantly explain the observed variability. This suggests

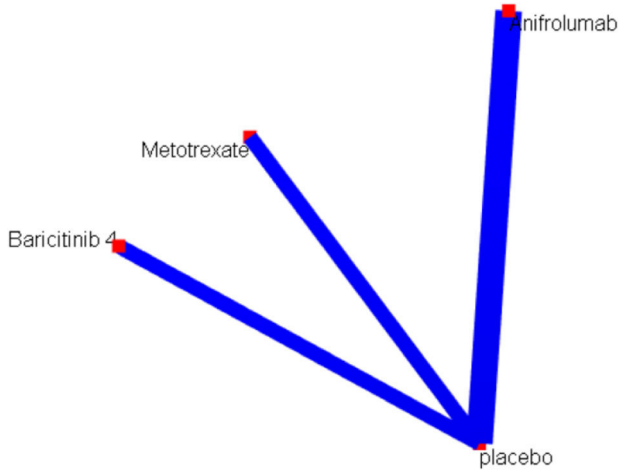

Fig. 4. Network structure.

that other factors, such as clinical or methodological differences between studies, could be contributing to the inconsistency of the estimated effects.

Discussion

The treatment of joint manifestations in lupus includes limited evidence regarding joint count control for both synthetic and biologic disease-modifying antirheumatic drugs (DMARDs). Our research demonstrated only three direct comparisons, from which three indirect comparisons were obtained with high inconsistency. This may be attributed to the small number of studies, as well as methodological differences among them.

Treatment with Ani was the biologic with the most direct comparisons to placebo in the treatment network, given that its outcomes include joint response. Among the pivotal studies, TULIP-1 demonstrated a 50% reduction in the count of swollen and tender joints, numerically favouring the Ani 300 mg group versus placebo by 47% vs. 32%,[20] although it did not reach the primary outcome of the SLE Response Index (SRI-4), and it was not assessed whether the differences were statistically significant at the joint level.

The results regarding overall disease control favoured Ani in the TULIP-212 trial, where, at week 52 in the BILAG-based composite assessment (BICLA), efficacy was achieved in 47.8% for the Ani 300 mg group versus 31.5% in the placebo group (difference 16.5%, 95% CI 6.2–26.3%, $P = .001$). However, when specifically evaluating the joint domain in the reduction of swollen and tender joint counts, it remained higher in the Ani group at 42.2% versus 37.5%, but without statistical significance. These joint component variables were not evaluated in the three-year TULIP-LTE extension study, since it analysed changes in questionnaires related to quality of life and functionality, which favoured the intervention group compared to placebo.[22]

Other biological molecules exist for the overall disease control, but were not included in the network. One example is Bel, whose BLISS-52 study demonstrated significant efficacy in reducing SRI compared to placebo for both the 1 mg/kg and 10 mg/kg doses, but did not specifically discriminate the peripheral synovitis variable.[23] Similarly, BLISS-76 found a higher proportion of patients who maintained a response until week 76, in favour of the Bel group.[24]

Regarding treatment with CD20 inhibitors, the private trials evaluated in lupus with the EXPLORER study[25] found no differences in major and partial clinical response in patients who received Rituximab plus standard therapy versus placebo. No specific analysis of the joint component was performed but observational studies demonstrate its off-label use in up to .5%–1.5% of cases in European countries, primarily following the use of one or two prior immunosuppressants in 69% of cases, demonstrating effectiveness in the musculoskeletal and renal components.[26]

Our research included the JAK1 and2 inhibitor, baricitinib, through the SLE-BRAVE-I study, which performed a direct comparison with placebo. This study demonstrated that doses of 4 mg significantly achieved the primary endpoint SRI-4 (OR = 1.57 [95% CI 1.09–2.27], $P = .016$), as well as a significant reduction in the number of tender joints compared to placebo at week 24. Therefore, it was included in the treatment network,[27] despite a 10% adverse event rate. This treatment alternative ranked second only to MTX in the hierarchical ranking according to the P-score.

A significant limitation of this network meta-analysis is the heterogeneity in the definition of joint activity among the included studies. While some trials directly assessed joint response through arthritis resolution or joint count, others used global composite outcomes such as SRI-4 or BICLA, which include, but are not limited to, the musculoskeletal domain. This methodological variability may have contributed to the observed inconsistency and limits the interpretation of the treatment ranking as a definitive hierarchy of joint efficacy.

It was not possible to comprehensively evaluate all potential effect modifiers, such as interferon signature or exact disease duration, due to the lack of uniform reporting among the included studies.

The certainty of the evidence was assessed using the confidence in network meta-analysis (CINeMA) approach, considering the risk of bias, indirectness, inconsistency, imprecision, heterogeneity, and publication bias. Most comparisons showed low to moderate confidence, primarily due to the imprecision and indirectness associated with heterogeneity in the measurement of joint involvement. Consequently, the rankings derived from the P-score are interpreted as exploratory and descriptive and should not be used in isolation to establish clinical superiority between interventions.

MTX continues to be a useful therapy in the management of joint manifestations, as explored in the study by Carneiro et al. (1999).[21] Although this study had a small sample size, it included a significant representation of patients with joint manifestations, and it reported that only 5.5% of patients receiving MTX versus 84.2% in the placebo group presented with joint manifestations at the end of the study,[21] although with low statistical power. Although other reviews support its use due to its effect on reducing SLEDAI (OR = .444, 95% CI .279–.707, $P = .001$) as well as significantly reducing glucocorticoid doses (OR = .335, 95% CI .20–.55, $P = .001$).[28]

Given the limited sample size in some nodes of the network, particularly in the MTX group, the ranking results based on P-scores should be considered exploratory and not interpreted as evidence of clinical superiority.

Finally, when analysing the effects matrix of our research, no significant differences were observed in the measures of association between the direct and indirect comparisons, which had wide confidence intervals. These findings suggest the absence of statistically or clinically relevant differences in the comparative efficacy of the treatments evaluated. However, this lack of

difference does not necessarily reflect true therapeutic equivalence, but could be influenced by methodological limitations, such as small sample sizes, clinical heterogeneity among studies, and poor network connectivity resulting from the limited number of trials per intervention, which reduces the precision of the estimates.

Conclusions

No differences were found in the estimated effect of treatments for joint manifestations in patients with SLE. However, in the exploratory ranking analysis, the P-scores showed that MTX (P-score = 1.0), baricitinib (P-score = .62), and Ani (P-score = .37) ranked highest numerically; however, these estimates represent a probabilistic, not inferential, measure and should therefore be interpreted with caution.

Authors' contributions

- Pedro Arbey Quevedo Mayorga: Lead author, systematic review, research protocol and manuscript writing, data analysis.
- Diana Isabel Muñoz: Manuscript reviewer, PhD lecturer in epidemiology and biostatistics, research process guidance.
- Sebastián Giraldo: Systematic review, manuscript reviewer.
- Cristhian Camilo Guzmán: Systematic review, bias assessor.
- Javier Mauricio Mora: Bias assessor, summary tables.
- Jhon Jairo Tipasoca: Bias assessor.
- Sergio Daniel Montalvo: Summary tables.

Ethical considerations

This study was conducted through a systematic literature review, including studies already published in journals and reviewed by peer review and ethics committees. For greater transparency, the protocol was published on the PROSPERO platform, and statistical analyses were performed, including assessments of the effects of direct and indirect measurements, heterogeneity, inconsistency, and transitivity.

Declaration of Generative AI and AI-assisted technologies in the writing process

No artificial intelligence tools were used for the development of this analysis.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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