

# A systematic review on the efficacy of the biologic therapies Rituximab, Belimumab and Anifrolumab in Lupus Erythematosus

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## ABSTRACT

**Objective:** This systematic review presents the treatment efficacy of anifrolumab, belimumab and rituximab in non-renal Systemic Lupus Erythematosus using the main endpoints.

**Methods:** A search was done using Embase, Medline, PubMed and Web of Science for the mentioned biologics targeting SLE after 1 Jan 2019. A manual search was done with ClinicalTrials.gov for trials, and search engines for literature reviews.

**Results:** For anifrolumab, all trials reached their end point except TULIP-1 (OR=1.16, [95% CI 0.77,1.76]). Meanwhile, most trials for belimumab did not reach a response, with its only randomised controlled trial (RCT) not reaching its endpoint OR=1.40 CI [0.92,2.11]. The only trial with rituximab included 125 patients; 48 achieved remission after one cycle and 61 after 2 cycles.

**Conclusion:** The review displays evidence on the positive efficacy of anifrolumab, a varied and safe effect for belimumab and a good effect for rituximab. No trial revealed worsening by a biologic, which is a positive effect.

## INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease driven by a blurry convergence of genetic susceptibility and environmental factors. The disease manifests with the production of autoreactive B cells from recombination, immune incompetence or hypermutation.<sup>1</sup>

The disease is characterised by fatigue, skin rashes, fever, swelling and periods of worsening symptoms called flares, in mostly fertile women.<sup>2</sup> These symptoms are due to the production of autoantibodies by plasma cells which attack host tissue causing inflammation. Depending on severity, most adults can live a normal life whilst on medications such as corticosteroids, immunosuppressants, anti-malarial drugs and biologic therapies that precede adverse effects; but since there is no cure, many drugs have been trialled including those targeting B cells, such as belimumab and rituximab.<sup>3,4</sup> Recently, there has been evidence of increased type 1 interferon (IFN) in patients, therefore, drugs such as anifrolumab are being trialled.<sup>5</sup>

Despite common use of rituximab and belimumab, and the recent approval of anifrolumab, there is still uncertainty of the efficacy of biologic therapies. Thus, this systematic review aims to examine the efficacy using the main SLE measurements, of clinical trials published in the last five years across belimumab, rituximab and anifrolumab on SLE.

## METHODS

### Search strategy

Searches were conducted on four electronic databases: EMBASE, Medline, Scopus, PubMed, with keywords and MESH

terms, included in the appendix, related to the terms SLE and biologics. Papers dating back five years, published from 01/01/2019 to date of search 23/11/2023. Due to the lack of relevant trials, a manual search was done on ClinicalTrials.gov to include more relevant trials that were missed in the systematic search resulting in references 15, 16. Additionally, references 6, 7, 9, 12, 17, 18 were searched manually for the qualitative analysis. All citations were downloaded, and duplicates were removed.

### Selection criteria

After screening the titles, articles were included if any of the keywords were mentioned only. Papers including trials of adult patients (>18 years) with SLE receiving biologic therapies. Most trials had patients with moderate to severe SLE classified by different measures. After screening abstracts, any paper that was not relevant to the aim of the review was eliminated. Any paper that did not include primary research was discarded, unless deemed relevant for qualitative analysis.

### Outcome definitions

SLE uses multiple scales. The focus was the SLE Responder Index (SRI), "British Isles Lupus Assessment Group (BILAG)-Based Composite Lupus Assessment" (BICLA), "Safety of Estrogen in Lupus National Assessment – SLE Disease Activity Index" (SELENA-SLEDAI), The SLE Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI).

An SRI response comprises: (i)  $\geq 4$ -point reduction in SELENA-SLEDAI score; (ii) no new BILAG A or no more than one new BILAG B domain score, (iii) no deterioration from baseline in the physician's global assessment (PGA) by  $\geq 0.3$  points, (iv) no discontinuation of trial intervention, and (v) no use of restricted medications beyond the protocol. The usual SRI records responses with four points in the SELENA-SLEDAI but trials may choose to increase this (5/6/7/8).

The BILAG-2004 score comprises 97 clinical and laboratory variables for nine organ systems with letters depicting severity of condition: A(severe), B(moderate), C(mild), D(inactive). Using the BILAG is also the BICLA; a response defined as a reduction of all A or B disease activity at baseline to lower levels (B, C, or D and C or D, respectively) and no worsening in other organ systems (worsening defined as  $\geq 1$  new A item or  $\geq 2$  new B items); no worsening in SLEDAI-2K score (no increase from baseline) and by the PGA; no discontinuation of the trial intervention; and no use of restricted medications beyond protocol.

The SLEDAI-2K is a weighted score with 24 laboratory and clinical items with a total score of 0 to 105.<sup>6</sup> Similar to it but older, the SELENA-SLEDAI compiles a list of ranked clinical items scored 0 to 8 and laboratory items score 0 to 4, scoring 0 to 105.<sup>7</sup> Lastly, the SDI assesses damage in different organ systems, with 39 items and a score of 47.<sup>8</sup>

**RESULTS**

**Anifrolumab**

Type I interferon inhibitor anifrolumab in active SLE (TULIP-1) was the first phase 3 trial to measure the efficacy of anifrolumab with 457 patients using the SRI-4. 184 were assigned the placebo group and 180 the anifrolumab 300 mg group. Since 79 from the placebo group and 84 from the drug group had an SRI-4 response, there seemed to be no significant difference between both groups. (OR=1.16, [95% confidence interval (CI) 0.77,1.76]) Given that SRI-4 responses were similar between weeks 24 and 52, the endpoint of the trial was not reached. On the other hand, the BICLA recorded 46% responses in the intervention group compared to 20% in control. The SLEDAI-2K also had a small but significant greater reduction in the drugged group than the control, with a difference of -0.77[CI -1.6 to 0.2]. Lastly, the SDI showed no significant change.<sup>5</sup>

The successor of the previous study, TULIP-2, is a phase 3 clinical trial where 362 were randomised into 180 for the intervention group, and 182 for the placebo group. With BICLA being used as the primary efficacy endpoint after being informed of TULIP-1's results, and secondary outcomes including different SRI forms. By week 52, the intervention group had 100 responses while the control had 68 according to SRI-4 and a similar trend continued when switching SRI-5/6/7/8. The OR 2.10[CI 1.38, 3.19], therefore depicted a positive relationship with anifrolumab. The outcome for BICLA demonstrated more responses over time and for anifrolumab than placebo. Anifrolumab had 47.8% response whilst 31.5% in the placebo (OR 1.13[CI 0.73 to 1.74]). Unfortunately, the BILAG reported that 52.2% from placebo compared to 81% from intervention had 1 or more organs classed A. Lastly, the SDI, PGA and SLEDAI-2K showed no significant change.<sup>6</sup>

The third trial added for anifrolumab was a 3-year-old open label extension study following a previous RCT done using anifrolumab, where 139 patients completed it resulting in better outcomes using the SLEDAI-2K score. The trial then reports that approximately 64.9% of patients with a baseline SLEDAI-2K with a score  $\geq 6$  had a  $\geq 4$  reduction, and 27.9% with  $>0$  score had a 0 by week 160. Overall, the mean SLEDAI-2K was around five when treatment started, around three by the end of treatment (156 weeks) and 4.9 [+/-3.0] at the end of the trial (168 weeks). This in comparison to the mean score of 10.9[+/-4.1] from the RCT that happened previously shows a clear reduction in disease activity. The median and range of SLEDAI-2K also decreased for the open label study (4.0[0-22]) in comparison to the RCT (10.0[4-29]). The SDI score had no variation.<sup>3</sup>

The last trial is a placebo controlled 3-year long term extension (LTE) using the TULIP trials' patients. The trial mainly looks to observe adverse events and safety, but it includes secondary goals for efficacy with SLEDAI-2K and SDI. Overall, 547 patients were trialled, with 437 in the intervention group and 112 in the placebo. There was a marked reduction when 184 patients in the intervention group scored  $\geq 10$  points at the start compared to only 30 on week 52, on the other hand, 80 scored this in the placebo group at the start and 25 on week 52. The efficacy effect resulted in a SLEDAI-2K reduction from a mean of 11.2[SE +/- 3.7] on week 0 to 4.9[SE +/-3.5] on week 52 when using anifrolumab; meanwhile, the placebo group went from 11.3[SE +/-3.6] to 5.9[SE +/-4.3]. The same

trend continued until the end of the study. In summary, the disease manifestation decreased over time. Lastly, there was little difference in reduction and score for the PGA, while the SDI showed an insignificant increase.<sup>9</sup>

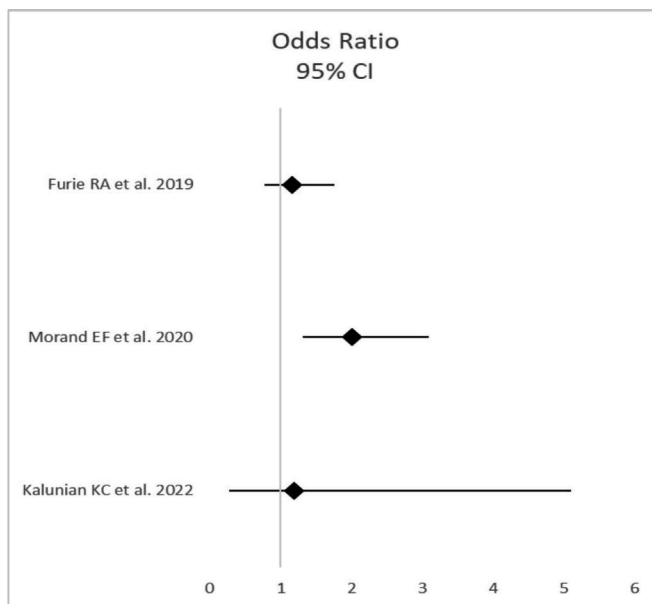


Table 1: Forest plot of primary outcomes for controlled trials with anifrolumab.<sup>5, 10, 13</sup>

**Belimumab**

The EMBRACE is a 52-week RCT followed by an open label trial which observes the efficacy of belimumab on black adults. Despite having higher prevalence of SLE, severity and risk in organ damage compared to a white population, black people are underrepresented in trials.<sup>7</sup> 501 patients were enrolled with 334 using belimumab and 167 in the control. The primary efficacy endpoint for them was the SRI, but instead of the SELENA-SLEDAI, the SLEDAI-2K was used: SRI-SLEDAI-2K. Secondary measures included the normal SRI. The SRI at the end of the trial showed a slight improvement with no statistical significance. Specifically, the belimumab group had 49% responders while the placebo had 41.6%, with an OR=1.42 [CI 0.94,2.15]. The mean SELENA-SLEDAI scores for belimumab and placebo were 9.9[SE +/-3.52] and 10.2[SE +/- 2.90], respectively, at baseline with no major difference by the start of the open label phase. For the BILAG, the placebo had lower scores by the start of the extension phase than at baseline of trial; 71.8% having  $\geq 1$  A organ or  $2 \geq B$  organs to a 22.9%. The belimumab group remained constant. As for the primary end point, the SRI-SLEDAI-2K demonstrated a 48.7% of responders in the intervention group, and a not far off 41.6% in the placebo. With an OR 1.40 CI [0.92,2.11] the end point was not reached. Only a clear numerical advantage is shown for SRI-SS and SRI-S2K starting from week 28.<sup>7</sup>

Continuing with an open label trial, a 2-year trial recruiting 401 active SLE patients evaluated response by SRI-4. SLEDAI-2K was a secondary outcome. SRI-4 was achieved by 68.2%, 73.3%, 74.7% and 68.3% of patients at 12, 24, 36 and 48 months, respectively. Despite the little difference shown by SRI, the SLEDAI-2K improved from a baseline of 8.05[+/-3.36] to 2.67[+/-2.05] at 48 months, showing a significant decrease in disease activity.<sup>10</sup>

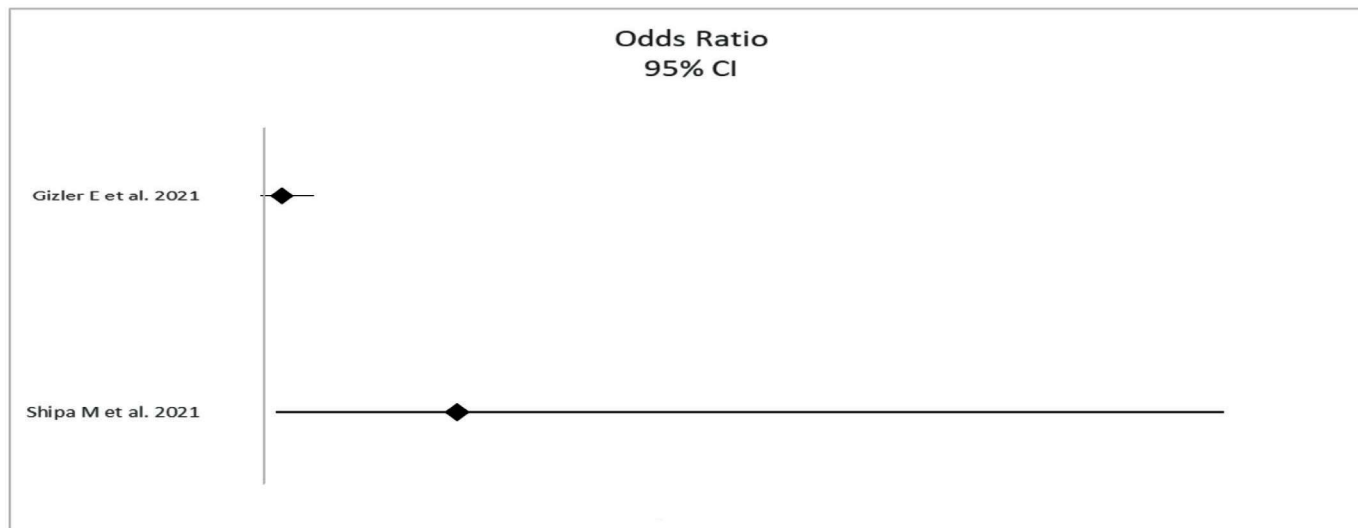


Table 2: Forest plot of primary outcomes for controlled trials with belimumab.<sup>7,12</sup>

Another open label trial included is an 8-year-old LTE with 368 patients from previous blinded trials (BLISS-52, BLISS-76). The main efficacy endpoint was the SDI, and the population was divided in subgroups for analysis such as by SELENA-SLEDAI. SDI remained stable till the end, with 0.2 mean change, meaning that by year 8 87.7% experienced no SDI change.<sup>11</sup>

**Rituximab to Belimumab**

Two trials where the drug was switched from rituximab to belimumab were found. In the first, 125 patients received rituximab and when another drug was needed, eight were changed to belimumab. After six months, only one patient achieved an SRI-4 response, but it was discontinued due to recurrent infections. Another two patients had a 4-point reduction in SLEDAI-2K but failed to achieve an SRI response. Additionally, there was no improvement in SLEDAI-2K from baseline (median score 11 to 10). Four patients continued with

belimumab after six months, and only one remained using it after three years. All of them required escalation in the additional treatment of immunosuppressants and prednisolone.<sup>4</sup> The second had 52 patients on standard therapy with rituximab, after which they switched to belimumab. The placebo had ten flares according to BILAG while the other had three flares.<sup>12</sup>

**Rituximab**

Lastly, only one trial previously mentioned with 125 patients was found to receive rituximab over a 15-year follow-up; from these 80% had a BILAG response from which 62% suffered relapse and had repeat rituximab cycles. Of the 77 that relapsed, 79% maintained a BILAG-2004 response, whilst two had inefficacy and 18% developed a bad response. The patients that changed to belimumab from rituximab had a mean SLEDAI-2K score of 11, but only one had an A or B BILAG scored organ.<sup>4</sup>

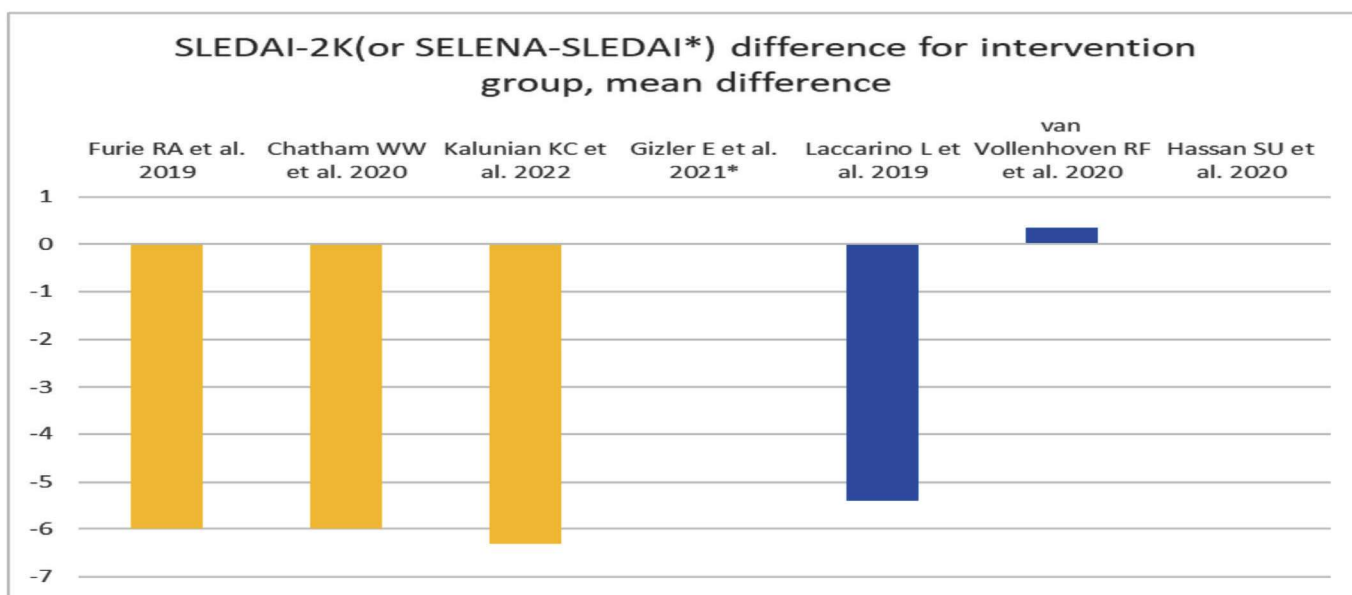


Table 3: Depicts mean difference in SLEDAI-2K (disease activity reduction) for all trials with available data starting with three for anifrolumab, then three for belimumab and a last one for rituximab, respectively.<sup>3, 4, 5, 7</sup>

## DISCUSSION

In the case of anifrolumab, all trials reached their endpoint except the first RCT, TULIP-1, which had better response to BICLA. Meanwhile, TULIP-2 had better SRI response despite using BICLA as primary response. The third and the last trial, the LTE, reported a response with SLEDAI-2K. Although the LTE reported significant disease reduction, the placebo also exhibited marked improvement, prompting consideration of corticosteroid side effects.<sup>3, 5, 6, 9</sup>

EMBRACE, the second belimumab and the open label trials did not reach their end point; the two former using SRI and the latter SDI. The second trial did see improvement with SLEDAI-2K as an additional measure. The last trial mentioned, where belimumab was received after rituximab, recorded a response with BILAG flaring.<sup>7, 10, 11, 12</sup>

The only trial for rituximab showed some response for BILAG.<sup>4</sup>

Regarding the tables, Table 1 showed TULIP-2 as having the greatest response while Kalunian KC et al.<sup>9</sup> displayed less exact results due to a broad CI. Meanwhile, Table 2 reaffirmed no effect for EMBRACE but some effect for the smaller trial, Shipa et al.,<sup>12</sup> SLEDAI-2K between weeks 0 and 52. Lastly, the SLEDAI-2K graph embraces anifrolumab as the most illness reductionist meaning that targeting the CD20 receptor over Blys may be more efficacious.

Additionally, both had a difference in population of around 100 when including all trials, but anifrolumab did have two RCTs. Regarding rituximab, no assumptions can be made off such a small trial, but it is the oldest with substantial clinical use.

In the case of biologics, as with other trials measuring efficacy for SLE, a standardised study design and measurement has not been established, therefore some results may report an improvement whilst others don't. For example, while some use the SRI as primary score due to SLE pathophysiology, the SELENA-SLEDAI only considers items that have completely resolved, therefore creating a blind spot for small improvements which to a physician may be classed as significant. On the other hand, the BICLA only considers clinical improvements and shuns serological ones, which in biologic drugs that target molecular pathways may be highly important. Additionally, the rules on restriction medications seem to impact the way we score, as TULIP-1 reported more responders once modifying its rules on drugs.<sup>5</sup>

Studies that discard both measurements may argue that irreversible organ damage is imminent regardless of treatment due to SLE long-term activity, so overestimating their importance may underscore drug efficacy.<sup>3</sup>

Regarding outcomes, a drop in mean SLEDAI-2K may be due to the stop of the biologic or drop out.<sup>3, 10</sup> The exclusion criteria are important to consider also, since studies such as EMBRACE excluded patients with severe lupus nephritis which has worse manifestations, but the belimumab LTE did not.<sup>11</sup> It is important to note that even if a drug conveys no improvement, no change may be a positive result.<sup>10</sup>

This review is not without faults as it includes only papers dating five years, and several open label studies that lack placebo groups which risks bias. The extended studies also carry selection bias as patients taken directly from RCT come with varying drug exposures and may tolerate the drug better whilst carrying lower disease levels.<sup>10</sup> Therefore, more standardised RCTs using a common SLE score, and criteria, should be performed in the future.

Declaration of conflicts of interest: No interest to declare.

## APPENDIX

Upon request.

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