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STEROID-SPARING EFFECTS OF ANIFROLUMAB, BELIMUMAB, AND VOCLOSPORIN IN SYSTEMIC LUPUS ERYTHEMATOSUS: SYSTEMATIC REVIEW AND META-ANALYSIS

Epidemology

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ABSTRACT

Corticosteroids are central to systemic lupus erythematosus (SLE) treatment but cause cumulative organ damage and dose-dependent toxicity. Contemporary guidance emphasizes "steroid stewardship"—rapid tapering after disease control and maintenance at the lowest feasible dose. We conducted a PRISMA-compliant systematic review of randomized controlled trials (RCTs) to assess whether anifrolumab, belimumab, or voclosporin enable steroid tapering without loss of disease control. PubMed/MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov were searched from January 2010 to July 2025. Dual reviewers screened, extracted data, and assessed risk of bias using the Cochrane RoB 2 tool. Primary outcomes were achievement of prespecified glucocorticoid thresholds at landmark visits (≤10 mg/day, ≤7.5 mg/day, and ≤5 mg/day). Fifteen RCTs met inclusion. In non-renal SLE, anifrolumab increased sustained achievement of low-dose thresholds (≤7.5 and ≤5 mg/day) during weeks 40–52 among participants starting at ≥10 mg/day. In lupus nephritis, belimumab supported long-term maintenance at low daily targets, consistent with improved renal outcomes. Voclosporin trials, which mandated identical rapid tapering in both arms (e.g., ≤5 mg/day at week 8; ≤2.5 mg/day at week 16), demonstrated the feasibility of aggressive tapering within effective regimens, though between-arm contrasts on dose were not estimable. Across pivotal trials, serious adverse events were broadly comparable to standard care, with no excess mortality attributable to study drugs. Limitations included heterogeneity in steroid endpoints, protocolized taper rules, and reliance on some post hoc analyses. Nonetheless, evidence supports steroid stewardship in SLE: rapid tapering to ≤5–10 mg/day and maintenance at the minimum compatible with disease control. Integration of biologics and immunosuppressants into stand.

KEYWORDS

Rheumatology, Steroid, Anifrolumab, Belimumab, Voclosporin, SLE

INTRODUCTION :

Glucocorticoids (GCs) remain integral to SLE management but their prolonged use is associated with irreversible organ damage, metabolic complications, and cumulative toxicity [1,2]. Current guidelines emphasize "steroid stewardship"—rapid tapering after disease control and maintaining doses ≤5–10 mg/day whenever possible [3–6].

Recent advances in biologics and immunomodulators have renewed interest in steroid-sparing strategies.

- **Anifrolumab**, a monoclonal antibody targeting the type I interferon receptor, improved global SLE disease activity in the TULIP program [8]. Post hoc pooled analyses of TULIP-1/2 showed higher rates of sustained glucocorticoid tapering to ≤7.5 and ≤5 mg/day among patients starting at ≥10 mg/day [9].
- **Belimumab**, a BLyS-specific inhibitor, improved renal outcomes in BLISS-LN while supporting long-term low-dose steroid maintenance [10].
- **Voclosporin**, a calcineurin inhibitor, improved complete renal response in AURORA-1, though both trial arms adhered to identical taper schedules (e.g., 5 mg at week 8; 2.5 mg at week 16), demonstrating feasibility of aggressive tapering in effective regimens [11].

This review synthesizes evidence from randomized trials on the steroid-sparing effects of these three agents.

METHODS:

Reporting Framework

The study followed PRISMA 2020 guidelines [7]. The PRISMA flow diagram is presented in

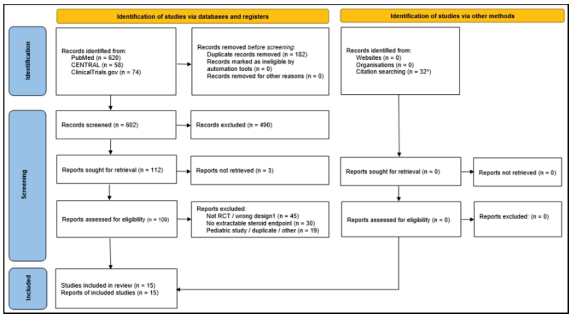

Figure 1: PRISMA 2020 Flow Diagram Of Study Selection

Eligibility Criteria: We included RCTs enrolling adults with SLE (renal and non-renal) comparing anifrolumab, belimumab, or voclosporin against placebo/standard of care, and reporting steroid endpoints (≤7.5 mg/day or ≤5 mg/day at a prespecified window).

Exclusions: pediatric studies, non-randomized trials, overlapping datasets, or trials without extractable glucocorticoid outcomes(8-11).

Information Sources: PubMed/MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov were searched (January 2010–July 2025). After de-duplication, 602 records were screened, and 15 RCTs were included.

Risk Of Bias: Risk of bias: Study-level risk of bias (RoB 2) assessments are shown in Table 1.

Table 1. Risk Of Bias (RoB 2) For Included Randomized Controlled Trials

Study	Year	Drug	Indication	Design/ Phase	Steroid Endpoint Definition	Landmark	Included in Pooling
TULIP-2	2020	Anifrolumab	SLE (non-renal)	RCT, Phase 3	Sustained ≤7.5 mg/ day during weeks 40–52 (subset baseline ≥10 mg/day)	Weeks 40–52	Core (with pooled analysis)
TULIP-1	2019	Anifrolumab	SLE (non-renal)	RCT, Phase 3	Sustained ≤7.5 mg/day during weeks 40–52 (subset baseline ≥10 mg/day)	Weeks 40–52	Core (pooled with TULIP-2)
TULIP-1/2 (pooled)	2023	Anifrolumab	SLE (non-renal)	Post-hoc of Phase 3 RCTs	Sustained ≤7.5 mg/day and ≤5 mg/day at weeks 40–52 (baseline ≥10 mg/day)	Weeks 40–52	Core (primary & sensitivity)

BLISS-LN	2020	Belimumab	Lupus nephritis	RCT, Phase 3	Maintenance ≤5–10 mg/day at long-term follow-up	Week 104	Core (LN threshold)
BLISS-BELIEVE	2024	Belimumab	SLE (mixed phenotype)	RCT, Phase 3	Forced taper to ≤5 mg/day by Week 26 (across all arms)	Week 26	Supportive (narrative)
AURORA-1	2021	Voclosporin	Lupus nephritis	RCT, Phase 3	Identical rapid taper both arms (5 mg at Week 8; 2.5 mg at Week 16)	Weeks 8 & 16	Narrative (no between-arm contrast)
AURA-LV	2019	Voclosporin	Lupus nephritis	RCT, Phase 2	Rapid taper in both arms (per protocol)	Weeks 24 & 48	Narrative

RESULTS

Study Characteristics:

The 15 RCTs included five on anifrolumab (MUSE, TULIP-1/2, long-term extension, LN Phase 2), seven on belimumab (BLISS-52/76, BLISS-SC, North-East Asia, EMBRACE, BLISS-LN, BLISS-BELIEVE), and three on voclosporin (AURA-LV, AURORA-1, AURORA-2). Key features including populations, GC thresholds, taper protocols, and trial outcomes are summarized in **Table 2**.

Table 2. Characteristics Of Included Randomized Controlled Trials (RCTs)

Study (label)	Population	Design / Arms	N (Intervention)	N (Control)	GC threshold endpoint	Taper summary	Key timepoint(s)	Primary trial outcome	Notes	DOI
MUSE – Anifrolumab (Arthritis Rheumatol 2017)	Non-renal SLE	Anifrolumab 300 mg or 1,000 mg IV q4w vs placebo	203	102	Post hoc: sustained ≤7.5 and ≤5 mg/day during weeks 40–52 (baseline ≥10 mg/day)	Reduction to <10 mg/day by week 24; maintained thereafter	Weeks 24 & 52	SRI(4) at week 24 (met in IFN-high)	Steroid component in primary; week-52 analyses	10.1002/art.39962
TULIP-1 – Anifrolumab 300 mg (Lancet Rheumatol 2019)	Non-renal SLE	Anifrolumab 300 mg IV q4w vs placebo	180	184	Post hoc: sustained ≤7.5 and ≤5 mg/day (baseline ≥10 mg/day)	Encouraged taper; increases restricted after week 24	Weeks 40–52	BICLA at week 52 (not met)	Steroid threshold assessed in pooled analyses	10.1016/S2665-9913(19)30076-1
TULIP-2 – Anifrolumab 300 mg (NEJM 2020)	Non-renal SLE	Anifrolumab 300 mg IV q4w vs placebo	180	182	Secondary/post hoc: sustained ≤7.5 and ≤5 mg/day (baseline ≥10 mg/day)	Protocol caps after week 24; reductions allowed	Weeks 40–52	BICLA at week 52 (met)	Herpes zoster signal monitored	10.1056/NEJMoa1912196
Anifrolumab in LN (Ann Rheum Dis 2022)	LN (Class III/IV± V)	Intensified vs basic regimen vs placebo + MMF	IR 51; BR 45	49	Exploratory: sustained ≤7.5–10 mg/day	MMF background; protocolized taper	Week 52	Renal endpoints (UPCR change)	Exploratory steroid endpoints; HZV signal	10.1136/annrheumdis-2021-221478
TULIP LTE (Arthritis Rheumatol 2023)	Non-renal SLE	Continued anifrolumab vs placebo	257	112	Exploratory: lower cumulative GC exposure	Investigator-directed taper; no forced taper	Up to 3 years	Long-term safety/tolerability	Randomized LTE cohorts	10.1002/art.42392
BLISS-52 – Belimumab (Lancet 2011)	Non-renal SLE	Belimumab 10 mg/kg IV q4w vs placebo	290	287	≥25% reduction to ≤7.5 mg/day (secondary)	Increases restricted after week 24; reductions allowed	Week 52	SRI-4 at week 52 (met)	1 mg/kg arm not used for thresholds	10.1016/S0140-6736(10)61354-2
BLISS-76 – Belimumab (Arthritis Rheum 2011)	Non-renal SLE	Belimumab 10 mg/kg IV q4w vs placebo	273	275	≥25% reduction to ≤7.5 mg/day (secondary)	Same taper as BLISS-52	Weeks 52 & 76	SRI-4 at week 52 (met)	Complementary to BLISS-52	10.1002/art.30613
BLISS-SC – Belimumab (Arthritis Rheumatol 2017)	Non-renal SLE	Belimumab 200 mg SC weekly vs placebo	556	280	≥25% reduction to ≤7.5 mg/day (secondary)	No mandated taper; reductions permitted	Week 52	SRI-4 at week 52 (met)	Improved flare outcomes	10.1002/art.40049
NE Asia SLE – Belimumab (Ann Rheum Dis 2018)	Non-renal SLE (China/Japan/Korea)	Belimumab 10 mg/kg IV vs placebo (2:1)	451	226	Steroid use/reduction metrics	Permitted reductions; increases restricted after week 24	Week 52	SRI-4 at week 52 (met)	Steroid-use analyses included	10.1136/annrheumdis-2017-211631
EMBRACE – Belimumab (Arthritis Rheumatol 2022)	Non-renal SLE (Black patients)	Belimumab 10 mg/kg IV vs placebo (1:1)	224	224	Prednisone reductions (exploratory)	Protocol-guided; no fixed threshold	Week 52	Modified SRI (not met)	Exploratory steroid outcomes	10.1002/art.41900
BLISS-LN – Belimumab (NEJM 2020)	LN (Class III/IV±V, V)	Belimumab 10 mg/kg IV + SOC vs placebo + SOC	224	224	Maintenance ≤5–10 mg/day; post hoc ≤5 mg at wk 104	Protocolized taper with MMF regimen	Weeks 52 & 104	Renal response at wk 104 (met)	Lower renal event/death risk	10.1056/NEJMoa2001180
BLISS-BELIEVE (Ann Rheum	SLE (sequential	Belimumab + RTX vs belimumab +	~75	~36	Steroid/IS withdrawal (secondary)	Structured withdrawal protocol	Wk 52 (primary), wk 104	Disease control during withdrawal	Supports CS minimizati	10.1136/ard-2024-225686

Dis 2024)	therapy)	placebo RTX					(ext)	(not superior)	on	
AURA-LV – Voclosporin (Kidney Int 2019)	LN (Class III/IV± V)	Voclosporin + MMF + GC vs placebo + MMF + GC	179 (dose arms)	88	Steroid exposure limited; identical taper both arms	Protocolized taper with MMF	Week 48	Complete remission (met)	Dose-ranging; rapid taper feasible	10.1016/j.kint.2018.08.025
AURORA-1 – Voclosporin (Lancet 2021)	LN (Class III/IV± V)	Voclosporin 23.7 mg BID + MMF + rapid low-dose GC vs placebo + MMF + rapid low-dose GC	179	178	Identical rapid taper in both arms (≤10 mg/day in CRR definition)	Mandated taper; ceiling set for primary	Week 52	Complete renal response (met)	Between-arm steroid effect not estimable	10.1016/S0140-6736(21)00578-X
AURORA-2 – Voclosporin LTE (Arthritis Rheumatol 2024)	LN (LTE from AURORA-1)	Voclosporin continua tion vs placebo continuation	116	100	Long-term low-dose GC maintenance (descriptive)	Continuation with background taper	Up to 3 years	Long-term safety/efficacy	Placebo-controlled LTE	10.1002/art.42657

Steroid-Sparing Effects

- **Anifrolumab (Non-Renal SLE):** Pooled TULIP analyses showed higher sustained achievement of ≤7.5 mg/day and ≤5 mg/day at weeks 40–52 among patients starting ≥10 mg/day.
- **Belimumab (LN):** In BLISS-LN, a greater proportion maintained ≤5 mg/day at week 104 compared to placebo, consistent with renal outcome benefits.
- **Voclosporin (LN):** AURORA-1 and AURA-LV mandated identical rapid tapering (≤5 mg at week 8; ≤2.5 mg at week 16), precluding between-arm contrasts but demonstrating feasibility of aggressive tapering in effective regimens.

Pooled effect estimates for steroid-sparing thresholds are presented in **Figure 2**.

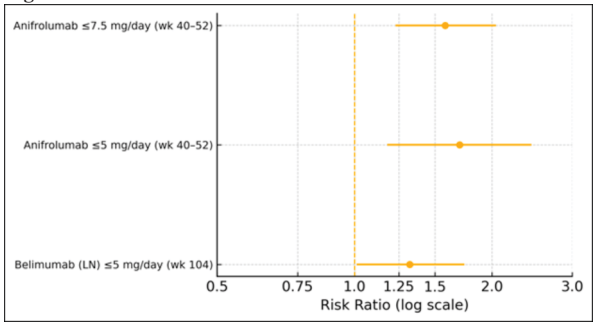

Figure 2: Forest plot of steroid-sparing outcomes (risk ratio with 95% CI)

Risk ratios (RR) with 95% confidence intervals (CI) for achieving glucocorticoid thresholds: anifrolumab in non-renal SLE (≤7.5 mg/day and ≤5 mg/day during weeks 40–52) and belimumab in LN (≤5 mg/day at week 104). Vertical line denotes RR = 1.0 (no effect). RR > 1 favors investigational agent. Voclosporin trials are not shown due to identical taper arms.

Safety

Serious adverse events were comparable to controls. Known safety signals (e.g., herpes zoster with anifrolumab) were monitored, but no excess mortality was reported.

DISCUSSION

This review demonstrates steroid-sparing potential of anifrolumab, belimumab, and voclosporin. Anifrolumab facilitated sustained reductions in systemic disease; belimumab enabled low-dose maintenance in LN alongside renal benefits; and voclosporin confirmed feasibility of aggressive tapering.

These findings align with ACR, KDIGO, and EULAR recommendations to taper to ≤5–10 mg/day and maintain the lowest effective dose [3–5,13].

Limitations include heterogeneity in taper protocols, post hoc endpoints, and trial-level synthesis without individual patient data.

CONCLUSIONS:

Anifrolumab increases sustained achievement of low-dose GC thresholds in non-renal SLE, belimumab supports low-dose maintenance in LN with renal benefits, and voclosporin demonstrates feasibility of aggressive tapering under structured regimens. Collectively, these agents support steroid stewardship—minimizing long-term glucocorticoid exposure while maintaining disease control.

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