Interferon Inhibition for Lupus with Anifrolumab: Critical Appraisal of the Evidence Leading to FDA Approval

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Journal Club. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatol 2017;69:376-86.

Objective. To assess the efficacy and safety of anifrolumab, a type I interferon (IFN) receptor antagonist, in a phase IIb, randomized, double-blind, placebo-controlled study of adults with moderate-to-severe systemic lupus erythematosus (SLE).

Methods. Patients (n = 305) were randomized to receive intravenous anifrolumab (300 mg or 1,000 mg) or placebo, in addition to standard therapy, every 4 weeks for 48 weeks. Randomization was stratified by SLE Disease Activity Index 2000 score (<10 or ≥10), oral corticosteroid dosage (<10 or ≥10 mg/day), and type I IFN gene signature status (high or low) based on a 4-gene expression assay. The primary end point was the percentage of patients achieving an SLE Responder Index (SRI [4]) response at week 24 with sustained reduction of oral corticosteroids (<10 mg/day and less than or equal to the dose at week 1 from week 12 through 24). Other end points (including SRI [4], British Isles Lupus Assessment Group [BILAG]–based Composite Lupus Assessment [BICLA], modified SRI [6], and major clinical response) were assessed at week 52. The primary end point was analyzed in the modified intent-to-treat (ITT) population and type I IFN–high subpopulation. The study result was considered positive if the primary end point was met in either of the 2 study populations. The Type I error rate was controlled at 0.10 (2-sided), within each of the 2 study populations for the primary end point analysis.

Results. The primary end point was met by more patients treated with anifrolumab (34.3% of 99 for 300 mg and 28.8% of 104 for 1,000 mg) than placebo (17.6% of 102) (P = 0.014 for 300 mg and P = 0.063 for 1,000 mg, versus placebo), with greater effect size in patients with a high IFN signature at baseline (13.2% in placebo-treated patients versus 36.0% [P = 0.004] and 28.2% [P = 0.029]) in patients treated with anifrolumab 300 mg and 1,000 mg, respectively. At week 52, patients treated with anifrolumab achieved greater responses in SRI(4) (40.2% versus 62.6% [P < 0.001] and 53.8% [P = 0.043] with placebo, anifrolumab 300 mg, and anifrolumab 1,000 mg, respectively), BICLA (25.7% versus 53.5% [P < 0.001] and 41.2% [P = 0.018], respectively), modified SRI(6) (28.4% versus 49.5% [P = 0.002] and 44.7% [P = 0.015], respectively), major clinical response (BILAG 2004 C or better in all organ domains from week 24 through week 52) (6.9% versus 19.2% [P = 0.012] and 17.3% [P = 0.025], respectively), and several other global and organ-specific end points. Herpes zoster was more frequent in the anifrolumab-treated patients (2.0% with placebo treatment versus 5.1% and 9.5% with anifrolumab 300 mg and 1,000 mg, respectively), as were cases reported as influenza (2.0% versus 6.1% and 7.6%, respectively), in the anifrolumab treatment groups. Incidence of serious adverse events was similar between groups (18.8% versus 16.2% and 17.1%, respectively).

Conclusion. Anifrolumab substantially reduced disease activity compared with placebo across multiple clinical end points in the patients with moderate-to-severe SLE.

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ANIFROLUMAB IN LUPUS

Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol 2019;1:E208-19.

Background. Type I interferons are involved in systemic lupus erythematosus (SLE) pathogenesis. In a phase 2 trial, anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1, suppressed interferon gene signatures and substantially reduced SLE disease activity. Here, we sought to confirm the efficacy of anifrolumab versus placebo in a phase 3 trial of adult patients with SLE and moderate-to-severe disease activity despite standard-of-care treatment.

Methods. TULIP-1 was a double-blind, randomised, controlled, phase 3 trial done at 123 sites in 18 countries. Included patients were aged 18–70 years, with moderate-to-severe SLE, and ongoing stable treatment with either prednisone or equivalent, an antimalarial, azathioprine, mizoribine, mycophenolate mofetil or mycophenolic acid, or methotrexate. Patients were randomly assigned (2:1:2) to receive placebo, anifrolumab 150 mg, or anifrolumab 300 mg intravenously every 4 weeks for 48 weeks. Stable standard-of-care treatment continued except for mandatory attempts at oral corticosteroid tapering for patients receiving prednisone or equivalent of 10 mg/day or more at baseline. The primary outcome was the difference between the proportion of patients who achieved an SLE responder index-4 (SRI-4) response at week 52 with anifrolumab 300 mg versus with placebo. Key secondary outcomes were the difference between the anifrolumab 300 mg group and the placebo group in: proportion of patients in the interferon gene signature test—high subgroup who achieved SRI-4 at week 52; proportion of patients on 10 mg/day or more corticosteroids at baseline who achieved a sustained dose reduction to 7.5 mg/day or less from week 40 to 52; proportion of patients with a cutaneous lupus erythematosus disease area and severity index (CLASI) activity score of 10 or higher at baseline who achieved a 50% or more reduction in CLASI score by week 12; proportion of patients who achieved SRI-4 at week 24; and annualised flare rate through week 52. Other measures of disease activity were also assessed at week 52, including the British Isles Lupus Assessment Group-based composite lupus assessment (BICLA). Safety was also assessed. Efficacy and safety analyses were done in the population of patients who received at least one dose of study drug. This trial was registered at ClinicalTrials.gov (NCT02446912).

Findings. Between June 9, 2015, and June 16, 2017, 457 patients were randomly assigned to the anifrolumab 300 mg group (n = 180), the anifrolumab 150 mg group (n = 93), or the placebo group (n = 184). The proportion of patients at week 52 with an SRI-4 response was similar between anifrolumab 300 mg (65 [36%] of 180) and placebo (74 [40%] of 184; difference −4.2 [95% CI −14.2 to 5.8], p = 0.41). Similarly, proportions of patients with an SRI-4 response at week 24, and at week 52 in patients in the interferon gene signature test—high subgroup, did not differ between the anifrolumab and placebo groups. In patients with baseline oral corticosteroids of at least 10 mg/day, sustained dose reduction to 7-5 mg/day or less was achieved by 42 (41%) of 103 patients in the anifrolumab 300 mg group and 33 (32%) of 102 patients in the placebo group (difference −8.9 [95% CI −4.1 to 21.9]). In patients with CLASI activity score of at least 10 at baseline, at least 50% reduction by week 12 was achieved by 24 (42%) of 58 patients in the anifrolumab 300 mg group and 14 (25%) of 54 in the placebo group (difference 17.0 [95% CI −0.3 to 34.3]). Annualised flare rates were 0.60 for anifrolumab and 0.72 for placebo (rate ratio 0.83 [95% CI 0.60 to 1.14]). BICLA response was achieved by 67 (37%) of 180 patients receiving anifrolumab 300 mg versus 49 (27%) of 184 receiving placebo (difference 10.1 [95% CI 0.6 to 19.7]). Anifrolumab’s safety profile was similar to that observed in phase 1, with similar proportions of patients having a serious adverse event between groups (25 [14%] of 180 for anifrolumab 300 mg, ten [11%] of 93 for anifrolumab 150 mg, and 30 [16%] of 184 for placebo).

Interpretation. The primary endpoint was not reached. However, several secondary endpoints, including reduction in oral corticosteroid dose, CLASI responses, and BICLA responses, suggest clinical benefit of anifrolumab compared with placebo. Conclusive evidence for the efficacy of anifrolumab awaits further phase 3 trial data. Despite the inherent limitations of a 1-year phase 3 study, such as incomplete knowledge of applicability to the general population and scarce detection of rare safety signals, in addition to complications from prespecified restricted medication rules, our results suggest that anifrolumab might have the potential to provide a treatment option for patients who have active SLE while receiving standard therapy.

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Morand EF, Furie R, Tanaka Y, Bruce IN, Askanease AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med 2020;382:211-21.

**Background.** Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1 investigated for the treatment of systemic lupus erythematosus (SLE), did not have a significant effect on the primary end point in a previous phase 3 trial. The current phase 3 trial used a secondary end point from that trial as the primary end point.

**Methods.** We randomly assigned patients in a 1:1 ratio to receive intravenous anifrolumab (300 mg) or placebo every 4 weeks for 48 weeks. The primary end point of this trial was a response at week 52 defined with the use of the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA). A BICLA response requires reduction in any moderate-to-severe baseline disease activity and no worsening in any of nine organ systems in the BILAG index, no worsening on the Systemic Lupus Erythematosus Disease Activity Index, no increase of 0.3 points or more in the score on the Physician Global Assessment of disease activity (on a scale from 0 [no disease activity] to 3 [severe disease]), no discontinuation of the trial intervention, and no use of medications restricted by the protocol. Secondary end points included a BICLA response in patients with a high interferon gene signature at baseline; reductions in the glucocorticoid dose, in the severity of skin disease, and in counts of swollen and tender joints; and the annualized flare rate.

**Results.** A total of 362 patients received the randomized intervention: 180 received anifrolumab and 182 received placebo. The percentage of patients who had a BICLA response was 47.8% in the anifrolumab group and 31.5% in the placebo group (difference, 16.3 percentage points; 95% confidence interval, 6.3 to 26.3; P = 0.001). Among patients with a high interferon gene signature, the percentage with a response was 48.0% in the anifrolumab group and 30.7% in the placebo group; among patients with a low interferon gene signature, the percentage was 46.7% and 35.5%, respectively. Secondary end points with respect to the glucocorticoid dose and the severity of skin disease, and in counts of swollen and tender joints; and the annualized flare rate.

**Conclusions.** Monthly administration of anifrolumab resulted in a higher percentage of patients with a response (as defined by a composite end point) at week 52 than did placebo, in contrast to the findings of a similar phase 3 trial involving patients with SLE that had a different primary end point. The frequency of herpes zoster was higher with anifrolumab than with placebo. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT02446899.)

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**Introduction**

Systemic lupus erythematosus (SLE) can present with multiple different patterns of organ involvement, which poses diagnostic and therapeutic challenges. Treatment options often have limited efficacy and poor tolerability (1–3), and many of the medications recommended by the 2012 American College of Rheumatology (ACR) lupus nephritis (LN) guidelines (4) and 2019 European League Against Rheumatism (EULAR) lupus management guidelines (5) are used off-label for SLE.

Naturally, there has been interest in exploring new therapeutic options, including type I interferon (IFN) antagonists. Type I IFNs are collectively mediated by the type I IFN-α/β/ω receptor (IFNAR) (6). A phase 1 study of global type I IFN inhibition with anifrolumab, a fully human immunoglobulin G1κ antibody that binds IFNAR, showed promise in patients with scleroderma (7). Given known similarities in type I IFN in scleroderma and SLE (8), the phase 2b MEDI-546 in Uncontrolled Systemic lupus Erythematosus (MUSE) trial (9) was designed to assess safety and efficacy of anifrolumab in SLE. The MUSE trial was then followed by the phase 3 trials Treatment of Uncontrolled Lupus via the Interferon Pathway-1 (TULIP-1) (10) and Treatment of Uncontrolled Lupus via the Interferon Pathway-2 (TULIP-2) (11), which led to US Food and Drug Administration approval of anifrolumab for patients with moderate-to-severe SLE, excluding patients with LN or central
nervous system (CNS) involvement. Here we critically appraise these three trials.

MUSE

**Patients and methods.** MUSE was a multicenter phase 2b double-blind randomized controlled trial (RCT) of 307 patients assigned in a 1:1:1 ratio into groups receiving anifrolumab 300 mg, anifrolumab 1000 mg, or placebo every 4 weeks for 48 weeks, with a 52-week follow-up. Groups were stratified on the basis of type I IFN signature (high vs low), glucocorticoid dose (≥10 mg prednisone equivalent vs <10 mg), and SLE Disease Activity Index 2000 (SLEDAI-2K) score (≥10 vs <10). Inclusion criteria were the following: age 18 to 65 years; weight ≥40 kg; meeting 1997 ACR SLE classification criteria; stability on current medications for ≥6 months; SLEDAI-2K score ≥6, excluding headache, with ≥4 points from clinical criteria; British Isles Lupus Assessment Group (BILAG) 2004 organ domain score ≥1 A or ≥2 B, and physician’s global assessment (PGA) of disease activity of ≥1. Exclusion criteria included ongoing therapy with other biologic agents, active and severe LN, neuropsychiatric SLE, history of cancer other than basal or squamous cell carcinoma, primary immunodeficiency, other inflammatory joint or skin disease, and any infection requiring hospitalization or intravenous antimicrobial therapy within the last 60 days.

The primary outcome was a composite of the SLE Responder Index (SRI) 4 at week 24 with sustained reduction in oral corticosteroids from weeks 12 to 24. The SRI-4 response is defined as a ≥4-point reduction in the SLEDAI-2K score, no new BILAG 2004 A domain score with a new BILAG 2004 B domain score ≤1, and <0.3-point worsening in PGA. Seventeen secondary outcomes were assessed, with an α level of 0.10 and no multiplicity adjustment. Notable secondary outcomes included the following: 1 and 2) SRI-4 response at week 52 with and without corticosteroid reduction from weeks 40 to 52, 3) percentage of patients with ≥50% improvement in Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI) scores, 4) percentage of patients with ≥50% improvement in swollen and tender joint counts, 5) BILAG-based Composite Lupus Assessment (BICLA) response, 6 to 9) modified SRIs with SLEDAI-2K score improvements of 5 to 8 points, 10) PGA improvements, 11 and 12) percentage achieving an SLEDAI-2K score ≤2 or 0, and 13) annualized SLE flare rate.

**Results.** The primary end point was met by more patients in both anifrolumab arms than in the placebo arm (34% anifrolumab 300 mg, 29% 1000 mg, and 18% placebo), with a greater effect size in the high IFN subset (36% anifrolumab 300 mg, 28% 1000 mg, and 13% placebo). Secondary outcomes that reached significance were the modified SRI-4 responses, the BICLA response, improvement in joint counts, improvement in CLASI scores, major clinical responses, PGA improvement, and achieving SLEDAI-2K scores of ≤2 or 0. There was not a significant difference in SLE flare rates as assessed by BILAG scoring.

At least one adverse event was reported in 77%, 85%, and 86% of the placebo, 300 mg anifrolumab, and 1000 mg anifrolumab groups, with serious adverse events reported in 19%, 16%, and 17% of each group, respectively. Intervention was discontinued because of adverse events in 8% of the placebo group, 3% of the 300 mg group, and 10% of the 1000 mg group. The most common adverse events were headaches (11%-12% across groups), upper respiratory tract infections (10%-13% across groups), bronchitis (4% placebo, 7%-9% anifrolumab groups), and herpes zoster infections (2% placebo, 5% 300 mg group, 10% 1000 mg group). There was one reported death due to macrophage activation syndrome following acute colitis occurring in the anifrolumab 1000 mg group.

TULIP-1

**Patients and methods.** TULIP-1 was a multicenter phase 3 double-blind RCT that used block randomization with stratification to assign 457 patients in a 2:1:2 ratio to anifrolumab 300 mg, anifrolumab 150 mg, or placebo. Anifrolumab or placebo was administered every 4 weeks for 48 weeks, with 52 weeks of follow-up. Entry criteria was nearly identical to that of the MUSE trial, except 2019 ACR classification criteria were used in place of the 1997 criteria and the age range was broadened up to 70 years. Exclusion criteria included severe LN, neuropsychiatric SLE, and comorbid autoimmune disease.

The primary outcome was SRI-4 responses at week 52 in the high-dose anifrolumab group versus the placebo group. Predefined secondary outcomes not adjusted for multiplicity included 1) BICLA response, 2 to 5) SRI-5 to SRI-8 responses, 6) BILAG score, 7 and 8) joint response in 20% and 50%, and 9) CLASI score reduction ≥50%. Key secondary outcomes adjusted for multiplicity on post hoc testing were the following: 1) SRI-4 response in the high-IFN group, 2) sustained prednisone dose reduction ≤7.5mg/day, 3) CLASI score reduction ≥50% by week 12, 4) SRI-4 response at week 24, and 5) annualized SLE flare rate.

**Results.** TULIP-1 failed to reach the primary end point of SRI-4 response at week 52 (36% high-dose anifrolumab vs 40% placebo, confidence interval −14.2 to 5.8, P = 0.41). Because the primary end point was not met, adjustments for secondary analyses were abandoned and the authors amended their medication restriction rules, which initially considered new nonsteroidal anti-inflammatory drug (NSAID) use to indicate anifrolumab failure. Following this amendment and removal of multiplicity correction, the high-dose anifrolumab group achieved higher rates of glucocorticoid dose reduction (49% vs 32%), CLASI score reduction ≥50% (44% vs 25%), joint tenderness or swelling improvement ≥50% (47% vs 32%), and BICLA response (46% vs 30%) compared with the placebo group.
Adverse events occurred in 89% in the 300 mg anifrolumab group, 86% in the 150 mg anifrolumab group, and 78% in the placebo group. Herpes zoster was more common in both anifrolumab groups (6% high dose, 5% low dose, 2% placebo). Other adverse events, including infusion reactions (7%-9%), pneumonia (1%-2%), and upper respiratory tract infections (1%), were similar across groups.

**TULIP-2**

**Patients and methods.** TULIP-2 was a multicenter phase 3 double-blind RCT that used stratification to assign 365 patients 1:1 to anifrolumab 300 mg and placebo groups. Inclusion criteria, exclusion criteria, medication protocol, and follow-up were the same as in TULIP-1. The primary end point was BICLA response at week 52. Key secondary end points adjusted for multiplicity were the following: 1) BICLA response in the high IFN group, 2) reduction in glucocorticoid dose ≤7.5 mg daily, 3) CLASI score reduction ≥50%, 4) joint swelling or tenderness count reduction ≥50%, and 5) annualized flare rate.

**Results.** The primary end point was achieved with the anifrolumab group reaching a greater BICLA response than the placebo group (48% vs 32%). Secondary outcomes that achieved significance were BICLA response in the high IFN group (48% vs 31%), glucocorticoid reduction ≤7.5 mg (52% vs 30%), and ≥50% improvement in CLASI activity (49% vs 25%). In contrast to TULIP-1, there was no significant difference in reduction in swollen and tender joint counts in the anifrolumab group versus the placebo group. There was a trend toward a lower annualized flare rate in the placebo group (0.64 vs 0.43); however, this did not reach statistical significance (P = 0.08).

Adverse events occurred in 84% of patients in the placebo group and in 88% of patients in the anifrolumab group. The rate of discontinuation due to adverse events was lower in the anifrolumab group (2.8% vs 7.1%); worsening SLE was included as an adverse event. The most common adverse events in the anifrolumab group were upper respiratory tract infections (22%), nasopharyngitis (16%), infusion reactions (14%), and bronchitis (12%). There were 13 cases (7%) of mild herpes zoster reported.

**Discussion**

SLE poses diagnostic, therapeutic, and research challenges given heterogeneity in presentation and clinical progression. Many medications used in clinical practice and recommended by the ACR and EULAR are used off-label with variable efficacy. MUSE, TULIP-1, and TULIP-2 aimed to broaden our armamentarium against SLE with IFN inhibition with anifrolumab.

**Efficacy.** The phase 2b MUSE trial showed positive efficacy in its primary composite end point of SRI-4 response with corticosteroid reduction without worsening BILAG or PGA score. Multiple secondary outcomes, including variations of the SRI response and BICLA response and improvements in joint and skin manifestations, also showed a positive treatment effect. The wide α level of 0.10 and lack of adjustment for multiplicity on 17 secondary tests limited clinical applicability of this study but did provide the framework for two phase 3 trials: TULIP-1 and TULIP-2.

TULIP-1 borrowed much of its design from MUSE, with similar inclusion and exclusion criteria and many of the same outcome measures. Key differences were that TULIP-1 compared different doses of anifrolumab with placebo (150 and 300 mg rather than 300 and 1000 mg), used a stricter α level of 0.05, and adjusted secondary analyses for multiplicity. With this stricter design, TULIP-1 failed to reach its primary outcome of SRI-4 response at week 52. This negative outcome led to interesting reflexivity from the authors, in which they noted that their design might have been too strict. Specifically, the initial study design considered new NSAID use equivalent to treatment failure, and the authors highlighted that the SRI cannot capture partial symptomatic improvement. Because failure to reach the primary outcome made all secondary end points nonsignificant, the authors did not enact their multiplicity adjustments. With that revision, they found better responses in BICLA scores, skin improvements, and success in tapering glucocorticoids, with a trend toward better joint response, mirroring MUSE.

In response to TULIP-1’s negative results, investigators in TULIP-2 changed their primary end point to BICLA response at week 52. Unlike the SRI, BICLA can capture partial improvements in disease activity. With this adjustment, TULIP-2 reached its primary end point, showing better BICLA responses in the anifrolumab group than in the placebo group. Given the positive outcome, the authors did adjust for multiplicity in their secondary analyses, which showed better BICLA responses in the anifrolumab group regardless of baseline IFN levels, successful glucocorticoid tapering, and CLASI score improvement ≥50%. Unlike the preceding MUSE and TULIP-1 trials, improvement in joint tenderness and swelling was not statistically different between the anifrolumab and placebo groups, and there was a lower annualized flare rate in the anifrolumab group.

**Safety.** Anifrolumab was fairly well tolerated across the MUSE, TULIP-1, and TULIP-2 trials. In these trials, upper respiratory tract infections (11%-21%) (9–11), infusion reactions (9%-14%) (10,11), and herpes zoster (1%-10%) (9–11) were reported as leading adverse events. Although adverse event rates of 85% to 89% for anifrolumab seem high, they are comparable to the rates of adverse events (77%-84%) seen in the placebo groups in these trials and are numerically lower than the adverse event rates reported in the trials leading to approval for belimumab (92%-93%) (12,13) and voclosporin (91%) (14). Serious adverse events were reported in 8% to 17% of anifrolumab groups and in 16% to 19% of placebo groups in MUSE, TULIP-1, and
TULIP-2 (9–11) compared with 7% to 13% in the voclosporin and belimumab trials (12–14).

Limitations. The MUSE, TULIP-1, and TULIP-2 trials all successfully built on their predecessors. MUSE’s biggest limitation was including a wide α level of 0.10 and not controlling for multiplicity in 17 secondary analyses, which would predict an 83% chance of a type I error. However, this is appropriate for a phase 2 study aiming to assess drug safety and efficacy. TULIP-1 attempted to build on the positive outcomes in MUSE, but with a higher level of rigor, and failed by overcorrection. Unadjusted secondary analyses in TULIP-1 hinted that anifrolumab may be effective for musculoskeletal and cutaneous manifestations of SLE and for BICLA response, which is sensitive for partial improvements (whereas SRI responses only capture complete resolution within an organ system). TULIP-2 devised its end points from the lessons learned in TULIP-1 to show the efficacy of anifrolumab in SLE. Benefitting from the lessons in MUSE and TULIP-1, TULIP-2 was well designed. However, clinicians should interpret the safety data from TULIP-2 with caution because it included SLE activity as an adverse event. Finally, these trials excluded patients with CNS or active severe renal manifestations of SLE, which can limit their clinical applicability.

Conclusions

Clinicians should critically appraise MUSE, TULIP-1, and TULIP-2 collectively when considering anifrolumab for their patients with SLE. Together these trials show that anifrolumab can reduce SLE activity, particularly cutaneous and likely musculoskeletal manifestations, and lower glucocorticoid requirements in addition to standard of care for patients without renal or CNS involvement. Adverse event rates were similar to those for placebo and those in prior reports of belimumab and voclosporin. When considering anifrolumab, clinicians should counsel patients on the risk of infusion reactions, upper respiratory tract infections, and herpes zoster. Further study assessing the safety and efficacy of anifrolumab in patients with severe renal or CNS involvement could broaden the spectrum of use, and there is an ongoing study of anifrolumab in patients with active proliferative LN (15). Finally, evaluating anifrolumab compared with standard of care, rather than in addition to standard of care, could likewise expand its use.

AUTHOR CONTRIBUTIONS

Drs. Loncharich and Anderson drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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