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Effectiveness of Anifrolumab in Patients with Systemic Lupus Erythematosus Who Did Not Achieve LLDAS: Findings from the LOOPS Registry

Satsuki Matsunaga
University of Occupational and Environmental Health, Japan
Satoshi Kubo
University of Occupational and Environmental Health, Japan
Yusuke Miyazaki
University of Occupational and Environmental Health, Japan
Masashi Funada
University of Occupational and Environmental Health, Japan
Naoaki Ohkubo
University of Occupational and Environmental Health, Japan
Masanobu Ueno
University of Occupational and Environmental Health, Japan
Ippei Miyagawa
University of Occupational and Environmental Health, Japan
Hiroaki Tanaka
University of Occupational and Environmental Health, Japan
Yurie Satoh-Kanda
University of Occupational and Environmental Health, Japan
Yasuyuki Todoroki
University of Occupational and Environmental Health, Japan
Ryuichiro Kanda
University of Occupational and Environmental Health, Japan
Yuya Fujita
University of Occupational and Environmental Health, Japan
Katsuhide Kusaka
University of Occupational and Environmental Health, Japan
Hidenori Sakai
University of Occupational and Environmental Health, Japan
Yoshiya Tanaka
University of Occupational and Environmental Health, Japan

Shingo Nakayamada

s-nakaya@med.uoeh-u.ac.jp

University of Occupational and Environmental Health, Japan

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Effectiveness of Anifrolumab in Patients with Systemic Lupus Erythematosus Who Did Not Achieve LLDAS: Findings from the LOOPS Registry

Satsuki Matsunaga[1], Satoshi Kubo[1], Yusuke Miyazaki[1], Masashi Funada[1], Naoaki Ohkubo[3], Masanobu Ueno[1], Ippei Miyagawa[1,2], Hiroaki Tanaka[1], Yurie Satoh-Kanda[1], Yasuyuki Todoroki[1], Ryuichiro Kanda[1], Yuya Fujita[1], Katsuhide Kusaka[1,2], Hidenori Sakai[1], Yoshiya Tanaka[1,2], Shingo Nakayamada[1]

[1] The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

[2] Department of Molecular Targeted Therapies, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

[3] Department of Environmental Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

Address for correspondence and reprint requests:

Prof. Shingo Nakayamada, MD, PhD

The First Department of Internal Medicine,

School of Medicine, University of Occupational and Environmental Health, Japan,

1-1 Iseigaoka, Yahata-nishi-ku, Kitakyushu, Fukuoka, 807-8555, Japan

Tel. +81-93-603-1611 (ext. 2426); Fax +81-93-691-9334

Email: s-nakaya@med.uoeh-u.ac.jp

ABSTRACT

Objective: To evaluate the real-world effectiveness of anifrolumab (ANI) in achieving treat-to-target outcomes, including Lupus Low Disease Activity State (LLDAS) and Definition of Remission in Systemic Lupus Erythematosus (DORIS) remission, among lupus patients who did not achieve LLDAS.

Methods: Patients with SLE who did not achieve LLDAS and subsequently underwent treatment intensification were included. Patients receiving ANI in addition to standard-of- care (SoC) were assigned to the SoC+ANI group, whereas those treated with glucocorticoid escalation and/or addition or escalation of immunosuppressive agents were assigned to the standard-of-care (SoC) group. The primary endpoints were LLDAS attainment and DORIS remission at week 52. Stabilized inverse probability of treatment weighting (IPTW) and doubly robust analyses were performed to adjust for baseline characteristics. The SoC+ANI group was further classified into patients with minor flares, defined as relapse after previous LLDAS attainment, and non-achievers, defined as persistent failure to achieve LLDAS after induction therapy.

Results: A total of 134 patients were included (SoC+ANI, n=88; SoC, n=46). After stabilized IPTW adjustment, LLDAS attainment and DORIS remission rates at week 52 were higher in the SoC+ANI group than in the SoC group (both $p<0.01$). Doubly robust analyses in the overall cohort showed that ANI treatment was independently associated with LLDAS attainment (aOR, 15.5; 95% CI, 5.4–51.7) and DORIS remission (aOR, 8.4; 95% CI, 2.7–34.0), compared with SoC treatment. The SoC+ANI group demonstrated sustained reductions in disease activity and glucocorticoid dose, with a 52-week retention rate of 80.6%. In subgroup analyses, patients with minor flares achieved LLDAS earlier and more frequently than non-achievers, and higher anti-SS-A antibody titers were associated with LLDAS re-attainment.

Conclusion: In real-world practice, ANI was associated with improved LLDAS attainment and DORIS remission, together with glucocorticoid-sparing effects, in patients with SLE who did not achieve LLDAS. These findings suggest that ANI may be an effective treatment option for achieving treat-to-target goals while reducing glucocorticoid exposure, particularly among patients with minor flares.

KEYWORDS

systemic lupus erythematosus, anifrolumab, treat-to-target, LLDAS, DORIS, minor flare, glucocorticoid sparing

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by recurrent flares and remission[1]. Persistent disease activity is associated with irreversible organ damage accrual and poor survival outcomes[2]. Consequently, the importance of the treat-to-target (T2T) strategy has been increasingly recognized, and Lupus Low Disease Activity State (LLDAS) has been proposed as an initial therapeutic target[3]. LLDAS is considered a clinically meaningful treatment target and has been associated with reduced organ damage accrual and improved long-term outcomes[4,5]. Furthermore, achievement of Definition of Remission in SLE (DORIS) remission, a more stringent therapeutic target, has also been associated with improved long-term prognosis and reduced organ damage accrual[6].

Glucocorticoids (GCs) remain a cornerstone of SLE treatment. However, their use is associated with multiple adverse events, including infections, cardiovascular events, and osteoporosis[3,7,8]. Cumulative GC exposure is a major risk factor for irreversible organ damage accrual[9], and minimizing GC use is recommended in the European Alliance of Associations for Rheumatology (EULAR) recommendations[3,10]. Both LLDAS and DORIS incorporate not only disease activity control but also restrictions on GC use within their definitions, making them clinically important composite outcomes that reflect both disease activity and GC exposure in real-world practice. Nevertheless, many patients fail to achieve LLDAS despite receiving standard-of-care (SoC) treatment[11]. In these patients, persistent disease activity, GC dependence, and progressive organ damage remain major clinical challenges.

Anifrolumab (ANI) is a monoclonal antibody targeting the type I interferon receptor subunit[12], and its efficacy has been demonstrated in phase III clinical trials of patients with moderately to severely active SLE[13]. Post hoc analyses further showed that ANI improved the rates of LLDAS attainment and DORIS remission[14]. However, patients enrolled in clinical trials generally have higher disease activity than those

treated in routine practice. In the phase III trials, approximately two-thirds of patients had a SLEDAI-2K score greater than 10 and approximately 40% had at least one BILAG A domain, whereas ANI is often used in real-world settings for patients with lower disease activity. Therefore, real-world data are needed to clarify the effectiveness of ANI as part of a treat-to-target strategy in patients who have not achieved LLDAS.

In clinical practice, patients who have not achieved LLDAS represent a heterogeneous population, including non-achievers, who have never attained LLDAS despite remission induction therapy, and patients with minor flares, who relapse after previously achieving LLDAS. Although both groups are categorized as LLDAS non-achievers, they may differ in treatment refractoriness and reversibility of disease activity.

Therefore, this study used a real-world clinical registry to evaluate the effectiveness of treatment intensification with ANI compared with SoC treatment in patients with SLE who did not achieve LLDAS. In addition, exploratory analyses were performed to assess whether responsiveness to ANI differed between the non-achiever and minor flare subgroups.

MATERIALS AND METHODS

Human participants and study design: This multicenter retrospective observational study included patients with SLE and was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (approval numbers: UOEHCRB21-054 and UOEHCRB21-103). Patients enrolled in the LOOPS registry[15,16], an SLE registry system involving the study institution and affiliated hospitals, fulfilled at least one of the following classification criteria: the American College of Rheumatology (ACR) classification criteria (1997), the Systemic Lupus International Collaborating Clinics classification criteria (2012), or the EULAR/ACR classification criteria for SLE (2019). Among registered patients, those who did not achieve LLDAS were identified.

Patients who underwent treatment intensification between May 2016 (approval of mycophenolate mofetil in Japan) and June 2017 (before approval of belimumab in Japan) were assigned to the SoC group (n=46). Treatment intensification consisted of GC dose escalation and/or initiation or dose escalation of immunosuppressive agents, including mycophenolate mofetil (MMF), tacrolimus (TAC), methotrexate (MTX), and azathioprine (AZ). Patients who underwent treatment intensification with ANI in addition to standard of care after December 2021 (approval of ANI in Japan) were assigned to the SoC+ANI group (n=88). The study design is shown in Supplemental Figure 1. Study transparency was maintained in accordance with the STROBE statement (Supplemental Material).

Primary outcomes: The primary outcomes were LLDAS attainment and DORIS remission[4,6] at 52 weeks after treatment intensification. Outcome rates were adjusted using stabilized inverse probability of treatment weighting (IPTW).

Secondary outcomes: Secondary outcomes included the 52-week treatment retention rate, incidence and type of adverse events, longitudinal changes in SLEDAI-2K scores, and changes in oral GC dose. Adverse events were defined as grade ≥2 events according to the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Exploratory outcomes: Within the SoC+ANI group, patients who did not achieve LLDAS within 6 months after initiation of remission induction therapy were classified as the non-achiever subgroup. Patients who experienced mild-to-moderate

organ flares according to the SELENA-SLEDAI flare index (SFI)[17] after prior LLDAS attainment were classified as the minor flare subgroup (Supplemental Figure 2).

LLDAS attainment and DORIS remission rates at 52 weeks after ANI initiation, as well as longitudinal changes in SLEDAI-2K scores and oral GC dose, were compared between the non-achiever and minor flare subgroups. Rates of LLDAS attainment and DORIS remission were reported as stabilized IPTW-adjusted proportions.

Statistical analysis

1) Patient background: Continuous variables (e.g., age) were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), according to data distribution. Categorical variables (e.g., sex) were expressed as numbers and percentages. Between-group comparisons were performed using Student's t-test or the Mann–Whitney U test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

2) Comparative analysis between ANI and SoC: To reduce confounding and selection bias arising from imbalances in baseline characteristics between the ANI and SoC groups, stabilized IPTW based on propensity scores (PSs) was applied[18]. PSs were estimated using multivariable logistic regression analysis, with ANI treatment as the dependent variable and the following covariates as independent variables: age, sex, disease activity (SLEDAI-2K), GC use and dose, hydroxychloroquine (HCQ) use, concomitant immunosuppressive agents (MMF, TAC, MTX, and AZ), mucocutaneous involvement, arthritis, history of lupus nephritis, and history of neuropsychiatric SLE (NPSLE). Stabilized weights were calculated as follows: for the ANI group, the proportion of ANI-treated patients in the overall cohort divided by the PS; and for the SoC group, the proportion of SoC-treated patients in the overall cohort divided by (1 − PS). Covariate balance after weighting was assessed using standardized mean differences (SMDs), with SMD <0.1 considered indicative of acceptable balance. Residual imbalance persisted after weighting, particularly for immunological variables such as anti-dsDNA antibody titers and complement levels. Therefore, additional adjustment was performed using a doubly robust logistic regression model incorporating these covariates at the

primary evaluation time point of 52 weeks. Rates of LLDAS attainment and DORIS remission for the primary and exploratory outcomes were reported as stabilized IPTW-adjusted proportions.

3) Comparative analysis within the SoC+ANI group (non-achiever vs. minor flare): In subgroup analyses restricted to patients treated with SoC+ANI, PSs were calculated using a partially modified covariate set based on clinical relevance and sample size considerations. Multivariable logistic regression analysis included age, sex, disease activity (SLEDAI-2K), GC use and dose, HCQ use, concomitant immunosuppressive agents (MMF, TAC, MTX, and AZ), mucocutaneous involvement, history of lupus nephritis, and history of NPSLE as independent variables.

4) Other statistical analysis and software: All p values were two-sided, and $p<0.05$ was considered statistically significant. The primary analysis was conducted at 52 weeks. For patients who discontinued treatment during follow-up, the last observation carried forward (LOCF) method was applied. Retention rates were analyzed using the Kaplan–Meier method. All statistical analyses were performed using JMP Student Edition version 19.0 (SAS Institute, Cary, NC, USA).

RESULTS

Comparison of LLDAS Attainment and DORIS Remission between SoC Treatment and ANI

Baseline patient characteristics are summarized in Table 1. After stabilized IPTW adjustment, intergroup differences in most baseline variables were reduced, and acceptable balance was achieved for major demographic and clinical characteristics, including age, sex, disease duration, mucocutaneous involvement, arthritis, and leukopenia. Nevertheless, residual imbalance remained in several immunological and treatment-related variables, including anti-dsDNA antibody titers (SMD 0.42), CH50 levels (SMD 0.35), and GC use (SMD 0.32). These variables were further adjusted using a doubly robust analytical approach. Detailed distributions of individual SLEDAI-2K items and BILAG domains are shown in Supplementary Tables 1–3.

Figures 1A and 1B present rates of LLDAS attainment and DORIS remission at each evaluation time point. In the SoC+ANI group, LLDAS attainment rates increased progressively, reaching 69.7% at week 12, 79.8% at week 24, and 86.5% at week 52 (Figure 1A). In the SoC group, corresponding rates were 40.5%, 32.4%, and 43.2%, respectively. LLDAS attainment rates were higher in the SoC+ANI group at all evaluated time points (all $p<0.01$). In doubly robust analysis, treatment intensification with ANI remained independently associated with LLDAS attainment at week 52 (adjusted odds ratio [aOR], 15.5; 95% confidence interval [CI], 5.4–51.7; $p<0.001$).

Similarly, DORIS remission rates increased over time in the SoC+ANI group, reaching 22.4% at week 12, 34.8% at week 24, and 42.7% at week 52. In contrast, remission rates in the SoC group remained low at 5.4%, 1.9%, and 10.8%, respectively (Figure 1B). The SoC+ANI group demonstrated higher DORIS remission rates at all evaluation points (week 12, $p=0.03$; weeks 24 and 52, both $p<0.01$). Similar results were observed in the doubly robust analysis (aOR, 8.4; 95% CI, 2.7-34.0; $p<0.001$).

ANI Retention and Incidence of Adverse Events

Figure 2A presents the 52-week retention rate of ANI and reasons for treatment discontinuation. Among 88 patients with SLE who did not achieve LLDAS and initiated ANI, 71 (80.6%) remained on treatment at week 52. The most common reason for discontinuation was worsening SLE activity, observed in 13 patients (14.8%), including refractory arthritis in seven patients (7.9%), worsening cutaneous manifestations in five (5.6%), and worsening lupus nephritis in one (1.1%). Two patients (2.3%) discontinued treatment because of recurrent upper respiratory tract infections. Additionally, two patients (2.3%) electively discontinued ANI after remission achievement because of planned pregnancy.

Figure 2B shows adverse events through week 52 after treatment intensification. The overall incidence of adverse events was 52.2% (24/46) in the SoC group and 42.0% (29/88) in the SoC+ANI group. Infections occurred in 48.8% (21/46) of patients in the SoC group and 27.3% (24/88) in the SoC+ANI group.

As shown in Figure 2C, stabilized IPTW analysis demonstrated a lower incidence of infections in the SoC+ANI group than in the SoC group (26.6% [24/89] vs. 46.3% [17/37], respectively). In doubly robust analysis using infection as the outcome, ANI treatment was independently associated with reduced infection risk (aOR, 0.4; 95% CI, 0.2–0.9; p=0.02). Regarding infection type, upper respiratory tract infections occurred in 10.8% of patients in the SoC group and 11.3% in the SoC+ANI group. Herpes zoster occurred in 6.5% and 5.6%, respectively, whereas influenza occurred in 6.5% and 1.1%, respectively. COVID-19 was observed only in the SoC+ANI group and affected seven patients (8.0%). Total follow-up duration during the observation period was 46 person-years in the SoC group and 77.1 person-years in the SoC+ANI group.

Comparison of SLEDAI-2K Trajectories and GC Reduction between SoC Treatment and ANI

Longitudinal changes in SLEDAI-2K scores are shown in Figure 3A. Baseline SLEDAI-2K scores were 4.5 ± 1.8 in the SoC group and 5.0 ± 2.7 in the SoC+ANI group. At week 12, scores decreased to 2.4 ± 1.5 and 2.5 ± 2.6, respectively; at week 24, to 2.6 ± 1.8 and 2.1 ± 2.5; and at week 52, to 2.6 ± 2.0 and 1.7 ± 2.2. The SoC+ANI group demonstrated progressive reduction in disease activity and significantly lower SLEDAI-2K scores than the SoC group at week 52 ($p<0.01$). No

significant between-group differences were observed at weeks 12 or 24 (p=0.7 and p=0.2, respectively). Doubly robust analysis yielded consistent findings, showing that treatment intensification with ANI was significantly associated with lower SLEDAI-2K scores at week 52 (p<0.002).

Figure 3B shows longitudinal changes in oral GC dose expressed as prednisolone-equivalent dose. Baseline GC doses were 4.4 ± 3.0 mg/day in the SoC group and 4.0 ± 4.7 mg/day in the SoC+ANI group. At week 12, doses were 5.2 ± 4.0 mg/day and 2.8 ± 3.0 mg/day, respectively; at week 24, 4.7 ± 3.2 mg/day and 2.1 ± 2.7 mg/day; and at week 52, 4.0 ± 2.9 mg/day and 1.7 ± 2.5 mg/day. GC doses progressively decreased in the SoC+ANI group and were significantly lower than those in the SoC group at weeks 12, 24, and 52 (all p<0.001). Similar results were observed in doubly robust analysis, in which treatment intensification with ANI was significantly associated with lower GC doses at week 52 (p<0.001).

Figure 3C shows organ damage accrual through week 52, assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI).[19] SDI progression was less frequent in the SoC+ANI group than in the SoC group (4.5% [4/89] vs. 21.6% [8/37], respectively). In doubly robust analysis, ANI treatment remained independently associated with a lower risk of SDI progression (p=0.048). Subsequent treatment intensification due to worsening disease activity occurred in 13.5% (12/89) of patients in the SoC+ANI group and 32.4% (12/37) of those in the SoC group (p=0.019).

Comparison of ANI Effectiveness between Patients who did not achieve LLDAS after Induction Therapy and those with Relapse after LLDAS Attainment

The findings described above demonstrated that treatment intensification with ANI was associated with higher rates of LLDAS attainment and DORIS remission among patients with SLE who did not achieve LLDAS. To identify clinical settings in which ANI may provide greater benefit, the SoC+ANI group was subdivided according to treatment indication. The non-achiever subgroup comprised patients who did not achieve LLDAS within 6 months after remission induction therapy, whereas the minor flare subgroup comprised patients who relapsed after previous LLDAS attainment.

Baseline characteristics of both subgroups are summarized in Table 2. Compared with the minor flare subgroup, the non-achiever subgroup showed a higher

frequency of cutaneous manifestations and higher GC doses. In contrast, arthritis and lymphopenia were more common in the minor flare subgroup.

After adjustment for baseline characteristics, rates of LLDAS attainment are shown in Figure 4A. In the minor flare subgroup, LLDAS attainment rates were 78.3% (47/60) at week 12, 85.0% (51/60) at week 24, and 91.6% (55/60) at week 52. Corresponding rates in the non-achiever subgroup were 37.0% (10/27), 55.6% (15/27), and 70.3% (19/27), respectively. LLDAS attainment rates were significantly higher in the minor flare subgroup at all evaluation time points (week 12, $p<0.001$; week 24, $p<0.01$; week 52, $p=0.02$), with the greatest between-group difference observed at week 12.

DORIS remission rates, SLEDAI-2K scores, and oral GC doses are presented in Figures 4B, 4C, and 4D, respectively. The difference in DORIS remission rates was most pronounced at week 24, reaching 50.0% (30/60) in the minor flare subgroup and 18.5% (5/27) in the non-achiever subgroup ($p<0.01$). By week 52, remission rates increased to 50.0% (30/60) and 36.4% (10/27), respectively, without a significant between-group difference ($p=0.2$). SLEDAI-2K scores decreased in both groups; however, the minor flare subgroup demonstrated more rapid improvement and significantly lower scores at weeks 12 and 24 (both $p<0.01$). Oral GC doses also decreased in both groups, although no significant between-group differences were observed at any evaluation point.

To identify factors associated with LLDAS re-attainment at week 52 in the minor flare subgroup, multivariable logistic regression analysis was performed (Figure 4E). Higher anti-SS-A antibody titers positivity were significantly associated with LLDAS re-attainment (aOR per 100 U/mL increase, 1.20; 95% CI, 1.04–1.44; $p=0.010$). In our institution, anti-SS-A antibody titers primarily reflect anti-Ro60 antibody reactivity. Concomitant HCQ use was also significantly associated with LLDAS re-attainment (aOR, 11.13; 95% CI, 1.46–132.0; $p=0.019$). In contrast, anti-U1-RNP antibody titers, disease duration, SLEDAI-2K scores, and oral GC dose at treatment intensification were not significantly associated with LLDAS re-attainment. Using the cutoff value identified by receiver operating characteristic analysis (1120 U/mL), patients were classified into high anti-SS-A antibody titer (≥1120 U/mL) and lower-titer groups. Patients with high anti-SS-A antibody titers showed significantly

319 higher rates of LLDAS re-attainment than those with lower titers (89.6% vs. 60.3%,
320 $p<0.01$) (Figure 4F).
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DISCUSSION

The present study evaluated the effectiveness of a treatment intensification strategy incorporating ANI in achieving T2T goals among patients with SLE who did not achieve LLDAS. Compared with SoC treatment, ANI was associated with significantly higher rates of LLDAS attainment and DORIS remission at week 52. Notably, more than 90% of patients in the minor flare subgroup re-achieved LLDAS by week 52.

A major finding of this study is that treatment intensification incorporating ANI was associated with improvement not only in disease activity but also in clinically meaningful treatment targets incorporating GC reduction. These associations remained significant after doubly robust adjustment. Accumulating evidence indicates that cumulative GC exposure substantially contributes to irreversible organ damage accrual in patients with SLE[20]. Additionally, GCs are recognized as major risk factors for infection in autoimmune diseases[21]. Consequently, minimizing GC exposure while maintaining disease control has become a central objective in contemporary SLE management. Both LLDAS and DORIS remission incorporate GC use into their definitions. Therefore, achievement of these targets reflects both disease control and successful reduction of GC dependence. In the present study, patients treated with ANI achieved higher rates of LLDAS and DORIS remission together with GC reduction, supporting the clinical utility of GC-sparing therapeutic strategies in real-world practice. In addition, SDI progression at week 52 was less frequent in the SoC+ANI group than in the SoC group, and this association remained significant after doubly robust adjustment. Although longer-term follow-up is required, these findings suggest that treatment strategies incorporating ANI may contribute to reducing irreversible organ damage accrual.

Traditionally, GC escalation has frequently been used to manage patients with SLE experiencing minor flares[22]. However, cumulative GC exposure is strongly associated with irreversible organ damage accrual and infection risk. Moreover, because SLE predominantly affects young females[1], cosmetic adverse effects of GC therapy, including weight gain, moon face, and hirsutism, may substantially impair quality of life[23,24]. Therefore, achieving disease control while limiting GC exposure remains a major challenge in SLE management[3,7].

In the present study, approximately 80% of patients in the minor flare subgroup re-achieved LLDAS by week 12, and more than 90% re-achieved LLDAS by week 52. These findings suggest that treatment intensification strategies incorporating ANI may help restore disease control without requiring GC escalation. Accordingly, ANI may represent a useful treatment intensification strategy for patients experiencing minor flares.

This study also subdivided patients who did not achieve LLDAS into minor flare and non-achiever subgroups. Among patients treated with ANI, the minor flare subgroup demonstrated earlier and higher rates of LLDAS re-attainment than the non-achiever subgroup. Although some patients in the non-achiever subgroup also achieved LLDAS by week 52, a longer period was generally required. These findings suggest that prior LLDAS attainment may predict treatment responsiveness after initiation of ANI.

Exploratory analyses further demonstrated that high anti-SS-A antibody titers and concomitant HCQ use were associated with LLDAS re-attainment at week 52 in the minor flare subgroup. Anti-SS-A antibody titers have been associated with type I interferon activation[13,25-27], and may represent an exploratory factor associated with responsiveness to ANI[28,29]. Notably, anti-SS-A antibody measurements in our institution primarily reflect anti-Ro60 antibody reactivity. These observations are biologically plausible given the mechanism of action of ANI. However, potential effects of cutoff selection, assay methodology, and residual confounding also cannot be excluded. Therefore, further validation studies are warranted.

This study has some limitations. First, potential calendar time bias may have affected the results. The SoC group included patients treated between May 2016 and June 2017, whereas the SoC+ANI group included patients treated after December 2021. During this interval, SLE management strategies evolved, particularly regarding emphasis on GC reduction. In addition, healthcare-seeking behavior during the COVID-19 pandemic may have influenced comparisons between groups. Furthermore, because this was a retrospective observational study, residual and unmeasured confounding could not be completely eliminated despite adjustment using PS weighting and doubly robust analyses. Second, this study was conducted at a limited number of centers. Subgroup analyses comparing the minor flare and non-achiever subgroups, as well as analyses involving anti-SS-A antibodies and HCQ use, should therefore be considered exploratory. Therefore, the observed benefits may reflect not only the introduction of

ANI but also temporal changes in SLE management, including wider HCQ use, implementation of T2T strategies, and greater emphasis on GC minimization. Validation in larger prospective studies is warranted.

CONCLUSION

In conclusion, a treatment intensification strategy incorporating ANI was associated with higher rates of LLDAS attainment and DORIS remission, lower GC exposure, and reduced organ damage accrual among patients with SLE who did not achieve LLDAS. In particular, among patients with minor flares, ANI was associated with restoration of disease control without GC escalation, suggesting potential utility within T2T strategies aimed at reducing GC dependence. In this subgroup, high anti-SS-A antibody titers and concomitant HCQ use may help identify patients most likely to benefit from ANI. Prospective multicenter studies are needed to confirm these findings and further define patient populations most likely to benefit from ANI -containing treatment strategies.

ABBREVIATIONS

ANI: anifrolumab; LLDAS: Lupus Low Disease Activity State; DORIS: Definition of Remission in Systemic Lupus Erythematosus; SLE: systemic lupus erythematosus; SoC: standard- of- care; IPTW: inverse probability of treatment weighting; T2T: treat-to-target; GC: glucocorticoids; EULAR: European Alliance of Associations for Rheumatology; ACR: American College of Rheumatology; MMF: mycophenolate mofetil; TAC: tacrolimus; MTX: methotrexate; AZ: azathioprine; CTCAE: Common Terminology Criteria for Adverse Events; SFI: SELENA-SLEDAI flare index; SD: standard deviation; IQR: interquartile range; PS: propensity score; NPSLE: neuropsychiatric systemic lupus erythematosus; SMD: standardized mean difference; LOCF: last observation carried forward; aOR: adjusted odds ratio; CI: confidence interval; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

DECLARATIONS

Ethical approval information

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Occupational and Environmental Health School of Medicine (#UOEHCRB21-054 and UOEHCRB21-103). Owing to the retrospective observational design, the requirement for informed consent was waived, and an opt-out approach was implemented in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour and Welfare.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

SK has received speaking fees from Eli Lilly, Otsuka Pharmaceutical, Boehringer Ingelheim, AstraZeneca, UCB Japan, AbbVie, Eisai, and Taisho, and research grants from AbbVie, Daiichi-Sankyo.

YM has received consulting fees, speaking fees, lecture fees, and/or honoraria from AstraZeneca, GlaxoSmithKline, Bristol-Myers, Astellas, Asahi Kasei, AbbVie, Chugai, Sanofi, Eisai, Eli Lilly, and Boehringer Ingelheim.

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Author contributions

All authors contributed to manuscript drafting and revision and approved the final version for submission. SM and SK had full access to all study data. SK supervised the study and assumes responsibility for data integrity and analytical accuracy.

Concept and study design: SM, SK, SN.

Data collection: SM, SK, YM, MF.

Data analysis and interpretation: SM, SK, YM, MF, NO, MU, IM, HT, YSK, YT, RK, YF, KK, HS, YT, SN.

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REFERENCES

1. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011; **365**(22): 2110–21.
2. Tanaka Y. Systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2022; **36**(4): 101814.
3. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024; **83**(1): 15–29.
4. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016; **75**(9): 1615–21.
5. Golder V, Tsang ASMWP. Treatment targets in SLE: remission and low disease activity state. *Rheumatology (Oxford)* 2020; **59**(Suppl5): v19–v28.
6. van Vollenhoven RF, Bertsias G, Doria A, et al. 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2021; **8**(1).
7. Tanaka Y. Novel therapies in treatments of SLE. *Best Pract Res Clin Rheumatol* 2025; **39**(4): 102101.
8. Tanaka Y. State-of-the-art treatment of systemic lupus erythematosus. *Int J Rheum Dis* 2020; **23**(4): 465–71.
9. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000; **43**(8): 1801–8.
10. Thamer M, Hernán MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009; **36**(3): 560–4.
11. Tanaka Y. Viewpoint on anifrolumab in patients with systemic lupus erythematosus and a high unmet need in clinical practice. *RMD Open* 2023; **9**(3).
12. Riggs JM, Hanna RN, Rajan B, et al. Characterisation of anifrolumab, a fully human anti-interferon receptor antagonist antibody for the treatment of systemic lupus erythematosus. *Lupus Sci Med* 2018; **5**(1): e000261.
13. Morand EF, Furie R, Tanaka Y, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med* 2020; **382**(3): 211–21.
14. Morand EF, van Vollenhoven R, Furie RA, et al. LLDAS and remission attainment with anifrolumab treatment in patients with systemic lupus erythematosus:

525 results from the TULIP and long-term extension randomised controlled trials. *Ann*
526 *Rheum Dis* 2025; **84**(5): 777–88.
527 15. Miyazaki Y, Funada M, Nakayamada S, et al. Safety and efficacy of
528 anifrolumab therapy in systemic lupus erythematosus in real-world clinical practice:
529 LOOPS registry. *Rheumatology (Oxford)* 2024; **63**(9): 2345–54.
530 16. Ohkubo N, Iwata S, Nakano K, et al. Efficacy and safety of high-dose of
531 mycophenolate mofetil compared with cyclophosphamide pulse therapy as induction
532 therapy in Japanese patients with proliferative lupus nephritis. *Mod Rheumatol* 2022;
533 **32**(6): 1077–85.
534 17. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE
535 clinical trials. *Lupus* 1999; **8**(8): 685–91.
536 18. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of
537 stabilized inverse propensity scores as weights to directly estimate relative risk and its
538 confidence intervals. *Value Health* 2010; **13**(2): 273–7.
539 19. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial
540 validation of the Systemic Lupus International Collaborating Clinics/American College
541 of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*
542 1996; **39**(3): 363–9.
543 20. Petri M, Purvey S, Fang H, Magder LS. Predictors of organ damage in
544 systemic lupus erythematosus: the Hopkins Lupus Cohort. *Arthritis Rheum* 2012;
545 **64**(12): 4021–8.
546 21. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed
547 impact of oral glucocorticoid therapy on risk of serious infection in older patients with
548 rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012; **71**(7): 1128–
549 33.
550 22. Martin-Iglesias D, Paredes-Ruiz D, Ruiz-Irastorza G. Use of Glucocorticoids
551 in SLE: A Clinical Approach. *Mediterr J Rheumatol* 2024; **35**(Suppl 2): 342–53.
552 23. Jolly M, Pickard AS, Mikolaitis RA, et al. Body image in patients with
553 systemic lupus erythematosus. *Int J Behav Med* 2012; **19**(2): 157–64.
554 24. Hale ED, Radvanski DC, Hassett AL. The man-in-the-moon face: a
555 qualitative study of body image, self-image and medication use in systemic lupus
556 erythematosus. *Rheumatology (Oxford)* 2015; **54**(7): 1220–5.

557 25. Vital EM, Merrill JT, Morand EF, et al. Anifrolumab efficacy and safety by
558 type I interferon gene signature and clinical subgroups in patients with SLE: post hoc
559 analysis of pooled data from two phase III trials. *Ann Rheum Dis* 2022; **81**(7): 951–61.
560 26. Weckerle CE, Franek BS, Kelly JA, et al. Network analysis of associations
561 between serum interferon-α activity, autoantibodies, and clinical features in systemic
562 lupus erythematosus. *Arthritis Rheum* 2011; **63**(4): 1044–53.
563 27. Foulquier N, Le Dantec C, Bettacchioli E, Jamin C, Alarcón-Riquelme ME,
564 Pers JO. Machine Learning for the Identification of a Common Signature for Anti-
565 SSA/Ro 60 Antibody Expression Across Autoimmune Diseases. *Arthritis Rheumatol*
566 2022; **74**(10): 1706–19.
567 28. Niewold TB, Rivera TL, Buyon JP, Crow MK. Serum type I interferon
568 activity is dependent on maternal diagnosis in anti-SSA/Ro-positive mothers of children
569 with neonatal lupus. *Arthritis Rheum* 2008; **58**(2): 541–6.
570 29. Matsui T, Tsuchida Y, Itamiya T, et al. Anti-U1-RNP antibody positivity is
571 associated with elevated interferon-stimulated gene expression scores in systemic lupus
572 erythematosus irrespective of disease activity: a transcriptome analysis in Japanese
573 patients. *Mod Rheumatol* 2025; **36**(1): 32–8.
574

575 Table 1. Baseline characteristics of the patients

	Before Stabilized IPTW			After Stabilized IPTW		
	SoC n=46	SoC+ANI n=88	SMDs	SoC n=37	SoC+ANI n=89	SMDs
Age (years)	39.5 (±14.1)	46.0 (±13.7)	0.47	44.5 (±14.0)	44.5 (±13.5)	0.00
Female, n (%)	40 (87.0)	83 (94.3)	0.27	35 (92.6)	80 (90.9)	0.06
Disease duration (months)	142.7 (±98.6)	143.3 (±114.0)	0.01	157.0 (±104.1)	147.9 (±113.3)	0.08
SLEDAI-2K score	4.2 (±2.1)	5.4 (±2.8)	0.46	4.5 (±1.8)	5.0 (±2.7)	0.22
BILAG A1 or B2, n (%)	0 (0.0)	0 (0.0)	0.00	0 (0.0)	0 (0.0)	0.00
Arthritis, n (%)	24 (52.1)	60 (61.4)	0.33	22 (58.4)	49 (55.5)	0.06
Skin involvement, n (%)	26 (56.5)	55 (62.5)	0.12	23 (60.5)	54 (61.5)	0.02
Leukopenia, n (%)	7 (15.2)	11 (12.5)	0.08	2 (10.1)	2 (10.1)	0.00
History of lupus nephritis, n (%)	21 (45.7)	22 (23.7)	0.44	15 (40.6)	32 (36.5)	0.08
History of NPSLE, n (%)	18 (39.1)	25 (28.4)	0.23	11 (29.1)	29 (32.5)	0.07
Anti-dsDNA antibody (U/mL)	14.7 (±33.2)	8.0 (±19.5)	0.27	18.1 (±35.8)	6.7 (±16.6)	0.42
CH50 (U/mL)	51.9 (±11.9)	48.6 (±11.3)	0.29	52.0 (±12.2)	47.7 (±12.2)	0.35
GC dose, PSL equivalent (mg/day)	4.4 (±2.9)	3.7 (±5.3)	0.15	4.4 (±3.1)	4.0 (±4.7)	0.10
GC use, n (%)	40 (87.0)	45 (51.1)	0.74	29 (78.6)	57 (64.3)	0.32
HCQ use, n (%)	31 (67.4)	76 (86.4)	0.47	28 (74.7)	72 (81.6)	0.17
MMF use, n (%)	6 (13.0)	11 (12.5)	0.02	6 (16.6)	14 (16.2)	0.01
Classical immunosuppressant use* n (%)	24 (52.1)	23 (26.1)	0.55	18 (47.9)	30 (33.6)	0.29

576

577 Data are presented as mean (standard deviation) or number of patients (%).

578 GC, glucocorticoid; PSL, prednisolone; HCQ, hydroxychloroquine; MMF,

579 mycophenolate mofetil; NPSLE, neuropsychiatric systemic lupus erythematosus; SMD,

580 standardized mean difference; SoC, standard of care; ANI, anifrolumab

581 *Classical immunosuppressants included methotrexate (MTX), tacrolimus (TAC), and

582 azathioprine (AZA).

583

584 Table 2. Baseline characteristics of patients in the minor flare and non-achiever subgroups

	Before Stabilized IPTW			After Stabilized IPTW		
	Non-achiever N=30	Minor flare N=58	SMDs	Non-achiever N=27	Minor flare N=60	SMDs
Age (years)	44.7 (±13.4)	46.0 (±13.8)	0.10	44.4 (±13.8)	44.4 (±14.0)	0.00
Female, n (%)	27 (90.0)	56 (96.6)	0.26	26 (93.9)	58 (96.3)	0.09
Disease duration (months)	141.2 (±92.3)	150.7 (±124.4)	0.09	145.6 (±83.9)	144.3 (±118.3)	0.01
SLEDAI-2K score	5.9 (±3.3)	5.1 (±2.4)	0.29	5.9 (±3.1)	5.6 (±2.5)	0.11
BILAG A1 or B2, n (%)	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	0.00
Arthritis, n (%)	15 (50.0)	39 (67.2)	0.35	16 (59.4)	43 (71.9)	0.27
Skin involvement, n (%)	21 (70.0)	34 (58.6)	0.23	17 (63.1)	37 (60.6)	0.05
Leukopenia, n (%)	1 (3.3)	10 (17.2)	0.43	1 (5.1)	15 (24.8)	0.56
History of lupus nephritis, n (%)	13 (22.4)	13 (22.4)	0.00	7 (27.0)	16 (25.7)	0.03
History of NPSLE, n (%)	10 (33.3)	15 (25.8)	0.17	6 (22.2)	13 (22.1)	0.00
Anti-dsDNA antibody (U/mL)	7.1 (±24.0)	8.0 (±17.0)	0.04	8.8 (±26.1)	7.7 (±16.5)	0.05
CH50 (U/mL)	48.4 (±13.1)	48.9 (±10.4)	0.04	48.5 (±11.8)	47.0 (±12.1)	0.13
GC dose, PSL equivalent (mg/day)	7.0 (±6.7)	2.0 (±3.2)	0.89	4.1 (±5.4)	4.1 (±5.3)	0.00
GC use, n (%)	22 (73.3)	23 (40.0)	0.70	15 (53.9)	32 (53.1)	0.02
HCQ use, n (%)	25 (83.3)	51 (87.9)	0.12	24 (86.7)	53 (87.3)	0.02
MMF use, n (%)	6 (20.0)	5 (8.6)	0.36	4 (14.9)	8 (12.3)	0.08
Classical immunosuppressant use* n (%)	10 (33.3)	13 (22.4)	0.25	8 (31.0)	15 (25.3)	0.13

585

586 Data are presented as mean (standard deviation) or number of patients (%).

587 GC, glucocorticoid; PSL, prednisolone; HCQ, hydroxychloroquine; MMF,

588 mycophenolate mofetil; NPSLE, neuropsychiatric systemic lupus erythematosus; SMD,

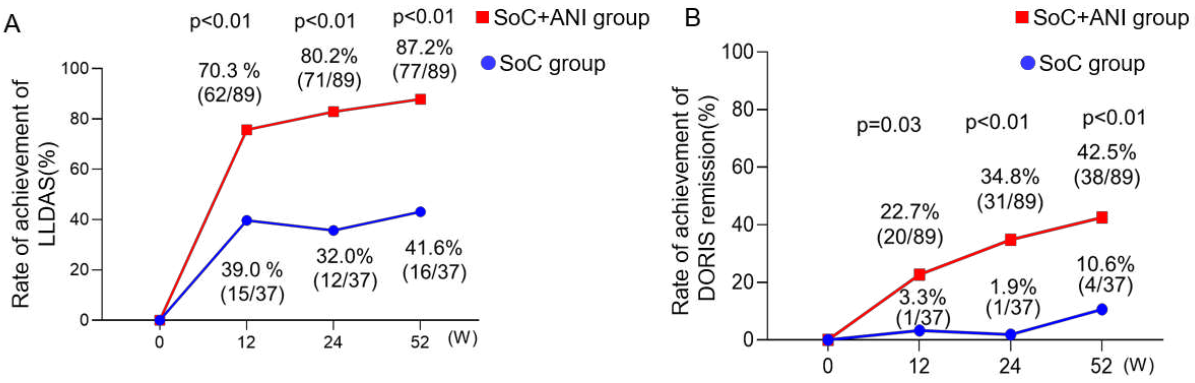
589 standardized mean difference.

590 *Classical immunosuppressants included methotrexate (MTX), tacrolimus (TAC), and

591 azathioprine (AZA).

592 **FIGURE LEGENDS**

593 **Figure 1. Efficacy of anifrolumab**

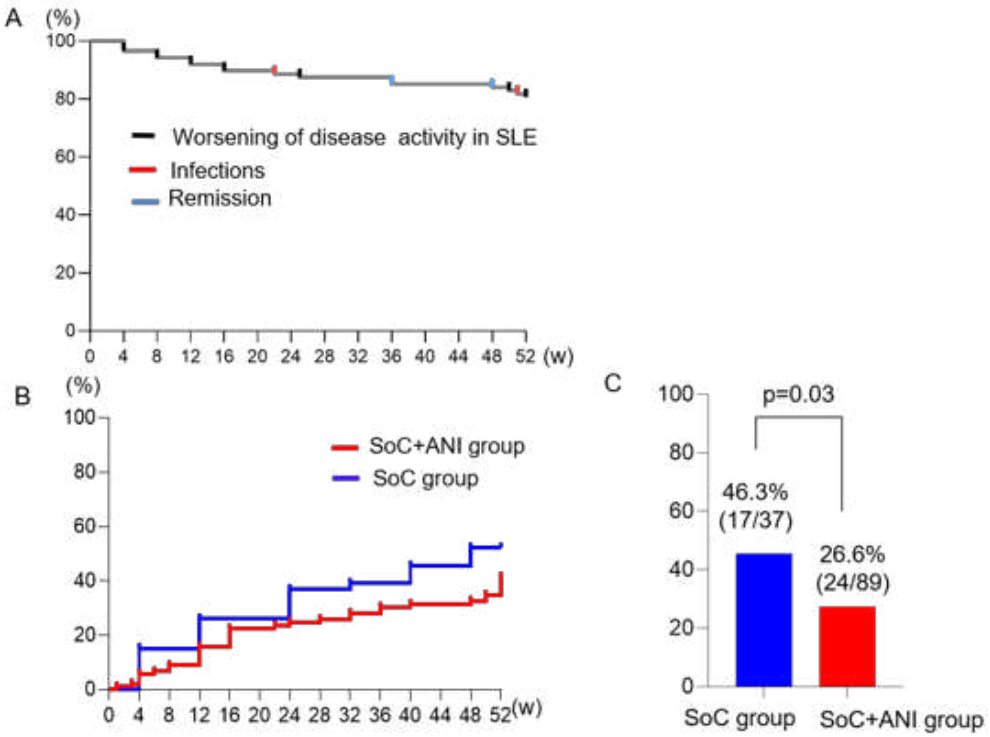


594

595 (A) LLDAS attainment rates over 52 weeks after treatment intensification in the SoC
596 and SoC+ANI groups following stabilized IPTW adjustment.
597 (B) DORIS remission rates over 52 weeks after treatment intensification in the SoC
598 and SoC+ANI groups following stabilized IPTW adjustment.
599 Values are presented as weighted proportions. Between-group comparisons were
600 performed at each time point.
601 LLDAS, Lupus Low Disease Activity State; DORIS, Definition of Remission in
602 SLE; IPTW, inverse probability of treatment weighting; SoC, standard of care; ANI,
603 anifrolumab; w, week.

604

Figure 2. Retention rate, discontinuation reasons, and adverse events associated with anifrolumab



(A) Kaplan–Meier curve showing retention rates and reasons for discontinuation over 52 weeks after anifrolumab initiation.

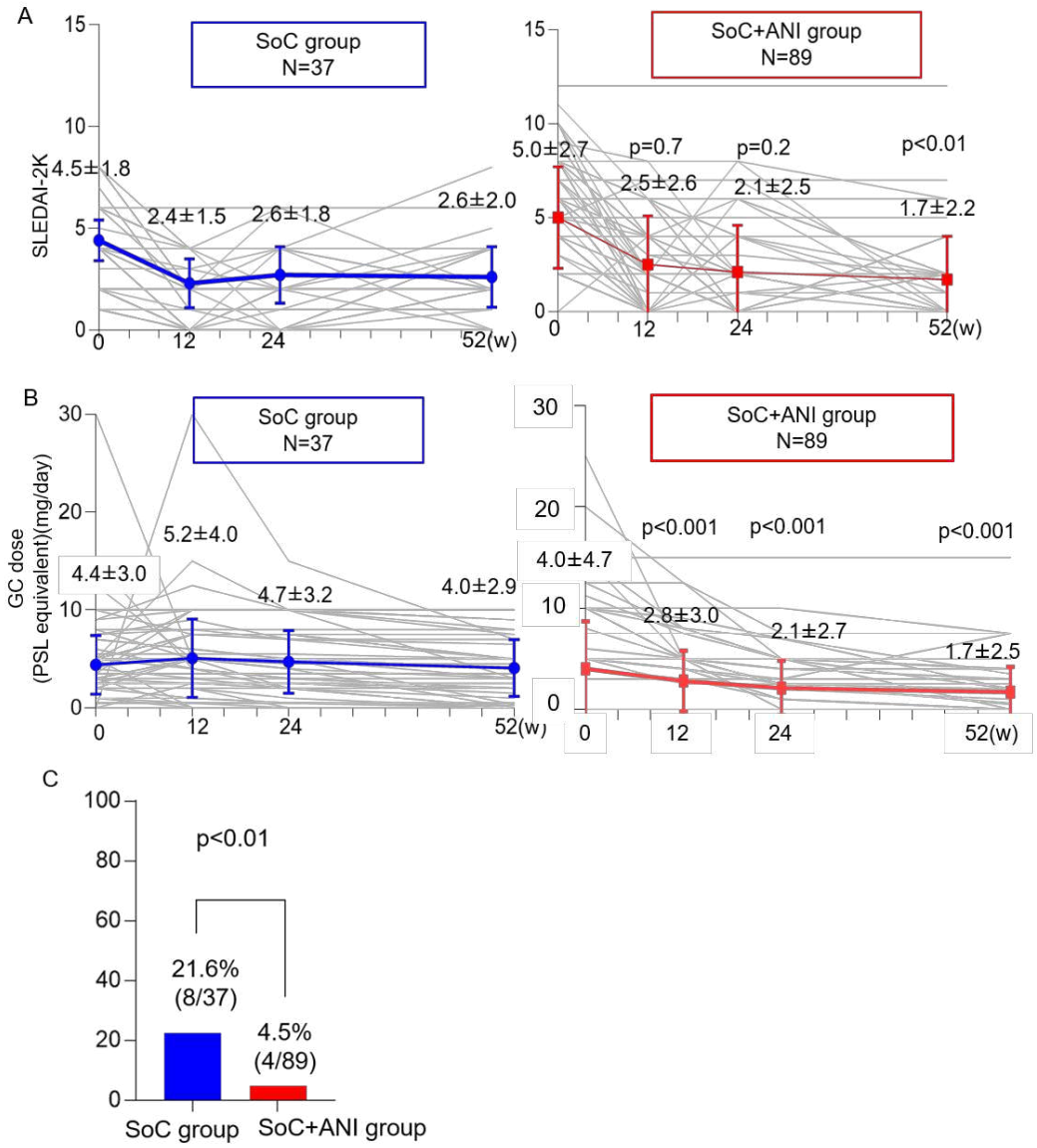
(B) Overall adverse event rates over 52 weeks after treatment intensification in the SoC and SoC+ANI groups.

(C) Infection rates over 52 weeks after treatment intensification in the SoC and SoC+ANI groups following stabilized IPTW adjustment.

Values in panel (C) are presented as weighted proportions.

IPTW, inverse probability of treatment weighting; SoC, standard of care; ANI, anifrolumab.

Figure 3. Disease activity and glucocorticoid dose after treatment intensification



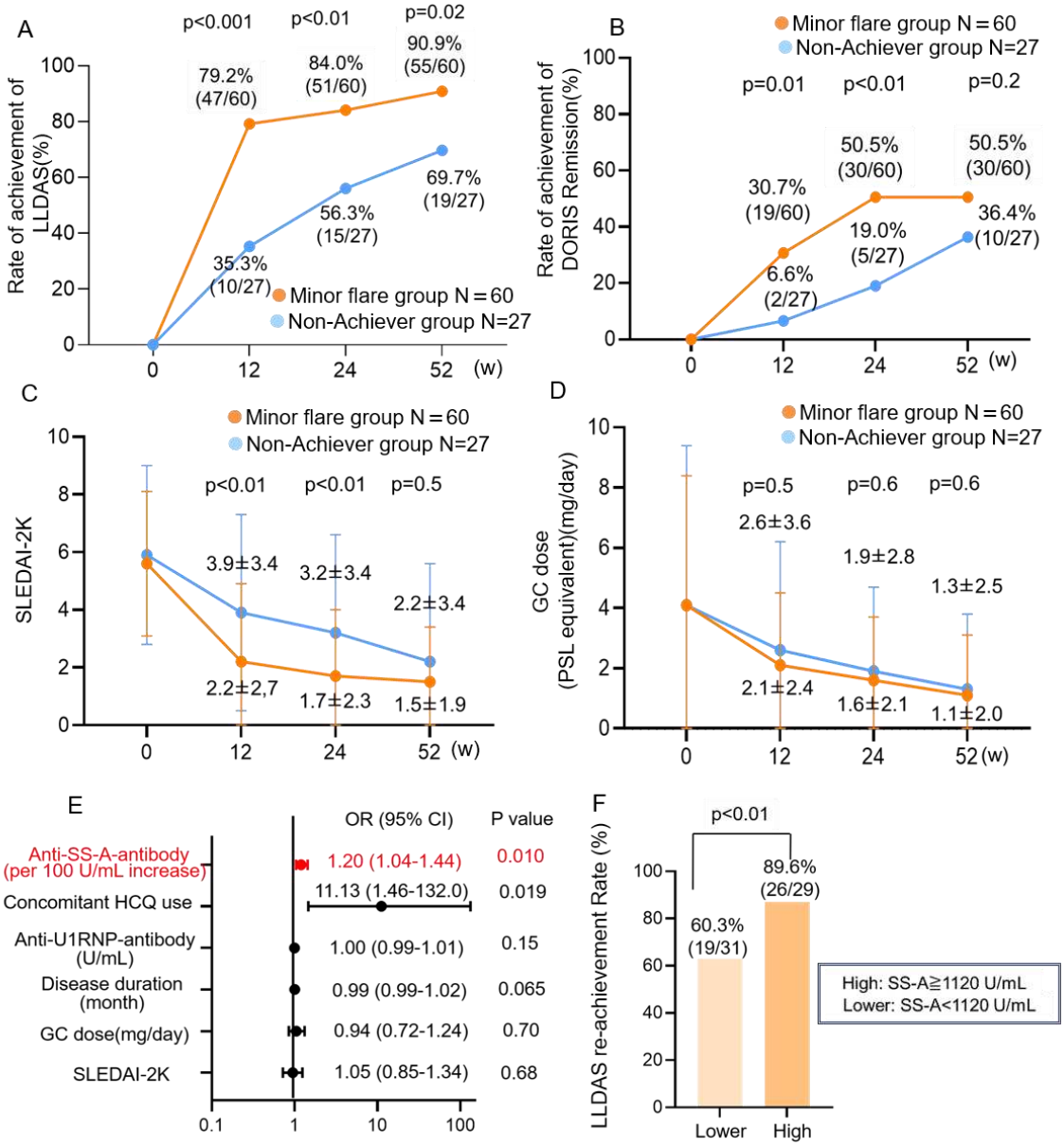
(A) SLEDAI-2K scores over 52 weeks after treatment intensification in the SoC and SoC+ANI groups following stabilized IPTW adjustment.

(B) Glucocorticoid dose (prednisolone equivalent) over 52 weeks after treatment intensification in the SoC and SoC+ANI groups following stabilized IPTW adjustment.

Values are presented as mean ± standard deviation.

SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; GC, glucocorticoid; IPTW, inverse probability of treatment weighting; SoC, standard of care; ANI, anifrolumab.

Figure 4. Comparison of treatment responses to anifrolumab between the minor flare and non-achiever subgroups



(A) LLDAS attainment rates over 52 weeks after anifrolumab initiation in the minor flare and non-achiever subgroups following stabilized IPTW adjustment.

(B) DORIS remission rates over 52 weeks after anifrolumab initiation in the minor flare and non-achiever subgroups following stabilized IPTW adjustment.

(C) SLEDAI-2K scores over 52 weeks after anifrolumab initiation in the minor flare and non-achiever subgroups following stabilized IPTW adjustment.

(D) Glucocorticoid dose (prednisolone equivalent) over 52 weeks after anifrolumab initiation in the minor flare and non-achiever subgroups following stabilized IPTW adjustment.

(E) Multivariable logistic regression analysis of factors associated with LLDAS re-attainment at week 52 in the minor flare subgroup.

(F) LLDAS re-attainment rates in patients with high versus low anti-SS-A antibody titers according to the cutoff value determined by ROC analysis.

Values in panels (A), (B), and (F) are presented as weighted proportions, whereas values in panels (C) and (D) are presented as mean ± standard deviation.
LLDAS, Lupus Low Disease Activity State; DORIS, Definition of Remission in SLE; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; GC, glucocorticoid; IPTW, inverse probability of treatment weighting.

Supplemental Figure 1. Study design

Patients with systemic lupus erythematosus (SLE) who did not achieve Lupus Low Disease Activity State (LLDAS) were retrospectively classified according to treatment intensification strategy. Patients who underwent treatment intensification with anifrolumab after regulatory approval were assigned to the SoC+ANI group, whereas patients treated with glucocorticoid escalation and/or addition or escalation of immunosuppressive agents before anifrolumab approval were assigned to the standard-of-care (SoC) group.

GC, glucocorticoid; MMF, mycophenolate mofetil; TAC, tacrolimus; AZA, azathioprine; MTX, methotrexate; ANI, anifrolumab.

Supplemental Figure 2. Definitions of subgroup analyses

The SoC+ANI group was further divided into two subgroups according to prior LLDAS achievement. The non-achiever subgroup comprised patients who had never achieved LLDAS after 6 months from remission induction therapy initiation. The minor flare subgroup comprised patients who developed mild-to-moderate flare according to the SELENA-SLEDAI flare index (SFI) after previous LLDAS achievement.

LLDAS, Lupus Low Disease Activity State; SFI, SELENA-SLEDAI flare index; ANI, anifrolumab.

Supplementary Files

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