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Association of Modified Systemic Lupus Erythematosus Responder Index Attainment With Long-Term Clinical Outcomes: A Five-Year Prospective Study

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Objective. In trials of systemic lupus erythematosus (SLE), the SLE Responder Index (SRI) is the most commonly used primary efficacy end point but has limited validation against long-term outcomes. We aimed to investigate associations of attainment of a modified version of the SRI (mSRI) with key clinical outcomes in SLE patients with up to 5 years of follow-up.

Methods. We used data from a large multicenter, longitudinal SLE cohort in which patients received standard of care. The first visit with active disease (defined as SLE Disease Activity Index 2000 [SLEDAI-2K] score ≥6) was designated as baseline, and mSRI attainment (defined as a reduction in SLEDAI-2K ≥4 points with no worsening in physician global assessment ≥0.3 points) was determined at annual intervals from baseline up to 5 years. Associations between mSRI attainment and outcomes including disease activity, glucocorticoid dose, flare, damage accrual, Lupus Low Disease Activity State (LLDAS), and remission were studied.

Results. We included 2,060 patients, with a median baseline SLEDAI-2K score of 8. An mSRI response was attained by 56% of patients at 1 year, with similar responder rates seen at subsequent annual time points. Compared to nonresponders, mSRI responders had significantly lower disease activity and prednisolone dose and higher proportions of LLDAS and remission attainment at each year, and less damage accrual at years 2 and 3. Furthermore, mSRI responder status at 1 year predicted clinical benefit at subsequent years across most outcomes, including damage accrual (odds ratio [OR] range 0.58–0.69, $P < 0.05$ for damage accrual ORs at all time points).

Conclusion. In SLE patients with active disease receiving standard of care, mSRI attainment predicts favorable outcomes over long-term follow-up, supporting the clinical meaningfulness of SRI attainment as an SLE trial end point.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease of high unmet need (1). Despite significant interest in therapeutic development, the vast majority of promising treatments entering late-phase clinical trials over the last 20 years have not met their primary efficacy end points (2) and thus failed to obtain regulatory approval. It is widely acknowledged that in addition to therapeutic

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target selection, factors related to trial design have contributed to this lack of success. In particular, selection of clinical trial end points in SLE remains an unresolved issue (3), and has been identified as a top research priority among lupus patients, researchers and clinicians alike (4).

The SLE Responder Index (SRI) is a composite responder definition that is the most common primary efficacy end point used in SLE phase II and III randomized controlled trials (RCTs) over the last 10 years (5). An SRI-4 response is defined as a reduction in the SLE Disease Activity Index (SLEDAI) by ≥4 points, with no worsening of the British Isles Lupus Assessment Group (BILAG) index (new grade 1A or 2B score) or deterioration from baseline ≥0.3 points in the physician global assessment (PhGA) (6). Several analyses have shown that SRI responder classification is almost entirely determined by meeting the SLEDAI reduction criteria, which ascertains improvement in overall disease activity. In contrast, inclusion of the BILAG and PhGA criteria is intended to detect significant worsening not captured by the SLEDAI alone, and the BILAG and PhGA criteria were rarely discordant with the SLEDAI criteria when the 3 component measures of the SRI have been individually analyzed in trial data (6–8).

The SRI was initially developed through retrospective analysis of belimumab phase II trial data (6), then successfully employed as an end point in the phase III belimumab trials (9,10). However, subsequent use of the SRI in major lupus RCTs has produced mixed results, including in some cases failure to discriminate therapies that had clinically important efficacy suggested by other end points (11–16). This has raised questions about the performance and suitability of the SRI as a trial end point and highlighted the need for further empirical assessment of its measurement properties.

The SRI has been predominantly validated via post hoc analyses of clinical trial data sets in which the SRI was used as an end point. These studies have shown an association of SRI response with important outcomes, including reduction in glucocorticoid exposure, joint and skin score improvements, and improved patient-reported outcomes (8,17,18). However, validation of SRI attainment outside the constraints of a clinical trial, such as protection against important long-term clinical outcomes, including damage accrual, is lacking. Therefore, the aim of this study was to investigate associations between attainment of SRI response and SLE clinical outcomes over multiple years of follow-up. To achieve this, we performed an analysis of outcomes following attainment of a modified SRI response, omitting BILAG, at the 1-year time point commonly used in SLE RCTs.

PATIENTS AND METHODS

Study design. We used prospectively collected data from the Asia Pacific Lupus Collaboration (APLC) cohort (19) from 2013 to 2020. Adult patients fulfilling the American College of Rheumatology (ACR) revised criteria for SLE as updated in 1997 (20) or the Systemic Lupus International Collaborating Clinics (SLICC) revised criteria for SLE (21) were recruited from 25 centers in 13 countries. Disease activity, assessed by SLEDAI 2000 (SLEDAI-2K) (22) and PhGA (23), treatment, and laboratory data for patients in the APLC cohort were recorded at routine clinic visits every 3 to 6 months, and damage was assessed annually using the SLICC/ACR Damage Index (SDI) (24). Ethics approval for this study was obtained from the Monash University Human Research Ethics Committee (MUHREC Project no. 18778).

To be included in this analysis (Figure 1), patients had to have ≥1 documented episode of active disease defined as a SLEDAI-2K score ≥6. A SLEDAI-2K score threshold of 6 was chosen as this is a common entry criterion for clinical trials (9,11,14,16,25). This visit was designated as the baseline, and data subsequent to that visit were used for analysis. As the BILAG is not collected in the APLC cohort, a modified version of SRI (mSRI) response was defined as a reduction in SLEDAI-2K ≥4 points with no worsening in PhGA ≥0.3 points, omitting the BILAG criteria from the original SRI definition. Attainment of mSRI was determined for each patient with available data at 1 year and

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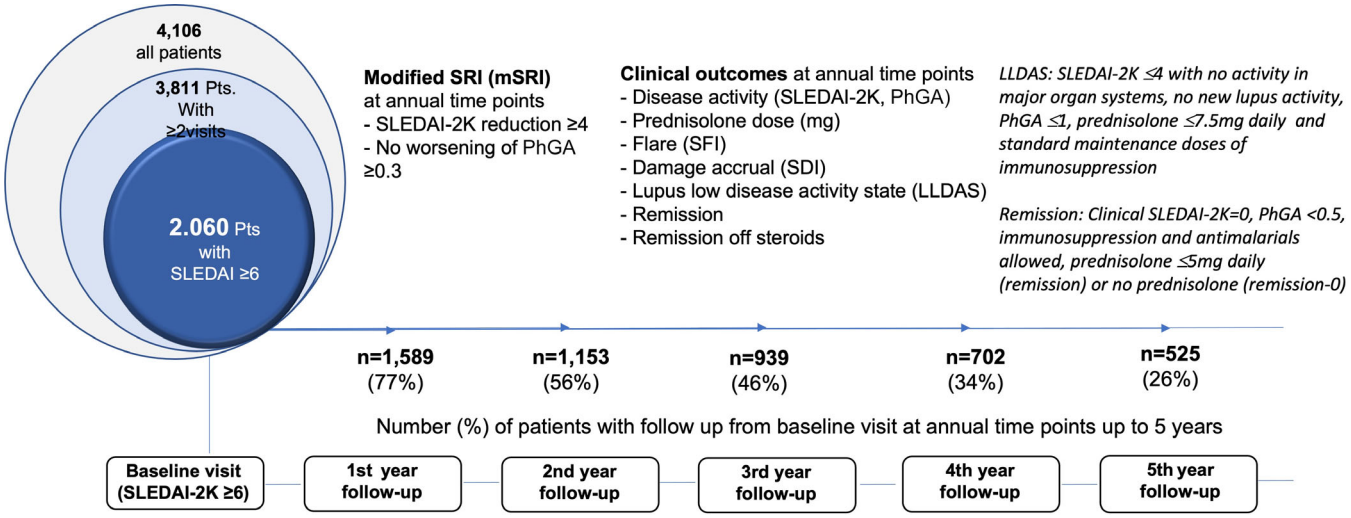

Figure 1. Inclusion and 5-year follow-up of systemic lupus erythematosus (SLE) patients (Pts) from the Asia Pacific Lupus Collaboration cohort in a prospective study to investigate associations between attainment of a modified version of the SLE Responder Index (mSRI) and clinical outcomes at annual time points. Patients at baseline had an SLE Disease Activity Index 2000 (SLEDAI-2K) score ≥6. Clinical outcomes included disease activity (measured by SLEDAI-2K and physician global assessment [PhGA]), glucocorticoid dose, flare (measured by Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI flare index [SFI]), damage accrual (measured by Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SDI]), Lupus Low Disease Activity State (LLDAS) attainment, and remission. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42350/abstract.

subsequent annual time points (up to 5 years of follow-up), with response defined from the baseline visit for each patient.

Outcomes. Clinical outcomes assessed at each annual time point were disease activity (SLEDAI-2K and PhGA), glucocorticoid use (prednisolone dose in mg/day), flare (Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI flare index [SFI]) (26), attainment of Lupus Low Disease Activity State (LLDAS) (27), attainment of remission according to the definition of remission in SLE (DORIS) (28) and a modification of DORIS requiring patients not be receiving glucocorticoids (termed remission-0), and damage accrual (increase in SDI score from baseline) (24).

In addition to analyzing outcomes at each annual time point, we also analyzed each outcome considering all data available across the study period. For continuous variables (SLEDAI-2K, PhGA, and prednisolone dose) we calculated time-adjusted mean values (29) as an average over the preceding annual period from the time point of interest and as an average since baseline. Binary outcomes (flare, LLDAS, and remission) were additionally analyzed according to whether they occurred at any visit in the preceding year and at any visit since baseline.

Statistical analysis. The associations between mSRI attainment and clinical outcomes were determined using univariable linear and logistic regression analyses. To assess the predictive capacity of mSRI attainment at 1 year on future outcomes, we also analyzed the associations of achieving mSRI at 1 year with clinical outcomes at subsequent annual time points. Visits with missing data were omitted from analysis. All analyses were performed using STATA version 15.1 (StataCorp).

RESULTS

Patient characteristics. Of 4,106 patients in the APLC cohort, 2,060 were included in this analysis, each having a visit with active disease (SLEDAI-2K score ≥6) designated as baseline. The number of patients assessed at each follow-up time point, ranging from 1 year to 5 years, is shown in Figure 1. The characteristics of the study cohort are shown in Table 1. Most patients were female (92%), were Asian (89%), and had established SLE. The median SLEDAI-2K score at active disease baseline visit was 8 (interquartile range [IQR] 6, 10), and 52% of patients met criteria for flare at this visit. Most patients were receiving glucocorticoids at baseline (86%) with a median daily prednisolone dose of 7.5 mg (IQR 5, 15 mg). At baseline, 42% of included patients had organ damage (SDI score >0).

Attainment of mSRI. At 1 year, mSRI response was attained by 884 [56%] of 1,589 patients. Compared to patients who did not attain mSRI, mSRI responders had higher baseline disease activity (including SLEDAI-2K total score, activity across multiple SLEDAI-2K domains, and flare), higher glucocorticoid doses, lower damage scores, and shorter disease duration (Table 1).

At subsequent annual time points, mSRI attainment rates remained similar to that seen at 1 year, ranging 54–57% over up

Table 1. Characteristics of SLE patients included from the Asia Pacific Lupus Collaboration cohort at baseline visit, including comparison of mSRI responders and nonresponders at 1 year follow-up*

Characteristic	Total patients (n = 2,060)	mSRI responder at year 1 (n = 884)	mSRI nonresponder at year 1 (n = 682)	*P*
Age at baseline visit, median (IQR) years	37 (28, 47)	37 (28, 48)	38 (30, 48)	0.11
Disease duration, median (IQR) years	8 (3, 15)	7 (2, 14)	9 (5, 16)	<0.001
Female	1,903 (92.4)	821 (92.9)	632 (92.7)	0.9
Asian	1,819 (88.6)	792 (89.7)	598 (87.8)	0.24
ANA-positive	1,823 (93.4)	570 (90.3)	791 (94.5)	0.002
aPL-positive	471 (24.1)	165 (26.1)	204 (24.4)	0.44
SLEDAI-2K total score, median (IQR)	8 (6, 10)	8 (6, 12)	6 (6, 8)	<0.001
SLEDAI-2K domain				
Neurologic	77 (3.7)	34 (3.8)	7 (1.0)	<0.001
Vasculitis	76 (3.7)	47 (5.3)	13 (1.9)	<0.001
Musculoskeletal	478 (23.2)	240 (27.1)	107 (15.7)	<0.001
Renal	1,197 (58.1)	549 (62.1)	389 (57.0)	0.043
Cutaneous	736 (35.7)	310 (35.1)	250 (36.7)	0.53
Serositis	45 (2.2)	22 (2.5)	9 (1.3)	0.1
Serologic	1,789 (86.8)	762 (86.2)	624 (91.5)	0.001
Anti-dsDNA	1,445 (70.9)	503 (74.7)	608 (69.4)	0.021
Low C3/C4	1,323 (64.4)	450 (66.2)	562 (63.6)	0.30
Constitutional	40 (1.9)	26 (2.9)	6 (0.9)	0.004
Hematologic	177 (8.6)	78 (8.8)	48 (7.0)	0.2
PhGA, median (IQR) score	1.0 (0.5, 1.5)	1.0 (0.6, 1.5)	0.9 (0.5, 1.2)	<0.001
SFI				
Any flare	1,061 (51.5)	460 (52.0)	277 (40.6)	<0.001
Mild/moderate flare	952 (46.2)	408 (46.2)	246 (36.1)	<0.001
Severe flare	346 (16.8)	168 (19.0)	80 (11.7)	<0.001
Accrued damage (SDI >0)	801 (42.2)	335 (40.8)	295 (46.9)	0.019
Prednisolone use	1,765 (85.7)	763 (86.3)	579 (84.9)	0.4
Prednisolone dose, median (IQR) mg/day	7.5 (5, 15)	8.5 (5.0, 20.0)	6.6 (4.0, 10.0)	<0.001
Antimalarials	1,457 (70.7)	478 (70.1)	614 (69.5)	0.79
Immunosuppressants	1,310 (63.6)	430 (63.0)	561 (63.5)	0.87
Azathioprine	447 (21.7)	166 (24.3)	171 (19.3)	0.017
Mycophenolate	591 (28.6)	192 (28.1)	252 (28.5)	0.72
Methotrexate	113 (5.5)	34 (5.0)	44 (5.0)	0.9
Other	289 (14.0)	79 (11.7)	141 (15.9)	–

* Except where otherwise indicated, values are number (%) of patients. SLE = systemic lupus erythematosus; mSRI = modified SLE Responder Index; IQR = interquartile range; ANA = antinuclear antibody; aPL = antiphospholipid antibody; SLEDAI-2K = SLE Disease Activity Index 2000; anti-dsDNA = anti–double-stranded DNA; PhGA = physician global assessment; SFI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI flare index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

to 5 years of follow-up (Figure 2A). Most mSRI responders at 1 year (range 71–75%) remained mSRI responders at subsequent annual time points (Figure 2B).

Association of mSRI attainment with clinical outcomes at annual time points. Table 2 summarizes the results of univariable linear and logistic regression analyses of associations between mSRI attainment and clinical outcomes present at annual time points for years 1, 3, and 5. Full results, including additional annual time points at years 2 and 4, are presented in Supplementary Table 1 available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42350. At each annual visit, mSRI responders had significantly lower disease activity as measured by SLEDAI-2K and PhGA ($P < 0.001$ for regression coefficients at all annual time points), in addition to significantly lower glucocorticoid doses ($P < 0.001$ for regression coefficients at all time points) and lower odds of flare ($P < 0.001$ for odds ratios [ORs] at all time points). Attainment of LLDAS, remission, and remission-0 was significantly greater among mSRI responders at all annual visits, with ORs ranging from 10.4 to 13.3, 2.83 to 5.52, and 3.19 to 7.65, respectively, $P < 0.001$ for all ORs. Fewer mSRI responders at each annual time point had accrued damage from baseline visit (OR range 0.67–0.78, significant at years 2 and 3).

We next analyzed associations between mSRI responder status at each annual time point and outcome variables considering all data available across the study period (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42350). Time-adjusted mean disease activity (adjusted mean SLEDAI-2K and time-adjusted mean PhGA) was consistently lower among mSRI responders at each annual time point when considering mean results from the year preceding each annual visit and when including all visits from baseline. Time-adjusted mean prednisolone doses and occurrence of flare were lower

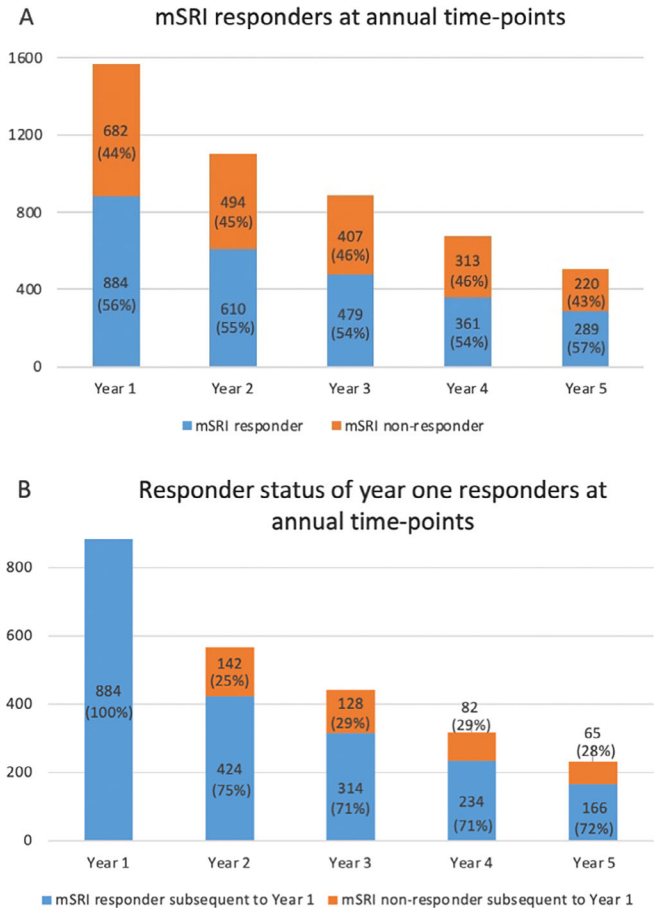

Figure 2. Bar graphs showing the number (%) of included systemic lupus erythematosus (SLE) patients who attained a modified version of the SLE Responder Index (mSRI) at annual time points over 5-year follow-up (**A**) and the number (%) of mSRI responders at year 1 who remained mSRI responders versus those who did not over 5-year follow-up (**B**).

among mSRI responders in the year preceding each annual visit from the second year onward, but not when considering all visits from baseline. Patients who were mSRI responders were also significantly more likely to attain LLDAS, remission, and remission-0 in the year preceding each annual visit and when including all visits from baseline.

Association of mSRI attainment at 1 year with future clinical outcomes. Table 3 shows the association of mSRI response attainment at 1 year with future clinical outcomes assessed at annual time points from 2 to 5 years. Full results are presented in Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.42350. Compared to nonresponders at year 1, mSRI responders at year 1 had significantly lower future disease activity, measured with either SLEDAI-2K or PhGA, at virtually all subsequent time points, considering values at the time of each annual visit (Table 3) as well as time-adjusted means in the year preceding each annual visit and from baseline (Supplementary Table 2).

The strength of these associations, while generally maintaining statistical significance, gradually weakened over time. Prednisolone use, including time-adjusted mean doses, was lower in year 1 mSRI responders compared to year 1 nonresponders, with between-group differences attenuating from year 4 onward. In contrast, there was no significant association of year 1 mSRI attainment with rates of flare in subsequent years. Year 1 mSRI responders were more likely to achieve LLDAS and remission when analyzed according to whether outcomes were achieved at annual time points, at any visit in the preceding year, and at any visit since baseline. However, like other outcomes, the strength of associations lessened over time. A similar pattern of association was seen for remission-0, but as a more stringent outcome, this was achieved by fewer patients, limiting the power of statistical comparisons. Importantly, damage accrual was significantly lower in year 1 mSRI responders compared to nonresponders across all 5 years of follow-up (OR range 0.58–0.69).

DISCUSSION

Research in the development of measurement end points for SLE continues to evolve. For example, recent years have seen the definition and validation of LLDAS and remission as treat-to-target

Table 2. Associations of mSRI attainment with clinical outcomes at 1-, 3-, and 5-year annual time points*

	Year 1			Year 3			Year 5		
	mSRI response			mSRI response			mSRI response		
	No (n = 682)	Yes (n = 884)	RC (95% CI) or OR (95% CI)†	No n = 407	Yes n = 479	RC (95% CI) or OR (95% CI)†	No n = 220	Yes n = 289	RC (95% CI) or OR (95% CI)†
Outcomes analyzed using linear regression, mean ± SD									
SLEDAI-2K score‡	7.4 ± 3.7	2.7 ± 2.5	−4.63 (−4.9, −4.3)§	6.9 ± 3.7	2.5 ± 2.1	−4.42 (−4.8, −4.0)§	6.4 ± 3.0	2.5 ± 2.3	−3.89 (−4.4, −3.4)§
Adjusted mean SLEDAI¶	6.7 ± 2.8	5.2 ± 2.9	−1.47 (−1.8, −1.2)§	6.0 ± 2.5	4.5 ± 2.5	−1.46 (−1.8, −1.1)§	5.8 ± 2.4	4.6 ± 2.3	−1.18 (−1.6, −0.8)§
PhGA score‡	0.9 ± 0.6	0.5 ± 0.5	−0.38 (−0.4, −0.3)§	0.9 ± 0.6	0.4 ± 0.4	−0.48 (−0.6, −0.4)§	0.8 ± 0.6	0.3 ± 0.3	−0.44 (−0.5, −0.4)§
Prednisolone dose, mg/day‡	9.8 ± 21.5	5.8 ± 5.1	−4.01 (−5.5, −2.5)§	8.1 ± 8.3	4.8 ± 4.9	−3.25 (−4.1, −2.4)§	7.8 ± 10.6	4.5 ± 4.7	−3.32 (−4.7, −1.9)§
Outcomes analyzed using logistic regression, no. (%) of patients									
Flare‡	245 (36)	81 (9.2)	0.18 (0.1, 0.2)§	113 (28)	39 (8)	0.23 (0.2, 0.3)§	56 (26)	8 (3)	0.08 (0.0, 0.2)§
LLDAS attainment‡	62 (9.5)	445 (53)	10.7 (8.0, 14.4)§	50 (13)	270 (61)	10.4 (7.3, 14.8)§	26 (12)	172 (63)	12.0 (7.5, 19.5)§
Remission‡	141 (21)	375 (42)	2.83 (2.3, 3.6)§	76 (20)	265 (59)	5.52 (4.0, 7.6)§	60 (29)	175 (64)	4.30 (2.9, 6.3)§
Remission-0‡#	19 (2.8)	75 (8.5)	3.19 (1.9, 5.3)§	8 (2)	66 (14)	7.65 (3.6, 16.1)§	9 (4)	54 (19)	5.23 (2.5, 10.9)§
Damage accrual¶	70 (10)	67 (8)	0.72 (0.5, 1.0)	104 (26)	95 (20)	0.72 (0.5, 1.0)**	78 (36)	87 (30)	0.78 (0.5, 1.1)

* Full results, including data at years 2 and 4, are available in Supplementary Table 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42350). mSRI = modified SLE Responder Index; SLEDAI-2K = SLE Disease Activity Index 2000; PhGA = physician global assessment; LLDAS = Lupus Low Disease Activity State.
† Comparative values for each outcome represent either regression coefficients (RCs) with 95% confidence intervals (95% CIs) when analyzed using univariable linear regression, or odds ratios (ORs) with 95% CIs when analyzed using univariable logistic regression.
‡ Assessed at annual time point.
§ $P < 0.001$.
¶ Assessed from baseline.
# Remission-0 was defined as meeting remission criteria according to the definition of remission in systemic lupus erythematosus (SLE) (see ref 28) plus having no glucocorticoid use.
** Between $P > 0.01$ and $P < 0.05$.

Table 3. Predictive value of mSRI attainment at 1 year for clinical outcomes at subsequent 2-, 3-, 4-, and 5-year annual time points*

	Year 2			Year 3			Year 4			Year 5		
	mSRI response at year 1			mSRI response at year 1			mSRI response at year 1			mSRI response at year 1		
	No (n = 499)	Yes (n = 594)	RC (95% CI) or OR (95% CI)†	No (n = 425)	Yes (n = 475)	RC (95% CI) or OR (95% CI)†	No (n = 344)	Yes (n = 333)	RC (95% CI) or OR (95% CI)†	No (n = 265)	Yes (n = 240)	RC (95% CI) or OR (95% CI)†
Outcomes analyzed using linear regression, mean ± SD												
SLEDAI-2K score‡	5.4 ± 3.7	3.8 ± 3.6	−1.60 (−2.0, −1.2)§	5.1 ± 3.7	3.7 ± 3.5	−1.31 (−1.8, −0.8)§	5.1 ± 3.6	3.8 ± 3.4	−1.26 (−1.8, −0.7)§	4.5 ± 3.1	3.8 ± 3.3	−0.71 (−1.3, −0.1)¶
Adjusted mean SLEDAI#	6.4 ± 2.6	4.4 ± 2.5	−1.98 (−2.3, −1.7)§	6.0 ± 2.4	4.3 ± 2.4	−1.73 (−2.1, −1.4)§	5.9 ± 2.3	4.3 ± 2.4	−1.63 (−2.0, −1.3)**	5.8 ± 2.3	4.3 ± 2.3	−1.51 (−1.9, −1.1)§
PhGA score‡	0.7 ± 0.6	0.5 ± 0.5	−0.18 (−0.3, −0.1)§	0.7 ± 0.6	0.5 ± 0.5	−0.16 (−0.2, −0.1)§	0.6 ± 0.5	0.5 ± 0.5	−0.09 (−0.2, −0.0)¶	0.6 ± 0.5	0.5 ± 0.5	−0.03 (−0.11, 0.1)
Prednisolone dose, mg/day‡	7.7 ± 8.3	6.0 ± 7.0	−1.70 (−2.6, −0.8)§	6.9 ± 7.4	5.8 ± 6.3	−1.16 (−2.1, −0.3)**	6.1 ± 5.8	6.1 ± 8.0	−0.01 (−1.1, 1.0)	6.0 ± 6.1	6.1 ± 9.7	0.11 (−1.3, 1.5)
Outcomes analyzed using logistic regression, no. (%) of patients												
Flare‡	97 (19)	111 (19)	0.95 (0.7, 1.3)	70 (17)	77 (16)	0.98 (0.7, 1.4)	59 (17)	53 (16)	0.91 (0.6, 1.4)	38 (14)	25 (10)	0.69 (0.4, 1.2)
LLDAS attainment‡	128 (28)	246 (47)	2.28 (1.8, 3.0)§	127 (33)	180 (45)	1.66 (1.2, 2.2)**	100 (31)	135 (47)	1.91 (1.4, 2.7)§	90 (36)	100 (46)	1.51 (1.0, 2.2)¶
Remission‡	87 (18)	217 (38)	2.79 (2.1, 3.7)§	86 (21)	164 (38)	2.21 (1.6, 3.0)§	79 (24)	120 (38)	1.93 (1.4, 2.7)§	80 (32)	88 (38)	1.35 (0.9, 1.0)
Remission-0‡,††	24 (5)	47 (8)	1.71 (1.0, 2.8)¶	26 (7)	47 (11)	1.74 (1.1, 2.9)¶	27 (8)	36 (12)	1.43 (0.9, 2.4)	28 (11)	31 (14)	1.26 (0.7, 2.2)
Damage accrual#	104 (21)	79 (13)	0.58 (0.4, 0.8)**	114 (27)	86 (18)	0.60 (0.4, 0.8)§	101 (29)	74 (22)	0.69 (0.5, 1.0)¶	94 (36)	65 (27)	0.68 (0.5, 1.0)¶

* Full results are available in Supplementary Table 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.42350). mSRI = modified SLE Responder Index; SLEDAI-2K = SLE Disease Activity Index 2000; PhGA = physician global assessment; LLDAS = Lupus Low Disease Activity State.
† Comparative values for each outcome represent either regression coefficients (RCs) with 95% confidence intervals (95% CIs) when analyzed using univariable linear regression, or odds ratios (ORs) with 95% CIs when analyzed using univariable logistic regression.
‡ Assessed at annual time point.
§ $P < 0.001$.
¶ Between $P > 0.01$ and $P < 0.05$.
# Assessed from baseline.
** Between $P > 0.001$ and $P < 0.01$.
†† Remission-0 was defined as meeting remission criteria according to the definition of remission in systemic lupus erythematosus (SLE) (see ref 28) plus having no glucocorticoid use.

end points, and LLDAS has also shown utility as an outcome measure in RCTs (30–33). In addition, recommendations for development of clinical trial end points now include the requirement to stringently demonstrate that measurements deliver outcomes that impact patient health (34). Despite being the most commonly used primary efficacy end point in SLE RCTs over the last decade, the SRI has limited validation against long-term clinical outcomes. To address this knowledge gap, we used prospectively collected data from a large, multinational lupus cohort to examine whether patients with active disease who attain a modified version of the SRI, omitting the BILAG criteria, have better outcomes than those who do not. We found that mSRI attainment at annual time points portends favorable clinical outcomes over up to 5 years of follow-up. Furthermore, mSRI attainment at 1 year, the typical timing of efficacy assessment in SLE clinical trials, predicted ongoing benefit in subsequent years.

Using data from a longitudinal cohort, we identified over 2,000 SLE patients who had a visit with active disease (SLEDAI-2K score ≥6) and synchronized these visits to set a baseline visit from which to follow outcomes. The rate of mSRI attainment at 1 year in our study was 56%. In comparison, typical SRI response rates in recent clinical trials have ranged from 32% to 48% in the placebo (i.e., standard of care) arms (35), with these lower rates most likely reflecting the restrictions on concomitant medications such as glucocorticoid bursts applied in a trial setting and potential differences in an RCT population compared to an unselected observational cohort. We also examined persistence of mSRI attainment (relative to the baseline active disease visit for each patient) over up to 5 years of follow-up, and found that 71–75% of mSRI responders at 1 year continued to meet the responder definition at subsequent annual time points. The maintenance of similar rates of mSRI response from 1 year up to 5 years of follow-up suggests that mSRI response, once achieved, is more likely than not to be maintained over time.

We found that mSRI responders consistently achieved better clinical outcomes compared to nonresponders for up to 5 years of follow-up. This included, at each annual time point from 1 to 5 years, significantly lower disease activity measured by SLEDAI-2K and PhGA, lower rates of flare, lower glucocorticoid doses, higher rates of attainment of treat-to-target end points, as well as 22–33% lower odds of accruing damage after the baseline visit. Associations were detected when analyzing outcomes at each annual time point and when analyzed over time considering all available visits. These associations were largely true when we analyzed year 1 mSRI responder status with future outcomes. At annual time points from years 2 to 5, we found that compared to mSRI nonresponders, mSRI responders at year 1 consistently had significantly lower disease activity scores, higher rates of LLDAS and remission attainment, and lower glucocorticoid doses that were significant for up to 4 years from baseline.

While benefit of year 1 mSRI attainment persisted at future time points, there was a consistent attenuation of the magnitude of benefit for most outcomes as time progressed. This was not unexpected given the fluctuating nature of SLE and our cohort being observational in nature. Importantly, damage accrual, a cumulative outcome which tends to take longer to develop, was significantly lower in year 1 mSRI responders compared to nonresponders at all subsequent time points through 5 years of follow-up. Together, these findings support the benefit of mSRI attainment at 1 year on future outcomes.

These results support and extend existing post hoc analyses of trial data seeking to validate the SRI as a meaningful end point. Prior studies have shown that at 1-year follow-up, SRI-4 response is significantly associated with improvements in SLEDAI, BILAG, and PhGA, as well as other outcomes not included in the SRI definition itself, including flare rates, glucocorticoid reduction, improvements in joint counts and skin scores, and positive associations with patient-reported outcomes, including Short Form 36 and Functional Assessment of Chronic Illness Therapy–Fatigue scores (8,17,18). In addition to these associations, we also found novel associations of mSRI attainment with the prognostically important outcomes of LLDAS and remission attainment, as well as reduced damage accrual. The current study extends the timeframe of analyses beyond the typical 1-year clinical trial window and shows that benefits of mSRI response extend for up to 5 years, with a comparable level of benefit seen at all time points over follow-up. Furthermore, by analyzing associations of mSRI response at 1 year with clinical outcomes across subsequent years, our findings suggest that outcomes observed at a 1-year time point predict improved outcomes over up to 5 years, albeit with the magnitude of benefit gradually attenuating with the passage of time.

While our study results support the long-term validity of the SRI as a treatment response measure, we did not examine all characteristics relevant to the suitability of an instrument as a clinical trial efficacy end point. Other characteristics of the SRI include poor sensitivity to change due to the use of binary thresholds in the SLEDAI, a factor which may contribute to inconsistent discrimination between treatment arms in clinical trials. Thus, although our study addresses an important gap in the construct validity of the SRI as a trial outcome measure, it does not negate other limitations of the SRI as a measure for SLE trials.

Limitations of this study include the use of a modified version of the SRI, due to the BILAG not being collected in our study cohort. It is unlikely that this would substantially affect results, as multiple studies have shown the BILAG criteria to be only very rarely discordant with responder status as determined by the SLEDAI and PhGA criteria (6–8). For example, in analyses of SRI response data from phase III tabalumab trials, and combined phase II anifrolumab and sifalimumab data, only 0.5% and 1.5% of patients, respectively, met the SLEDAI reduction but were deemed SRI nonresponders due to failure to meet BILAG or PhGA criteria (7,8). Baseline characteristics of mSRI

responders and nonresponders at 1 year differed, with mSRI responders at 1 year having higher disease activity, higher glucocorticoid doses, and less baseline damage than nonresponders. We do not consider it likely that these differences would contribute to mSRI responders having more favorable outcomes.

Other study limitations relate to the use of cohort data, although we designated active disease (SLEDAI-2K score ≥ 6) as the baseline visit, which is similar to thresholds used to recruit patients to typical SLE clinical trials. Patients in our cohort were predominantly Asian, which likely contributed to the observation of higher rates of renal and serologic activity and lower rates of musculoskeletal and mucocutaneous features compared to typical SLE trial cohorts (5). Baseline disease activity was also slightly lower in our cohort (median SLEDAI-2K score of 8) than in typical trial populations. Nonetheless, significant disease activity and severity in our cohort are suggested by the high proportions of glucocorticoid use and rates of damage already accrued at baseline. The nature of our data set also meant we were unable to analyze the influence of different medications and/or changes in treatment on observed outcomes.

Despite these limitations, applying the mSRI in an observational setting in a real-world context supports the validity of SRI as a trial outcome measure. Strengths of this study also include the cohort size and duration of follow-up, as well as the investigation of a broad range of relevant clinical outcomes, with the consistency of results supporting the robustness of our findings.

In conclusion, this study represents the most comprehensive analysis to date evaluating SRI attainment against longer-term clinical outcomes, albeit using a modified definition. Although SRI attainment may be an imperfect measure of treatment response, this study provides important and reassuring data regarding its clinical meaningfulness when used in SLE clinical trials.

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AUTHOR CONTRIBUTIONS

All the authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Connelly and Kandane-Rathnayake had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of the data. Hoi, Louthrenoo, Hamijoyo, Luo, Wu, Cho, Lateef, Lau, Chen, Navarra, Zamora, Li, An, Sockalingam, Hao, Zhang, Chan, Katsumata, Harigai, Oon, Bae, O'Neill, Gibson, Basnayake, Kikuchi, Takeuchi, Ling Ng, Tugnet, Kumar, Goldblatt, Law, Tee, Tee, Tanaka, Ohkubo, Tan, Karyekar, Nikpour, Golder, Morand.

Analysis and interpretation of the data. Connelly, Kandane-Rathnayake, Golder, Morand.

ROLE OF THE STUDY SPONSOR

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