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Prevalence, Determinants, and Outcomes of Low Disease Activity and Remission Attainment in Patients With Systemic Lupus Erythematosus That Is Clinically Active

Yanjie Hao,[1] Dylan Hansen,[2] Rangi Kandane-Rathnayake,[3] Worawit Louthrenoo,[4] Yi-Hsing Chen,[5] Jiacai Cho,[6] Aisha Lateef,[7] Laniyati Hamijoyo,[8] Shue Fen Luo,[9] Yeong-Jian Jan Wu,[9] Sandra Navarra,[10] Leonid Zamora,[10] Zhanguo Li,[11] Sargunan Sockalingam,[12] Yasuhiro Katsumata,[13] Masayoshi Harigai,[13] Zhuoli Zhang,[14] Madelynn Chan,[15] Jun Kikuchi,[16] Tsutomu Takeuchi,[16] Sang-Cheol Bae,[17] Fiona Goldblatt,[18] Sean O'Neill,[19] Kristine (Pek Ling) Ng,[20] Annie Law,[21] B. M. D. B. Basnayake,[22] Nicola Tugnet,[23] Sunil Kumar,[24] Cherica Tee,[25] Michael Tee,[25] Naoaki Ohkubo,[26] Yoshiya Tanaka,[26] Shirley Chan,[27] C. S. Lau,[27] Vera Golder,[3] Alberta Hoi,[3] Shereen Oon,[28] Eric Morand,[3] and Mandana Nikpour,[29] for the Asia-Pacific Lupus Collaboration

Objective. This study aimed to identify in patients with systemic lupus erythematosus (SLE) with clinically active disease the attainment of frequency and determinants of Lupus Low Disease Activity State (LLDAS) and Definition of Remission in SLE (DORIS) and the frequency and determinants of flare and damage accrual after target attainment.

Methods. Patients in a multinational cohort with SLE who had clinical disease activity but were not in LLDAS or DORIS were observed prospectively.

Results. A total of 1,991 patients (93.2% female) were observed for a median (interquartile range) of 2.5 (0.7–4.5) years, with 70.9% and 55.6% achieving LLDAS and DORIS, respectively. Nephritis and low complements were associated with a longer time, and antimalarial and immunosuppressant use were associated with a shorter time to LLDAS attainment. After the first LLDAS and DORIS attainment, 47.0% and 47.5% of the patients experienced flare(s), respectively, and 9.5% and 7.9 % of patients accrued organ damage within 24 months, respectively. Longer cumulative time at target and antimalarial use was associated with a longer time to flare and damage accrual, whereas dose reduction in glucocorticoids and immunosuppressants was associated with a shorter time to flare. Reduction in immunosuppressants also correlated with a shorter time to damage accrual.

Conclusion. In patients with SLE with clinical disease activity, the proportion attaining LLDAS and DORIS under usual care conditions is suboptimal. Longer maintenance of these states is significantly associated with reduced risk of flare. Because flares and damage accrual still occur frequently following initial target attainment, further research is needed to inform strategies for maintaining these targets.

INTRODUCTION

There is increasing interest in adopting the principle of treat-to-target in systemic lupus erythematosus (SLE). The recommendations for the management of SLE have emphasized the importance of treat-to-target in SLE and proposed "remission, as defined by the Definition of Remission in SLE (DORIS) criteria, or alternately, low disease activity states, such as the Lupus Low Disease Activity State (LLDAS), as treatment targets."[1] Multiple large prospective and retrospective studies have demonstrated

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SIGNIFICANCE & INNOVATIONS

- The present study focused on patients with systemic lupus erythematosus (SLE) with clinically active disease, defined according to the clinical domains of the Systemic Lupus Erythematosus Disease Activity Index-2000.
- Target attainment, including low disease activity and remission, is not optimal in this group of patients under usual care conditions, primarily managed with conventional therapies, with 30% not achieving either target over a median of 2.5 years.
- Flare and damage accrual are still substantial after reaching low disease activity or remission. Maintaining these targets for longer may reduce the risk of flares and organ damage, and tapering immunosuppressive treatment after target attainment is a risk factor for these adverse outcomes.
- This is the first study to comprehensively evaluate target attainment and subsequent clinical outcomes in patients with clinically active disease in a large prospective cohort with SLE in the Asia–Pacific region. Prospective clinical trials of a treating-to-target strategy in SLE are needed, and data from the present study can inform the design of such clinical trials.

that in patients with SLE, attainment of these targets is associated with improved outcomes, including reduced damage accrual, better health-related quality of life (HRQoL), and improved survival.[2–6] Although studies have indicated that attainment of low disease activity or remission is protectively associated with reduced damage accrual in patients with high disease activity (Systemic Lupus Erythematosus Disease Activity Index-2000 [SLEDAI-2K] ≥ 6) at baseline,[3] significant knowledge gaps remain concerning the timing and impacts of remission or low disease activity attainment in the larger subset of patients who have any clinically active disease, who are likely to be the patients recruited into future treating-to-target intervention studies.[7]

We undertook a retrospective analysis of patients in the large multinational prospective Asia-Pacific Lupus Collaboration (APLC) cohort, under usual care conditions. We observed patients from their first visit with any clinical disease activity to identify (i) frequency and time to attainment of low disease activity and remission, defined by the LLDAS and DORIS criteria, respectively,[2,8] (ii) determinants of attaining these targets, (iii) frequency and time to flare and damage accrual subsequent to LLDAS or DORIS attainment, and (iv) determinants of developing flare and damage accrual following target attainment.

PATIENTS AND METHODS

Patients. This study included all patients enrolled in the APLC cohort between March 2013 and December 2020 who newly developed any clinical disease activity following at least one visit with clinical inactivity. Clinical disease activity was defined as the clinical domains of the SLEDAI-2K (cSLEDAI-2K) >0 but were not in DORIS or LLDAS. Baseline was defined as the first observed clinical activity following an observed period of inactivity to ensure time from the onset of activity to LLDAS or DORIS could be correctly calculated. Patients were observed from this baseline. A subgroup of patients who newly developed high disease activity, defined as SLEDAI-2K ≥10, was also observed from their first fulfilling high disease activity criteria.

The APLC cohort is a prospective multinational observational cohort of patients with SLE, including 25 sites across

and Union Chimique Belge to support data collection and data and project management.

[1]Yanjie Hao, MD: The University of Melbourne and St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia, and Peking University First Hospital, Beijing, China; [2]Dylan Hansen, MBioStat: St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia; [3]Rangi Kandane-Rathnayake, PhD, Vera Golder, PhD, Alberta Hoi, PhD, Eric Morand, PhD: Monash University, Melbourne, Victoria, Australia; [4]Worawit Louthrenoo, MD: Chiang Mai University Hospital, Chiang Mai, Thailand; [5]Yi-Hsing Chen, MD: Taichung Veterans General Hospital, Taichung, Taiwan; [6]Jiacai Cho, MBBS: National University Hospital, University Medicine Cluster, Singapore; [7]Aisha Lateef, MBBS: Woodlands Health, Singapore; [8]Laniyati Hamijoyo, MD: Padjadjaran University, Hasan Sadikin General Hospital, Bandung, Indonesia; [9]Shue Fen Luo, MD, Yeong-Jian Jan Wu, MD: Chang Gung Memorial Hospital, Taoyuan City, Taiwan; [10]Sandra Navarra, MD, Leonid Zamora, MD: University of Santo Tomas Hospital, Manila, Philippines; [11]Zhanguo Li, PhD: People's Hospital Peking University Health Science Center, Beijing, China; [12]Sargunan Sockalingam, MBBS: University of Malaya, Kuala Lumpur, Malaysia; [13]Yasuhiro Katsumata, PhD, Masayoshi Harigai, PhD: Tokyo Women's Medical University, Tokyo, Japan; [14]Zhuoli Zhang, PhD: Peking University First Hospital, Beijing, China; [15]Madelynn Chan, MD: Tan Tock Seng Hospital, Singapore; [16]Jun Kikuchi, MD, Tsutomu Takeuchi, PhD: Keio University, Tokyo, Japan; [17]Sang-Cheol Bae, PhD: Hanyang University Hospital for Rheumatic Diseases, Hanyang University Institute for Rheumatology Research, and Hanyang Institute of Bioscience and Biotechnology, Seoul, South Korea; [18]Fiona Goldblatt, PhD: Flinders Medical Centre, Adelaide, South Australia, Australia; [19]Sean O'Neill, PhD: Liverpool Hospital, Liverpool, New South Wales, Australia; [20]Kristine (Pek Ling) Ng, BScMed, MBBS: Health New Zealand Waitemata, Auckland, New Zealand; [21]Annie Law, MBBS: Singapore General Hospital, Singapore; [22]B. M. D. B. Basnayake, MD: Teaching Hospital Kandy, Kandy, Sri Lanka; [23]Nicola Tugnet, MBChB: Greenlane Clinical Centre, Auckland, New Zealand; [24]Sunil Kumar, MBBS: Middlemore Hospital, Auckland, New Zealand; [25]Cherica Tee, MD, Michael Tee, MD: University of the Philippines, Manila, Philippines; [26]Naoaki Ohkubo, MD, Yoshiya Tanaka, PhD: University of Occupational and Environmental Health, Kitakyushu, Japan; [27]Shirley Chan, MBBS, C. S. Lau, MD: The University of Hong Kong, Hong Kong, China; [28]Shereen Oon, PhD: The University of Melbourne and St. Vincent's Hospital Melbourne, Melbourne, Victoria, Australia; [29]Mandana Nikpour, PhD: The University of Melbourne and St. Vincent's Hospital, Melbourne, Victoria and The University of Sydney and Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.

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Address correspondence via email to Mandana Nikpour, PhD, at mandana.nikpour@sydney.edu.au.

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12 countries in the Asia–Pacific region. Patients eligible for enrollment into the APLC cohort are those with newly diagnosed or pre-existing adult patients with SLE (≥18 years old), fulfilling either the 1997 American College of Rheumatology (ACR) Modified Classification Criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for SLE.[9,10] Patients are treated under standard care conditions and are seen every three to six months. No specific treatment algorithm was predefined.

Ethics. Human research ethical approval for data collection, storage of the central dataset, analysis, and publication of data collected by the APLC were obtained from the Monash University Human Research Ethics Committee (project 18778). Local ethics approvals have also been obtained at each participating site. Informed consent was obtained from each participant before enrollment.

Data collection. In the APLC cohort, patient demographics and SLE-related history were collected at enrollment. SLE manifestations; SLEDAI-2K score[11]; Physician Global Assessment (PGA; scale 0–3) score[12]; medication use including antimalarials, prednisolone (or equivalent), methotrexate (MTX), leflunomide (LEF), azathioprine (AZA), mycophenolate/mycophenolic acid (MMF/MPA), cyclosporin (CsA), tacrolimus (Tac), cyclophosphamide (CYC), rituximab, and belimumab; and disease flares were collected at each visit. The SLICC/ACR Damage Index (SDI) and the HRQoL 36-Item Short-Form Health Survey (SF36) were completed annually.[13,14] All data were recorded in a standardized electronic case report form.[15]

Data availability. Access to APLC pooled data is subject to the specific guidelines outlined in the APLC Data Access Policy (available on request). The APLC welcomes requests for aggregate (summary) data or to perform analyses of new research questions, and such requests can be submitted to the APLC Steering Committee via the APLC Project Manager.

Definitions. LLDAS was defined as SLEDAI-2K ≤4, with no activity in any major organ, no new disease activity since the previous assessment, PGA ≤1, and prednisolone (or equivalent) dosage ≤7.5 mg/day, with standard maintenance doses of immunosuppressant (IS) and approved biologic agents allowed.[3] The DORIS criteria require a cSLEDAI-2K of 0 (disregarding serology including anti–double-stranded DNA and complements) and PGA <0.5. It allows a maximum prednisolone dosage of 5 mg/day and IS treatment.[8] Disease flare was assessed using the flare definition used in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial—the SELENA-SLEDAI Flare Index (SFI).[16] Cumulative organ damage was defined according to SDI. An SDI score >0 was an indication of the presence of organ damage overall, and an increase in SDI of 1 unit or greater was defined as damage accrual.[13] Minimum clinically important difference (MCID) in the mental component summary (MCS) and physical component summary (PCS) scores of the SF36 were defined as a +2.5 increase in MCS and PCS scores.[17]

Statistical analysis. Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as numbers (percentages). Time to first LLDAS or DORIS attainment was measured from the first visit that met the inclusion criteria (study baseline) to the first subsequent visit that met the LLDAS or DORIS criteria. After first reaching LLDAS or DORIS, patients were further followed up, and time to first flare or damage accrual was defined from the first LLDAS or remission point to the first subsequent visit that met the definition for SFI or damage accrual. The duration of the first episode of LLDAS or DORIS was measured from the first visit that met the LLDAS or DORIS criteria to the first subsequent visit that did not. Univariable and multivariable time-varying covariate Cox regression analyses across consecutive visits were used to account for time-varying clinical features to determine factors associated with time to first LLDAS or DORIS attainment and factors associated with time to first flare and damage accrual following first LLDAS or DORIS attainment. Age, gender, disease duration, ethnicity, current smoking status, education level, clinical and serologic features according to SLEDAI-2K, and treatment-related variables, including prednisolone equivalent glucocorticoids dose, antimalarial use, and IS use (categorized as MMF/MPA use and other IS use including MTX, LEF, AZA, CsA, Tac, and CYC), were included in the univariable analysis for determinants of target attainment. Age, gender, disease duration, ethnicity, current smoking status, education level, serologic features, cumulative time in LLDAS or DORIS post-first target attainment until the current visit, time-adjusted mean (TAM) daily prednisolone dose from cohort enrollment up to the current visit, antimalarial use, reduction of prednisolone dose, and reduction of IS dose were included in the univariate analyses for flares and damage accrual after first LLDAS or DORIS attainment. Dose reduction was defined as any decrease in dose from the previous visit in prednisolone equivalent glucocorticoids or oral IS therapy, including MTX, LEF, AZA, MMF/MPA, CsA, and Tac, excluding antimalarials. All the dose reductions were at the physician's discretion. We selected variables for multivariable Cox regression analysis based on the results of univariate analyses and clinical relevance. All analyses were performed with STATA version 17.0 (StataCorp), and a P value of ≤0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics at baseline. Among 4,106 patients enrolled in the APLC cohort from March 2013 to December 2020, 1,991 patients newly developed clinical disease activity during follow-up, including

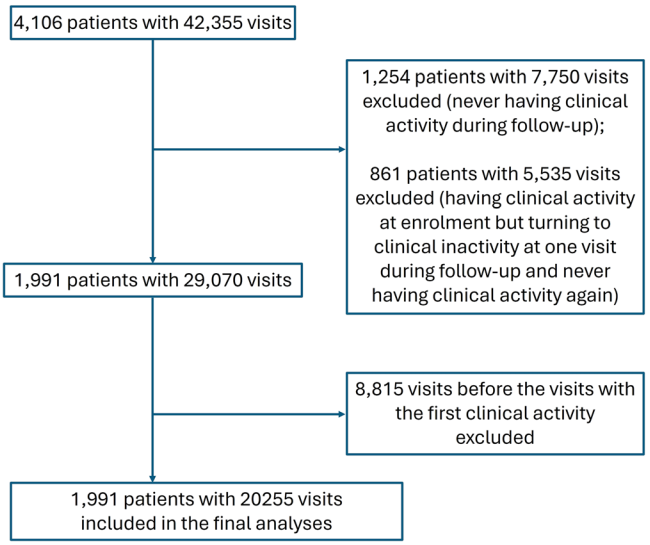

Figure 1. Flow diagram depicting selection of patients and visits for inclusion in analyses.

756 patients who newly developed high disease activity (SLEDAI-2K ≥ 10) on at least one occasion. For the included 1,991 patients, 8,815 visits that occurred before their first clinical activity visit were excluded, leaving 20,255 visits in the analyses (Figure 1). The 1,991 patients had a median (IQR) age at baseline of 41 (32–51) years; 93.2% were female, and 87.7% had Asian ethnicity. The median (IQR) disease duration at baseline was 10 (5–17) years, and the median (IQR) follow-up duration from baseline was 2.5 (0.7–4.5) years. The median (IQR) SLEDAI-2K score at baseline was 6 (4–8), with nephritis (41.2%), mucocutaneous involvement (32.5%), and arthritis (16.0%) as the most common clinical features (Table 1). During follow-up, antimalarial, prednisolone, IS, and biologics were used in 76.1%, 85.8%, 73.5%, and 3.1% of patients, respectively, with a median (IQR) TAM prednisolone dosage of 5 (2.5–9.2) mg/day. Compared to the analyzed cohort overall, the high disease activity subgroup was younger (36 [28–47] years old), had a shorter disease duration at baseline (9.0 [4.0–15.0] years), were more likely to be of Asian ethnicity (88.7%), and had a significantly higher frequency of nephritis (78.7%) and a higher median SLEDAI-2K score (12 [10–14]) at baseline. During follow-up, more patients with high disease activity were taking prednisolone (95.5%), IS (85.2%), and biologics (6.9%), with a higher TAM prednisolone dosage (7.9 [5–12.9] mg/day; Supplementary Table 1).

Target attainment from baseline. During follow-up, 1,412 (70.9%) patients attained LLDAS at least once, with a median (IQR) time to first LLDAS attainment of 0.5 (0.3–1.0) years. 1,107 (55.6%) patients attained DORIS, with a median (IQR) of 0.6 (0.3–1.4) years to first attainment. The duration of the first episodes of LLDAS and DORIS were 0.5 (0.3–1.0) and 0.6 (0.3–1.2) years, respectively (Table 2). Compared to the analyzed cohort overall, the high disease activity subgroup showed a markedly lower proportion of LLDAS (56.1%) and DORIS (39.7%) attainment, with a longer time to attain the targets and a shorter duration in the targets (Supplementary Table 2).

Table 1. Patient characteristics*

Baseline	Cohort (n = 1,991)
Age at baseline visit,[a] median (IQR), y	41 (32–51)
Age at diagnosis, median (IQR), y	29 (21–39)
Disease duration at baseline visit,[a] median (IQR), y	10.0 (5.0–17.0)
Female, n (%)	1,856 (93.2)
Family history of SLE, n (%)	153 of 1,963 (7.8)
Asian ethnicity, n (%)	1,738 of 1,982 (87.7)
Smoker at baseline visit,[a] n (%)	110 of 1,972 (5.6)
Tertiary education, n (%)	908 of 1,819 (49.2)
Clinical features at baseline visit according to SLEDAI-2K,[a] n (%)	
Nephritis	820 (41.2)
Mucocutaneous	647 (32.5)
Arthritis	319 (16.0)
Leukopenia	241 (12.1)
Thrombocytopenia	101 (5.1)
NPSLE	34 (1.7)
Serositis	29 (1.5)
Fever	23 (1.2)
Vasculitis	24 (1.2)
Myositis	8 (0.4)
SLEDAI-2K at baseline visit,[a] median (IQR)	6 (4–8)
PGA at baseline visit,[a] median (IQR)	0.7 (0.3–1.0)
Follow-up	
Follow-up duration from baseline visit,[a] median (IQR), y	2.5 (0.7–4.5)
Total visits per patient including baseline visit, median (IQR)	8 (3–14)
Medication ever used during follow-up	
Antimalarial use,[b] n (%)	1,515 (76.1)
Prednisolone use, n (%)	1,709 (85.8)
TAM daily prednisolone dosage, median (IQR), mg/day	5 (2.5–9.2)
Immunosuppressant use,[c] n (%)	1,464 (73.5)
Biologic use,[d] n (%)	61 (3.1)
Deaths during follow-up, n (%)	45 (2.3)

* IQR, interquartile range; NPSLE, neuropsychiatric systemic lupus erythematosus; PGA, Physician Global Assessment; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; TAM, time-adjusted mean.
[a] Baseline visit was defined as the first visit with clinically active disease following a visit without clinical activity.
[b] Antimalarials include hydroxychloroquine and chloroquine.
[c] Immunosuppressants include methotrexate, leflunomide, azathioprine, mycophenolate/mycophenolic acid, cyclosporin, tacrolimus, and cyclophosphamide.
[d] Biologics include rituximab and belimumab.

Main outcomes following first target attainment. After the first attainment of LLDAS, 663 of 1,412 (47.0%) of the patients experienced flare(s) within a median (IQR) follow-up of 2.4 (0.8–4.0) years. The median (IQR) time to first flare was 0.6 (0.3–1.4) years. After the first attainment of DORIS, 526 of 1,107 (47.5%) patients had flare(s) within a median (IQR) of 2.7 (1.0–4.2)

Table 2. Target attainment from baseline and associated outcomes*

LLDAS- and DORIS-associated outcomes	Cohort (n = 1,991)
LLDAS attainment from baseline,[a] n (%)	1,412 of 1,991 (70.9)
Time to first LLDAS attainment, median (IQR), y	0.5 (0.3–1.0)
Duration of first LLDAS, median (IQR), y	0.5 (0.3–1.0)
Flare following first attainment of LLDAS, n (%)	663 of 1,412 (47.0)
Time to first flare, median (IQR), y	0.6 (0.3–1.4)
Damage accrual over 24 months following first attainment of LLDAS, n (%)	68 of 717 (9.5)
Time to first damage accrual, median (IQR), y	1.9 (1.0–3.1)
MCS MCID[b] attainment over 24 months following first attainment of LLDAS, n (%)	207 of 642 (32.2)
PCS MCID[b] attainment over 24 months following first attainment of LLDAS, n (%)	155 of 642 (24.1)
TAM prednisolone dosage over 24 months following first attainment of LLDAS, median (IQR), mg/day	4.5 (1.5–6.0)
Death following first attainment of LLDAS, n (%)	22 of 1,412 (1.6)
DORIS attainment from baseline,[a] n (%)	1,107 of 1,991 (55.6)
Time to first DORIS attainment, median (IQR), y	0.6 (0.3–1.4)
Duration of first DORIS, median (IQR), y	0.6 (0.3–1.2)
Flare following first attainment of DORIS, n (%)	526 of 1,107 (47.5)
Time to first flare, median (IQR), y	0.7 (0.3–1.5)
Damage accrual over 24 months following first attainment of DORIS, n (%)	47 of 592 (7.9)
Time to first damage accrual, median (IQR), y	2.1 (1.2–3.4)
MCS MCID[b] attainment over 24 months following first attainment of DORIS, n (%)	177 of 543 (32.6)
PCS MCID[b] attainment over 24 months following first attainment of DORIS, n (%)	144 of 543 (26.5)
TAM prednisolone dosage over 24 months following first attainment of DORIS, median (IQR), mg/day	3.7 (0.9–5.1)
Death following first attainment of DORIS, n (%)	16 of 1,107 (1.4)

* DORIS, Definitions of Remission in SLE; IQR, interquartile range; LLDAS, Lupus Low Disease Activity State; MCID, minimum clinically important difference; MCS, mental component summary; PCS, physical component summary; SLE, systemic lupus erythematosus; TAM, time-adjusted mean.
[a] Baseline visit was defined as the first visit with clinically active disease following a visit without clinical activity.
[b] MCID in the MCS or PCS scores of the 36-Item Short-Form Health Survey was defined as a +2.5 increase in MCS or PCS score.

years, and the time to first flare was 0.7 (0.3–1.5) years. The incidences of flare during the follow-up period from first reaching LLDAS and DORIS to the end of follow-up (*after* first LLDAS and DORIS attainment) were 45 and 44 per 100 person-years, respectively. However, for the same group of patients, the incidences of flare from baseline to first reaching LLDAS and DORIS (*before* first LLDAS and DORIS attainment) were 200 and 116 per 100 person-years, respectively. After the first LLDAS and remission attainment, 68 of 717 (9.5%) and 47 of 592 (7.9%) patients had damage accrual over two years, respectively, with a median (IQR) of 1.9 (1.0–3.1) and 2.1 (1.2–3.4) years to first damage accrual, respectively (Table 2). With HRQoL, the proportions of patients attaining SF36 PCS and MCS MCID over two years after the first LLDAS or DORIS attainment were similar (24.1% vs 26.5% for PCS and 32.2% vs 32.6% for MCS, respectively). The median (IQR) TAM prednisolone dosages over two years after the first LLDAS and DORIS attainment were 4.5 (1.5–6.0) and 3.7 (0.9–5.1) mg/day, respectively. Concerning mortality rates, 22 of 1,412 (1.6%) patients died following the first LLDAS attainment over a median (IQR) follow-up of 2.4 (1.1–3.8) years; similarly, 16 of 1,107 (1.4%) of patients died over a median (IQR) of 3.1 (1.4–4.2) years following the first DORIS attainment (Table 2). In the high disease activity subgroup, more patients flared (58.0% and 59.3% after the first LLDAS and DORIS attainment, respectively) and accrued damage (11.2% and 9.6% after the first LLDAS and DORIS attainment over 24 months, respectively), compared to the analyzed cohort overall, with a relatively shorter time to first flare and damage accrual. However, the frequency of PCS and MCS MCID attainment was higher than the overall cohort, and the mortality rate was similar to the overall cohort (1.4% and 1.7% after the first LLDAS and DORIS attainment, respectively; Supplementary Table 2).

Determinants of target attainment from baseline. Multivariable time-varying covariate Cox regression analysis in the analyzed overall cohort identified nephritis, low complements, and higher prednisolone dose were independently associated with a longer time to attainment of LLDAS or DORIS. In addition, thrombocytopenia showed a significant association with a longer time to DORIS attainment. In contrast, older age, arthritis, antimalarial use, and MMF/MPA or other IS use were associated with a shorter time to attainment of LLDAS (Table 3).

Determinants of flare from first target attainment. In the analyzed cohort overall, after first achieving LLDAS or DORIS, longer cumulative time in LLDAS or DORIS (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.89–0.94, $P < 0.0001$ for LLDAS, and HR 0.92, 95% CI 0.89–0.94, $P < 0.0001$ for DORIS) and antimalarial use were each found to be protectively associated with subsequent flare, but prednisolone dose reduction increased the risk of subsequent flare (HR 1.21, 95% CI 1.02–1.45, $P = 0.033$ in the LLDAS model, and HR 1.23, 95% CI 1.00–1.51, $P = 0.047$ in the DORIS model). In addition, IS dose reduction was also associated with a shorter time to flare after LLDAS attainment (HR 1.27, 95% CI 1.02–1.60, $P = 0.036$) but did not reach statistical significance

Table 3. Multivariable models for time to first LLDAS or DORIS attainment from baseline*

Variables[a]	LLDAS		DORIS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per 10 years	1.05 (1.00–1.10)	0.036	1.02 (0.97–1.08)	0.47
Clinical features according to SLEDAI-2K				
Mucocutaneous	0.98 (0.85–1.13)	0.78	0.88 (0.75–1.03)	0.11
Arthritis	1.19 (1.02–1.40)	0.031	1.09 (0.98–1.32)	0.42
Leukopenia	1.03 (0.87–1.23)	0.73	0.83 (0.67–1.02)	0.072
Thrombocytopenia	0.80 (0.58–1.11)	0.178	0.36 (0.21–0.61)	0.0002
Vasculitis	0.48 (0.21–1.12)	0.091	0.21 (0.03–1.50)	0.12
Nephritis	0.58 (0.51–0.67)	<0.0001	0.69 (0.59–0.80)	<0.0001
Serological features according to SLEDAI-2K				
Anti-dsDNA positive	0.94 (0.84–1.05)	0.30	0.90 (0.79–1.03)	0.13
Low complements	0.85 (0.84–1.05)	0.0024	0.78 (0.68–0.89)	0.0003
Treatments				
Prednisolone dosage, mg/day	0.93 (0.91–0.94)	<0.0001	0.89 (0.87–0.90)	<0.0001
Antimalarial use	1.16 (1.02–1.31)	0.024	0.98 (0.86–1.13)	0.81
Immunosuppressant use				
No immunosuppressant	Reference	Reference	Reference	Reference
MMF/MPA	1.16 (1.00–1.34)	0.044	1.16 (0.97–1.37)	0.095
Other immunosuppressants[b]	1.15 (1.00–1.31)	0.046	0.98 (0.84–1.14)	0.75

* Multivariable time-varying covariate Cox regression analysis was performed. CI, confidence interval; DORIS, Definitions of Remission in SLE; dsDNA, double-stranded DNA; HR, hazard ratio; LLDAS, Lupus Low Disease Activity State; MMF/MPA, mycophenolate/mycophenolic acid; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.
[a] Variables were at any visit from baseline to the first LLDAS or DORIS attainment. The baseline was defined as the first visit with clinically active disease following a visit without clinical activity.
[b] Other immunosuppressants include methotrexate, leflunomide, azathioprine, cyclosporin, tacrolimus, and cyclophosphamide.

after DORIS attainment (HR 1.23, 95% CI 0.96–1.60, $P = 0.10$; Table 4).

Determinants of damage accrual from first target attainment. In terms of determinants of damage accrual after first LLDAS or DORIS attainment, older age and higher TAM daily prednisolone dose from cohort enrollment were associated with a shorter time to damage accrual, whereas antimalarial use was associated with a longer time to damage accrual in both LLDAS and DORIS models. Longer cumulative time in target since first attainment positively related to a longer time to damage accrual, especially the cumulative time in DORIS, which showed a statistically significant protective effect for subsequent damage accrual (HR 0.97, 95% CI 0.94–1.01, $P = 0.109$ for LLDAS, and HR 0.96, 95% CI 0.93–0.99, $P = 0.036$ for DORIS). In addition, IS dose reduction was associated with an increase in risk of damage accrual, and this association reached statistical significance in the LLDAS model (HR 1.87, 95% CI 1.29–2.73, $P = 0.001$ in the

Table 4. Multivariable models for time to first flare from first LLDAS or DORIS attainment*

Variables[a]	LLDAS		DORIS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per 10 years	0.94 (0.88–1.01)	0.085	0.91 (0.85–0.99)	0.020
Disease duration, per 5 years	1.01 (0.95–1.06)	0.84	1.02 (0.96–1.08)	0.46
Cumulative time in LLDAS/DORIS, per 3 months[b]	0.91 (0.89–0.94)	<0.0001	0.92 (0.89–0.94)	<0.0001
Treatments				
Antimalarial use	0.66 (0.56–0.78)	<0.0001	0.70 (0.58–0.83)	<0.0001
Prednisolone reduction[c]	1.21 (1.02–1.45)	0.033	1.23 (1.00–1.51)	0.047
Immunosuppressant reduction[d]	1.27 (1.02–1.60)	0.036	1.23 (0.96–1.60)	0.10

* Multivariable time-varying covariate Cox regression analysis was performed. CI, confidence interval; DORIS, Definitions of Remission in SLE; HR, hazard ratio; LLDAS, Lupus Low Disease Activity State; SLE, systemic lupus erythematosus.
[a] Variables were at any visit between the first LLDAS or DORIS attainment and the first flare.
[b] Cumulative time in LLDAS or DORIS was defined as being since the first LLDAS or DORIS attainment up to this visit. It was cumulative time in LLDAS for the LLDAS model and cumulative time in DORIS for the DORIS model.
[c] Prednisolone reduction was defined as any decrease in dose from the previous visit in prednisolone equivalent glucocorticoids.
[d] Immunosuppressant reduction was defined as any decrease in dose from the previous visit in any of the oral immunosuppressants, including methotrexate, leflunomide, azathioprine, mycophenolate/mycophenolic acid, cyclosporin, and tacrolimus, excluding antimalarials.

Table 5. Multivariable models for time to first damage accrual from first LLDAS or DORIS attainment*

Variables[a]	LLDAS		DORIS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per 10 years	1.26 (1.11–1.42)	<0.0001	1.38 (1.20–1.57)	<0.0001
Disease duration, per 5 years	1.07 (0.97–1.18)	0.155	1.11 (1.01–1.23)	0.035
Cumulative time in LLDAS/DORIS, per 3 months[b]	0.97 (0.94–1.01)	0.109	0.96 (0.93–0.99)	0.036
Treatments				
Antimalarial use	0.66 (0.49–0.90)	0.008	0.66 (0.47–0.92)	0.016
TAM prednisolone dosage, per 1 mg/day[c]	1.03 (1.00–1.06)	0.029	1.04 (1.01–1.08)	0.022
Immunosuppressants reduction[d]	1.87 (1.29–2.73)	0.001	1.47 (0.92–2.35)	0.108

* Multivariable time-varying covariate Cox regression analysis was performed. CI, confidence interval; DORIS, Definitions of Remission in SLE; HR, hazard ratio; LLDAS, Lupus Low Disease Activity State; SLE, systemic lupus erythematosus; TAM, time-adjusted mean.
[a] Variables were at any visit between the first LLDAS or DORIS attainment and the first damage accrual.
[b] Cumulative time in LLDAS or DORIS was defined as being since the first LLDAS or DORIS attainment up to this visit. It was cumulative time in LLDAS for the LLDAS model and cumulative time in DORIS for the DORIS model.
[c] TAM daily dose of prednisolone equivalent glucocorticoids was from cohort enrollment up to this visit.
[d] Immunosuppressant reduction was defined as any decrease in dose from the previous visit in any of the oral immunosuppressants, including methotrexate, leflunomide, azathioprine, mycophenolate/mycophenolic acid, cyclosporin, and tacrolimus, excluding antimalarials.

LLDAS model, and HR 1.47, 95% CI 0.92–2.35, $P = 0.108$ in the DORIS model; Table 5).

DISCUSSION

Patients enrolled in typical clinical trials of novel therapies in SLE are recruited based on having moderate or severe disease activity.[18,19] In contrast, future studies of treating-to-target approaches in SLE are likely to include a wider subset of patients, namely all those who are not in remission or LLDAS and have any clinical activity. Less is known about the rates, determinants, and consequences of treating-to-target goal attainment in these patients, and filling this knowledge gap may improve the design of such trials. In this study, we have reported the prevalence of attainment of LLDAS and DORIS "targets" in patients with any clinically active disease in a large multinational, multiethnic cohort in the Asia–Pacific region receiving standard-of-care therapy and some clinically important outcomes such as flare, damage accrual, and HRQoL following target attainment. In addition to the wider subset of patients with any clinical activity, we also reported these outcomes in a subgroup with high disease activity.

Cohort studies reported variable rates of attainment of LLDAS and remission. For example, Golder et al previously reported that 78.0% of the patients in the APLC cohort attained LLDAS during a mean follow-up of 2.2 years,[3] whereas 60.9% of the patients attained DORIS.[6] However, the reports were based on the entire APLC population, including a substantial proportion of patients who were in LLDAS or remission throughout the observation period; such patients would not be enrolled in a treating-to-target intervention study. The present study analyzed all patients with any clinically active disease who were not in LLDAS or remission and found relatively lower frequencies of target attainment. This means that almost one-third of patients with active disease were unable to attain a low activity disease state after a median of 2.6 years of usual care, and this number even increased to 44% in patients with high disease activity, underlining the need for a target-driven approach to SLE management. In the present study, the median time to achieve LLDAS and DORIS was 0.5 and 0.7 years, respectively; this is shorter than those reported by Babaoğlu et al and Wilhelm et al from the Hopkins Lupus cohort (1.1 years for LLDAS and 1.8 years for DORIS) despite a lower mean disease activity at baseline in the Hopkins patients.[20,21] However, the duration of the DORIS in the present report was longer than the Hopkins Lupus cohort (7.2 vs 3 months).[21] Different cohort compositions may explain these differences. In the Hopkins cohort, 61.8% of the patients were Caucasian, 30.1% were African American, and less than 10% were of other ethnicities, and patients with African American ethnicity had a lower frequency of LLDAS attainment than the other ethnicities.[20] There was another cohort study from Europe by Pitsigavdaki et al evaluating LLDAS and DORIS attainment rates in a population with moderate to high disease activity, defined as PGA ≥1.5 and/or SLEDAI-2K ≥6. Similar to the Hopkins cohort, they also reported a relatively longer time to target attainment (9 months for LLDAS and 15 months for DORIS) compared to our cohort. Different patient populations with varying ethnicities and disease activities may influence this result. In this European cohort, 96.3% of the patients were of White ethnicity, and the median disease activity was higher than ours.[22]

The subgroup analyses showed that patients with high disease activity were less likely to attain treatment targets than the overall cohort. Moreover, they were less likely to maintain low disease activity or remission status and had a higher chance of flaring, indicating that current management strategies still do not meet the needs of this group of patients. HRQoL is a key outcome, and improvement in HRQoL is one of the primary treatment objectives for patients with SLE. In the current study, over

30% and approximately 25% of the patients achieved an MCID in the mental and physical components of SF36 after reaching the targets, respectively. The high-activity subgroup achieved MCID at a greater frequency than the group overall. These findings suggest that target attainment can benefit HRQoL, especially in patients with high disease activity. Additionally, mental health improved more with target attainment than physical health, and DORIS attainment contributed more to improvement than LLDAS attainment in physical components.

Our results showed that lupus nephritis prolonged the time to LLDAS and remission attainment, whereas thrombocytopenia may impede remission attainment. Several previous studies from large cohorts have also shown that lupus nephritis was negatively associated with low disease activity or remission attainment,[20,23,24] but only one study by Zen et al reported that hematologic manifestations were negatively associated with remission attainment.[24] We also found that low complement was associated with a longer time to both LLDAS and DORIS attainment, consistent with some previous studies.[20,21,23] Regarding treatment effects, our analyses showed a positive association of antimalarial use with LLDAS attainment. In addition, IS use also showed a positive association with LLDAS attainment.

Although a series of studies have reported flare frequencies in patients with SLE,[25–28] we investigated flare frequency *following* LLDAS or remission attainment; this has rarely been reported in large multinational cohorts. We found that the incidence of flare after the target attainment was significantly lower compared to the period before target attainment in the same group of patients (45 vs 200 per 100 person-years after and before LLDAS attainment; 44 vs 116 per 100 person-years after and before DORIS attainment), confirming the protective association of target achievement with flare. However, almost half of the patients still experienced flare(s) following LLDAS and remission attainment within less than one year. In addition, organ damage accrued in almost 10% of the patients after target attainment. Longer cumulative time in LLDAS or DORIS states following the first target attainment was significantly associated with reduced subsequent flare, and longer cumulative time in remission was significantly associated with less subsequent damage accrual. Therefore, management strategies that aim to maintain low disease activity or remission states after attaining these targets could help delay or prevent flares and damage accrual, and longer duration in remission compared to LLDAS is more desirable given its stronger protective association with reduced damage accrual.

Because long-term adverse effects of glucocorticoids are widely recognized, tapering and maintaining the lowest possible dose are recommended in treatment guidelines.[1] Our damage accrual models demonstrated that higher glucocorticoid exposure increased the risk of damage accrual, which further emphasizes the importance of maintaining the lowest possible glucocorticoid dose. However, we found that reducing the dose of glucocorticoids below the 7.5 mg/day prednisolone threshold after LLDAS attainment or the 5 mg/day prednisolone threshold after DORIS attainment increased the risk of flare. The CORTICOLUP randomized trial by Mathian et al also demonstrated that withdrawal of low-dose prednisolone in clinically inactive disease resulted in excess flares compared to the maintenance of prednisolone.[29] These results indicate that more effective and safer glucocorticoid tapering strategies need to be defined and that close monitoring is necessary during the tapering process. Our models showed that IS tapering was associated with a higher risk of flare after LLDAS attainment, suggesting that maintaining IS treatment could potentially prevent flares because glucocorticoids are tapered. A meta-analysis has also reported glucocorticoid-sparing and flare-prevention effects of IS medications.[30] In addition to preventing flare, our models also suggested the effects of IS in preventing damage accrual because IS dose reduction was associated with an increased risk of subsequent damage accrual after LLDAS attainment. However, IS reduction did not significantly increase the risk of flare or damage accrual in the DORIS models, indicating that tapering IS during DORIS may be safer than tapering during LLDAS in terms of risk of flare and damage accrual. Overall, our findings suggest that current treatments are inadequate for flare and damage accrual prevention and highlight the need for interventions and strategies that maintain LLDAS or remission while allowing for the tapering of glucocorticoids.

A key strength of this study is the inclusion of a large number of patients with clinically active disease at baseline. This is important in treat-to-target clinical trial design because these are the patients most suitable to enroll while differing from those enrolled in classic phase 2 or 3 trials. Subgroup analyses for patients with high disease activity provide important information for clinical practice and inform the design of studies and clinical trials that target those with high disease activity.

There are, however, some limitations to this study. First, clinically active disease in the present study was defined according to the clinical domains of SLEDAI-2K. However, SLEDAI-2K omits several clinical manifestations, including hemolytic anemia and cardiac, pulmonary, and gastrointestinal involvement. Secondly, there is increasing use of biologics such as rituximab, belimumab, and anifrolumab in SLE and voclosporin in lupus nephritis. However, we were unable to evaluate the impact of this on target attainment and subsequent outcomes due to their very limited use in this cohort at the time the data were collected. Therefore, the current analysis offers an overview of how targets are achieved and maintained in patients with clinically active disease mainly under the current standard of care, primarily with conventional therapies. Varying factors may contribute to the low usage of biologics, including rituximab, belimumab, and anifrolumab, in this cohort, such as socioeconomic conditions, the availability of these biologics by the time of data collection, and regulatory limitations for access to biologics imposed by local authorities. In addition to limited biologic use, the proportion of conventional IS

use was also relatively low in this cohort (73.5% in the overall cohort and 85.2% in the high disease activity subgroup), which may also have some impact on glucocorticoid use, target attainment, and subsequent outcomes because our models showed that IS use was associated with increased target attainment and IS reduction was associated with increased flare and damage accrual. Thirdly, although the APLC cohort represents a multinational and multiethnic population, non-Asian patients make up less than 20% of the total group. As a result, the generalizability of the findings on a global scale is limited. However, it is important to note that the Asian ethnicity encompasses various races in the APLC cohort, including North-East Asian, South-East Asian, and Southern and Central Asian. The non-Asian ethnicity in the APLC cohort includes Caucasian, Hispanic, Aboriginal and/or Torres Strait Islander, Pacific Islander, Sub-Saharan African, African Caribbean, Egyptian, Latin American, Samoan, and Māori.

In conclusion, LLDAS and DORIS are both achievable goals in patients with clinically active disease. However, a significant proportion of patients receiving usual care, primarily with conventional therapies, do not attain these targets. This could potentially be improved with more target-driven approaches and more effective treatments. Flares and damage accrual occurred frequently following target attainment, highlighting the remaining unmet need in this population. Longer durations of target maintenance and antimalarial use protected patients against flare and damage accrual. Conversely, glucocorticoid dose reduction after target attainment increased the risk of flare, and IS dose reduction increased the risk of both flare and damage. Prospective treat-to-target strategy clinical trials are needed to inform monitoring and treatment adjustment in SLE to maintain states associated with optimal outcomes.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Nikpour confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

AstraZeneca had no role in the study design or in the collection, analysis, or interpretation of the data or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AstraZeneca.

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