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BRIEF REPORT

Implementation of the Lupus Low Disease Activity State in Pediatric Rheumatology Care: The Role of the Visual Analog Scale

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Objective. We compared the measurement properties of a traditional physician global assessment of disease activity (PhGA) 10-cm visual analog scale ($PhGA_{0–10}$) with that of the three-point numeric scale ($PhGA_{0–3}$) in childhood-onset systemic lupus erythematosus (cSLE) as part of the childhood Lupus Low Disease Activity State (cLLDAS).

Methods. We used a secondary data analysis from a convenience sample of 100 patients with cSLE followed every three months for up to seven visits. Ratings of $PhGA_{0–10}$, $PhGA_{0–3}$, parent assessment of patient well-being (ParGA) (range: 0= very poorly, 10 = very well), disease activity as measured by the SLE disease activity index 2000 (SLEDAI-2k), Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI, and the British Isles International Lupus Activity Group index (BILAG; A = 9, B = 3, C = 1, D/E = 0) were compared. After linear transformation of $PhGA_{0–10}$ to a 0 to 3 range ($tPhGA_{0–10}$), the frequency of $PhGA_{0–3} \leq 1$ was assessed to estimate the impact of scale type on the scoring of the cLLDAS.

Results. In 600 visits, the median (range) scores of $PhGA_{0–10}$, $PhGA_{0–3}$, SLEDAI-2k, SELENA-SLEDAI, and BILAG were 2 (0–10), 1(0–3), 4 (0–28), 4 (0–32), and 2 (0–28), respectively. $PhGA_{0–10}$ and $PhGA_{0–3}$ ratings were strong to moderately correlated with (r = 0.73; $P < 0.0001$) and with more variability for $PhGA_{0–3} \geq 2$. SELENA-SLEDAI and SLEDAI-2k scores were moderately correlated with $PhGA_{0–10}$ (r = 0.56/0.54; $P < 0.0001$). ParGA values were weakly correlated with all other measures considered (all r = −0.19 to −0.34). There were 490 of 600 visits with $PhGA_{0–3} \leq 1$ and 497 of 600 visits with $tPhGA_{0–10} \leq 1$ (κ (SE) =0.59 (0.04), McNemar $P = 0.4$).

Conclusion. $PhGA_{0–3}$ and $PhGA_{0–10}$ have comparable measurement properties and yield almost identical cLLDAS rates when used in cSLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disease that continues to result in considerable morbidity and mortality. Patients with childhood-onset SLE (cSLE) have been found to have more multiorgan involvement, including lupus nephritis, and persistently active disease when compared to adult-onset SLE.[1]

In recent years, treat-to-target strategies for managing SLE and cSLE have been formulated to improve disease outcomes and avoid damage development.[2] To operationalize the above concept, the Lupus Low Disease Activity State (LLDAS) was developed and proposed as a treat-to-target goal of adults and children with SLE.[2,3] LLDAS determination requires patients to tolerate immunosuppressive medication, use no more than low dose glucocorticosteroids (GCs), and to maintain a low level of

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SIGNIFICANCE & INNOVATIONS

- The physician global assessment of disease activity (PhGA) 10-cm visual analog scale ($PhGA_{0–10}$) can be reliably used for childhood Lupus Low Disease Activity State (cLLDAS) assessment in childhood-onset systemic lupus erythematosus (cSLE).
- Use of the $PhGA_{0–10}$ and PhGA with a three-point numeric scale ($PhGA_{0–3}$) scales in cLLDAS assessment in cSLE showed comparable measurement properties.
- The $PhGA_{0–10}$ scale is routinely assessed in pediatric rheumatology practices and as a measure in the Provisional Pediatric Rheumatology International Trials Organization/American College of Rheumatology (ACR) criteria for treatment response, the Preliminary ACR Criteria for Flare and the Provisional Criteria of Minimally important improvement of cSLE, hence, potentially enabling easier widespread adoption of the $PhGA_{0–10}$ in cLLDAS assessment in cSLE.

SLE activity.[3] Indeed, achievement and maintenance of LLDAS in adults is associated with reduced damage accrual and improved survival in both adults and children.[4,5] Recently, the childhood LLDAS (cLLDAS) was derived by consensus to facilitate life course studies. This is a modification of the adult derived LLDAS and includes similar parameters such as a physician global assessment (PhGA) scale, but with steroid dosing based on body weight.[6]

Visual analog scales (VASs) of disease activity are widely used in rheumatology and allow for continuous scaling of disease activity, that is, allow physicians the consideration of disease activity features of a patient that are not considered in traditional disease activity measures. Furthermore, VASs provide an opportunity for studies to determine clinically significant changes, rather than relying on predetermined glossary-based definitions as indicators of disease severity. Unfortunately, past studies of VASs in SLE have yielded inconsistent results, likely because of the potential variations in how clinicians interpret these scales.[7]

Specifically in pediatric rheumatology, the 10-cm VAS to score PhGA of disease activity ($PhGA_{0–10}$) is widely used for assessing disease activity in juvenile idiopathic arthritis, juvenile dermatomyositis, and cSLE.[8–10] Conversely, the cLLDAS repurposes a three-point numeric Likert scale ($PhGA_{0–3}$) that is part of the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE disease activity index (SLEDAI) and its flare tool.[6,11] Therefore, comparison between the measurement properties of the $PhGA_{0–10}$ and $PhGA_{0–3}$ scales is needed because the completion of the $PhGA_{0–3}$ is currently not routine in pediatric rheumatology practice and to enhance the integration of the cLLDAS as a treat-to-target goal in cSLE. Thus, we aimed to evaluate the impact of using the $PhGA_{0–10}$ as opposed to the $PhGA_{0–3}$ as part of the cLLDAS. We hypothesized that the associations between various measures of disease activity used in cSLE with the $PhGA_{0–3}$ and the $PhGA_{0–10}$ are comparable.

METHODS

Patients and data. An exploratory analysis of an available dataset from aNational Institutes of Health–supported study in cSLE was performed. The original dataset was assembled to assess the intrarater reliability, construct validity, and responsiveness of the disease indices in cSLE.[8] There were a total of 600 visits from a total of 100 patients with cSLE fulfilling the 1997 revised American College of Rheumatology classification criteria for SLE before the age 18 years.[12] For these patients, serial assessments were done about every three months to document the course of cSLE. Collected data included the measurement of disease damage, medication usage, including the dose of prednisone equivalent, and patient characteristics. The study used fully registry data from an institutional review board–approved protocol. All patients and/or caretakers signed assent and consent forms approved by the Cincinnati Children's Institutional Review Board (IRB 2008-0635). The datasets generated and/or analyzed during the current study are not publicly available due to individual data privacy but may be available from the corresponding author on reasonable request.

Outcomes. Patient assessments included measurement of disease activity, patient well-being, and the physician assessment of global disease activity. The following disease activity indices were evaluated: British Isles International Lupus Activity Group index (BILAG; numeric conversion of the domain ratings [A–E]: A = 9, B = 3, C = 1, D/E = 0),[13] the SLEDAI (version 2000; range 0–105),[14] and the SELENA-SLEDAI.[11] The latter features a three-point numeric Likert scale of disease activity ($PhGA_{0–3}$), which provides distinct markers when assessing disease activity. These are inactive for a value of 0; mild for a value of 1, moderate or severe for values of 2 and 3, respectively. The rater can assign any value on the $PhGA_{0–3}$ between 0 and 3 in response to the question "How do you assess your patient's current disease activity?" The treating physician also rated patient global disease activity on a 10-cm VAS with the anchors "inactive" for a value of 0 and "very active" for a value of 10, in response to the question: "Considering the findings at today's visit, the overall disease activity of the patient is."

The patient global assessment of well-being (Pat-well) was also rated on a traditional 10-cm VAS with the anchors "very poor" for a value of 0 and "very well" corresponding to a value of 10, in response to the question: "When considering your medications, school, work, life at home, doctor visits, pains, and feelings, how would you rate your overall well-being?"

Table 1. Demographics and SLE features at baseline*

Parameter	N	Mean ± SD
Age, y	98	15.3 ± 2.85
Disease duration, y	98	1.5 ± 2.0
Current medications		
Prednisone, mg/day	82	15.1 ± 1.8
Azathioprine, mycophenolate mofetil, methotrexate	47	
Cyclophosphamide	6	
Hydroxychloroquine	73	
Nonsteroidal anti-inflammatory drugs	24	
At least one antihypertensive medication	38	
Biopsy-proven lupus nephritis[a]	39	
Disease damage, SDI score (0 = no damage)	98	0.42 ± 0.1
Physician assessment of overall disease activity ($PhGA_{0–10}$)	98	2.5 ± 1.93
Physician assessment of overall disease activity ($PhGA_{0–3}$)	99	0.85 ± 0.59
Disease activity score	98	
SLEDAI-2k		4.93 ± 4.25
SELENA-SLEDAI		4.82 ± 4.04
BILAG (0–9)		5.31 ± 5.44

*BILAG, British Isles Lupus Activity Group Index; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2k, Systemic Lupus Erythematosus Disease Activity Index 2000; VAS, visual analog scale.
[a]There were 21 patients without proteinuria, as defined by a protein to creatinine ratio of <0.2. All smaller values were rounded up to 0.15.

From the available data, cLLDAS was present if all of the following were met: SLEDAI-2k score of ≤4 without activity in major organ systems, no new features of disease activity compared to the previous assessment, physician global assessment ($PhGA_{0–3}$) of ≤1 (scale 0–3), daily prednisone equivalent dose of ≤7.5 mg (or a maximum of 0.15 mg/kg body weight per day for children under 50 kg), and well-tolerated standard maintenance doses of immunosuppressives.[6]

Statistical analysis. Descriptive analysis was done for the baseline status of the patients at the time of the enrollment into the study. Numeric values were summarized as arithmetic mean (SD) and median (range) and ordinal and nominal variables as frequencies, respectively. We also determined mean (SD) and median (range) of Pat-well and the disease activity measures (SLEDAI-2k, SELENA-SLEDAI, BILAG, $PhGA_{0–10}$, $PhGA_{0–3}$) for all study visits.

To study the concurrent validity of the disease activity measures (SLEDAI-2k, SELENA-SLEDAI, BILAG, $PhGA_{0–10}$, $PhGA_{0–3}$) and the Pat-well values, Spearman correlation coefficients (r) were calculated, which can be interpreted as follows: values of $r < 0.2$ were considered not correlated. Weak correlation is defined by $r \geq 0.2–0.4$; moderate correlation by $r \geq 0.4–0.6$; strong to moderate correlation by $r \geq 0.6–0.8$; and strong correlation by $r \geq 0.8$. Smooth plots were generated using locally estimated scatterplot smoothing to further evaluate the relationship between $PhGA_{0–3}$ and $PhGA_{0–10}$. To test the effect of the use of the $PhGA_{0–10}$ for determining cLLDAS, we first performed a linear transformation of the physician-provided ratings on the $PhGA_{0–10}$ to yield values between 0 and 3 ($tPhGA_{0–10}$). McNemar test and kappa (SE) statistics were then used to compare cLLDAS frequencies during the study period when using the $tPhGA_{0–10}$ or the traditional $PhGA_{0–3}$ scale in the cLLDAS algorithm. Agreement, based on kappa values can be interpreted as $\kappa \leq 0$, no agreement; $\kappa = 0.01–0.20$, no more than slight agreement; $\kappa = 0.21–0.40$, fair agreement; $\kappa = 0.41– 0.60$, moderate agreement; $\kappa = 0.61–0.80$, substantial agreement; and $\kappa = 0.81–1.00$, almost perfect agreement. McNamar agreement test $P > 0.05$ indicate that there is no statistically significant disagreement between measures.

RESULTS

Patients and visits. There were 600 visits for 100 patients available for this analysis. Complete $PhGA_{0–3}$ and $PhGA_{0–10}$ data were missing for 2 of the 100 enrolled patients from sites in the United States and Canada (Table 1).

Rating and association of outcome measures during the study. Across all 600 visits mean (SD) and median (range) of the SLEDAI-2k were 4.63 (4.14) and 4 (0–28) and of the SELENA-SLEDAI were 4.51 (4.1) and 4 (0–32). Mean (SD) and median (range) of the BILAG was 2.82 (3.34) and 2 (0–28) and that of Pat-well was 7.74 (1.77) and 8 (1–11). Table 2 shows the correlations of the $PhGA_{0–3}$ and the $PhGA_{0–10}$ to Pat-well and disease activity index scores to be almost identical.

Comparison of ratings of PhGA of disease activity. Across all study visits, the mean (SD) and median (range) ratings

Table 2. Associations of well-being with disease activity and PhGA measures*

	$PhGA_{0–10}$	$PhGA_{0–3}$	SLEDAI-2k	SELENA-SLEDAI	BILAG
Par-well	−0.34 (<0.0001)	−0.30 (<0.0001)	−0.19 (<0.0001)	−0.20 (<0.0001)	−0.28 (<0.0001)
SLEDAI-2k	0.54 (<0.0001)	0.53 (<0.0001)	1.00 (NA)	0.97 (<0.0001)	0.58 (<0.0001)
SELENA-SLEDAI	0.52 (<0.0001)	0.52 (<0.0001)	0.97 (<0.0001)	1.00	0.57

*All values are Spearman correlation coefficient r (*P* value). BILAG, British Isles International Lupus Activity Group index; Par-well, parent assessment of patient well-being; $PhGA_{0–3}$, three-point numeric scale for physician global assessment of disease activity; $PhGA_{0–10}$, 10-cm visual analog scale for physician global assessment of disease activity; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

of the $PhGA_{0–10}$ were 2.13 (1.87) and 2 (0–10) and of the $PhGA_{0–3}$ were 0.79 (0.64) and 1 (0–3). Figure 1A depicts the relationship between the rating on these two scales. Notably, 95% confidence intervals increase for $PhGA_{0–3}$ >2.

Impact of the use of the $PhGA_{0–3}$ versus the $PhGA_{0–10}$ on the scoring of the cLLDAS. Scoring of the cLLDAS using complete data was available for 600 visits. Figure 1B depicts the comparison of the two PhGA scales in measurement of the cLLDAS in cSLE. When using the $PhGA_{0–3}$, there were 456 visits with values of ≤1 compared to 489 visits when considering the $tPhGA_{0–1}$ (κ [SE] = 0.59 [0.04]; McNemar P = 0.4). Misclassification rates were ≤6.7%. There was a larger variability between the $PhGA_{0–10}$ and $PhGA_{0–3}$ ≥2 (unpooled t-test, t = −11.93; Satterthwaite $P \leq 0.0001$).

DISCUSSION

Routine standardized assessment of disease activity in pediatric rheumatic diseases is advocated. Thus, the VAS of physician assessment of disease activity is relevant and commonly performed. In the past, the $PhGA_{0–10}$ was almost universally used for measuring flare and treatment response in juvenile idiopathic arthritis and cSLE. More recently, the cLLDAS has been proposed as a treat-to-target for cSLE. This is because patients with cSLE in LLDAS experienced fewer disease flares and limited the accrual of disease damage in cSLE compared to patients not reaching LLDAS.[4–6] In our study, we show that correlations with validated disease activity indices using the two types of VAS ($PhGA_{0–3}$ and $PhGA_{0–10}$) are almost identical. Further, rates of cLLDAS using either $PhGA_{0–3}$ or $PhGA_{0–10}$ are comparable, with misclassifications rates of 5% to 7%. This can be interpreted as that, in 93% of the patient assessments, the choice of the VAS type had no impact on whether the patient with cSLE was deemed inactive. We noted that there is larger variability (≥2) between the $PhGA_{0–10}$ and $PhGA_{0–3}$. This indicates a potential ceiling effect of the $PhGA_{0–3}$ and suggests that the $PhGA_{0–10}$ is preferable because it would allow a wider numeric range to better discriminate the various levels of disease activity in patients with cSLE.

An assessment of cLLDAS in clinical practice for the purpose of treat-to-target strategies requires information from patient medical records, which are more often in electronic format in pediatric rheumatology centers in North America and several countries around the world. Arguably, to measure the LLDAS in adult SLE cohorts, it is sensible to use $PhGA_{0–3}$ because this is the predominant type of VAS to measure disease activity in clinical practice and research. Conversely, considering the widespread use of the $PhGA_{0–10}$ in pediatric rheumatology, the authors opine that the new introduction of this $PhGA_{0–3}$ scale may add to the documentation burden of physicians and impede the ease of adaptation of treat-to-target strategies for cSLE in routine clinical practice.

Our study provides quantitative assessment of the measurement properties of both $PhGA_{0–10}$ and $PhGA_{0–3}$ in cSLE. Based on the results of this study, an alternate approach for the adaptation of the cLLDAS[5,6] could be to incorporate the $PhGA_{0–10}$ in addition to the already modified low steroid criterion that adjusts the ≤7.5 mg of prednisone equivalent for pediatric patients with smaller body weights. Notably, the $PhGA_{0–10}$ scale is already

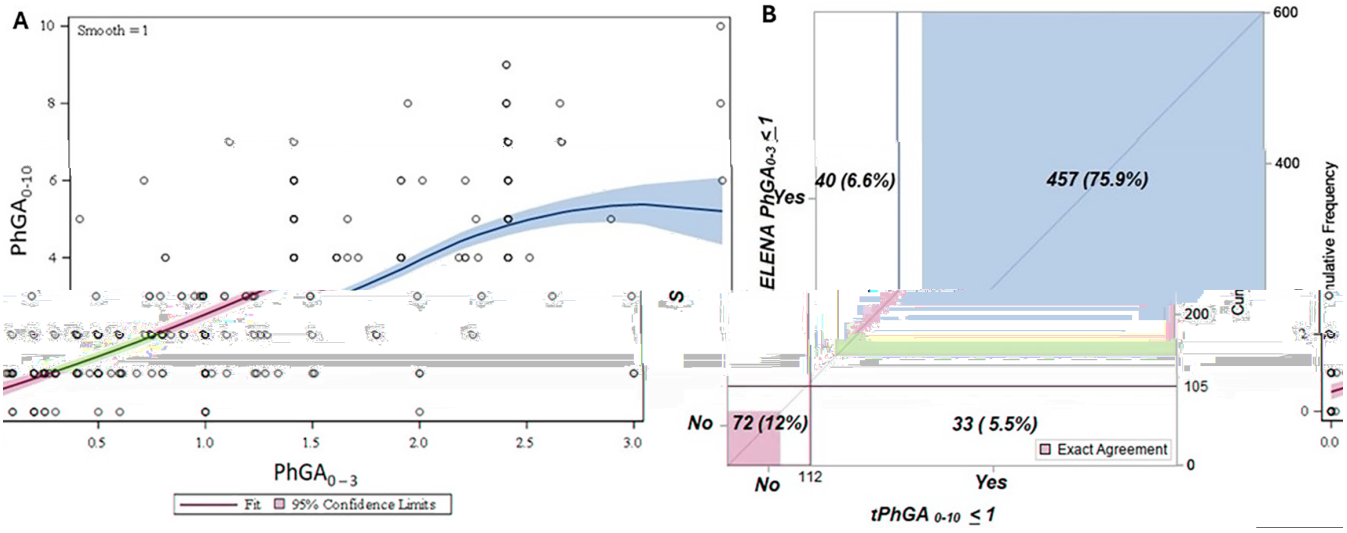

Figure 1. (A) LOESS fit of relationship of $PhGA_{0–10}$ with the $PhGA_{0–3}$. (B) Agreement plot of $PhGA_{0–3}$ ≤1 and $tPhGA_{0–10}$ ≤1 scales to fulfill LLDAS cut-offs: κ (SE) = 0.59 (0.04), McNemar P = 0.4. LLDAS, Lupus Low Disease Activity State; LOESS, locally estimated scatterplot smoothing; PhGA, physician global assessment of disease activity; $PhGA_{0–10}$, PhGA of disease activity traditional 10-cm visual analog scale; $PhGA_{0–3}$, PhGA with a three-point numeric scale; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; $tPhGA_{0–10}$, linear transformation of $PhGA_{0–10}$.

used as a measure in the Provisional Pediatric Rheumatology International Trials Organization/ACR criteria for treatment response,[10] the Preliminary ACR Criteria for Flare,[15] and the Provisional Criteria of Minimally important improvement of cSLE.[9]

In conclusion, the $PhGA_{0-3}$ and $PhGA_{0-10}$ have comparable measurement properties and yield almost identical cLLDAS rates when used in cSLE. This may suggest that both scales can be used to score the cLLDAS in cSLE. Further studies are needed to understand the measurement properties of both $PhGA_{0-3}$ and $PhGA_{0-10}$ scales in the Provisional Pediatric Rheumatology International Trials Organization/ACR criteria for treatment response, the Preliminary ACR Criteria for Flare, and the Provisional Criteria of Minimally important improvement of cSLE.

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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 Brunner 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/Helsinki Declaration requirements.

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