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Evaluation of the LFA-REAL clinician-reported outcome (ClinRO) and patient-reported outcome (PRO): prespecified analysis of the phase III ustekinumab trial in patients with SLE

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ABSTRACT

Objective The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) system is a novel and simple SLE disease activity instrument, consisting of a tandem clinician-reported (ClinRO) and patient-reported (PRO) outcome measure. The aim of this study was to compare the LFA-REAL system with other SLE activity measures in the phase III trial of ustekinumab in patients with active SLE.

Methods This was a prespecified analysis of data from a randomised, double-blind, placebo-controlled, parallel-group trial conducted at 140 sites in 20 countries. Correlations were evaluated between the LFA-REAL ClinRO and PRO with a panel of clinician-reported and patient-reported disease activity measures commonly used in SLE clinical trials at baseline, week 24 and week 52. All p values are reported as nominal.

Results Trial participants included 516 patients with SLE with a mean (SD) age of 43.5 (8.9), of whom 482 (93.4%) were female. The LFA-REAL ClinRO correlated with Physician Global Assessment (r=0.39, 0.65 and 0.74, p<0.001), British Isles Lupus Assessment Group Index (r=0.43, 0.67 and 0.73, p<0.001) and SLE Disease Activity Index-2000 (r=0.35, 0.60 and 0.62, p<0.001). The LFA-REAL ClinRO arthralgia/arthritis score correlated well with active joint counts (r=0.54, 0.73 and 0.68, p<0.001) and the mucocutaneous global score correlated strongly with Cutaneous Lupus Erythematosus Disease Area and Severity Index total activity (r=0.57, 0.77 and 0.81, p<0.001). The LFA-REAL PRO demonstrated a moderate correlation with Functional Assessment of Chronic Illness Therapy-Fatigue (r=−0.60, −0.55 and −0.58, p<0.001), Lupus QoL physical health (r=−0.42, −0.47 and −0.46, p<0.001), SF-36v2 vitality (r=−0.40, −0.43 and −0.58, p<0.001) and SF-36v2 Physical Component Summary (r=−0.45, −0.53 and −0.53, p<0.001). The LFA-REAL ClinRO and PRO showed a moderate correlation with each other (r=0.32, 0.45 and 0.50, p<0.001).

Conclusions The LFA-REAL ClinRO and PRO showed varied levels of correlations (weak to strong) with existing physician-based lupus disease activity measures and patient-reported outcome instruments, respectively and were able to more accurately capture organ-specific mucocutaneous and musculoskeletal manifestations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ SLE is a complex multisystem autoimmune disease and it remains challenging to accurately measure SLE disease activity in both clinical practice and research.

WHAT THIS STUDY ADDS

⇒ The study evaluated the correlations between the Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) clinician-reported (ClinRO) and patient-reported (PRO) with a panel of clinician-reported and patient-reported disease activity measures commonly used in SLE clinical trials in a prespecified analysis of data from the phase III trial of ustekinumab in patients with active SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data from this study support further development of the LFA-REAL ClinRO and PRO as a flexible resource in the evaluation of lupus disease activity and its potential as a simple, user-friendly outcome measure for SLE studies.

More analyses are needed to determine areas in which patient-reported outcomes are most similar or different to physician-reported end points and the basis for differences.

INTRODUCTION

SLE is a complex multisystem autoimmune disease characterised by clinical heterogeneity and unpredictable flares that can affect virtually any organ.[1] Multiple clinical assessment tools have attempted to capture the heterogeneity and variability of SLE clinical pattern and disease course yet over 20 late phase therapeutic trials failed to produce interpretable results.[2] It remains challenging to accurately

measure SLE disease activity in both clinical practice and research.[3]

The SLE Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group Index (BILAG) and Physician Global Assessment (PGA) are the most extensively used disease activity measures in large, international, multicentre trials, and each has well-known limitations.[4–6] SLEDAI includes only 24 items which misses a number of possible manifestations, and does not include severity grading thus cannot capture variations in the severity of individual manifestations once a minimal threshold has been met for a defined manifestation.[7 8] BILAG-2004 includes a comprehensive list of 97 items categorised within 9 organ systems. Changes in severity are captured; however, glossary-based definitions lead to inaccurate quantification of change at the threshold between severity grades, and the consolidation of various features within one organ system into a single score impedes comparisons between patients with one or multiple active features within an organ.[9] The PGA is an overall summation of the clinical encounter that allows physicians to quantify both the degree of disease activity and also whether there has been clinically significant change from visit to visit. However, there is conflicting data on the interobserver reliability of PGA among lupus experts.[10 11] The PGA is widely used alone and in composite end points, including the SLE Responder Index 4 (SRI-4),[12] BILAG-Based Composite Lupus Assessment (BICLA),[13 14] remission[15] and Lupus Low Disease Activity (LLDAS) definitions.[16] However, moderate changes are difficult to distinguish or compare from patient to patient on a limited 100 mm scale, and since all manifestations are consolidated into one score major improvement in one organ cannot be distinguished from moderate improvement in multiple organs. All these instruments have been problematic to interpret in clinical trials and are often inconsistent with patient-reported outcomes.[17 18] There is no built-in methodology to explore the reasons for this inconsistency.

The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) system is a new SLE disease activity measure that consists of a tandem clinician-reported outcome (ClinRO) and patient-reported outcome (PRO) that were developed using standard psychometric methodology and input from patients with lupus and clinicians.[19–21] LFA-REAL ClinRO includes nine organ domain Visual Analogue Scale (VAS) and subscales for individual symptoms to allow evaluation of patient progress at the level of individual manifestations, organs and total disease activity and to distinguish moderate change in all organs from major change in one organ. LFA-REAL PRO generates information on lupus disease activity that is parallel to the ClinRO assessments and could help to address reasons for discordance in differing opinions between physicians and patients.

The current study evaluated the construct validity of the LFA-REAL ClinRO and LFA-REAL PRO compared with established disease activity measures and PROs in the phase III, randomised, placebo-controlled study (LOTUS; ClinicalTrials.gov: NCT03517722) of ustekinumab in patients with active SLE.[22]

METHODS

Patient cohort

This is a prespecified analysis of data from a randomised, double-blind, placebo-controlled, parallel-group trial conducted at 140 sites in 20 countries.[22] Following the planned interim analysis, the sponsor discontinued the study due to lack of efficacy; accordingly, the number of patients included in the week 52 of current analysis is lower. Eligible patients were 18–75 years of age, fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) 2012 SLE classification criteria[23] and had moderately to severely active SLE, as measured by a SLEDAI-2000 (SLEDAI-2K) score of ≥6 with at least 4 points for clinical (non-laboratory) manifestations. Additionally, either severe disease activity in one or more organs or moderate activity in two or more organs were required (BILAG-2004 organ scores of ≥1 A item or ≥2 B items). At screening, patients were required to be seropositive for ANAs, antidouble-stranded DNA antibodies or anti-Smith antibodies and to be receiving stable treatment with at least one of the following medications: prednisone or equivalent, an antimalarial agent or immunosuppressant agent (azathioprine, mycophenolate mofetil or methotrexate). Patients with active severe lupus nephritis or neuropsychiatric SLE were excluded. Disease activity was assessed using clinician-reported outcomes including SLEDAI-2K, BILAG, PGA, Clinician Global Impression of Change (CGIC), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), swollen and tender joint counts, LFA-REAL ClinRO and SRI-4. BILAG Total Scores were calculated based on the numerical scoring proposed by Yee *et al*.[24] Patients completed several PROs including 36-item Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Patient Global Assessment, Patient Global Impression of Change (PGIC) and LFA-REAL PRO. The LFA-REAL PRO was only available in English at the study start, accordingly the data presented here were limited to the investigators and sites in the USA only.

LFA-REAL system

The LFA-REAL ClinRO includes eight domains: mucocutaneous, musculoskeletal, cardiorespiratory, neuropsychiatric, renal, haematological, constitutional and vasculitis; clinicians are asked to score only active lupus manifestations over the past month. In addition, for this trial, up to three 'other' domains could be assessed. Subscales are prespecified or can be added to record individual scores when there is more than one manifestation in each organ. For example, the mucocutaneous domain consists of one overall scale and three subscales (rash, alopecia and mucosal ulcers). The musculoskeletal includes one global scale and two subscales (arthralgia/arthritis and myalgia/myositis). This keeps the instrument quite

simple but allows flexibility for comprehensive scoring of all SLE manifestations. Each organ or individual item score is entered on a VAS from 0 to 100 mm, with anchors separating mild, moderate and severe disease, similar to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI PGA.[5] The total score is the sum of each organ domain score including global scores of mucocutaneous and musculoskeletal domains.

The LFA-REAL PRO has seven domains: rash, symptoms of arthritis, muscle pain or aches, fatigue, fever, hair loss and body symptoms (which include chest pain, shortness of breath, swelling in legs and other); patients are asked to score only active lupus symptoms over the past month. It was developed as a measurement of disease activity from patient's perspective. The symptoms of arthritis domain were intentionally split into three subscales (joint pain, joint swelling and joint stiffness) and overall arthritis scale. After first scoring each of the arthritis subscales separately, the patient is asked to put them together and provide an overall arthritis score. This simple, stepwise process trains the patient to consider arthritis the same way that a clinician does. Furthermore, if the patient's report is inconsistent with that of the clinician, it can be determined which aspect of the arthritis is the basis for the discrepancy. For each manifestation, a VAS (0–100 mm) is used. The summary results which range from 0 to 700 with the overall arthritis scale are reported.

Further description of the LFA-REAL can be found elsewhere.[19–21]

Statistical analyses

Correlation coefficients and nominal p values were generated for correlations between the LFA-REAL ClinRO or LFA-REAL PRO and the other disease measures using the Spearman's rank-order or Pearson's correlations based on appropriateness. Analyses were performed to ascertain relationships between different disease severity measurements and not treatment efficacy. Therefore, pooled (combined) treatment groups were used. Corresponding domains of the LFA-REAL ClinRO and the LFA-REAL PRO were compared, as were correlations between the LFA-REAL ClinRO and PRO skin domains and the CLASI as well as the LFA-REAL arthritis measures versus the active (tender and swollen) joint counts. A p value (two-sided) <0.05 was considered clinically relevant in all analyses. Data are exploratory and were not adjusted for multiple comparisons. A receiver operating curve (ROC) was generated to evaluate the LFA-REAL ClinRO Score change from baseline in terms of other response measures (SRI-4, BICLA, SLEDAI-2K Improvement or BILAG Improvement). Area under the curve (AUC) estimates were based on a logistic regression model for response (yes) with the LFA-REAL ClinRO Score change from baseline as the single covariate; 95% CIs were estimated using the Wald method. As a post hoc summary, estimates of sensitivity and specificity for multiple cut-off points of LFA-REAL ClinRO Score change from baseline at week 52 in terms of SRI-4 and BICLA response were generated at three selected points of clinical interest and three optimal cut-off points identified by commonly used methods (sensitivity/specificity equity, closest distance to ROC 'ideal point' and Youden index).

RESULTS

Five hundred sixteen patients were evaluated of whom 482 (93.4%) were female, the mean age was 43.5 years and mean disease duration 8.9 years. The demographic and clinical characteristics of the patients are included in online supplemental table 1 and were described in detail elsewhere.[22] The LFA-REAL ClinRO and PRO evaluations were performed at the baseline, week 24 and week 52 study visits. The LFA-REAL PRO was only available in English at the time of this study and as such was completed only in the USA by patients with good English proficiency.

The number of patients included in each correlation analysis shown in tables 1–4 are available in online supplemental table 2. The numbers of patients available for ClinRO analyses at baseline, week 24 and week 52 were 494, 426 and 241, respectively. The numbers of patients available for PRO analyses at baseline, week 24 and week 52 were 117, 116 and 77, respectively.

Correlations between the LFA-REAL ClinRO and other SLE disease activity measures

At baseline, the total LFA-REAL ClinRO Score correlated weakly with SLEDAI-2K and PGA (r=0.35 and 0.39, p<0.001), and moderately with BILAG (r=0.43, p<0.001). At weeks 24 and 52, the total LFA-REAL ClinRO Score strongly correlated to the SLEDAI-2K score (r=0.60 and 0.62, p<0.001), the BILAG score (r=0.67 and 0.73, p<0.001) and the PGA (r=0.65 and 0.74, p<0.001) (see table 1A).

Correlations between PGA and BILAG or SLEDAI-2K were very weak at baseline (r=0.17 and 0.09, p<0.001), and were moderate at week 24 (r=0.51 and 0.45, p<0.001) and week 52 (r=0.57 and 0.52, p<0.001) (table 1C). The estimated AUC for LFA-REAL ClinRO Score change from baseline to weeks 24 and 52 were 0.76 for SRI-4 (fair) and 0.70 for BICLA (fair) at both time points (online supplemental table 3). As a post hoc summary, LFA-REAL ClinRO change from baseline at week 52 cut-off points to discriminate SRI-4 and BICLA responders from non-responders were assessed and are included in online supplemental table 3 and figure 4. Based on the closest distance to ROC 'ideal point', the sensitivity and specificity of LFA-REAL ClinRO were 75% and 68% at the cut-off point of −55 in discriminating SRI-4 response, and 76% and 57% at the cut-off point of −58 in discriminating BICLA response.

Correlations between the numerical change in the LFA-REAL ClinRO and SRI-4 response between baseline and weeks 24 and 52 were moderate (r=−0.38 and −0.40, p<0.001), and even less robust with BICLA (r=−0.31 and

Table 1 Correlations between LFA-REAL ClinRO and SLE disease activity measures, LFA-REAL PRO and other PRO measures, PGA with SLEDAI and BILAG at baseline, 24 and 52 weeks

	LFA-REAL ClinRO				LFA-REAL PRO				PGA		
A	Baseline	Week 24	Week 52	B	Baseline	Week 24	Week 52	C	Baseline	Week 24	Week 52
PGA	0.39	0.65	0.74	FACIT-F	−0.60	−0.55	−0.58	BILAG	0.17	0.51	0.57
BILAG	0.43	0.67	0.73	Lupus QoL	−0.42	−0.47	−0.46	SLEDAI-2K	0.09	0.45	0.52
SLEDAI-2K	0.35	0.60	0.62	SF-36v2 vitality	−0.40	−0.43	−0.58				
				SF-36 PCS	−0.45	−0.53	−0.53				

Correlation scale: very weak: 0–0.2; weak: 0.2–0.4; moderate: 0.4–0.6; strong: 0.6–0.8; very strong: 0.8–1.0. P<0.001 across all correlation analyses.
(A) Correlations between LFA-REAL ClinRO Total Score and SLE disease activity measures. LFA-REAL ClinRO; LFA-REAL PRO; SLEDAI-2K; BILAG; PGA.
(B) Correlations between LFA-REAL PRO Total Score and PRO measures. LFA-REAL PRO; SF-36; SF-36 PCS; Lupus QoL; FACIT-F. The LFA-REAL PRO increases with disease severity while the other PROs increase with improvement, accounting for the inverse correlations observed.
(C) Correlations between PGA and SLEDAI and BILAG.
BILAG, British Isles Lupus Assessment Group 2004 Index Total Score; ClinRO, clinician-reported outcome; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; Lupus QoL, Lupus Quality of Life questionnaire; PGA, Physician Global Assessment; PRO, patient-reported outcome; SF-36, 36-item Short-Form Health Survey; SF-36 PCS, 36-item SF-36 Physical Component Summary; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

−0.33, p<0.001), and LLDAS (r=−0.11, p=0.064; r=−0.27, p=0.002) (table 2A and 2B).

Further analyses were performed to estimate AUC value (estimated AUC (95% CI)) for the LFA-REAL ClinRO Score change from baseline to weeks 24 and 52 and showed 0.76, 95% CI (0.71 to 0.80) and 0.76, 95% CI (0.70 to 0.83) in terms of SRI-4 response, and 0.70, 95% CI (0.65 to 0.75) and 0.70, 95% CI (0.64 to 0.77) BICLA response (online supplemental table 3); LFA-REAL ClinRO Score change from baseline to week 52 was 0.74, 95% CI (0.67 to 0.81) in terms of SLEDAI-2K (≥4) Improvement and 0.68, 95% CI (0.62 to 0.75) in terms of BILAG Improvement.

Correlations between the LFA-REAL PRO and other PRO measures

A correlation was observed between LFA-REAL PRO and FACIT-F at baseline (r=−0.60, p<0.001), which slightly decreased at week 24 (r=−0.55, p<0.001) and week 52 (r=−0.58, p<0.001). Similar correlations were present at baseline, week 24 and week 52 between LFA-REAL PRO and Lupus QoL physical health (r=−0.42, −0.47 and

Table 2 Correlation between LFA REAL ClinRO Total Score from baseline and composite response measures/disease activity measures, and LFA-REAL PRO change form baseline with other PROs at 24 and 52 weeks

	LFA-REAL ClinRO change from baseline			LFA-REAL PRO change from baseline	
A	Week 24	Week 52	B	Week 24	Week 52
DORIS remission	−0.09	−0.20	FACIT-F	−0.32	−0.44
LLDAS	−0.11	−0.27	Lupus QoL	−0.22	−0.44
BICLA response	−0.31	−0.33	SF-36v2 vitality	−0.21	−0.49
SRI-4 response	−0.38	−0.40	SF-36 PCS	−0.32	−0.42
PGA	0.48	0.53			
BILAG	0.43	0.40			
SLEDAI-2K	0.51	0.51			

Correlation scale: very weak: 0–0.2; weak: 0.2–0.4; moderate: 0.4–0.6; strong: 0.6–0.8; very strong: 0.8–1.0.
(A) Correlations between the change in LFA-REAL ClinRO Total Score from baseline and composite response measures and change from baseline in other disease measures. P<0.001 across all correlation analyses except with DORIS remission at week 24 (p=0.064) and week 52 (p=0.002), and LLDAS at week 24 (p=0.029).
(B) Correlations between change in LFA-REAL PRO score from baseline with change in other PRO measures from baseline to weeks 24 and 52. P<0.001 across all correlation analyses except Lupus QoL at week 24 (p=0.024), and SF-36v2 vitality at week 24 (p=0.033). The LFA-REAL PRO increases with disease severity while the other PROs increase with improvement, accounting for the inverse correlations observed.
BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group 2004 Index Total Score; ClinRO, clinician-reported outcomes; DORIS remission, clinical temission on treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; LLDAS, Lupus Low Disease Activity State; Lupus QoL, Lupus Quality of Life questionnaire; PGA, Physician Global Assessment; PRO, patient-reported outcomes; SF-36, 36-item Short-Form Health Survey; SF-36 PCS, 36-item SF-36 Physical Component Summary; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4, SLEDAI-2K SLE Responder Index.

Table 3 Correlations between LFA-REAL ClinRO and PRO scores, ClinRO rash and PRO rash, ClinRO alopecia and PRO hair loss, ClinRO arthralgia/arthritis and PRO overall arthritis at baseline, week 24 and week 52 visits as well as change from baseline to week 24 and week 52

	At visit			Change from baseline	
	Baseline	Week 24	Week 52	Week 24	Week 52
ClinRO arthralgia/arthritis and PRO overall arthritis	0.38	0.49	0.56	0.24	0.37
ClinRO alopecia and PRO hair loss	0.38	0.50	0.61	0.38	0.30
ClinRO rash and PRO rash	0.51	0.49	0.66	0.43	0.49
ClinRO total and PRO total	0.32	0.45	0.50	0.27	0.37

Correlation scale very weak: 0–0.2; weak: 0.2–0.4; moderate: 0.4–0.6; strong: 0.6–0.8; very strong: 0.8–1.0. P≤0.015 across all correlation analyses.
ClinRO, clinician-reported outcomes; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; PRO, patient-reported outcomes.

–0.46, p<0.001), SF-36 PCS (r=–0.45, –0.53 and –0.53, p<0.001) and SF-36v2 vitality (r=–0.40, –0.43 and –0.58, p<0.001) (see table 1B). The LFA-REAL PRO increases with disease severity while the other PROs increase with

Table 4 Correlation between LFA REAL ClinRO PRO musculoskeletal and mucocutaneous components and individual components of disease activity measures

	LFA-REAL ClinRO: arthralgia/arthritis				LFA-REAL PRO symptoms of arthritis: overall arthritis		
A	**Baseline**	**Week 24**	**Week 52**		**Baseline**	**Week 24**	**Week 52**
SLEDAI arthritis	0.54	0.66	0.65		0.27	0.44	0.33
Subset: subjects with ≥8 active counts at baseline	0.30	0.72	0.79		0.29	0.59	0.51
Subset: subjects with ≥4 active counts at baseline	0.38	0.73	0.69		0.19	0.48	0.42
All subjects active joint count	0.54	0.73	0.68		0.22	0.51	0.42
B	**LFA-REAL ClinRO**				**LFA-REAL PRO**		
	Baseline	**Week 24**	**Week 52**		**Baseline**	**Week 24**	**Week 52**
ClinRO mucosal ulcers/ SLEDAI mucosal ulcers	0.82	0.82	0.85		NA	NA	NA
ClinRO alopecia/SLEDAI alopecia	0.79	0.73	0.74	PRO hair loss/ SLEDAI alopecia	0.36	0.35	0.48
ClinRO rash/SLEDAI rash	0.58	0.65	0.73	PRO rash/ SLEDAI rash	0.25	0.31	0.60
ClinRO mucocutaneous global/BILAG mucocutaneous	0.48	0.66	0.76	PRO rash/BILAG mucocutaneous	0.22	0.30	0.53
ClinRO mucocutaneous global/CLASI total activity	0.57	0.77	0.81	PRO rash/CLASI erythema	0.42	0.42	0.61

Correlation scale very weak: 0–0.2; weak: 0.2–0.4; moderate: 0.4–0.6; strong: 0.6–0.8; very strong: 0.8–1.0. P≤0.05 across all correlation analyses.
(A) Correlations between LFA-REAL ClinRO arthralgia/arthritis and LFA-REAL PRO symptoms of arthritis, and their correlations with active joint counts, and SLEDAI arthritis. Active joint counts (62 joints) are defined as joints with pain and signs of inflammation. Tender (pain) joint count (64 joints) are defined as joints with pain on examination; LFA-REAL PRO symptoms of arthritis consist of three individual symptom domains each scored on 0–100 mm VAS. Overall arthritis is a 0–100 mm VAS indicating patient's global consideration of joint pain, swelling and stiffness.
(B) Correlations between LFA-REAL ClinRO mucocutaneous global and components with CLASI, BILAG and SLEDAI, LFA-REAL PRO rash and LFA-REAL PRO hair loss, with CLASI, BILAG and SLEDAI. CLASI is a measure of skin disease severity, with scores ranging from 0 (least severe) to 70 (most severe). LFA-REAL ClinRO mucocutaneous global is a 0–100 mm VAS as an overall consideration of three mucocutaneous domains: rash, alopecia, mucosal.
BILAG, British Isles Lupus Assessment Group Index; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinRO, clinician-reported outcomes; LFA-REAL, Lupus Foundation of America Rapid Evaluation of Activity in Lupus; PRO, patient-reported outcomes; SLEDAI, SLE Disease Activity Index; VAS, Visual Analogue Scale.

improvement, accounting for the inverse correlations observed.

Correlations between the LFA-REAL ClinRO and PRO

The two components of the LFA-REAL system, ClinRO and PRO, correlated with each other weakly at baseline (r=0.32, p<0.001) but strengthened at week 24 and week 52 (r=0.45 and 0.50, p<0.001). The change from baseline of these two components correlated weakly at week 24 (r=0.27, p=0.005) and at week 52 (r=0.37, p=0.001) (see table 3).

Musculoskeletal and mucocutaneous subcomponents of the LFA-REAL

LFA-REAL ClinRO arthralgia/arthritis and LFA-REAL PRO overall arthritis joint involvements correlated moderately with each other (table 4A) at week 24 and week 52 (r=0.49 and 0.56, p<0.001). Each component of the patient-reported joint involvement was examined and showed similar degrees of correlation to the LFA-REAL ClinRO arthralgia/arthritis at week 24 and week 52, including joint pain (r=0.47 and 0.49, p<0.001), joint swelling (r=0.50 and 0.56, p<0.001) and joint stiffness (r=0.43 and 0.56, p<0.001). Strong correlations were observed between the LFA-REAL ClinRO and active joint counts (r=0.73 and 0.68, p<0.001), these correlations increased in strength in patients with higher active joint counts ≥4 (r=0.73 and 0.69, p<0.001) and ≥8 (r=0.72 and 0.79, p<0.001). On the other hand, joint involvement reported by patients (LFA-REAL PRO symptoms of arthritis) correlated only moderately with active joint counts (r=0.51 and 0.42, p<0.001) at week 24 and week 52. This correlation also gained strength in patients with active joint counts ≥8 (r=0.59 and 0.51, p<0.001). The evaluation of individual components of the LFA-REAL ClinRO and PRO (joint pain and joint swelling) did not change the strength of these correlations.

Mucocutaneous involvement (table 4B) scored by the clinicians (LFA-REAL ClinRO mucocutaneous global) correlated strongly with CLASI total activity score at week 24 (r=0.77, p<0.001) and week 52 (r=0.81, p<0.001). Hair loss reported by patients (LFA-REAL PRO hair loss) correlated moderately with physicians' assessment of alopecia (LFA-REAL ClinRO alopecia) at week 24 (r=0.50, p<0.001) and more strongly at week 52 (r=0.61, p<0.001). Additionally, rash scored on the LFA-REAL ClinRO and LFA-REAL PRO correlated moderately at baseline and week 24 (r=0.51 and 0.49, respectively, p<0.001), and strongly at week 52 (r=0.66, p<0.001). The evaluation of individual components of the LFA-REAL ClinRO (rash, mucosal ulcers and alopecia) and PRO (rash and hair loss) did not change the strength of these correlations.

DISCUSSION

The LFA-REAL system was developed to capture evaluations of the same manifestations by both clinicians and patients so that a more complete picture of lupus disease activity can be evaluated.[19–21] The data presented here describe the measurement properties of the LFA-REAL compared with both clinician-reported and patient-reported outcome measures in a phase III clinical trial of ustekinumab which involved patients with moderate-to-severe SLE. The trial did not meet its primary end point and was stopped based on the futility analysis but provided significant data for this analysis.

The data show that the LFA-REAL ClinRO correlated moderately or strongly with SLEDAI-2K, BILAG and PGA. Previous smaller studies reported similar correlations between LFA-REAL ClinRO and Hybrid SLEDAI or PGA.[19 21 25 26] In the current analysis, the LFA-REAL ClinRO showed a stronger correlation with PGA (r=0.39, 0.65 and 0.74, p<0.001) than SLEDAI-2K (r=0.35, 0.60 and 0.62, p<0.001). The LFA-REAL ClinRO Total Score correlated well with BILAG Total Index (r=0.43, 0.67 and 0.73, p<0.001) in this international trial, although lower than that reported from the preliminary test done in 2015 by the authors (r=0.933, p<0.001),[21] and a second study carried out in 2017 by lupus clinicians (r=0.81, p<0.001) and clinical investigators (r=0.88, p<0.001).[25] However, the change in LFA-REAL ClinRO from baseline at weeks 24 and 52 correlated weakly with BICLA (r=−0.31 and −0.33, p<0.001) and SRI-4 (r=−0.38 and −0.40, p<0.001).

The LFA-REAL correlates well with the PGA, since it is a summation of organ or symptom-specific PGA scales added together. The relatively weaker correlations of BILAG and SLEDAI-2K with PGA compared with the LFA-REAL at baseline, week 24 and week 52 suggest that the LFA-REAL has the potential to integrate various aspects of disease activity similar to the PGA.

The LFA-REAL PRO Total Score, as a disease activity PRO, correlated moderately with SF-36 PCS (r=−0.53, p<0.001), Lupus QoL physical health (r=−0.46, p<0.001), SF-36v2 vitality (r=−0.58, p<0.001) and FACIT-F (r=−0.58, p<0.001). These correlations from international patients were lower than those reported from an Italian cohort of 110 consecutive patients with SLE where the correlation between the LFA-REAL PRO and FACIT-F (r=−0.817, p<0.001) and SF-36 PCS (r=−0.753, p<0.001) were strong or very strong.[27] Taken together, the accumulating data do suggest a potential utility for the LFA-REAL PRO in reflecting fatigue and overall physical functioning.

Many of the correlations evaluated in this study grew stronger postbaseline visits, indicating a potential learning curve that brings both patients and clinicians into increasingly analogous frames of reference over time. The LFA-REAL ClinRO and PRO correlated moderately with each other at week 52, suggesting some progress in integrating the perspective of the clinician and patient when focus is purposefully directed to similar aspects of disease. This possibility is supported by the fact that none of the three components of arthritis that the patients were instructed to score to build their total arthritis score showed greater or less correlation to the clinicians' arthritis scoring than the others. Nevertheless, more work needs to be done to fully understand the reasons for the discordance between patient report and physician assessment of SLE disease

activity, a problem which has been demonstrated by multiple previous studies.[18 26 28–30]

One goal of developing the LFA-REAL is to provide a simple, user-friendly system that can provide an accurate global disease activity score while also providing reliable individual organ scores. The LFA-REAL clinicians' arthralgia/arthritis scores correlated with active joint counts moderately (r=0.54, p<0.001) at baseline and strongly at week 24 and week 52 (r=0.73 and 0.68, p<0.001); the mucocutaneous score correlated moderately, strongly and very strongly with CLASI total activity (r=0.57, 0.77 and 0.81, p<0.001) at baseline, week 24 and week 52, respectively. The strong correlations with arthritis and rash support the potential of LFA-REAL as an end point measurement in clinical trials.[7–9]

Strengths of the LFA-REAL include the simplicity and speed of its use and the minimal requirement for specialised training to accurately score the instrument. This was confirmed in a past study in which the scoring of clinicians untrained on outcome measures was compared with the scoring of expert trialists.[23] Weaknesses of the current study include the fact that the instrument was designed to be scored monthly but was only applied in the current trial three times, with each scoring date many months apart. Despite our efforts to simplify the LFA-REAL, there appears to be a learning curve in its use over time, so it might be interesting to try this application in a study using a washout or run-in period so that both patients and clinicians could gain experience before the time when randomisation to an intervention occurs. Another problem with intermittent scoring is that the gold standard of PGIC and CGIG could not be used, since they involve a recall involving change of disease activity from 1 month to the next. The optimal cut-off points to identify improvement in LFA-REAL ClinRO derived from these data will be further evaluated against CGIC improvement.

In sum, these data support the further development of the LFA-REAL ClinRO and PRO as a flexible resource in the evaluation of lupus disease activity and its potential as a simple, user-friendly outcome measure for SLE studies.

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