Arthritis Care & Research
Vol. 72, No. S10, October 2020, pp 163–170
DOI 10.1002/acr.24212

American College of Rheumatology
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Update on Outcome Measures for Pediatric Systemic Lupus Erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune, multisystem inflammatory disease of unknown etiology that is characterized by protean clinical manifestations, unpredictable course, and substantial risk of morbidity and mortality (1). It is estimated that 10% to 20% of all patients with SLE have their onset before 16 years of age. Pediatric SLE (pSLE) is thought to have a worse prognosis than adult-onset SLE, particularly in respect to multiorgan and kidney involvement (2,3).

In the past two decades, there has been a marked improvement in survival among patients with pSLE. Explanations for the prolonged life expectancy include earlier diagnosis, recognition of mild forms, and better approaches to therapy. However, as a result of the increased life span, children and adolescents with SLE are now faced with considerable morbidity because of the sequelae of disease activity, side effects of medications, and comorbid conditions such as recurrent infections, accelerated atherosclerosis, osteoporosis, and hypertension (4). This morbidity may affect their long-term quality of life, raising problems related to the physical and psychological adaptation to a chronic severe illness. Thus, the contemporary management of patients with pSLE should be directed not only at controlling disease activity and preventing death but also at minimizing cumulative organ damage.

These issues emphasize the need for a careful long-term follow-up of currently treated patients in order to monitor the patient disease state and global health and the effectiveness of therapy. This goal requires the regular assessment of the level of disease activity and organ damage as well as of the parent and the patient's perception of disease burden through the use of outcome measures validated for use in children and adolescents.

In a 2011 issue of *Arthritis Care & Research*, we reviewed the measures of disease activity and damage that were available at that time (5). However, since then, there has been a great deal of effort aimed at refining existing tools and developing novel instruments aiming to address the various aspects of disease impact. The purpose of the present review is to provide an overview of the newer outcome measures specifically developed for use in patients with pSLE.

Criteria for inactive disease and clinical remission

Although the global disease activity tools developed for adult SLE, which include the British Isles Lupus Assessment Group (BILAG) (6), the European Consensus Lupus Activity Measurement (ECLAM) (7), the Systemic Lupus Activity Measure (SLAM) (8), and the Systemic Lupus Erythematous Disease Activity Index (SLEDAI) (9), are also applicable to patients with pSLE, these measures are intended to provide a quantitative estimation of the absolute level of disease activity and do not enable the determination of a particular disease state. Because the current and future therapeutic advances will increase the likelihood of achieving complete disease control, there is a need to develop criteria that precisely define the state of disease remission.

In 2012, Mina et al (10) undertook a consensus survey aimed at defining the states of inactive disease (ID) and clinical remission (CR) in pSLE and selecting the variables that can be used to measure such states. After the selection of the articles relevant to the project through a systematic literature review, Delphi questionnaires were sent to an international group of pediatric rheumatologists with expertise in pSLE. There was a consensus that ID refers to a certain point in time, irrespective of treatment, whereas CR requires the presence of ID for 6 months or more and should consider the use of medications. There was also consensus that patients with ID/CR must have a normal physical examination (with the exception of malar rash, livedo reticularis, alopecia, or Raynaud phenomenon, which can be present if considered expression of disease damage and not of active disease), but may have persistence of select laboratory abnormalities, including antinuclear antibody positivity, any damage-related laboratory changes, low levels of complement C4 if presumed to be due to null allele, low and stable

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication March 9, 2020; accepted in revised form April 7, 2020.

levels of antiphospholipid antibodies, and mildly elevated erythrocyte sedimentation rate. Patients with ID can also have up to two mild nonlimiting symptoms (ie, fatigue, arthralgia, headache, myalgia) but not Raynaud's phenomenon, chest pain, or objective physical signs of SLE. Complete blood count, liver function testing, and complement C3 or CH50 levels must all be normal, and there cannot be an abnormal urinary sediment due to lupus nephritis (LN). Importantly, although the scores of disease activity indices (SLAM, SLEDAI, BILAG, and ECLAM) were deemed important for determining ID/CR, it was agreed that none of these tools are adequate to identify ID/CR and that these states can be present even if their score is more than 0.

The selected variables revealed strong capacity to discriminate patients with ID/CR from patients with minimally active lupus (MAL) (area under the receiver operating curve of more than 0.85). Disease activity scores with or without the physician global assessment of disease activity and patient symptoms were found to be suitable for differentiating children with ID from those with MAL.

The proposed definitions of ID and CR in pSLE and the permissible signs, symptoms, and laboratory abnormalities of patients with ID are presented in Table 1 and Table 2, respectively.

Damage assessment

A critical appraisal of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SDI) (11,12) and its modified pediatric version (Ped-SDI) (13) has been made in our former review (5). To further explore the validity of the SDI in pSLE, Holland et al investigated prospectively the frequency and types of SDI items in 1048 patients (14). They also assessed the ability of the instrument to reflect damage severity by asking the physician to rate the damage severity on a visual analog scale (MD VAS damage) in a subgroup of 559 patients. After these exercises, an international consensus conference was held to discuss, by means of nominal group technique, the appropriateness of both SDI and Ped-SDI for capturing damage and its severity in pSLE.

After a mean disease duration of 3.8 years, 44.2% of patients had an SDI score of more than 0 (maximum score of 14). The most commonly recorded SDI items were proteinuria, scarring alopecia, and cognitive impairment (Figure 1). Although there was a moderately strong association between SDI summary scores and MD VAS damage (Spearman's $r = 0.49$; $P < 0.0001$), in patients with damage (ie, patients with an SDI score of more than 0) mixed-effects analysis revealed that only four SDI items, each registered in less than 2% of patients, were significantly associated with MD VAS damage.

Based on these results and on the consensus among pediatric SLE experts, it was concluded that neither the original SDI nor its pediatric adaptation is adequate for estimating the severity of damage associated with pSLE. A criticism was raised that the SDI only provides an enumeration of damage items rather than quantifying their severity. Because physician perception of damage severity is influenced by both type of damage and related prognosis (eg, a stroke resulting in hemiparesis will likely lead to a greater impairment in patient function than a cataract), item weighting or scaling was thought to better capture the extent and impact of damage observed. There was full consensus (100%) that a separate measure or approach to capture damage severity of pSLE was needed.

Consensus was also reached on a definition of pSLE-associated damage and damage severity as the first step toward improving measurement of damage-related constructs. Damage was defined as "impairment of anatomy or physiology that may be associated with scarring, may accumulate, and is not completely reversible. Damage may be caused by disease, adverse effects of medication, or associated comorbidity. In children this may lead to stunted cognitive, and physical development." Damage severity was defined as follows: "severity of damage is measured by the organs involved, and the extent of anatomical and physiologic derangement as judged by the expected impact on mortality, degree of support required, activity limitation, restriction in social

Table 1. Definition of inactive disease and clinical remission in pSLE*

Construct	Time Frame		Medication Usage			
	Point in Time	Minimal Time Interval, mo	Glucocorticosteroids	Immunosuppressives	Preventive Medications†	Medications to Treat Damage
ID‡	Yes	–	Permissible	Permissible	Permissible	Permissible
CR						
CR on medication for pSLE	No	6	Permissible	Permissible	Permissible	Permissible
CR on preventive medication	No	6	No	No	Permissible	Permissible
CR off medication for pSLE	No	12	No	No	No	Permissible

* Adapted from Mina et al (10). ACE = angiotensin-converting enzyme; CR = clinical remission; ID = inactive disease; mo = months; pSLE = pediatric systemic lupus erythematosus.
† Preventive medications include systemic medications that can be used to prevent disease damage such as statins, aspirin, ACE inhibitors, angiotensin receptor blockers, bisphosphonates, vitamin D, and omega-3 fatty acids.
‡ See Table 2 for details on permissible signs, symptoms, and laboratory abnormalities of patients with inactive disease. Medication exposure is not considered.

Table 2. Details on permissible signs, symptoms, and laboratory abnormalities of patients with inactive disease*

Descriptors	Permissible Even if Potentially Due to cSLE Activity	Not Permissible Unless Due to Disease Damage
Signs of cSLE activity on physical examination	None	Malar rash, livedo reticularis, Raynaud's phenomenon, and alopecia†
Symptoms associated with cSLE activity		
Types of symptoms	Fatigue, arthralgia, myalgia, and headaches	Intermittent chest pain without radiologic or ECG abnormalities
Number of symptoms	2 or fewer	3 or 4
Severity of symptoms	Mild and nonlimiting	1 or more are moderate/severe
Laboratory abnormalities	Antinuclear antibodies positivity; any damage-related laboratory abnormalities (including proteinuria and decreased creatinine clearance); abnormally low levels of complement C4 if presumed to be due to null allele; abnormal but stable levels of antiphospholipid antibodies ≤ twice ULN; and erythrocyte sedimentation rate ≤ twice ULN	Abnormal urinary sediment due to lupus nephritis; abnormal liver function testing; abnormally low complement C3 or CH50 levels; and anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia‡

* Adapted from Mina et al (10). cSLE = childhood-onset systemic lupus erythematosus; ECG = electrocardiogram; HPF = high-power field; ULN = upper limit of normal.
† Raynaud's phenomenon determined by physical examination or by credible patient report.
‡ Lupus nephritis determined by urine sediment with white blood cells > 5 cells/HPF, red blood cells > 5 cells/HPF, or cellular cast.

participation, and patient-centered quality of life." These two definitions achieved an agreement of 83% and 77%, respectively, among experts (14).

Flare criteria

The course of SLE is often fluctuating, with episodes of disease exacerbation followed by periods of improvement, generally because of intensification of treatment. Precise measurement of disease flare is important to monitor the course of pSLE over time and to assess the effectiveness of drug therapies in clinical trials. In the context of an international collaborative effort, consensus was achieved on a definition of a flare of pSLE as "a measurable worsening of disease activity in at least one organ system, involving new or worse SLE symptoms; depending on the severity of the flare, more intensive therapy may be required." Furthermore, it was established that flares should be distinguished based on their severity into mild/minor, moderate, and major/severe categories. Using consensus formation techniques, agreement was reached on preliminary criteria for global flares in pSLE together with flare descriptors (15). However, these criteria were not validated until recently in an independent data set.

The preliminary flare criteria were validated using patient profiles rated by 268 international pediatric rheumatologists experienced in the care of pSLE. Each profile included data obtained at a baseline and a follow-up visit. The following descriptors were provided for each visit: 1) physician global assessment of over-

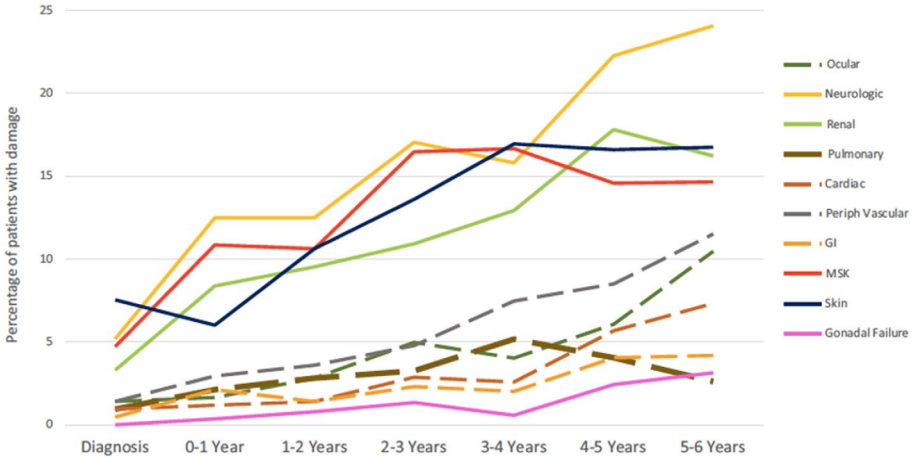

Figure 1. The relationship of the presence of damage in nine organ domains of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) is shown for disease duration of up to 6 years. Lines are moving averages of annual values. The most commonly damaged organ systems were the neuropsychiatric, musculoskeletal (MSK), renal, and skin systems. Malignancies and diabetes mellitus were present in less than 0.4% of the composite cohort, and both SDI organ systems are excluded from the figure. This figure is reproduced from Holland et al (14). GI = gastrointestinal.

all disease activity on a 0- to 10-cm visual analog scale (VAS), 2) parent assessment of patient overall well-being in a 0- to 10-cm VAS, 3) proteinuria, 4) erythrocyte sedimentation rate, 5) C3 and C4 levels, and 6) item and summary score of the SLEDAI 2000 or the domain and summary score of the BILAG. Using physician ratings, the preliminary criteria were tested for their ability to discriminate between patients who developed minor, moderate, and major flares. In a subsequent consensus conference, the validity of the criteria was further scrutinized on the basis of literature information, statistical performance, and metrological properties. The preliminary flare criteria were then ranked as per the ACR recommendations, and threshold scores for minor, moderate, and major flares were defined.

The four highest-ranked flare algorithms identified in the first consensus conference were considered. Two of them (SLEDAI-based criteria and BILAG-based criteria) were derived by multinomial logistic regression, whereas the other two (SLEDAI-classification tree analysis [CART] and BILAG-CART) were derived from CART. The first two candidate criteria, which consider the absolute change of each flare descriptor between the baseline and the follow-up visit, revealed the best accuracy (area under the curve [AUC] of more than 0.93 for both). Based on the comparable validation performances, consensus conference participants agreed that the two selected algorithms are equally valuable and suitable for use in clinical trials. Conversely, consensus was achieved that CART-based algorithms were not suited for use in clinical trials because they cannot be used to discriminate minor from moderate flares. The score calculation and the performance of the preliminary flare algorithms in the development and validation data sets are shown in Table 3.

The threshold scores for type of flare were calculated by computing the point on the receiver operating characteristic curves with the highest precision of correctly classifying the severity of a flare or by calculating the average of means of scores in two neighboring flare states weighted by the SDs of the scores. For the SLEDAI-based criteria, scores greater than or equal to 6.4, 3.0, and 0.6 constituted major, moderate, and minor flares, respectively. For the BILAG-based algorithm, scores greater than or equal to 7.4, 3.7, and 2.2 delineated major, moderate, and minor flares, respectively. All threshold values proved to be more than 82% sensitive and specific for capturing flare severity (16).

Response criteria

The Pediatric Rheumatology International Trials Organization (PRINTO)/ACR provisional criteria for the evaluation of response to therapy in pSLE were published in 2006 (17). Subsequently, Mina et al (18) found that the SLE Responder Index developed for adult-onset SLE was highly specific but had poor sensitivity for capturing improvement in pSLE. In the same study, the PRINTO/ACR provisional criteria were found to be well-suited to capturing major improvement but were less apt to detect moderate or major improvement. Thus, Brunner et al (19) sought to define clinically relevant improvement (CRI); to develop and validate criteria to measure CRI; and to categorize minor, moderate, and major responses to therapy in children and adolescents with SLE.

The project was conducted throughout seven subsequent steps, which included an initial Delphi survey among pediatric rheumatologists and nephrologists with expertise in pSLE aimed at selecting the key features for judging whether a patient experienced CRI, the rating of patient profiles, consensus procedures, and statistical analyses on patient profiles. Patient profiles included the following core set response variables (CRVs): 1)

Table 3. Comparison of the performance of the preliminary flare algorithm in the development and validation data set*

	Algorithm	Flare Category	AUC	
			2010 Data	2017 Data
SLEDAI-based flare score†	Score = 0.5 × SLEDAI + 0.45 × PCR + 0.5 × MD + 0.02 ESR	Major flare	0.95	0.93
		At least moderate flare	0.85	0.94
		At least minor flare	0.86	0.93
BILAG-based flare score†	Score = 0.4 × BILAG + 0.65 × PCR + 0.5 × MD + 0.02 ESR	Major flare	0.93	0.91
		At least moderate flare	0.85	0.92
		At least minor flare	0.85	0.93
SLEDAI-based CART rule	Score = 4 if 3 ≤ SLEDAI; score = 3 if 0.7 ≤ PCR and 3 > SLEDAI; score = 2 if 2 ≤ MD and 0.7 > PCR and 3 > SLEDAI; and score = 1 otherwise	Major flare	0.85	0.76
		At least moderate flare	0.80	0.80
		At least minor flare	0.84	0.89
BILAG-based CART rule	Score = 4 if 2 ≤ BILAG; score = 3 if 0.7 ≤ PCR and 2 > BILAG; score = 2 if 2 ≤ MD and 0.7 > PCR and 2 > BILAG; score = 1 otherwise	Major flare	0.86	0.71
		At least moderate flare	0.80	0.75
		At least minor flare	0.82	0.84

*Adapted from Brunner et al (16). Values presented represent the area under the receiver operating characteristic curve (AUC) considering the patient profile with consensus as defined by the 67% rule. Numeric values larger than or equal to flare score signify a flare; higher scores are seen with more severe flare. BILAG = British Isles Lupus Assessment Group; CART = classification tree analysis; ESR = erythrocyte sedimentation rate; MD = physician global assessment of disease (measured on a 0 to 10 visual analog scale, where 0 = inactive disease); PCR = urine protein/creatinine ratio from random urine sample; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.
† Algorithm considers for the change (baseline to follow-up) of each of the flare descriptors included.

global assessment of patient well-being, 2) physician assessment of overall disease activity, 3) SLEDAI score, 4) urine protein-to-creatinine ratio, and 5) Child Health Questionnaire physical summary score. Development of candidate algorithms and validation of their measurement properties was based on the evaluation of the percentage and absolute changes in the CRVs between baseline and follow-up visits.

During an international consensus conference, participants agreed that the preferred Childhood Lupus Improvement Index (CHILI) should consider absolute changes in CRVs. After conversion to a range of 0 to 100, a CHILI score of 54 or more revealed high accuracy for identifying CRI, with an AUC of 0.93, a sensitivity of 81.1%, and a specificity of 84.2%. CHILI scores greater than 15, 68, and 92 corresponded to minor, moderate, and major improvement, respectively (all with AUCs of more than 0.92, sensitivity of more than 93.1%, and specificity of more than 73.4%).

Organ-specific measures

Apart from the above-described global outcome measures, a number of organ-specific instruments, which aim to assess neurologic, renal, and cutaneous involvement in patients with pSLE, have been recently developed or adapted and validated.

Pediatric Automated Neuropsychological Assessment Metrics and Pediatric Automated Neuropsychological Assessment Metrics–Cognitive Performance Score

A number of studies have documented neurocognitive dysfunction in patients with pSLE, including deficits in attention or concentration, cognitive flexibility, free recall memory, visuoconstructional ability, and speed of information processing (20–22). The detection of these defects is generally based on formal neuropsychologic testing (20,22), which is, however, costly, lengthy, and not always easily available and necessitates highly specialized assessors. Computer-administered tests have been found as more cost-effective screening tools for neurocognitive dysfunction in various diseases (23).

Brunner et al (24) validated a pediatric version of the Automated Neuropsychological Assessment Metrics (25), which was found to be well suited to screening the cognitive abilities of adults with SLE. The instrument, which was named the Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) and adapted for use in children aged 10 years or more, was tested in a case-control study that enrolled 40 patients with pSLE. Formal neuropsychological tests were used as external standards.

The PedANAM is a computerized library of 10 subtests designed to measure sustained concentration and attention, spatial processing, cognitive-processing efficiency, verbal reasoning, learning, recall, and working memory. In the validation study, the PedANAM was found to possess moderate to substantial reproducibility, criterion and construct validity, and potential responsiveness to change.

In a subsequent analysis, it was noted that the use of the PedANAM in daily practice is hampered by its complexity and lack of a validated summary of overall performance statistics. This shortcoming prevents an easy synthesis of its data and, as a result, a reliable determination of whether the child's overall cognitive performance has changed. To overcome this limitation, a global cognitive performance score for the PedANAM (PedANAM-CPS) was devised to serve as a summary measure of children's cognitive performance on the PedANAM.

By means of supervised and unsupervised statistical approaches, four candidate composite indices were proposed, which were found to be able to differentiate patients' cognitive status in validation analysis. Based on the relative performance of the four candidate indices, the PedANAM-CPS Principal Components Analysis (PedANAM-CPS_{PCA}) score and the PedANAM-$CPS_{multiscore}$, as summary statistics, were proposed for systematic screening of cognitive impairment in children with pSLE. In detail, further neurocognitive assessment was recommended in subjects with a PedANAM-CPS_{PCA} score of less than 0.05 or a PedANAM-$CPS_{multiscore}$ of more than 0.09. Longitudinal testing with the PedANAM-CPS was advised for monitoring the course of cognitive ability over time. The software for the tests can be purchased online by contacting Vista LifeSciences on their website (www.vistalifesciences.com).

In a study of blood-based candidate biomarkers of the presence of neuropsychiatric involvement, select brain-reactive proteins were found to be associated with neurocognitive deficits and cognitive performance on the PedANAM in patients with pSLE. These proteins also helped predict the course of cognitive ability over time (26). This observation may open the way for using blood-based biomarkers in the screening and monitoring of neurocognitive deficits in pSLE.

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and the pediatric adaptation of Skindex29 (pSkindex27)

The CLASI has been developed to assess the extent of skin manifestations in adult patients with isolated cutaneous SLE and SLE (27). It includes a skin activity summary score (CLASI-A) and a damage summary score (CLASI-D). The activity score is determined by assessing mucocutaneous ulceration, hair loss, erythema, and scale/hypertrophy in 13 body areas, mucous membrane lesions, and alopecia due to active lupus. The CLASI-A score is calculated as the sum of the above item scores and ranges from 0 (no active mucocutaneous lesions) to 70 (maximum activity of mucocutaneous lesions). Values between 1 and 9, between 10 and 20, and of 21 or more correspond with mild, moderate, and severe mucocutaneous inflammation,

respectively. In addition, a 20% and 50% decrease in CLASI-A score are considered partial and major improvement in inflammatory skin lesions, respectively (28). Damage items contained in the CLASI-D include dyspigmentation and skin scarring and/or panniculitis of the same 13 body areas assessed by the CLASI-A. Its score ranges from 0 (no skin damage) to 56 (maximum skin damage).

The Skindex29 is a questionnaire aimed at measuring the impact of cutaneous disease on health-related quality of life (HRQOL) (29). It consists of 30 items grouped into the following three domains: emotions, symptoms, and functioning. Each item is rated on a five-point Likert scale as never, rarely, sometimes, often, or all the time. Responses are transformed to range from 0 (no effect or never) to 100 (experienced all the time). The summary score of the tool reflects the unweighted average of the three domain scores, with higher scores indicating a more profound impact of skin disease on HRQOL.

AIE'ed et al (30) evaluated the validity of the CLASI and Skindex29 in pSLE after adapting the latter instrument for use in children. The pediatric adaptation of the Skindex29 was formed by removing two items from the functioning domain (one pertaining to sex life and the other questioning affection difficulty) that were felt to be age inappropriate. The resulting pSkindex27 was composed of 28 items, one of which addresses adherence to treatment and is not scored. In validation analyses conducted in 48 patients with pSLE, both the CLASI and pSkindex27 were found to possess good measurement properties and to be well suited for use in epidemiological and therapeutic studies of children with pSLE. A subsequent study, which involved both rheumatologists and dermatologists, confirmed the validity and reliability of the CLASI and showed its superiority over the physician global assessment (31).

Validation of clinical indices of LN activity and damage in pSLE

It is still unclear whether clinical indices for LN can be used to monitor and quantify renal disease activity and damage in children with pSLE. Mina et al (32) investigated the validity of the renal domain scores of the SLEDAI (SLEDAI-R) and of the BILAG index (BILAG-R) (33), the Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS) (34), and the Systemic Lupus International Collaborating Clinics Damage Index Renal Domain Score (SDI-R) (35) against the criterion standard, represented by the findings of kidney biopsy. Overall, all clinical indices were found to be unable to differentiate among patients by the International Society of Nephrology/Renal Pathology Society class of renal histology. Despite its limitations, the SLEDAI-R revealed the best capacity for measuring LN activity in clinical practice. The SDI was poorly correlated with kidney damage.

Renal Activity Index for Lupus

In recent years, there has been a great deal of effort to identify biomarkers or panels of laboratory tests that allow the noninvasive estimation of the degree of inflammation seen on kidney biopsies in LN. Brunner et al (36) devised the Renal Activity Index for Lupus (RAIL), an instrument based solely on laboratory measures, and investigated whether it accurately reflected histological LN activity.

Traditional LN laboratory tests and 16 urine biomarkers were measured in 47 patients with pSLE at the time of kidney biopsy. Histological LN activity was measured by the National Institutes of Health Activity Index (NIH-AI) and the Tubulointerstitial Activity Index (TIAI). Candidate components of the RAIL were scrutinized by deriving RAIL algorithms that predicted the NIH-AI LN activity status and the TIAI LN activity status through stepwise multivariate logistic regression. The accuracy of the RAIL in discriminating patients by LN activity status was also examined. The following six urine biomarkers were included in the RAIL: NGAL, MCP-1, ceruloplasmin, adiponectin, hemopexin, and KIM-1. These biomarkers predicted LN activity status, defined by both NIH-AI and TIAI, with high accuracy and minimal influence of concomitant kidney damage.

CONCLUSIONS

In the past decade, a number of novel outcome measures for patients with pSLE have been developed by means of sophisticated and innovative statistical methods. These tools will help increase the reliability and precision of the assessment of disease status and course as well as treatment response. The availability, separate from composite instruments, of well-designed individual organ or system outcome measures will facilitate best approaches for treating specific disease manifestations such as LN, neuropsychiatric lupus, and cutaneous lupus erythematosus. The advances achieved so far will foster longitudinal observational studies and collaborative clinical trials in pSLE and improve their quality. In addition, the new outcome measures, in conjunction with the availability of new medications targeting recently discovered molecular pathways and mediators, will favor the implementation of better personalized therapeutic strategies.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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