The use of the British Isles Lupus Assessment Group (BILAG) index as a valid tool in assessing disease activity in childhood-onset systemic lupus erythematous

S. D. Marks, C. Pilkinson¹, P. Woo¹ and M. J. Dillon

Objectives. The British Isles Lupus Assessment Group (BILAG) index is a standardized systemic lupus erythematous (SLE) disease activity assessment. The main aim of this study was to correlate the BILAG index with laboratory measures of disease activity in childhood-onset SLE with and without biopsy-proven lupus nephritis.

Method. Prospective observational comparison study of the BILAG index in 21 SLE patients under 18 yr of age over a 12-month period in a tertiary referral paediatric outpatient clinic.

Results. Eleven patients with lupus non-nephritis and 10 patients with lupus nephritis were reviewed. The lupus nephritis patients had significantly ($P < 0.001$) more admissions over a similar time interval since diagnosis. The renal BILAG disease activity scores were significantly greater ($P = 0.013$) in the lupus nephritis group (range 1–9, median 3.0, compared with 0–3 and 1.0 in the lupus non-nephritis group). The total BILAG scores and patient visual analogue scores (VAS) were higher in the lupus nephritis groups, unlike the lower physician VAS, but these differences were not statistically significant compared with other laboratory indices of disease activity.

Conclusions. The BILAG index is a useful tool in monitoring disease activity in children and adolescents with SLE. The data collected for the BILAG index can be used serially and effectively by different clinicians over time to enable recording of disease status at sequential assessments. The lower patient VAS in the lupus non-nephritis group was not significant and may reflect the patients' own perception of lethargy at times of increased disease activity.

KEY WORDS: Systemic lupus erythematous, Childhood, Lupus nephritis, Disease activity score, BILAG index.

Systemic lupus erythematosus (SLE) is an episodic, multisystem, autoimmune disease with significant morbidity and mortality due to widespread inflammation of blood vessels and connective tissues within many systems, and is often progressive. In clinical studies patients are identified using the American College of Rheumatology criteria [1, 2]. Childhood-onset SLE has variable clinical manifestations and an unpredictable natural history. The minimum incidence in a paediatric population is 0.28 per 100 000 children at risk per yr [3] and the prevalence in children and adults from various epidemiological studies varies between 12.0 and 50.8 per 100 000 [4–10]. It has been shown that haematological and renal disease is more severe in patients with childhood-onset lupus than in those with adult-onset disease [11]. Evidence of renal involvement with biopsy-proven lupus nephritis is a major determinant of the prognosis of childhood-onset SLE.

The monitoring of outcome in lupus patients depends on the use of reproducible, reliable and validated disease activity, damage and patient health perception indices. The BILAG index is based on the principle of the physician’s intention to treat, and is a clinical measure of disease activity in SLE patients which has been validated to be reliable, comprehensive and sensitive to change [12–15]. It was developed to report disease activity in eight systems (general, mucocutaneous, neurological, musculoskeletal, cardiorespiratory, vasculitis, renal and haematological), which differentiates it from other lupus activity indices.

Each category has up to 18 questions, which are scored according to whether or not clinical features are present and whether they are improving (in the previous 4 weeks), the same, worse or new.

The BILAG scores include renal and haematological assessments within these systems, with confirmation of abnormal results due to active lupus (rather than drug side-effects, for example). The renal BILAG consists of assessment of blood pressure, proteinuria (dipstick and/or 24 h quantification), active urine sediment, nephrotic syndrome, renal function (creatinine and creatinine clearance or glomerular filtration rate) and histological evidence of active nephritis. The BILAG score does not include immunological data.

Although the BILAG system was originally devised for adult patients, its use has been adapted for and fully assessed in children [16]. The SDI [Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology Damage Index] [17, 18] is a damage index for lupus which has been developed and widely accepted. However, it had not yet been validated in children at the time of this trial so this assessment was not included in the present study.

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The methods of assessing disease severity are always open to discussion in relation to children with lupus. Many believe that clinical assessment should take precedence over laboratory investigations. However, it is well recognized that there may be changes in the results of investigations suggesting a flare in disease activity even though the patient is clinically well, and at other times clinical evidence of disease activity without commensurate laboratory abnormalities.

The main aim of this study was to compare the validity of the BILAG index in children and adolescents with SLE between two groups of patients: those with biopsy-proven lupus nephritis and those without. Our hypothesis was that if the BILAG index is valid, then it will be scored significantly higher in those patients with lupus nephritis. We also wanted to determine the correlation between the total BILAG score and clinical and laboratory measures of disease activity [such as erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, antidualle-stranded DNA antibody, complement C3 and C4 and anticardiolipin immunoglobulin (Ig) G and IgM antibody].

**Subjects and methods**

This was a cohort study of paediatric and adolescent patients with SLE reviewed at the tertiary referral clinics of the Departments of Nephrology and/or Rheumatology at Great Ormond Street Hospital for Children NHS Trust.

Due to the nature of tertiary referrals, these patients tend to be at the severe end of the spectrum of childhood disease activity. All the patients were seen at additional out-patient appointments in a joint nephrology and rheumatology clinic specifically set up for lupus patients at Great Ormond Street Hospital for Children NHS Trust for the purpose of this study. The subjects of the study were identified by a search of the hospital’s Patient Information Management Systems (PIMS) and the Nephrology Patient Database.

Twenty-five lupus patients were invited to attend the clinic, of whom 21 consented: 10 patients had lupus nephritis (clinical and biopsy-proven), referred to as the ‘lupus nephritis’ group, and 11 had no clinical or laboratory evidence of renal involvement at the time of analysis, referred to as the ‘lupus non-nephritis’ group.

Full clinical assessment (history, examination and investigations) was undertaken on all patients. The severity of disease activity in the cases was analysed manually using version 3 of the BILAG index [13] assessment form, which rates clinical and laboratory manifestations in each of the eight organ systems.

To provide numerical scores, we used a previous weighting system that assigned a score of 9 to active manifestations (grade A in the BILAG), 3 to grade B manifestations, 1 to grade C manifestations, and 0 to grade D and E manifestations. We used the sum of these scores as a summary index (possible range 0–72) [15].

One unblinded physician (S.D.M.) and all patients completed visual analogue scales (VAS); the patients marked on a 10-cm scale how well they felt in general, 0 denoting very ill and 10 denoting completely well [19].

The data were analysed with SPSS 11.0 software for Windows. Statistical significance was derived using non-parametric tests such as the Mann–Whitney U, Wilcoxon W and Kruskal–Wallis tests.

Ethical approval was obtained for this study from the Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust Research Ethics Committee, and written consent was obtained for all cases.

### Results

**Baseline characteristics**

Baseline characteristics of the patients in the lupus nephritis and lupus non-nephritis groups, in terms of age, sex ratio, time since diagnosis and number of admissions since diagnosis were identified. These are shown in Table 1, with time from diagnosis and comparisons between the groups showing similarity in age and sex ratio. Due to the expected severity of disease activity in the lupus nephritis group, this group showed a statistically significant increase in the number of hospital admissions over a similar time-interval since diagnosis. All 10 patients with lupus nephritis had evidence of active renal disease at the time of their previous biopsy, which was undertaken between 0.1 and 1.8 (median of 0.8) yr prior to the BILAG index assessment.

**Clinical disease activity**

The individual system BILAG scores are shown in Table 2. As might be expected, the lupus nephritis group had statistically

### Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Age range (median) (yr)</th>
<th>Sex ratio (F:M)</th>
<th>Range of years since diagnosis (median)</th>
<th>Range of number of admissions (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus non-nephritis</td>
<td>11</td>
<td>11.8–17.8 (15.7)</td>
<td>8:3</td>
<td>0.3–12.8 (2.6)</td>
<td>1–12 (8)</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>10</td>
<td>11.3–17.7 (15.3)</td>
<td>7:3</td>
<td>1.9–12.6 (4.4)</td>
<td>9–91 (17)</td>
</tr>
<tr>
<td>P&lt;0.43</td>
<td></td>
<td></td>
<td>P=0.92</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

*P<0.001

### Table 2. Individual system BILAG scores in lupus case groups

<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>Mucocutaneous</th>
<th>Nervous system</th>
<th>Musculoskeletal</th>
<th>Cardiorespiratory</th>
<th>Vasculitis</th>
<th>Renal</th>
<th>Haematological</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>D</td>
<td>1</td>
<td>0</td>
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<td>1</td>
<td>1</td>
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<td>E</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. of patients</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Category A = score of 9 (see [13] for individual system definitions); B = score of 3 (see [13] for individual system definitions); C = score of 1 (see [13] for individual system definitions); D = score of 0 as previous (but no current) involvement; E = score of 0 as no previous or current involvement.
significantly higher renal and higher total BILAG scores than the lupus non-nephritis group (Table 3). The lower patient VAS in the lupus non-nephritis group is not significant and may possibly be due to pain and psychological problems associated with the arthralgia and/or arthropathy. Patients with lupus nephritis may not have symptoms until severe disease progression, although their lower physician VAS may reflect the physician’s knowledge of their underlying disease activity, renal involvement and laboratory results.

The renal BILAG was able to differentiate between the lupus non-nephritis and the lupus nephritis groups. Using Mann–Whitney non-parametric tests, there were statistically significant differences between the lupus non-nephritis and lupus nephritis groups. Using Mann–Whitney non-parametric tests, there were statistically significant differences between the lupus non-nephritis and lupus nephritis groups. Using Mann–Whitney non-parametric tests, there were statistically significant differences between the lupus non-nephritis and lupus nephritis groups.

Laboratory measures of disease activity
The findings from this study (Table 4) showed no statistically significant differences between the groups. The lupus non-nephritis group, however, were more likely to have higher anticardiolipin IgG antibodies, which would suggest an increased likelihood of thrombotic events, although this was not statistically significant.

Clinical and laboratory measures of disease activity
There was no relationship between clinical disease activity (documented by the total BILAG score) and evidence of disease activity by investigation (for example, hypocomplementaemia).

Discussion
This was a prospective observational comparison study of the disease activity score of lupus nephritis and lupus non-nephritis patients at the tertiary referral paediatric nephrology and rheumatology out-patient clinics of Great Ormond Street Hospital for Children NHS Trust. The multisystem nature of SLE necessitates the individualized management of each patient. Constant vigilance is required in the monitoring of evolution of disease within each organ system of every patient, and the BILAG disease activity index is an excellent clinical indicator of disease activity.

All of the information from the history, examination and the evaluation of laboratory evidence of disease activity is required for optimal management. The BILAG has been shown to be highly sensitive to clinical change in children and can be used to study the response to treatment in children with SLE [16], which can be beneficial in randomized controlled studies of different therapeutic regimens.

The methods of assessing disease severity in childhood SLE are still open to discussion. Scales of indices of disease activity continue to evolve and include SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), SLAM (Systemic Lupus Activity Measure) and ECLAM (European Consensus Lupus Activity Measure) [16–18, 20, 21]. These have all been used in the evaluation of disease activity in adults and are being validated for use in children with SLE.

In our study, the lower patient VAS values in the lupus non-nephritis group are not significant and may reflect the patients’ own perception of lethargy at times of increased disease activity. Patients and physicians assess disease activity differently using the 10-cm VAS; as expected, physicians place more emphasis on laboratory features, whereas patients emphasize function [19]. This may explain the differences seen between the physician and patient VAS results.

This study is limited by the relatively small number of patients reviewed with regard to the BILAG index, patient and physician VAS. All of this needs to be re-assessed frequently with more patients as part of a multicentre study.

SLE is a multisystem disease that can affect different systems over time, and therefore physicians need to continuously assess clinical and laboratory results to monitor disease activity. Documentation in the notes of clinical symptoms and signs is, therefore, imperative in the management of children with SLE.

However, problems can be encountered when different physicians are assessing patients at out-patient clinic attendances and during admissions. The BILAG index allows effective monitoring of disease progress serially over time by using standardization of questions and data recorded, even if patients are seen by different clinicians.

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**Key messages**
- The BILAG index is a useful tool in monitoring disease activity in childhood SLE.
- Data collected for the BILAG can be used serially and effectively by different clinicians.
The authors have declared no conflicts of interest.

References