Institution: University of Birmingham

Unit of Assessment: A1

Title of case study: Assessment of disease activity in lupus

1. Summary of the impact (indicative maximum 100 words)

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that is subject to relapses (flares) and remissions. Measuring disease activity in multiple systems, some of which may be worsening while others are improving, is a challenge in the management of patients with SLE and also in the conduct of clinical trials of new drugs for the treatment of SLE. The British Isles Lupus Assessment Group (BILAG) disease activity index for measuring lupus was developed by Professors Paul Bacon and Caroline Gordon at the University of Birmingham and has been validated and implemented for clinical trials and routine clinical practice. The instrument is able to capture significant improvement or worsening in lupus disease activity on a system based approach, leading to improved management and treatment of patients. It is the preferred disease activity instrument for international SLE trials recommended by the US Food and Drug Administration and European Medicines Agency, demonstrating impact on health and welfare and public policy and health services.

2. Underpinning research (indicative maximum 500 words)

SLE is an autoimmune disease which can affect any system in the body, varies in severity from mild to life-threatening and is more common in women. Research conducted at the University of Birmingham in the 1990s (by Professors Caroline Gordon, at UoB from 1989 and Paul Bacon, at UoB from 1981-2003; Honorary Professor thereafter) showed the incidence is 3.8/100,000/year (6.8/100,000/year in women and 0.5/100,000/year in men) with a median age at diagnosis of 37 years. The prevalence of lupus is 1 in 2000 in adult women in the UK (actually 49.6/100,000), but it is about tenfold less common in men. It is more common, more severe and presents younger in people of Afro-Caribbean and South Asian origin than in those of white European origin. The prevalence in adult women is about 1 in 500 for Afro-Caribbeans and 1 in 1000 in South Asians in Birmingham. The average age of death of patients with lupus is 52 years.

Clinical assessment of this disease is problematic due to the complex multi-system nature of the disease, with fluctuating levels of disease activity, which may vary between patients and within the same patient over time. In the 1980s there were about 40 reports of different ways of assessing disease activity in lupus but none had been validated and most resulted in a total numerical score. The Birmingham Rheumatology Unit (Professors Caroline Gordon and Paul Bacon) and other BILAG collaborators were pioneers in developing the BILAG disease activity index. Version 3 of this system-based approach to the assessment of lupus disease activity was validated and published in 1993 by Professors Gordon and Bacon from the University of Birmingham and Professors Hay and Symmons from the University of Manchester (1). This system differed from other disease activity instruments in being a comprehensive, transitional index that assessed how disease activity changes over time with a score for each of eight systems and not just a total score based on whether features are present or absent. The BILAG disease activity index was adapted for use in children and has been used widely for observational studies and clinical trials.

Over time it became apparent that there were still some deficiencies with this instrument. In particular it did not capture ophthalmic or gastrointestinal systems well and there was need to improve certain aspects of the terminology and scoring to reflect current opinion about the disease. This led to a complete revision of the instrument in 2003-2004 which was led by Prof Caroline Gordon at the University of Birmingham and Prof David Isenberg from University College London. The work was supported by a post-doctoral research fellow, Dr Chee-Seng Yee at the University of Birmingham and resulted in many publications (2-5). The revised instrument, called the BILAG-2004 index, was designed to have 9 rather than 8 systems, new terminology and scoring. It was shown to be a reliable assessment method with face, content and construct validity, was sensitive to change over time and was better than an alternative SLE Disease Activity Index (SLEDAI) (2-5).

The BILAG 2004 system allows for change in severity to be captured and incorporated in to the scoring, as well as each system having its own score, so that it is possible to see which systems improve on a given treatment and which do not. The alternative instrument SLEDAI from Canada and other lupus disease activity scores only provide a total score, which can be made up by different components. For example, two patients can have the same score on the same day or one patient can have the same score on different days but the components of the scores include different disease manifestations and levels of severity of disease on each occasion. The BILAG-2004 index improves the accuracy of reported disease manifestations, is sensitive to many types of change in disease activity, distinguishes different levels of severity in each system and importantly correlates with the simpler index SLEDAI. More recently a revised way of scoring the BILAG 2004 index has been proposed to capture lupus flare and was shown to perform better than an alternative lupus flare instrument (6).

3. References to the research (indicative maximum of six references)

1. Hay EM, **Bacon PA**, **Gordon C**, Isenberg DA, Maddison P, Snaith ML, Symmons DP, Viner N, Zoma A. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med. 1993, Jul;86(7):447-58. *PMID: 8210301*
2. Yee CS, Farewell V, Isenberg DA, Prabu A, Sokoll K, Teh LS, Rahman A, Bruce IN, Griffiths B, Akil M, McHugh N, D'Cruz D, Khamashta MA, Bowman S, Maddison P, Zoma A, Allen E, **Gordon C**. Revised British Isles Lupus Assessment Group 2004 index: A reliable tool for assessment of systemic lupus erythematosus activity. *Arthritis Rheumatism.* 2006; **54**(10):3300-3305. *DOI 10.1002/art.22162*
3. Yee CS, Farewell V, Isenberg DA, Rahman A, Teh LS, Griffiths B, Bruce IN, Ahmad Y, Prabu A, Akil M, McHugh N, D'Cruz D, Khamashta MA, Maddison P, **Gordon C**. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. *Arthritis & Rheumatism*. 2007;**56**:4113-4119. *DOI 10.1002/art.23130*
4. Yee CS, Isenberg DA, Prabu A, Sokoll K, Teh LS, Rahman A, Bruce IN, Griffiths B, Akil M, McHugh N, D'Cruz D, Khamashta MA, Bowman S, Maddison P, Zoma A, **Gordon C**. BILAG-2004 Index captures SLE disease activity better than SLEDAI-2000. *Annals Rheumatic Diseases.* 2008; **67**: 873 – 876 *DOI 10.1136/ard.2007.070847*
5. Yee CS, Farewell V, Isenberg DA, Griffiths B, Teh LS, Bruce IN, Ahmad Y, Rahman A, Prabu A, Akil M, McHugh N, Edwards C, D'Cruz D, Khamashta MA, Maddison P, **Gordon C**. The BILAG-2004 index is sensitive to change for assessment of SLE disease activity. *Rheumatology (Oxford)* 2009; 48(6):691-695. *DOI 10.1093/rheumatology/kep064*
6. Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcon GS, Aranow C, Bruce IN, Dooley MA, Fortin PR, Ginzler EM, Gladman DD, Hanly JG, Inanc M, Kalunian K, Khamashta M, Merrill JT, Nived O, Petri M, Ramsey-Goldman R, Sturfelt G, Urowitz M, Wallace DJ, **Gordon C**, Rahman A. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. *Ann Rheum Dis* 2011;70:54-59. *DOI 10.1136/ard.2010.132068*

4. Details of the impact (indicative maximum 750 words)

Measurement of disease activity in SLE is central to evaluating the severity of the disease and identifying patients at risk of developing chronic damage or dying, indicating what type of treatment a patient needs, evaluating whether or not they respond to therapy and can be used to identify differences in disease manifestations amongst patient groups. The BILAG 2004 index has been used increasingly worldwide for the assessment of disease activity in lupus patients in clinical trials and clinical practice since it was shown to be reliable, valid and sensitive to change, as it is the only validated index that shows activity in nine individual systems rather than a combined global score. The BILAG 2004 index has had an impact on **clinical practice**, **patient management** and the ability of **pharmaceutical companies** to obtain approval for the use of new treatments for lupus.

Impact on Pharmaceutical Companies and Guidance for Industry

Until recently the only drugs licensed for lupus were hydroxychloroquine and corticosteroids. Other drugs have been used but both steroids and other immunosuppressants cause a lot of toxicity. Until the late 1990s pharmaceutical companies were not keen to undertake trials in a complex multisystem disease like lupus because of uncertainty about how to measure appropriate disease end-points. However with increasing need for better therapies due to the significant mortality and morbidity of lupus, multiple clinical trials of new SLE treatments have been conducted in the UK and internationally over the last 10 years, that have incorporated the use of the BILAG system of assessing disease activity (1, 2). Many of these trials were set up by investigators or companies that were not involved in the design and validation of the BILAG 2004 index. Recommendations produced in 2009 by international members of the SLE Task Force of EULAR included the use of the BILAG system for the assessment of activity in clinical trials (3). Furthermore, guidance relating to the use of the BILAG 2004 index has also been incorporated into the US Federal Food and Drug Administration Guidance for Industry: Systemic Lupus Erythematosus — Developing Medical Products for Treatment, which was published in 2010. On page 7 of the document (4) it is stated: "*Several indices exist that mirror the assessment of experienced clinicians and are sensitive to changes in disease activity. The BILAG is the preferred index to study reduction in disease activity in clinical trials. The BILAG scores patients based on the need for therapy; therefore, the clinical interpretation of a change in score is apparent.*" This document goes on to discuss how the BILAG indices can be used in clinical trials in more detail (4).

Over the last 5 years there has been increasing use of composite end-points in lupus clinical trials using several disease activity instruments so that efficacy of treatment is demonstrated as improvement without worsening by more than one instrument (2). The BILAG 2004 index has been incorporated as the central score to show improvement in the BILAG based Combined Lupus Assessment (BICLA) (5). A representative of the company UCB wrote (5) "*It was important to have a sensitive efficacy assessment instrument, endpoints that are clinically meaningful to the treatment of this patient cohort and a placebo response which is limited enough to reveal the response of an effective treatment…Composite endpoints have greater power than individual tools to identify differences between treatment groups, which is particularly useful in SLE, where patient populations are heterogeneous and disease progression is unpredictable. The BILAG-2004 index was selected as the central score on the basis of its comprehensiveness, ability to capture partial improvement, incremental changes in disease activity, changes in individual involved body systems and the clinical relevance of its scoring system…The positive results of EMBLEM™ study proved BICLA as a robust, sensitive, composite, endpoint incorporating multiple disease activity indices, each of which emphasises different aspects of SLE activity…. The BILAG-2004 index, used as the key compartment of BICLA in EMBLEM™, is a comprehensive validated tool for assessing disease activity in all organ systems, and is capable of measuring incremental improvement*." The BILAG index is also a component of the SLE Responder Index (SRI) that was set up by another independent panel of lupus investigators. The SRI is based on showing improvement in the SLEDAI without worsening by the more comprehensive BILAG index or physician's global assessment. Landmark trials with the SRI were published in 2011 (and tested Belimumab, the first drug licensed for SLE in 50 years) (2). The European Medicines Agency (EMA) draft guideline on clinical investigations of medicinal products for the treatment of SLE, cutaneous lupus and lupus nephritis was published in early 2013 and recommends the use of the validated composite indices that incorporate the BILAG indices, both the BICLA and the SRI (6). To promote optimal clinical trial data collection using the BILAG 2004 index and the SLEDAI, the Lupus Foundation of America (a charity supporting lupus research and education) has set up a training and testing site which is available for the training of investigators worldwide and for pharmaceutical company staff involved in clinical trials; reflecting the impact of these instruments on lupus research (7). This provides further evidence of impact that BILAG 2004 index has had on investigators and pharmaceutical companies wanting to demonstrate outcome of the disease and efficacy of new drugs for lupus which will benefit patients as they gain access to new drug options.

Impact on Clinical Practice

In 2010 the European League Against Rheumatism (EULAR), an organisation representing patient,

healthcare professionals and scientific societies across Europe, recommended the use of such a disease activity instrument for routine monitoring of lupus patients (8) and in 2011 it was recommended as a quality indicator (9). The NHS England Clinical Reference Group (CRG)for Specialised Rheumatology has recommended the BILAG 2004 system specifically in 2013 as a pre-requisite assessment for both eligibility and outcome assessment for SLE patients being considered for high cost drugs in the UK (10). The Rheumatology CRG Chair wrote "*The impact of the BILAG indices also extends directly into improving the routine NHS clinical practice and care of our patients. For people living with lupus, which can follow an unpredictable course, including the risk of major life threatening disease in any organ system, the ability to accurately assess disease activity and severity is a paramount importance to routine clinical care*" (10). Thus the BILAG 2004 index is becoming a routine assessment for patients with this complex, life-threatening multisystem disease in UK clinical practice and abroad, as well as a tool for clinical trials and observational studies on disease outcome.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Gayed M, Gordon C. Novel treatments for systemic lupus erythematosus. *Curr Opin Investig Drugs* 2010; 11(11):1256-1264.

2. Harvey PR, Gordon C: B-cell targeted therapies in systemic lupus erythematosus: successes and challenges. BioDrugs 2013;27:85-95 *DOI 10.1007/s40259-013-0015-8*

3. Gordon C, Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, Font J, Gilboe IM, Houssiau F, Huizinga TW, Isenberg D, Kallenberg CG, Khamashta MA, Piette JC, Schneider M, Smolen JS, Sturfelt G, Tincani A, van Vollenhoven R, Boumpas DT: EULAR points to consider for conducting clinical trials in systemic lupus erythematosus. *Annals Rheumatic Diseases* 2009;68:470-476. (published on line 3 Apr 2008) *DOI 10.1136/ard.2007.083022*

4. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf (published 2010)

5. Letter from the Medical Director, Lupus and Immunology, UCB, Brussels

6. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139615.pdf

7. https://www.lfa-point.org/ (discussed in http://www.lupus.org/webmodules/webarticlesnet/templates/new_empty.aspx?articleid=3530

8. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, Cervera R, Doria A, Jayne D, Khamashta MA, Kuhn A, Gordon C, Petri M, Rekvig OP, Schneider M, Sherer Y, Shoenfeld Y, Smolen JS, Talarico R, Tincani A, van Vollenhoven RF, Ward MM, Werth VP, Carmona L. EULAR Recommendations for monitoring systemic lupus erythematosus patients in clinical practice and in observational studies. *Ann Rheum Dis* 2010; 69(7):1269-1274 *DOI 10.1136/ard.2009.117200*

9. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Cervera R, Doria A, Jayne D, Khamashta MA, Kuhn A, Gordon C, Petri M, Schneider M, Shoenfeld Y, Smolen JS, Talarico R, Tincani A, Ward MM, Werth VP, Carmona L. Development of quality indicators to evaluate the monitoring of SLE patients in routine clinical practice. *Autoimmun Rev* 2011; 10(7):383-388 *DOI 10.1016/j.autrev.2010.12.008*

10. Letter from the Chair, NHS England Clinical Reference Group, Specialised Rheumatology, UK