European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies

M Mosca, C Tani, M Aringer, et al.

Ann Rheum Dis published online November 5, 2009
doi: 10.1136/ard.2009.117200

ARD Online First, published on April 21, 2010 as 10.1136/ard.2009.117200

European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies

M Mosca,[1] C Tani,[1] M Aringer,[2] S Bombardieri,[1] D Boumpas,[3] R Brey,[4] R Cervera,[5] A Doria,[6] D Jayne,[7] M A Khamashta,[8] A Kuhn,[9] C Gordon,[10] M Petri,[11] O P Rekvig,[12] M Schneider,[13] Y Sherer,[14] Y Shoenfeld,[15] J S Smolen,[16] R Talarico,[1] A Tincani,[17] R F van Vollenhoven,[18] M M Ward,[19] V P Werth,[20] L Carmona[21]

► Additional data (supplementary files 1 and 2 and appendices 1–3) are published online only. To view these files please visit the journal online (http://ard.bmj.com) and find the article

Correspondence to: Dr Marta Mosca, University of Pisa, via Roma 67, Ospedale S. Chiara, Pisa, 56126, Italy; marta.mosca@int.med.unipi.it

Accepted 19 October 2009

ABSTRACT

Objectives: To develop recommendations for monitoring patients with systemic lupus erythematosus (SLE) in clinical practice and observational studies and to develop a standardised core set of variables to monitor SLE.

Methods: We followed the European League Against Rheumatism (EULAR) standardised procedures for guideline development. The following techniques were applied: nominal groups, Delphi surveys for prioritisation, small group discussion, systematic literature review and two Delphi rounds to obtain agreement. The panel included rheumatologists, internists, dermatologists, a nephrologist and an expert related to national research agencies. The level of evidence and grading of recommendations were determined according to the Levels of Evidence and Grades of Recommendations of the Oxford Centre for Evidence-Based Medicine.

Results: A total of 10 recommendations have been developed, covering the following aspects: patient assessment, cardiovascular risk factors, other risk factors (osteoporosis, cancer), infection risk (screening, vaccination, monitoring), frequency of assessments, laboratory tests, mucocutaneous involvement, kidney monitoring, neuropsychological manifestations and ophthalmology assessment. A 'core set' of minimal variables for the assessment and monitoring of patients with SLE in clinical practice was developed that included some of the recommendations. In addition to the recommendations, indications for specific organ assessments that were viewed as part of good clinical practice were discussed and included in the flow chart.

Conclusions: A set of recommendations for monitoring patients with SLE in routine clinical practice has been developed. The use of a standardised core set to monitor patients with SLE should facilitate clinical practice, as well as the quality control of care for patients with SLE, and the collection and comparison of data in observational studies.

INTRODUCTION

Assessment of patients with systemic lupus erythematosus (SLE) in clinical practice relies upon the experience of the treating doctor and thus is subject to great variability between centres and between doctors. Much of this variability concerns the assessment of organ involvement, complicating comparisons among practices and potentially leading to poor outcomes.[1 2]

The aims of the present study were to address aspects for monitoring patients with SLE in clinical practice and observational studies, and to develop a standardised core set of variables for the assessment of patients with SLE in routine clinical practice.

METHODS

These recommendations have been developed following the methodology proposed by the European League Against Rheumatism (EULAR).[3] The following techniques were applied: nominal group, Delphi surveys for prioritisation, small group discussion and systematic literature review (SLR).

A first meeting was held, during which a list of questions for the SLR was agreed upon. The SLR results were discussed at the final meeting. Evidence was graded according to the levels proposed by the Oxford Centre for Evidence-Based Medicine, and agreement with each recommendation was collected by Delphi technique.[4] Additionally, the panellists provided an estimation of the cost and safety of individual monitoring strategies (for more information on the methodology followed see the Supplementary material).

RESULTS

Scope, target population and definitions

These recommendations have been elaborated with the intention of helping specialists involved in the care of patients with SLE in their decisions. See the Supplementary material for the definitions of monitoring, active disease and remission referred to in this document.

Recommendations

Table 1 shows the list of recommendations with the level of evidence, grade of recommendation, agreement and cost/risk ratio. (See Supplementary material for further information in the discussion that led to specific recommendations.)

Recommendation 1: patient assessment

The clinical picture of SLE is extremely variable and may be related to disease activity, organ damage, drug toxicity and quality of life (QoL).[5 6] Several indices have been developed and validated

Recommendations

Table 1 List of recommendations with level of evidence and grade of recommendation, agreement, cost/risk ratio

Recommendation	Level of evidence and grade of recommendation	Agreement	Cost/risk
1. Patient assessment.			
In addition to the standard care of patients without lupus of the same age and sex, the assessment of patients with SLE must include the evaluation of:			
disease activity by a validated index at each visit			
organ damage annually			
general quality of life by patient history and/or by a 0–10 VAS (patient global score) at each visit	5, D	97.6	L/VL
comorbidities			
drug toxicity			
2. Cardiovascular risk factors			
At baseline and during follow-up at least once a year:			
assess smoking, vascular events (cerebral/cardiovascular), physical activity, oral contraceptives, hormonal therapies and family history of cardiovascular disease			
perform blood tests: blood cholesterol, glucose	1b, B	98.1	L/VL
examine for blood pressure, body mass index (and/or waist circumference)			
NB: some patients may need more frequent follow-up (ie, patients on glucocorticoids)			
3. Other comorbidities			
Osteoporosis. All patients with SLE:			
should be assessed for adequate calcium and vitamin D intake, regular exercise and smoking habits			
should be screened and followed for osteoporosis according to existing guidelines (a) for postmenopausal women; (b) for patients on steroids, or on any other medication that may reduce BMD	2b, C	93.8	M/VL
Cancer. Cancer screening is recommended according to the guidelines for the general population, including cervical smear tests	2b, C	92.3	M/L
4. Infection risk			
Screening. We recommend that patients should be screened for:			
HIV based on the patient's risk factors	2b, C	98.8	M/VL
HCV, HBV based on the patient's risk factors, particularly before IS drugs including high dose glucocorticoids are given			
tuberculosis, according to local guidelines, especially before IS drugs including high dose glucocorticoids are given			
CMV testing should be considered during treatment in selected patients.			
Vaccination. Patients with SLE are at high risk of infections, and prevention should be recommended. The administration of inactivated vaccines (especially flu and pneumococcus), following the Centers for Disease Control (CDC) guidelines for patients who are immunosuppressed, should be strongly encouraged in patients with SLE on IS drugs, preferably administered when the SLE is inactive. For other vaccinations, an individual risk/benefit analysis is recommended.	5, D	93.5	M/M
Monitoring. At follow-up visits, continuous assessment of the risk of infection by taking into consideration the presence of			
severe neutropenia (<500 cells/mm^3)			
severe lymphopenia (<500 cells/mm^3)	1b, B	88.8	M/VL
low IgG (<500 mg/dl)			
5. Frequency of assessments			
In patients with no activity, no damage, no comorbidity we recommend assessments every 6–12 months. During these visits, preventive measures should be emphasised.	5, D	93.8	M/L
6. Laboratory assessment			
We recommend the monitoring of the following autoantibodies and complement:			
at baseline: ANA, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, anti-phospholipid, C3, C4			
re-evaluation in previously negative patients of: anti-phospholipid antibodies: prior to pregnancy, surgery, transplant and use of oestrogen-containing treatments, or in the presence of a new neurological or vascular event; anti-Ro and anti-La antibodies before pregnancy; anti-dsDNA/C3 C4 may support evidence of disease activity/remission	2b, C	92.3	M/VL
Other laboratory assessments. At 6–12 months intervals patients with inactive disease should have:			
complete blood count			
erythrocyte sedimentation rate			
C reactive protein			
serum albumin	5, D	89.5	M/VL
serum creatinine (or eGFR)			
urinalysis and urine protein/creatinine ratio			
NB: if a patient is on a specific drug treatment, monitoring for that drug is required as well			

Continued

Table 1 Continued

Recommendation	Level of evidence and grade of recommendation	Agreement	Cost/risk
7. Mucocutaneous involvement Mucocutaneous lesions should be characterised, according to the existing classification systems, as to whether they may be: LE specific LE non-specific LE mimickers drug-related Lesions should be assessed for activity and damage, using validated indices (ie, CLASI)	5, D	94.6	M/L
8. Kidney Patients with a persistently abnormal urinalysis or raised serum creatinine should have urine protein/creatinine ratio (or 24 h proteinuria), urine microscopy and renal ultrasound, and be considered for referral for biopsy. Patients with established nephropathy should have protein/creatinine ratio (or 24 h proteinuria) and immunological tests (C3, C4, anti-dsDNA), urine microscopy and blood pressure at least every 3 months for the first 2–3 years. Patients with established chronic renal disease (eGFR <60 ml or stable proteinuria >0.5 mg/24 h) should be followed according to the National Kidney Foundation guidelines for chronic kidney disease.	1b, B	94.2	H/M
9. Neuropsychiatric manifestations Patients with SLE should be monitored for the presence of neuropsychological symptoms (seizures, paresthesiae, numbness, weakness, headache, epilepsy, depression, etc) by focused history. Cognitive impairment may be assessed by evaluating attention, concentration, word finding and memory difficulties (ie, by asking the patient about problems with multitasking, with household tasks, or memory). If there is a suspicion of any cognitive impairment, then the patient should be assessed in further detail.	2b, D	87.7	M/VL
10. Eye assessment In patients treated with glucocorticoids or antimalarials, a baseline eye examination is recommended according to standard guidelines. An eye examination during follow-up is recommended: in selected patients taking glucocorticoids (high risk of glaucoma or cataracts) in patients on antimalarial drugs, and (a) low risk: no further testing is required until after 5 years of baseline, after the first 5 years of treatment eye assessment is recommended yearly; (b) high risk: eye assessment is recommended yearly.	2b, D	95.8	M/L

ANA, anti-nuclear antibodies; BMD, bone mineral density; CLASI, Cutaneous Lupus Disease Area and Severity index; CMV, cytomegalovirus; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; H, high; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IS, immunosuppressive; L, low; LE, lupus erythematosus; M, moderate; SLE, systemic lupus erythematosus; VAS, visual analogue scale; VH, very high; VL, very low.

to measure these parameters. Although there are some concerns about feasibility, the use of validated indices facilitates the collection of relevant data that otherwise may be overlooked. The evaluation of QoL in routine clinical practice by questionnaires appeared unlikely to be feasible, and therefore the Committee agreed on QoL routine evaluation based on the patient's history or with a 0–10 visual analogue scale (VAS). Validated questionnaires should be used to compare QoL between centres.

Recommendation 2: cardiovascular risk factors

Patients with SLE have an increased prevalence of hypertension (11.5% to 75%) and dyslipidaemia (11.5% to 75%), and usually have a sedentary lifestyle, but they do not smoke more than the general population. Fewer data are available on whether the prevalence of diabetes or obesity is increased.[7–12]

Although data from the literature have shown that the increased incidence of cardiovascular disease (CVD) and of premature atherosclerosis in SLE cannot be fully explained by traditional CVD risk factors, at present agreement exists on the need for monitoring traditional CVD risk factors and treating modifiable risk factors according to the existing guidelines.[9 10–12]

In view of the potential of drugs to affect the occurrence of CVD risk factors, more frequent assessments may be required in certain situations, for example, corticosteroid therapy.[7 9 12]

Recommendation 3: other comorbidities

The prevalence of osteoporosis among patients with SLE varies from 4% to 24% and from 10% to 20% when premenopausal patients are evaluated. Vertebral fracture prevalence ranges between 7.6% and 37%. Additional risk factors for osteoporosis in SLE include treatment with glucocorticoids, as well as other medications that may impact bone mass, and reduced levels of vitamin D related to the avoidance of sun exposure or ethnicity.[13–15]

Cancer incidence is increased in patients with SLE, particularly haematological malignancies, cervical cancer, breast cancer and lung cancer.[16 17] An abnormal cervicovaginal cytology is reported in up to 16% of examined patients and an association with cyclophosphamide therapy has been suggested.[17]

However Bernatsky *et al* have found that patients with SLE undergo cancer screening (mammogram, faecal occult blood and cervical smear test) even less frequently than the general population.[18] Therefore patients with SLE should at least follow cancer screening recommended for the general population. However, taking in consideration the epidemiological and clinical characteristics of patients with SLE, the development of SLE specific guidelines might be considered.

Recommendation 4: infection risk

Patients with SLE do not have an increased incidence of HIV, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.[19]

However, in view of the risks of infection reactivation following immunosuppressive therapy, particularly glucocorticoids, patients with any personal risk factor should be screened for HIV, HBV and HCV infections before administering these medications.

The frequency of tuberculosis (TB) among patients with SLE is higher than expected, varying with background incidence (2.5% to 13.8% in countries with endemic TB and 0% to 1.4% in countries with a low incidence of TB).[20] Routine TB testing in patients with SLE is not recommended in non-endemic areas. However, TB testing before glucocorticoids and immunosuppressive drugs is recommended according to the US Centers for Disease Control and Prevention (CDC) recommendations.[21]

Cytomegalovirus (CMV) antigenaemia has been reported in 18% to 44% of patients. Antigen concentrations appear higher in patients treated with pulse methylprednisolone and pulse cyclophosphamide. As CMV infection may mimic active SLE and might be frequent with high dose corticosteroid therapy, testing for CMV (antigenaemia) should be considered particularly in patients with active disease undergoing therapy with high dose glucocorticoids.[22 23]

In view of the morbidity and mortality associated with infections, patients with SLE would greatly benefit from vaccination.[24–26] Some data show that vaccination may be associated with the development of autoimmunity, which has raised concerns about its safety in subjects with autoimmune diseases. Several studies have shown that flu vaccination is safe and does not lead to SLE flares, with the majority of patients developing protective antibodies. Similarly, vaccination against *Pneumococcus* appears safe, although reduced anti-pneumococcal antibody production has been reported. Hepatitis B vaccination of 28 patients with SLE with currently inactive SLE has been reported. All patients developed protective antibodies and no increase in SLE flares was observed. Tetanus toxoid administration was not associated with disease flares either, and 90% of patients developed protective levels of antibodies.

Inactivated live vaccines are contraindicated in patients taking immunosuppressive drugs and/or glucocorticoids at a dose >20 mg/day.

Lymphocyte counts of ≤1×109/litre and low levels of IgG3 (≤60 µg/ml) or IgG4 (≤20 µg/ml) have been associated with an increased risk of infections.[27 28] Total IgG and subclass levels should be assessed at the patient first assessment and during follow-up visits particularly in patients taking immunosuppressive drugs.

Recommendation 5: frequency of assessments

No data are available in the literature to suggest an optimal frequency of clinical and laboratory assessment in patients with SLE. The committee arbitrarily agreed on the need to assess patients with inactive disease, in the absence of organ damage and comorbidities, every 6–12 months. During these evaluations, emphasis should be given to the discussion of preventive measures such as sun avoidance, adequate vitamin D and calcium intake, weight control and other measures to reduce cardiovascular risk, QoL, occupational problems and pregnancy planning. Patients in whom immunosuppressive therapy is being reduced need to be monitored for reactivation of disease, especially those with renal disease, which may recur without symptoms.

Recommendation 6: laboratory assessment

Changes in anti-double-stranded (ds)DNA antibody titres sometimes correlate with disease activity and active renal disease, and may be useful in monitoring disease activity. The available data, however, do not support the indication of treating patients with anti-dsDNA antibodies in the absence of clinical activity.[29–31] Few data are available on the association between anti-dsDNA and damage development.

Anti-Ro, anti-La and anti-ribonucleoprotein (RNP) antibodies may have prognostic value in SLE. Anti-Ro/Sjögren syndrome antigen A (SSA) and anti-La (SSB) antibodies have been associated with the occurrence of neonatal lupus.[31]

Anti-phospholipid (aPL) antibodies have been associated with general disease activity, thrombotic manifestations, damage development as well as pregnancy complications.[32–34] A possible role of aPL in early graft loss among patients with SLE undergoing kidney transplant has been suggested.[35]

Complement levels are sometimes associated with active disease, although no predictive value for the development of disease flares has been reported.[36]

Severe anaemia has been variably associated with organ involvement, disease progression and worse prognosis. Similarly, thrombocytopenia has been associated with renal disease, disease progression to end-stage renal disease and worse prognosis. Severe leucopenia and lymphopenia have been associated with the occurrence of infections.[27 31]

Serum albumin, creatinine, urinalysis and urine protein/creatinine ratio provide information on the presence and prognosis of renal involvement.[31 37–39]

The significance of C reactive protein (CRP) in SLE remains controversial. Many authors reported that patients with SLE rarely have elevated CRP levels and, in the case of a significant increase along with clinical suspicion, a superimposed infection should be excluded, especially in the presence of very high values (>50 mg/litre).[40]

Recommendation 7: mucocutaneous involvement

Cutaneous manifestations of lupus erythematosus include LE-specific (acute cutaneous LE (CLE), subacute CLE, chronic CLE and intermittent CLE) and LE-non-specific lesions.[41 42]

The diagnosis of CLE may be difficult, as many conditions may mimic LE, and therefore may require evaluation by an experienced dermatologist and a skin biopsy for histological analysis.

Follow-up repeat biopsy is recommended if there is a change in the clinical morphology of the lesions or if there is a lack of response to treatment.

The use of Cutaneous Lupus Disease Area and Severity index (CLASI) in clinical practice might be considered, at least in patients with SLE with prevalent cutaneous manifestations.[42]

Recommendation 8: kidney

Serum creatinine, urine sediment analysis, proteinuria and blood pressure have a predictive value for the presence and outcome of kidney involvement and the occurrence of flares.[39 43–45] Relapses of kidney disease are common, being observed in up to 45% with a flare rate of 0.1–0.2 flares/patient/year. The risk of doubling serum creatinine ranges between 7.4% and 8.5% at 5 years and between 14.3% and 18.2% at 10 years.

The following variables have been associated with renal survival at 5 years: age, ethnicity, serum creatinine, hypertension, C3 complement, kidney biopsy, activity index and chronicity index.[31–38]

Guidelines have been published for the monitoring of patients with chronic kidney disease (http://www.kidney.org).

Recommendation 9: neuropsychiatric manifestations

Neurological involvement (central, peripheral, autonomic) occurs frequently in SLE. The most frequent syndromes observed are

headache, mood disorders, seizures, cognitive impairment and cerebrovascular disease.[46 47]

The assessment of neurological symptoms is difficult and no specific instrument has been evaluated in clinical practice. Therefore, it has been suggested that patients should be monitored by clinical history. Cognitive impairment may be assessed by evaluating memory, attention, concentration and word-finding difficulties.

Recommendation 10: eye assessment

The incidence of retinopathy among patients with SLE treated with antimalarial drugs is low (0.5%).[48 49] Risk factors are age (above 60 years), presence of macular degeneration, retinal dystrophy, obesity, liver disease, renal insufficiency, duration of therapy >5 years, daily dose of hydroxychloroquine above 6.5 mg/kg, or chloroquine above 3 mg/kg.[48 49]

Recommendations on screening for antimalarial retinopathy include a baseline eye assessment according to published guidelines.[50] Thereafter, in low-risk patients, no further testing is required for the next 5 years; after the first 5 years of treatment, eye assessment is recommended yearly. In high-risk patients, an eye assessment is recommended yearly.[50]

Systemic glucocorticoids increase the risk of cataracts and of glaucoma. Authors have reported glaucoma in 19% of subjects with rheumatic diseases treated with >7.5 mg/day of prednisone versus 3% of those treated with 7.5 mg/day.[15]

In addition an eye assessment may be required if there are symptoms suggesting eye involvement by lupus.

Core set of variables for the assessment and monitoring of patients with SLE in clinical practice

In addition to the recommendations, other assessments were discussed and included in a core set of data to be collected in routine clinical practice (see Supplementary material). The core set is given as a paper chart that could serve as a guide for data collection (see Supplementary material).

DISCUSSION

We have developed a set of recommendations and a core set of variables that could be used for monitoring SLE in clinical practice. We do acknowledge the limitations of the present recommendations. First, these recommendations take into consideration only some aspects of the patients' assessment. Some issues were not included or removed as these were felt to be standard good clinical practice or the panellists could not agree as the evidence was contradictory. Second, there was no direct evidence to support most recommendations directly, as studies on specific monitoring protocols are few. Finally while several aspects may be very important (for instance checking blood pressure at least once a year), others may be less essential (for instance checking blood glucose yearly in patients not on corticosteroid therapy). Another product of this study is the future research agenda. This should include the development of quality indicators, an update based on new data on biomarkers for activity, the development of specific guidelines for cancer screening and the development of specific guidelines for kidney biopsy.

An evidence-based guide to the minimum requirements for monitoring patients with lupus should decrease unwanted variability in clinical practice. In addition the use of a standardised core set may improve the quality of care offered to patients with SLE and provide data that could be used in observational studies.

Acknowledgements: We are thankful to Anja Schönbächler from EULAR for supporting the meetings and to Juan Antonio Martínez from the Spanish Society of Rheumatology for helping in the search strategies and in the creation of the data collecting forms.

Provenance and peer review: Not commissioned; externally peer reviewed.

[1]Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy; [2]University Clinical Center Carl Gustav Carus at the Technical University of Dresden, Dresden, Germany; [3]University of Crete Medical School, Heraklion, Crete, Greece; [4]Department of Medicine/Neurology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA; [5]Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain; [6]Division of Rheumatology, University of Padova, Padova, Italy; [7]Renal Unit, Addenbrooke's Hospital, Cambridge, UK; [8]Lupus Research Unit, Rayne Institute, St Thomas Hospital, London, UK; [9]Department of Dermatology, University of Muenster, Muenster, Germany; [10]School of Immunity & Infection, University of Birmingham, Birmingham, UK; [11]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [12]Department of Biochemistry, Institute of Medical Biology, Medical Faculty, University of Tromsø, Tromsø, Norway; [13]Rheumatology, Clinic of Endocrinology, Diabetology and Rheumatology, Heinrich-Heine-University, Duesseldorf, Germany; [14]Hospital Management, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; [15]Department of Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [16]Department of Rheumatology, Medical University of Vienna, Austria; [17]UO Reumatologia e Immunologia Clinica, Spedali Civili e Università, Brescia, Italy; [18]The Karolinska Institute, Stockholm, Sweden; [19]Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, US Department of Health and Human Services, Bethesda, Maryland, USA; [20]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [21]Research Unit, Sociedad Española de Reumatología, Madrid, Spain

REFERENCES

1. **Yazdany J, Panopalis P, Gillis JZ**, *et al.*; Systemic Lupus Erythematosus Quality Indicators Project Expert Panels. A quality indicator set for systemic lupus erythematosus. *Arthritis Rheum* 2009;**61**:370–7.
2. **Demas KL, Costenbader KH**. Disparities in lupus care and outcomes. *Curr Opin Rheumatol* 2009;**21**:102–9.
3. **Dougados M, Betteridge N, Burmester GR**, *et al.*; EULAR. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;**63**:1172–6.
4. **Centre for Evidence-Based Medicine.** EBM Tools. Finding the Evidence. Levels of Evidence**. University of Oxford,** 2001. http://www.cebm.net/index.aspx?o=1025 (accessed 15 February 2009).
5. **Strand V, Gladman D, Isenberg D**, *et al.* Outcome measures to be used in clinical trials in systemic lupus erythematosus. *J Rheumatol* 1999;**26**:490–7.
6. **Ramsey-Goldman R, Isenberg DA**. Systemic lupus erythematosus measures. *Arthritis Care Res* 2003;**49**(5 Suppl): S225–33.
7. **Calvo-Alén J, Toloza SM, Fernández M**, *et al.*; LUMINA Study Group. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXV. Smoking, older age, disease activity, lupus anticoagulant, and glucocorticoid dose as risk factors for the occurrence of venous thrombosis in lupus patients. *Arthritis Rheum* 2005;**52**:2060–8.
8. **Asanuma Y, Oeser A, Shintani AK**, *et al.* Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2407–15.
9. **Bruce IN, Urowitz MB, Gladman DD**, *et al.* Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. *Arthritis Rheum* 2003;**48**:3159–67.
10. **Esdaile JM, Abrahamowicz M, Grodzicky T**, *et al.* Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;**44**:2331–7.
11. **Manzi S, Selzer F, Sutton-Tyrrell K**, *et al.* Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;**42**:51–60.
12. **Wajed J, Ahmad Y, Durrington PN**, *et al.* Prevention of cardiovascular disease in systemic lupus erythematosus – proposed guidelines for risk factor management. *Rheumatology (Oxford)* 2004;**43**:7–12.
13. **Almehed K, Forsblad d'Elia H, Kvist G**, *et al.* Prevalence and risk factors of osteoporosis in female SLE patients-extended report. *Rheumatology (Oxford)* 2007;**46**:1185–90.
14. **Bultink IE, Lems WF, Kostense PJ**, *et al.* Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. *Arthritis Rheum* 2005;**52**:2044–50.
15. **Da Silva JAP, Jacobs JWG, Kirwan JR**, *et al*. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. *Ann Rheum Dis* 2006;**65**:285–93.

16. **Bernatsky S, Boivin JF, Joseph L**, *et al.* An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum* 2005;**52**:1481–90.
17. **Ognenovski VM, Marder W, Somers EC**, *et al.* Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. *J Rheumatol* 2004;**31**:1763–7.
18. **Bernatsky SR, Cooper GS, Mill C**, *et al.* Cancer screening in patients with systemic lupus erythematosus. *J Rheumatol* 2006;**33**:45–9.
19. **Erdozain JG, Ruiz-Irastorza G, Egurbide MV**, *et al.* High risk of tuberculosis in systemic lupus erythematosus? *Lupus* 2006;**15**:232–5.
20. **Abu-Shakra M, El-Sana S, Margalith M**, *et al*. Hepatitis B and C viruses serology in patients with SLE. *Lupus* 1997;**6**:543–4.
21. http://www.cdc.gov/mmwr/preview/mmwrhtml/00001642.htm.
22. **Yoda Y, Hanaoka R, Ide H**, *et al.* Clinical evaluation of patients with inflammatory connective tissue diseases complicated by cytomegalovirus antigenemia. *Mod Rheumatol* 2006;**16**:137–42.
23. **Ramos-Casals M, Cuadrado MJ, Alba P**, *et al.* Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature. *Medicine (Baltimore)* 2008;**87**:311–18.
24. **Conti F, Rezai S, Valesini G**. Vaccination and rheumatic diseases: is there still a dilemma? *Curr Rheumatol Rev* 2007;**3**:79–91.
25. **Battafarano DF, Battafarano NJ, Larsen L**, *et al.* Antigen-specific antibody responses in lupus patients following immunization. *Arthritis Rheum* 1998;**41**:1828–34.
26. **Klippel JH, Karsh J, Stahl NI**, *et al.* A controlled study of pneumococcal polysaccharide vaccine in systemic lupus erythematosus. *Arthritis Rheum* 1979;**22**:1321–5.
27. **Ng WL, Chu CM, Wu AK**, *et al.* Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. *QJM* 2006;**99**:37–47.
28. **Tokano Y, Yagita H, Iida N**, *et al.* Relation between the level of IgG subclasses and infections in patients with systemic lupus erythematosus. *Int Arch Allergy Appl Immunol* 1988;**87**:55–8.
29. **Hoffman IE, Peene I, Meheus L**, *et al.* Specific antinuclear antibodies are associated with clinical features in systemic lupus erythematosus. *Ann Rheum Dis* 2004;**63**:1155–8.
30. **Kavanaugh AF, Solomon DH**; American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-DNA antibody tests. *Arthritis Rheum* 2002;**47**:546–55.
31. **Bertsias G, Ioannidis JP, Boletis J**, *et al.*; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008;**67**:195–205.
32. **Miyakis S, Lockshin MD, Atsumi T**, *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;**4**:295–306.
33. **Ruiz-Irastorza G, Egurbide MV, Martinez-Berriotxoa A**, *et al.* Antiphospholipid antibodies predict early damage in patients with systemic lupus erythematosus. *Lupus* 2004;**13**:900–5.
34. **Moroni G, Ventura D, Riva P**, *et al.* Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. *Am J Kidney Dis* 2004;**43**:28–36.
35. **Stone JH, Amend WJ, Criswell LA**. Outcome of renal transplantation in systemic lupus erythematosus. *Semin Arthritis Rheum* 1997;**27**:17–26.
36. **Ho A, Barr SG, Magder LS**, *et al.* A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 2001;**44**:2350–7.
37. **Gordon C, Jayne D, Pusey C**, *et al.* European consensus statement on the terminology used in the management of lupus glomerulonephritis. *Lupus* 2009;**18**:257–63.
38. **Mok CC, Ho CT, Chan KW**, *et al.* Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. *Arthritis Rheum* 2002;**46**:1003–13.
39. **Mok CC, Ying KY, Tang S**, *et al.* Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum* 2004;**50**:2559–68.
40. **Williams RC Jr, Harmon ME, Burlingame R**, *et al.* Studies of serum C-reactive protein in systemic lupus erythematosus. *J Rheumatol* 2005;**32**:454–61.
41. **Rothfield N, Sontheimer RD, Bernstein M**. Lupus erythematosus: systemic and cutaneous manifestations. *Clin Dermatol* 2006;**24**:348–62.
42. **Krathen MS, Dunham J, Gaines E**, *et al.* The Cutaneous Lupus Erythematosus Disease Activity and Severity Index: expansion for rheumatology and dermatology. *Arthritis Rheum* 2008;**59**:338–44.
43. **Ciruelo E, de la Cruz J, López I**, *et al.* Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. *Arthritis Rheum* 1996;**39**:2028–34.
44. **Illei GG, Takada K, Parkin D**, *et al.* Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum* 2002;**46**:995–1002.
45. **Moroni G, Quaglini S, Maccario M**, *et al.* "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int* 1996;**50**:2047–53.
46. **Denburg SD, Stewart KE, Hart LE**, *et al.* How "soft" are soft neurological signs? The relationship of subjective neuropsychiatric complaints to cognitive function in systemic lupus erythematosus. *J Rheumatol* 2003;**30**:1006–10.
47. **Hanly JG, Urowitz MB, Sanchez-Guerrero J**, *et al.*; Systemic Lupus International Collaborating Clinics. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. *Arthritis Rheum* 2007;**56**:265–73.
48. **Mavrikakis I, Sfikakis PP, Mavrikakis E**, *et al.* The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. *Ophthalmology* 2003;**110**:1321–6.
49. **Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P**, *et al*. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2009 August 28. [Epub ahead of print].
50. **Marmor MF, Carr RE, Easterbrook M**, *et al.*; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report by the American Academy of Ophthalmology. *Ophthalmology* 2002;**109**:1377–82.