Assessment of multiple organ systems in systemic lupus erythematosus: what will the new guidelines mean?

Systemic lupus erythematosus (SLE) is characterized by a complex and variable clinical picture. The assessment of SLE patients in everyday care is therefore difficult and relies upon the experience of the treating physician. This determines a great variability, complicating comparisons and potentially leading to poor outcomes. Guidelines are a way to decrease variability. The European League Against Rheumatism promotes studies aimed at the development of classification/diagnostic criteria, recommendation for designing/conducting clinical trials and for the monitoring, management and treatment of rheumatic diseases and the standardization of procedures. Two sets of recommendations and a core set of minimal variables to assess and monitor SLE patients in clinical practice have been recently developed, which may offer a synthesis of the existing evidence with the expert opinion and should decrease unwanted variability in clinical practice. In the present article the recommendations are briefly described and their application and impact in clinical practice are discussed.

KEYWORDS: clinical practice ■ core set variables ■ recommendations ■ systemic lupus erythematosus

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The clinical picture of systemic lupus erythematosus (SLE) is characterized by an extreme variability between patients, as well as within a single patient. Patients may present with many different protean clinical manifestations of SLE, with different degrees of severity, episodes of remission and of exacerbation over time, and manifestations related to reversible inflammation, coexisting with irreversible damage or drug toxicities. The assessment of SLE patients in everyday care is therefore difficult, relying greatly upon the experience of the treating physician. The importance, relevance and meaning of clinical information are likely to be informed by experience, however in the case of SLE, with so many presentations and complications, a significant experience is difficult to achieve. This determines a great variability between centers and between physicians [1–5].

Unexplained variability has a considerable impact on health outcomes, potentially leading to poor outcomes, complicating comparisons among practices and, finally, affecting healthcare [6,7]. In the absence of agreed guidelines regarding what information to collect, a plausible 'story' framed according to a colleague's expectations about clinical outcome may obscure omissions of critical information and appear more reliable and diagnostic than it may actually be.

In theory, the availability of guidelines on the items of information to be taken into account when assessing a patient should reduce variability. However, data reveal that major difficulties arise in the application of guidelines into clinical practice, a fact that might be related to the physician's preferences or circumstances, the environment and available resources, as well as to inner properties of the recommendations. Implementation of research findings in clinical practice, therefore, strongly depends on the subjects who are being treated, but it also depends on the content and strength of guidelines. Inevitably, only strong and realistic guidelines that are easy to implement, may at any point change clinical practice and decrease variability [8–11].

All these aspects should be taken into consideration during the development phase of guidelines or recommendations, which therefore need to be to be based on the best evidence available but should also be feasible in routine clinical practice and possibly in any clinical setting.

European League Against Rheumatism guidelines

The European League Against Rheumatism (EULAR) executive committee has been promoting studies aimed at the development of classification/diagnostic criteria, recommendation for designing and conducting clinical trials and for the monitoring, management and treatment of rheumatic diseases, and for the standardization of procedures, with the final goal of improving the care of rheumatic patients throughout Europe [11,12].

The EULAR endorsed and supported studies need be conducted according to standardized procedures [12]. Briefly, the steering group

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must include experts in the field and a clinical epidemiologist to ensure a high level of quality and homogeneity of methodological issues. In addition, a systematic literature research is mandatory for most projects. As the publication of the evidence-based approach alone might be too complicated to be used, a summary of the expert opinion might be included in the recommendations. Recommendations developed according to these procedures offer the final user a synthesis of the existing evidence plus the expert opinion. This latter should be aware of the difficulties in implementation and guide the user on how to apply them in routine clinical practice.

Two sets of EULAR endorsed recommendations have been recently developed for the management and monitoring of SLE patients, and will be briefly described in this article [13–15].

Box 1. EULAR recommendations for monitoring systemic lupus erythematosus patients in clinical practice and in observational studies.

Recommendation 1: patient assessment

- In addition to the standard care of non-lupus patients of the same age and sex, the assessment of the SLE patient must include the evaluation of:
  - Disease activity routinely with a validated index at each visit
  - Organ damage annually
  - General quality of life by patient history and/or by a 0–10 visual analogue scale (patient global) at each visit
  - Comorbidities
  - Drug toxicity

Recommendation 2: cardiovascular risk factors

- At baseline and during follow-up, with a minimum of at least once a year†:
  - Assess: smoking, vascular events (cerebral/cardiovascular), physical activity, oral contraceptives, hormonal therapies and family history of cardiovascular disease
  - Blood test: blood cholesterol, glucose
  - Examination: blood pressure, body mass index (and/or waist circumference)

Recommendation 3: other comorbidities

- Osteoporosis
  - All SLE patients should be assessed for adequate calcium and vitamin D intake, regular exercise and smoking habit
  - All SLE patients should be screened and followed for osteoporosis according to the existing guidelines
  - For postmenopausal women
  - For patients on steroids, or on any other medication that may reduce body mass index
- Cancer
  - Cancer screening is recommended according to the guidelines for the general population, including Pap smears

Recommendation 4: infection risk

- 4.1: screening: we recommend that patients should be screened for:
  - HIV based on patient's risk factors
  - Hepatitis C virus, Hepatitis B virus based on the patient's risk factors, particularly before initiating treatment or immunosuppressive drugs, including high-dose corticosteroids
  - Tuberculosis, according to local guidelines, especially before immunosuppressive drugs including high-dose corticosteroids are started
  - Cytomegalovirus testing should be considered during treatment in selected patients
- 4.2: vaccination
  - SLE patients are at high risk of infections and prevention should be recommended. The administration of inactivated vaccines (especially influenza and pneumococcus), following the CDC guidelines for immunosuppressed patients, should be strongly considered in SLE patients on IS drugs, preferably administered when the SLE is inactive. For other vaccinations, an individual risk/benefit analysis is recommended
- 4.3: monitoring
  - At follow-up visits, reassess the risk of infection by taking into consideration the presence of:
    - Severe neutropenia (<500 mmc)
    - Severe lymphopenia (<500 mmc)
    - Low IgG (<500 mg/dl)

Recommendation 5: frequency of assessments

- In the patient with no activity, damage nor comorbidity, we recommend assessments every 6–12 months. During these visits, preventive measures should be emphasized

†Some patients may need more frequent follow-up (i.e., patients on corticosteroids).
CDC: Centers for Disease Control; EULAR: European League Against Rheumatism; LE: Lupus erythematosus; SLE: Systemic lupus erythematosus.

Box 1. EULAR recommendations for monitoring systemic lupus erythematosus patients in clinical practice and in observational studies (cont.).

Recommendation 6: laboratory assessment

- 6.1: we recommend the monitoring of the following autoantibodies and complement:
  - At baseline: antinuclear antibodies, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid, C3, C4
  - Re-evaluation in previously negative patients:
    - Anti-phospholipid antibodies: prior to pregnancy, surgery, transplant, and estrogen containing treatments, or in the presence of new neurologic or vascular event
    - Anti-Ro and anti-La antibodies before pregnancy
    - Anti-dsDNA/C3 C4 may support evidence of disease activity/remission
- 6.2: other laboratories
  - At 6–12 months intervals patients with inactive disease should have:
    - Complete blood count
    - Erythrocyte sedimentation rate
    - C-reactive protein
    - Serum albumin
    - Serum creatinine (or estimated glomerular filtration rate)
    - Urinalysis and urine protein:creatinine ratio
- If a patient is on a specific drug treatment then monitoring for that drug is also required

Recommendation 7: mucocutaneous involvement

- Mucocutaneous lesions should be characterized, according to the existing classification systems, as to whether they may be:
  - LE specific
  - LE nonspecific
  - LE mimickers
  - Drug-related
- Lesions should be assessed for activity and damage, using validated indices (i.e., Cutaneous Lupus Disease Area and Severity Index)

Recommendation 8: kidney

- Patients with a persistently abnormal urinalysis or raised serum creatinine should have urine protein:creatinine ratio (or 24 h proteinuria), urine microscopy, 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 (estimated glomerular filtration rate < 60 ml or stable proteinuria > 0.5 gm/24 h) should be followed according to the National Kidney Foundation guidelines for chronic kidney disease

Recommendation 9: neuropsychiatric manifestations

- SLE patients should be monitored for the presence of neuropsychological symptoms (e.g., seizures, paresthesiae, numbness, weakness, headache, epilepsy and depression) by focused history
- Cognitive impairment may be assessed by evaluating attention, concentration, word finding and memory difficulties (i.e., by asking the patient about problems with multitasking, or with household tasks or memory). If there is a suspicion of any cognitive impairment, then the patient should be assessed in further detail

Recommendation 10: eye assessment

In patients treated with corticosteroids or antimalarials, a baseline eye examination is recommended according to standard guidelines

An eye examination during follow-up is recommended:

- In selected patients taking corticosteroids (high risk of glaucoma or cataracts)
- In patients on antimalarial drugs and
  - 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
  - High risk: eye assessment is recommended yearly

†Some patients may need more frequent follow-up (i.e., patients on corticosteroids).
CDC: Centers for Disease Control; EULAR: European League Against Rheumatism; LE: Lupus erythematosus; SLE: Systemic lupus erythematosus.

EULAR recommendations for the management and monitoring of systemic lupus erythematosus

In 2008, Bertsias *et al.* developed 12 recommendations on the prognosis, diagnosis, monitoring and treatment of SLE, including neuropsychiatric SLE, pregnancy, the antiphospholipid syndrome and lupus nephritis, which were based on a systematic literature review and experts agreement [13].

Five recommendations refer to the patients' general management concerning prognosis, monitoring, comorbidites and treatment, including adjunct therapy. In this respect, the

recommendations highlight the prognostic role of specific clinical and laboratory manifestations and the need for the assessment of comorbidities, such as infections, atherosclerosis, osteoporosis and malignancies, which have an increased incidence among SLE patients. The use of validated disease activity indices is encouraged as these have a demonstrated predictive value for damage development and mortality. Corticosteroids and antimalarial drugs might be used in the treatment of SLE without major organ manifestations, while immunosuppressive drugs should be used cautiously in these patients in view of the few data available in the literature. Adjunctive therapies should be considered with respect to the presence of specific comorbidities; estrogens may be used after the assessment of the patient's specific risks.

Two recommendations refer to the diagnosis and treatment of neuropsychiatric lupus. Experts recommend that SLE patients should be assessed in the same way as any patient presenting with the same neuropsychiatric manifestation. Immunosuppressive therapy should be considered in SLE patients with neuropsychiatric SLE of possible inflammatory origin.

Other recommendations highlight the need to be alert during pregnancy, as mothers are at risk of disease flares as well as of obstetrical complications. The fetus may be affected either by disease activity, or by the presence of antiphospholipid antibodies, or by maternal therapy. Prednisone, azathioprine and hydroxychloroquine may be used in pregnant patients with SLE according to recommendations.

It is also recommended that the primary prevention of thrombosis and pregnancy loss might be performed by administering low-dose aspirin to SLE patients with positive antiphospholipid antibodies. In nonpregnant patients oral anticoagulation appears effective in secondary prevention of thrombosis, while during pregnancy unfractionated or low-molecular-weight heparin and aspirin should be considered.

In addition, in patients with antiphospholipid antibodies, the presence of other risk factor for thrombosis should be considered and estrogen-containing drugs should be used with caution.

Three recommendations refer to the follow-up and treatment of lupus nephritis and to the management of end-stage renal disease. Renal biopsy, urine sediment analysis, proteinuria and kidney function predict clinical outcome and should be interpreted in conjunction. Corticosteroids and immunosuppressive drugs are effective in controlling lupus nephritis. Long-term efficacy has been demonstrated mainly for cyclophosphamide, although data support the efficacy of mycophenolate mofetil in inducing remission, therefore this drug might be considered in selected cases, albeit under strict monitoring and with frequent reassessment of response. Dialysis and kidney transplantation result in survival rates similar to those observed in nondiabetic non-SLE patients. Kidney transplantation is the treatment of choice.

These recommendations provide an overview on a number of important issues in the management of SLE patients, and remind the physicians important aspects related to patients' evaluation that should not be overlooked.

European League Against Rheumatism recommendations for monitoring SLE patients in clinical practice and in observational studies.

In November 2009, a new set of ten recommendations has been published. With respect to those developed by Bertsias *et al.*, the new recommendations have been specifically developed to provide standardized measures to monitor SLE patients in clinical practice [15]. One of the major aims of this second study was to develop the recommendations alongside a core set of minimal assessments required to evaluate SLE patients in clinical practice. Therefore, the EULAR Recommendations for Patients Monitoring in Clinical Practice and Observational Studies are practical recommendations focusing on important aspects of patients' assessment and one of their major features is its feasibility for implementation.

These new recommendations refer to general assessment, cardiovascular risk factors, and comorbidities, focusing on cancer, osteoporosis and infections. They also deal with the frequency of assessment, what laboratory test need to be ordered in particular cases, and how to carry out specific organ assessment: mucocutaneous, kidney, neuropsychiatric and eye. The recommendations are summarized in **Box 1**.

These recommendations are directed to physicians with an expertise in SLE, so that it is recommended that the use of validated indices to estimate disease activity and damage in routine clinical practice is used. It is also recommended that drug toxicity, quality of life and comorbidities need to be assessed in SLE patients (recommendation 1).

Although cancer incidence appears increased among SLE patients, the few available data demonstrate that SLE patients have low adherence to cancer screening. Therefore it is emphasized that patients should undergo cancer screening at least by following guidelines issued for the general population (recommendation 3).

Systemic lupus erythematosus patients are at increased risk for infection; therefore, it is recommended to screen for major infections before starting any immunosuppressive therapy, to immunize patients at least with influenza and antipneumococcal vaccination and to monitor signs of infection at visits (recommendation 4).

Literature has been examined to identify the minimal laboratory assessment required in clinical practice (recommendation 6), which include complete blood count, erythrocyte sedimentation rate, cholesterol, C-reactive protein, serum albumin, serum creatinine (or estimated glomerular filtration rate), urinalysis and urine protein:creatinine ratio. At baseline, the autoantibodies antinuclear antibodies, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid and C3 and C4 should be assessed.

Experts recommend re-evaluation of antiphospholipid antibodies prior to pregnancy, surgery, transplant and the use of estrogen-containing drugs, in the presence of a new neurological or vascular event. Anti-Ro and anti-La antibodies should be tested before pregnancy in previously negative patients. Anti-dsDNA/low C3 or C4 may support evidence of disease activity or remission.

Mucocutaneous lesions should be characterized according to the existing classification systems as to whether they may be: lupus erythematosus (LE)-specific, LE-nonspecific, LE mimickers or drug-related. Lesions should be assessed for activity and damage, using validated indices (i.e., Cutaneous Lupus Disease Area and Severity Index; recommendation 7).

A recommendation was developed to assess patients with different degrees of kidney involvement (recommendation 8). Patients with a

Table 1. Minimal requirements for the assessment of organ involvement in systemic lupus erythematosus.

Laboratory assessment	ESR, CRP, CBC count, serum albumin, serum creatinine (or estimated glomerular filtration rate), urinalysis, protein:creatinine ratio (or 24 h proteinuria), C3, C4
Autoantibody assessment	At baseline: antinuclear antibodies, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, aPL Re-evaluation in previously negative patients: Antiphospholipid antibodies: prior to pregnancy, surgery, transplant, and estrogen-containing treatments, or in the presence of new neurologic or vascular event Anti-Ro and anti-La antibodies before pregnancy
Joint involvement	Ask for the presence of arthralgias, assess joints for arthritis, if present perform a joint count
Mucocutaneous involvement	Mucocutaneous lesions should be characterized according to the existing classification systems (lupus specific, lupus nonspecific, lupus mimickers or drug-related)
Kidney involvement	Protein:creatinine ratio (or 24 h proteinuria), urine microscopy, immunological tests (C3, C4, anti-dsDNA) and blood pressure
CNS involvement	Focused history for neuropsychiatric symptoms (e.g., seizures, parasthesia, numbness, weakness, headache, epilepsy and depression)
Pulmonary involvement	History: pleuritic chest pain, dyspnea (NYHA), cough Examination: pulmonary crackles/rales, pleural effusion
Heart involvement	History: Chest pain, dyspnea (NYHA), atherosclerosis risk factors Examination: peripheral oedema, arterial blood pressure, heart and carotid murmurs and heart rate
Eye assessment	Examination by an ophthalmologist or an optitician
Vascular involvement	Inquire about Raynaud's, thrombotic risk factors and intermittent claudication
Gastrointestinal tract	Ask about symptoms

CBC: Complete blood count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NYHA: New York Heart Association.

persistently abnormal urinalysis or raised serum creatinine should have urine protein:creatinine ratio (or 24 h proteinuria), urine microscopy, 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), urinary sediment microscopy and blood pressure at least every 3 months for the first 2–3 years. Patients with established chronic renal disease should be followed according to the guidelines for chronic kidney disease.

The assessment of neuropsychiatric involvement in SLE in routine clinical practice is still difficult. Therefore the recommendation dealing with this aspect is mainly intended at reminding the acting physician to assess patients for the presence of neurological symptoms, with an emphasis on cognitive impairment, which is frequently observed.

Eye assessment is required in view of the potential toxic effect of drugs such as glucocorticoids and antimalarial drugs (recommendation 10).

The main limitation of these recommendations is that they consider only some aspects of the patients' assessment. Some issues were not included as they were felt to be part of good clinical practice. In addition, there was no evidence to support most recommendations directly, as studies on specific monitoring protocols are extremely scarce. Nonetheless, these recommendations may offer the treating physician a valuable support and guide in the routine assessment of SLE patients, dealing with important aspects that should not be overlooked.

As previously mentioned, with the aim to offer to the treating physician an additional tool to standardize patients evaluation, a core set of minimal assessments required in routine clinical practice has been developed and a clinical chart prepared (**Table 1**) [15].

Future perspective

In the assessment of complex diseases, clinicians need to have guidelines applicable to their clinical settings to offer patients a minimum standard of care. In addition, observational studies that are based on the collection of data during routine clinical practice (registries) may increase our knowledge on SLE outcome, its predictors, and on the most appropriate treatment. Indeed, in low prevalence diseases such as SLE, it is necessary to have standardized information on patient outcomes. Such information should derive not only from randomized clinical trials but from clinical practice, as trials do not always reflect the complexity of 'real life'.

The development of recommendations to be used in clinical practice also offers a guide to healthcare providers and to insurance holders, and therefore they may influence future reimbursement of care. This latter aspect, obviously, implies that guidelines are based on the association of the best evidence with the expert opinion and should be feasible and applicable to clinical practice in any setting.

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Executive summary

- The assessment of systemic lupus erythematosus (SLE) patients in everyday care is difficult, relying greatly upon the experience of the treating physician. This determines a great variability between centers and between physicians.
- Guidelines may be a first step to decrease variability. However, only strong and realistic guidelines easy to implement, may change clinical practice and decrease variability.
- The European League Against Rheumatism (EULAR) endorses studies aimed at the development of classification/diagnostic criteria, recommendation, which need be conducted according to standardized procedures.
- Two sets of EULAR endorsed Recommendations have recently been developed for the management and monitoring of SLE patients.
- EULAR recommendations for the management of SLE. These recommendations give an overview on a number of important issues in the management of SLE patients, and remind the physicians of important aspects related to patients' evaluation that should not be overlooked.
- EULAR Recommendations for monitoring SLE patients in clinical practice and in observational studies. These recommendations have been specifically developed to provide standardized measures to monitor SLE patients in clinical practice and therefore are practical recommendations focusing on important aspects of patients' assessment and one of their major features is its feasibility for implementation.
- The development of recommendations to be used in clinical practice offers a guide to the physician by reducing variability and also to healthcare providers and to insurance holders.

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