Disease-specific quality indicators, guidelines, and outcome measures in systemic lupus erythematosus (SLE)

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ABSTRACT

The assessment of quality of care is becoming increasingly important, but as yet no standard set of measures to assess quality has been developed. The ACR Quality Measures Committee has selected the following areas of study to develop quality indicators: diagnostic/classification criteria, outcome measures/response criteria, treatment guidelines/management recommendations, definition of quality indicators, and definition of data collection systems. The aim of the present review is to evaluate existing guidelines and outcome measures concerning disease/activity monitoring, autoantibody and laboratory assessment, outcomes, and therapy in systemic lupus erythematosus (SLE) that could be used to define disease-specific quality indicators.

Much data is available in the literature that could serve to define a starter set of quality indicators for SLE. Monitoring issues are discussed in the ACR and EULAR recommendations. As far as therapy is concerned, the ACR has provided indicators for rheumatoid arthritis that could also be applied to SLE, as well as indications for anti-malarial monitoring. The outcomes measures most frequently used in SLE are damage and death, but organ-specific definitions of outcome and response are being evaluated.

The development of quality measures for SLE is just beginning; existing information could serve to construct a starter set of indicators such as the one proposed here. Certainly much progress will be made in the near future. A practical, user-friendly tool for physicians that will help them deliver high quality care to populations is also needed.

Introduction

The assessment of quality of care is becoming increasingly important as it offers a means of evaluating whether appropriate care is being given to patients; such a tool could have a positive impact on patient treatment, as well as on the reimbursement of health care services. Assessing quality could improve patient outcome by promoting best practices among physicians (1). However, it is difficult to define what constitutes "quality of care" because no standard set of measures to assess quality has been developed to date (1-8). Health care quality can be measured in terms of patient access to the health care system, the process of care provided, outcomes of care (mortality, damage, reduction of disease activity, functional status, pain), or by evaluating the patient's point of view (8).

Quality indicators represent the minimum acceptable standard of care, are based on the scientific information currently available, and could be developed using explicit process of care measurements. The American College of Rheumatology (ACR) Quality Measures Committee has chosen to focus on the following areas: diagnostic/classification criteria, outcome measures/response criteria, treatment guidelines/management recommendations, definition of quality indicators, and definition of data collection systems (2, 3). It has drafted a starter set of quality indicators that covers rheumatoid arthritis, osteoporosis, gout and drug safety (2).

The aim of the present review is to evaluate existing guidelines and outcome measures for disease/activity monitoring, autoantibody and laboratory assessment, outcomes, and therapy that could be used to define a specific set of quality indicators for systemic lupus erythematosus (SLE).

The monitoring of SLE

Once an accurate diagnosis is made and proper therapy instituted, monitoring represents one of the cornerstones in the management of SLE patients.

Monitoring should address disease activity, damage, co-morbidities, and drug-related toxicities (9-14).

In 1999, the ACR published its recommendations for monitoring SLE; these were aimed at improving the quality of care delivered to patients by primary care physicians (15). Recently the European League Against Rheumatism (EULAR) drew up its own recommendations for the management of SLE patients, which addressed those aspects considered to be of greatest importance by the committee members (16), in particular: general management (prognosis, monitoring, co-morbidities, treatment, adjunct therapy), neuropsychiatric lupus, pregnancy in lupus, anti-phospholipid syndrome, and lupus nephritis (monitoring, treatment, end-stage renal disease).

The frequency of routine visits depends as a rule on disease activity/severity. Patients with stable disease may be seen every 3 to 6 months. More frequent assessments are required when new clinical manifestations appear, during disease flares, when new therapies are instituted, and during pregnancy and puerperium (13, 15, 16). Most studies suggest that pregnant patients should be seen every 4 weeks (16, 17).

SLE is a multi-faceted disease characterized by a clinical course involving flares and remission. Therefore, assessment of disease activity is of primary importance (9, 10, 14, 16). Four validated disease activity indices – the British Isles Lupus Assessment Group Scale (BILAG), the European Consensus Lupus Activity Measurement (ECLAM), the Systemic Lupus Activity Measurement (SLAM), and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) – are widely used in longitudinal studies and randomized controlled trials (9-12, 14, 15, 18). In the recently published EULAR recommendations on SLE, the committee stated that at least one of these indices should be used in monitoring disease activity (16).

Renal involvement is common in SLE, and a kidney biopsy may help to confirm the diagnosis, as well as providing useful input for the prognosis and decisions regarding therapy (19). In cases of suspected nephritis a biopsy should be considered (16), but the cut-off point for test results that would justify a biopsy have not yet been defined. ACR guidelines suggest that a kidney biopsy be performed when there are persistent abnormalities in the urinary sediment, such as hematuria and pyuria, urinary casts, or increased serum creatinine (15, 20-22). Follow-up biopsies could be decisive in distinguishing patients in true remission from those in apparent remission, but as yet there are no guidelines regarding when a kidney biopsy should be repeated during follow-up (20-22). Therefore, current practice is to conduct a repeat biopsy in those patients who do not respond to therapy or who experience a deterioration in their renal parameters (21).

The diagnosis and monitoring of neurological involvement in SLE is very difficult. Laboratory, immunological and imaging tests are used to make the diagnosis, but tests with high diagnostic specificity or that can differentiate between neuropsychiatric and non-neuropsychiatric SLE are lacking (16, 23-28). No recommendations therefore can be made in this area.

Further review of the literature will be required to assess how joint, skin, cardiovascular, and other organ involvement should be monitored.

Patients should be evaluated for a number of co-morbidities that are associated with SLE, although evidence from randomized controlled trials and longitudinal observational studies does not suggest that intensified screening for co-morbidities improves patient outcome (15, 16, 29-38). Premature atherosclerosis does seem to have an impact on patient survival, indicating that monitoring for traditional cardiovascular risk factors and treatment of these conditions based on published guidelines would be appropriate.

Antibody testing

SLE is characterized by the production of a wide array of autoantibodies, many of which (*e.g.*, anti-dsDNA, anti-C1q, anti-Ro/SSA, anti-P ribosomal protein, and anti-phospholipid antibodies) may play a pathogenetic role in tissue injury. Laboratory assays to determine a patient's antibody status could be useful in predicting both future organ involvement and disease flares (39-47).

Anti-dsDNA antibodies have been linked to active SLE, renal involvement, and active renal involvement (46-51). In some patients, however, anti-dsDNA antibodies may be positive in the absence of any other signs of disease activity (51-53). Therefore, in assessing disease activity the presence or absence of anti-dsDNA could add value but should be considered in conjunction with other clinico-serological manifestations (16, 48).

Studies evaluating the prognostic significance of longitudinal determinations have produced differing results; in some studies an increase in antibody titers was predictive of flares, whereas in others it had little, if any prognostic value. The conflicting data could perhaps be explained by the use of different tests or differences in the frequency of the antibody assessment. The current consensus appears to be that changes in anti-dsDNA antibody titers do not necessarily pre-date disease flares. However, in the presence of such changes attentive patient follow-up may be advisable (16, 51-54).

Less data is available on anti-C1q antibodies, which have been linked to renal involvement, active renal involvement, and renal flares (55-59). No data regarding the usefulness of longitudinal assessment or the frequency of follow-up visits is available and therefore EULAR recommends that patients presenting with changes in anti-C1q antibody titers should be closely monitored (16).

In view of the data on the associations between anti-Ro/SSA antibodies and neonatal lupus, and between antiphospholipid antibodies and pregnancy complications, these antibodies should be tested in pregnant patients or in those planning a pregnancy (16, 43).

Laboratory testing

Changes in laboratory test results for anemia, lymphopenia, thrombocytopenia, or complement levels could signal a disease flare (16) and these parameters should be regularly monitored. EULAR recommends doing a complete blood cell count, platelet count,

creatinine measurement and urinalysis at each routine follow-up visit. In patients with renal disease, a complete blood cell count, urinalysis, and determination of 24-hour urinary proteins, creatinine, cholesterol, calcium, phosphorus, alkaline phosphatase, sodium and potassium levels should be undertaken monthly during nephritis flares and more often if the patient's condition is unstable (16).

The frequency of monitoring should be based on disease severity and activity. In patients with active disease, tests should be performed weekly, whereas in cases of inactive disease testing once every 3 to 6 months may be sufficient. When changes in laboratory parameters are observed close monitoring is recommended (15, 16). When hematological manifestations such as hemolytic anemia or thrombocytopenia are present, the hematocrit, reticulocyte count and platelet count should be monitored weekly (15).

Outcome measures

In the literature, various outcomes have been evaluated in SLE patients based on the organ system involved and the type of study undertaken. Outcome can be measured in terms of changes in disease activity, damage accrual or death, or can be specific to the organ/system under scrutiny (9-12, 18, 30, 60-65). While the disease activity indices for SLE are all able to capture changes over time, there is little data to indicate the minimally significant differences or cut-off points for a given outcome (18, 65).

The SLICC/ACR damage index (DI) is the only instrument that measures damage independently of its cause (SLE, drugs, co-morbidities). There is considerable data to support a strong correlation between high disease activity, severe flares and early damage, and a correlation between damage and death. Furthermore, once damage has occurred, further deterioration is to be expected (66-72).

The renal outcomes considered in various studies include death, a doubling of serum creatinine, end stage renal disease, and the occurrence of renal flares (73-82). Recently the ACR has recommended criteria to evaluate renal involvement in SLE (83). They suggest that the Cockroft-Gault prediction equation, which considers the effects of age, sex and body weight on the generation of creatinine, should be used to calculate creatinine clearance. The committee also concluded that the urinary protein to creatinine ratio is a reliable measure of proteinuria, setting the normal value at ≤ 0.2. Physicians are advised to consider urinary sediment only when the reproducibility of the test has been verified, as considerable variation in the assay results has been found.

The following outcomes have been defined: complete renal remission, end stage renal disease, nephrotic range proteinuria, response criteria for the glomerular filtration rate (GFR), response criteria for urinary protein, and response criteria for urinary sediment. Complete renal remission is defined as an estimated GFR of > 90 ml/min/1.73 m^2, a urinary protein to creatinine ratio of < 0.2, and inactive urinary sediment. End stage renal disease is defined as renal replacement therapy by either renal transplant or dialysis lasting for at least 3 months. Nephrotic range proteinuria is defined as a urinary protein level of ≥ 3.5 gm/day or a urinary protein to creatinine ratio > 3.0. No other organ-specific response criteria have been published to date.

Despite the large number of published studies on pregnancy in SLE, clear definitions of pregnancy outcome – variably designated as full-term delivery, livebirths, and percentage of maternal/fetal complications – are still lacking (16).

Therapy

Many different aspects of treatment must be considered – when to begin a specific medication, the best therapy for each manifestation, how to monitor treatment, and when and how therapy could be stopped. The ACR quality measures starter set includes considerations of drug safety and disease-modifying anti-rheumatic drugs for RA, patient information on the risks of therapy, and the importance of laboratory monitoring (2). Specific recommendations have been proposed for the treatment of lupus nephritis, as data strongly point to the efficacy of high-dose corticosteroids and cyclophosphamide (68-71). Their possible long-term side effects – especially the risks of cancer and premature ovarian failure – must be taken into consideration, however (15, 16, 84-87).

The EULAR committee on SLE countenances the use of mycophenolate mofetil as induction therapy in selected patients on the condition that they are kept under close observation (16). If the patient fails to respond after a maximum of 6 months, the therapy should be changed.

In patients with end stage renal disease, kidney transplantation seems to have a better outcome than dialysis, although data is lacking on the risk of thrombosis in patients with positive anti-phospholipid antibodies (16).

Patients without major organ involvement can be treated with corticosteroids and anti-malarials (15, 16). Indeed, many studies suggest that anti-malarials may be used as a disease-modifying drug, a fact that SLE patients should be informed of (89-93). The ACR published a position statement on the ophthalmologic side effects of anti-malarials. First, patients should be informed of the risks of ocular toxicity. Then each patient should be carefully examined within the first 12 months of therapy. Low-risk patients can be examined again after 5 years of therapy, whereas high-risk patients should be evaluated once a year (94-96).

All SLE patients should receive information about photoprotection to reduce the risk of skin lesions. The use of NSAIDs in SLE patients appears to be advisable only in rare cases and for limited periods of time (16).

In patients with anti-phospholipid antibodies and venous as well as arterial thrombosis, the limited evidence available suggests the need for lifelong oral anticoagulant therapy, which should aim for INR values of 2.5–3.0. There is no data from clinical trials on the prophylactic effect of low-dose aspirin on thrombosis in patients with positive anti-phospholipid antibodies, although such therapy could be recommended

Table I. Tentative starter list of quality measures for SLE.

Topic	Indicator	References
Monitoring	IF a patient has been diagnosed with SLE THEN disease activity should be assessed using a validated disease activity index	
	IF the disease course is mild to moderate THEN a patient should receive anundergo assessment visit every 3 to 6 months	
	IF changes in clinical or laboratory manifestations are observed THEN the patient should be assessed more frequently for disease flares	
	IF there is suspected renal involvement (persistent urinary sediment abnormalities, such as hematuria and pyuria, urinary casts, or increased serum creatinine) THEN a renal biopsy should be performed	
	IF a patient is pregnant THEN she should be assessed at least every 4 weeks	
	IF a patient has SLE THEN monitoring for traditional cardiovascular disease risk factors should be performed	
Laboratory testing	IF a patient presents with hemolytic anemia THEN the hematocrit and reticulocytes should initially be performed measured weekly	
	IF a patient presents with thrombocytopenia THEN a platelet count should initially be performed weekly	
	IF a patient has previous a history of lupus nephritis THEN a complete blood cell count, urinalysis, 24-hour urinary proteins, creatinine measurement, complete blood cell count, cholesterol, calcium, phosphorus, alkaline phosphatase, sodium and potassium levels should be undertaken monthly during periods of nephrotic flare	
Autoantibody testing	IF a patient presents with an increase of in anti-dsDNA or anti-C1q antibodies THEN close monitoring for flares is required	
	IF a patient is planning a pregnancy THEN anti-Ro/SSA and anti-phospholipid antibodies should be tested	
Outcome measures	IF a patient has a diagnosis of SLE THEN the SLICC/ACR damage index should be assessed yearly	
Treatment	IF a patient starts therapy with antimalarials THEN ocular toxicity should be discussed	
	IF a patient starts therapy with anti-malarials THEN a baseline ocular eye examination evaluation should be performed	
	IF a patient is at low risk for antimalarial ocular toxicity THEN ocular evaluation after baseline should be performed after 5 years of therapy	
	IF a patient is at high risk for antimalarial ocular toxicity THEN ocular evaluation after baseline should be performed annually	
	IF a patient has active lupus nephritis THEN treatment with high-dose corticosteroids and cyclophosphamide should be started	
	IF a patient with active lupus nephritis refuses cyclophosphamide or the drug is contraindicated THEN treatment with high-dose corticosteroids and mycophenolate mofetil should be started	
	IF a patient is treated with corticosteroids THEN bone protection with calcium and vitamin D is necessary	
	If a patients have experienced thrombosis secondary to anti-phospholipid antibodies THEN life-long oral anticoagulation (INR 2.5-3) is required	
	IF a patient is diagnosed with SLE THEN photoprotection should be advised	

based on expert opinion (16, 97, 98).

There is little data on hormone therapy, either in the form of oral contraception or as replacement therapy, in SLE patients (99, 100). Decisions regarding such therapy should therefore be made on a case-by-case basis. It is contraindicated in patients with anti-phospholipid antibodies and/or thrombophilia, and the general guidelines for hormone replacement therapy should be taken into account, including the exclusion criteria of hypertension, high cholesterol, obesity, smoking habit, etc.

General measures such as a correct diet for the prevention or reduction of obesity, osteoporosis, and hypercholesterolemia also enter into the management of SLE patients. Patients should receive regular cancer screening; a recent study has shown that SLE patients undergo cancer screening (for cervical, colorectal and breast cancer) less frequently than the general population (101).

Based on a large body of evidence, adjunct therapy for the prevention of osteoporosis in patients on long-term corticosteroid treatment should also be recommended (2, 16, 29). As already noted above, treatment for traditional cardiovascular risk factors according to prevailing guidelines appears to be important. It is less clear whether patients should be treated with low-dose aspirin to prevent cardiovascular disease (37).

Conclusions

The assessment of quality of care is becoming increasingly important in the field of medicine. However, the rheumatic diseases are complex and a comprehensive list of quality indicators must take into account disease assessment, monitoring, therapy and outcomes, as well as the patient's perspective, which may not always agree with that of the physician. Although the task is complicated, there is a large body of data in the literature that could help to set initial standards for the assessment of quality of care and patient management in SLE. A tentative, although by no mean exhaustive, starter list of quality measures in SLE based on current knowledge is presented in Table I. The quality assessment tools for a specific disease should be user-friendly, easily available, and routinely updated. Such a tool that will help physicians deliver high quality care to the SLE populations needs to be developed (1, 102).

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