EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Report of a Task Force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT) *

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* This is an abbreviated version of the recommendations. The full-text version is available on-line (http://ard.bmj.com)

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Key words: nephritis, neuropsychiatric lupus, morbidity, adjunct therapy, antiphospholipid syndrome

Word count: 3,449

ABSTRACT

Objective: SLE is a complex disease with variable presentations, course and prognosis. We sought to develop evidenced-based recommendations addressing the major issues in the management of SLE.
Methods: The EULAR Task Force on SLE comprised 19 specialists and a clinical epidemiologist. Key questions for the management of SLE were compiled using the Delphi technique. A systematic search of PubMed and Cochrane Library Reports was performed using McMaster/Hedges clinical queries' strategies for questions related to the diagnosis, prognosis, monitoring, and treatment of SLE. For neuropsychiatric, pregnancy, and antiphospholipid syndrome questions, the search was conducted using an array of relevant terms. Evidence was categorized based on sample size and type of design and the categories of available evidence were identified for each recommendation. The strength of recommendation was assessed based on the category of available evidence and agreement on the statements was measured across the 19 specialists.
Results: Twelve questions were generated regarding the prognosis, diagnosis, monitoring, and treatment of SLE, including neuropsychiatric SLE, pregnancy, the antiphospholipid syndrome, and lupus nephritis. The evidence to support each proposition was evaluated and scored. After discussion and votes, the final recommendations were presented using brief statements. The average agreement among experts was 8.8 out of 10.
Conclusion: Recommendations for the management of SLE were developed using an evidence-based approach followed by expert consensus with high level of agreement among the experts.

Key words: nephritis, neuropsychiatric lupus, morbidity, adjunct therapy, antiphospholipid syndrome, pregnancy, prognosis, monitoring, diagnosis

INTRODUCTION

Approximately half a million people in Europe and a quarter of a million people in the United States of America (projections based on prevalence rates of 30-50 per 100,000) have systemic lupus erythematosus (SLE) [1]. The great majority of these patients are women in their childbearing years. SLE is a complex disease with variable presentations, course and prognosis characterized by remissions and flares [2, 3]. Because of the systemic nature of the disease, multiple medical specialties are involved in the care of these patients. To avoid fragmentation and optimize management there is a presently unmet need to establish an integrated approach based on widely accepted principles and evidence-based recommendations.

Recommendations and/or guidelines represent a popular way of integrating evidence-based medicine to clinical practice. These are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances [4]. To this end and under the auspices of EULAR, we undertook the task of developing guidelines for the management of various aspects of SLE. To assure a high level of intrinsic quality and comparability of this approach, we used the EULAR standard operating procedures [5]. We present here 12 key recommendations, selected from a panel of experts, for the management (diagnosis, treatment, monitoring) of SLE using a combination of research-based evidence and expert consensus.

METHODS

The EULAR standardised operating procedures suggest a discussion among experts in the field about the focus, the target population and an operational definition of the term "management", followed by consensus building based on the currently available literature (evidence-based), combined with expert opinion, as needed, to arrive at consensus for a set of recommendations [5]. The expert committee agreed on 12 topics, including general management of SLE (5 questions), neuropsychiatric lupus (2 questions), pregnancy in lupus (1 question), anti-phospholipid syndrome (1 question), and lupus nephritis (3 questions). A systematic search of PubMed the Cochrane library was performed, and retrieved items were screened for eligibility based on their title, abstract and/or full content. Evidence was categorized according to study design using a traditional rating scale and the strength of the evidence was graded combining information on the design and validity of the available data (see the full-text version for more details). The results of the literature search were summarized, aggregated and distributed to the expert committee. Following discussion, voting and adjusting the formulation, the expert committee arrived at 12 final recommendations for the management of SLE (**Table 1**). Further, the expert committee proposed topics for a Research Agenda.

RESULTS (TABLES 1 AND 2)

Prognosis

SLE runs a highly variable clinical course, and determination of prognosis together with the development of reliable indicators of active disease, disease severity and damage accrual is important. Several clinical manifestations (discoid lesions [6], arthritis [7], serositis [8], renal involvement [9, 10], psychosis or seizures [6, 11]), laboratory tests (anemia [8, 12, 13], thrombocytopenia [14], leucopenia [15], serum cretatinine [9]), immunological tests (anti-dsDNA [10, 14, 16], anti-C1q [17], anti-phospholipid [18-20], anti-RNP [18], anti-Ro/SSA [21, 22], anti-La/SSB antibodies [23], serum complement concentrations [12, 14, 23]), brain MRI [7], and renal biopsy [24, 25] correlate with outcome in terms of development of major organ involvement (nephritis, neuropsychiatric lupus), end-stage renal disease (ESRD), and damage accrual or decreased survival.

The small size and the large number of candidate predictors tested represent significant problems and raise the possibility for selective reporting of significant associations. Moreover, these prognostic variables have not been uniformly informative across patients in various clinical settings or backgrounds. Most importantly perhaps, no single predicting factor has emerged that could accurately predict the outcome. Thus, the various prognostic factors in a single patient need to be evaluated in conjunction. In general, involvement of major organs denotes a worse prognosis.

Monitoring

SLE is often complicated by exacerbations and flares of varying severity. Several global and organ-specific activity indices are used in the evaluation of SLE patients in routine clinical practice and in clinical trials [26-28]. More commonly used are the British Isles Lupus Assessement Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). These indices have been developed in the context of long-term observational studies, are good predictors of damage and mortality, and reflect changes in disease activity [29-31]. The committee encourages the use of at least one of these indices for the monitoring of disease activity. In addition, new clinical manifestations (skin lesions [32], anemia, lymphopenia, or thrombocytopenia [33, 34], low serum C3 and/or C4 concentrations [35, 36], anti-dsDNA [33, 37, 38], and anti-C1q titers [39] correlate with disease severity and can predict future flares.

While these indices and diagnostic tests may have some diagnostic ability for monitoring disease, none of them has been evaluated in randomized trials for their ability to alter management and patient outcome. The level of changes that should trigger changes in management is also unknown. For example, intensification of therapy based on serological activity alone especially a rise in anti-dsDNA titers [37, 40, 41] runs into the risk of over-treating patients although shown to prevent relapses in a RCT [42]. In these cases most experts advice closer follow-up for clinical disease activity.

Co-morbidities

SLE patients may be at increased risk for several co-morbidities and treatment-related morbidity may not be easily separable from disease-related morbidity raising the issue whether the two may have an additive or synergistic effect. Patients with SLE have a nearly 5-fold increased risk of death compared with the general population [43, 44]. Several observational cohorts and case-control studies have identified infections [10, 45, 46], hypertension [47], dyslipidaemia [47, 48], diabetes mellitus [47], atherosclerosis [48, 49], coronary heart disease [50], osteoporosis [51], avascular bone necrosis [10, 52], and certain types of cancer (non-Hodgkin's lymphoma, lung cancer, hepatobiliary cancer) [53] as a common cause of morbidity and mortality in SLE patients. However, no randomized trials exist suggesting that intensified screening for these comorbidities would improve outcome. Moreover, many of these data originate from tertiary referral centers that usually provide care to the most severe cases of lupus raising the possibility of spectrum of disease bias. Suboptimal selection of controls may also inflate the reported strength of some of these associations. Neverthless, clinical experience and available data suggest comorbities are a major component of the disease. The committee therefore recommends a high-index of suspicion and diligent follow-up.

Treatment of non-major organ involvement

Glucocorticoids [42, 54], antimalarials [55, 56], non-steroid anti-inflammatory drugs (NSAIDs), and in severe, refractory cases immunosuppressive agents [57-59] are used in the treatment of SLE patients without major organ involvement. Despite their widespread use, there are only few RCTs with variable outcome criteria demonstrating their efficacy in SLE. Moreover, while most studies have shown improvement it is not apparent whether patients were left with residual disease activity and its extent. The evidence is typically limited to small sample sizes, even when randomization has been used. The committee recommends judicious use of these agents, taking into consideration the potential harms associated with each of these drugs.

Adjunct-therapy

In a double blind, intra-individual comparative study, the use of sunscreens could prevent the development of skin lesions following photoprovocation [60]. Although no data are available in SLE specifically, the committee felt that low-dose aspirin may be considered in adult lupus patients receiving corticosteroids, in those with anti-phospholipid antibodies, and in those with at least one traditional risk factor for atherosclerotic disease [61].

In patients receiving long-term glucocorticoid therapy, calcium and vitamin D may protect from bone mass loss [62]. Two other studies have demonstrated beneficial effects of biphosphonates in mixed population of patients with SLE and other inflammatory diseases [63, 64]. Pregnancy should be postponed for 6 months after withdrawal of biphosphonates [65]. Although estrogen use has been associated with increased risk for developing SLE [66], two RCTs have concluded that oral estrogen contraceptives do not increase the risk for flare in stable disease [67, 68]. Hormone replacement therapy (HRT) results in significantly better change in bone mass density compared to placebo or calcitriol, without increasing the risk for flares [69, 70]. These results may not be generalized to patients with increased risk for thombo-occlusive incidents, and accompanying risks should be assessed before estrogen therapy is prescribed.

Despite the lack of SLE-specific literature, weight control, physical exercise, and smoking cessation are recommended, especially for SLE patients with increased CVD risk. Statins and anti-hypertensives (ACE-inhibitors) should also be considered in selected patients.

Diagnosis of neuropsychiatric lupus

Neurological and/or psychiatric manifestations occur often in SLE patients and may be directly related to disease itself (primary neuropsychiatric lupus) or to complications of the disease or its treatment (secondary neuropsychiatric lupus). There are several clinical, laboratory/immunological, neuropsychological, and imaging tests [20, 71-78]which have been used in SLE patients presenting with neuropsychiatric manifestations. Altogether, these studies suggest that no single clinical, laboratory, neuropsychological and imaging test can be used to differentiate NPSLE from non-NPSLE patients with similar neuropsychiatric manifestations. A combination of the aforementioned tests may provide useful information in assessment of selected SLE patients presenting with neuropsychiatric symptoms. The diagnostic evaluation should be similar to what the evaluation would be in patients without SLE who exhibit the same neuropsychiatric manifestations.

Treatment of severe, inflammatory neuropsychiatric lupus

Primary neuropsychiatric lupus occurs in the setting of lupus activity in other organs and involves a variety of pathogenic mechanisms including immune-mediated neuronal excitation/injury/death or demyelination (which is usually managed with immunosuppressive therapy) and/or ischemic injury due to impaired perfusion (due to microangiopathy, thrombosis, or emboli) commonly associated with the antiphospholipid antibodies which may require anticoagulation [2].

We found a single RCT conducted in 32 SLE patients presenting with active NPSLE manifestations such as peripheral/cranial neuropathy, optic neuritis, transverse myelitis, brainstem disease or coma [79]. Induction therapy with i.v. methylprednisolone (MP) was followed by either i.v.

monthly cyclophosphamide (CY) versus i.v. MP every 4 months for 1 year and then i.v. CY or i.v. MP every 3 months for another year. 18/19 patients receiving CY vs. 7/13 patients receiving MP (p=0.03) responded to treatment. Beneficial effects of CY in treatment of severe NPSLE have also been suggested in non-randomized controlled studies [80, 81].

Pregnancy in lupus

The management of a pregnant SLE patient has always been a challenge for the practicing physician since lupus may affect pregnancy and vice versa. There is not enough evidence to support a deleterious effect of SLE on fertility [82-84]. Pregnancy may increase lupus disease activity and cause mild-to-moderate flares, involving mostly skin, joints, and blood [85-87].

Lupus nephritis [88, 89] and anti-phospholipid antibodies [90, 91] have been identified as a risk factor for hypertensive complications and pre-eclampsia. SLE patients – especially those with nephritis or anti-phospholipid antibodies – are at risk for adverse pregnancy outcomes, including miscarriage, stillbirth, and premature delivery (relative risks ranging 2.2−5.8) [87, 92-95]. Anti-phospholipid antibodies and nephritis are also associated with low birth weight and intra-uterine growth restriction [96, 97]. Fetal heart block is another complication of SLE pregnancies (2–4.5%) [98, 99], and it is associated with anti-Ro/SSA or anti-La/SSB autoantibodies.

Prednisolone and other non-fluorinated glucocorticoids, azathioprine, cyclosporine A, and low-dose aspirin have been used in lupus pregnancy but their efficacy and safety has not been demonstrated in randomized trials. The efficacy and safety of hydroxychloroquine in lupus pregnancy has been evaluated in one RCT [100]. These recommendations may differ from the ratings of the United States Food & Drug Administration which in their current form are often not helpful for the clinician treating patients with chronic disease during pregnancy and lactation [65]. There is no evidence to support the use of mycophenolate mofetil or CY, and methotrexate and these agents must be avoided during pregnancy [101, 102].

Antiphospholipid syndrome in lupus

Anti-phospholipid antibodies are commonly encountered in SLE patients and are associated with increased risk for thrombo-occlusive incidents. In such patients, primary and/or secondary prevention of thrombosis is warranted but the clinical decision is often hampered by accompanying risks for treatment-related adverse effects (i.e. major bleeding). Despite the lack of evidence for primary prevention of thombosis and pregnancy loss, the expert committee recommends the use of low dose aspirin in SLE patients with anti-phospholipid antibodies, especially when other risk factors for thrombosis co-exist.

The effectiveness of oral anticoagulation over aspirin alone in prevention of thrombosis in (non-pregnant) SLE patients with anti-phospholipid antibodies and thrombosis has been established in retrospective controlled studies [103-106]. Two RCTs [107, 108] have demonstrated no superiority of high-intensity (target INR 3.1−4.0) over moderate-intensity warfarin (INR 2.0−3.0) for secondary prevention, and increased risk for minor bleeding in the high-intensity arm (28% vs. 11%) [108]. Their results, however, are limited in that most patients (>70%) had history of venous – rather than arterial – thrombosis, and that patients who had already had recurrent events on oral anticoagulation were excluded. Conversely, retrospective studies including more patients with previous arterial thrombosis or stroke have concluded that high-intensity warfarin is more efficacious in secondary prevention of thrombosis without increasing the risk for major bleeding [103-105, 109, 110]. The committee proposes that in patients with APS and a first event of venous thrombosis oral anticoagulation should target INR 2.0−3.0. In the case of arterial or recurrent thrombosis, high-intensity anticoagulation (target INR 3.0−4.0) is warranted.

As for pregnant SLE patients with APS, a recent Cochrane Review concluded that combined unfractionated heparin and aspirin may reduce the risk for pregnancy loss (RR 0.46, 95% CI: 0.29−0.71) [111]. The combination of low molecular weight heparin and aspirin also seems to be effective (RR 0.78, 95% CI: 0.39−1.57). There are no randomized trials assessing the usefulness of anticoagulation in prevention of recurrent thrombosis during pregnancy. The committee recommends the use of aspirin and heparin for the prevention of APS-related thrombosis during pregancy.

Lupus nephritis: diagnosis and monitoring

In patients with suspected lupus nephritis, renal biopsy may be used to confirm the diagnosis, evaluate disease activity, chronicity/damage, and determine prognosis and appropriate therapy. The predictive value of second renal biopsy (i.e. after treatment initiation) has been assessed in one prospective [112] and a few retrospective studies [113, 114]. It was found that some pathology findings were associated with clinical response and outcome in lupus nephritis. Nevertheless, repeat renal biopsies pose a risk to the patient and may not be feasible for all patients. There is some evidence to support the predictive ability of urine sediment analysis in monitoring lupus nephritis therapy [115 116]. Changes in proteinuria [117], serum creatinine [22, 36, 113, 117], anti-dsDNA and serum C3 concentations [36, 118, 119] correlate with renal flares and outcome. It should be emphasized, however, that these studies were not specifically designed to evaluate the efficacy of various tests in monitoring response to therapy of lupus nephritis. There are no randomized trials evaluating the benefits from various monitoring strategies.

Lupus nephritis: treatment

The treatment of lupus nephritis often consists of a period of intensive immunosuppressive therapy (*induction therapy*) followed by a longer period of less intensive *maintenance therapy*. In a recent Cochrane Review, CY plus steroids reduced the risk for doubling of serum creatinine level compared with steroids alone (RR = 0.6), but had no impact on overall mortality [120, 121]. Azathioprine plus steroids reduced the risk for all-cause mortality compared with steroids alone (RR = 0.6), but had no effect on renal outcomes. CY was superior to azathioprine and/or corticosteroids with high-dose, intermittent administration of CY (pulse therapy) demonstrating a more favourable efficacy-to-toxicity ratio than oral CY [122]. In a long-term follow-up (median 11 years) of a RCT combination therapy with glucocorticoids and CY demonstrated efficacy (83% preserved renal function), without substantially increasing the risk for adverse effects [123]. Ovarian failure after CY therapy remains a considerable problem and is both dose- and age-dependent [124]. Gonadal protection may be feasible with the use of GnRH-analogues, a finding that requires further confirmation [125].

The efficacy of MMF as induction therapy has been assessed in four RCTs which concluded that MMF was associated with reduced risk for treatment failure (RR = 0.7) and for the composite end-point of death or ESRD (RR = 0.4) compared to CY [126-129]. The usefulness of MMF as a maintenance agent has been assessed in a single RCT of 59 patients who received induction therapy with boluses of IV-CY and glucocorticoids and then were randomly assigned to IV-CY, oral azathioprine, or oral MMF for 1–3 years [130]. The event-free survival rate for the composite end-point of death or ESRD was higher in the AZA and MMF groups that in the CY group. There was a significantly higher incidence of sustained amenorrhea in the CY group.

The committee recommends that physicians use MMF as induction therapy for selected patients under close observation; failure to achieve a significant response by 6 months at the latest (defined as improvement of serum creatinine and reduction of proteinuria to <1 g/day [131]) should evoke discussions for intensification of therapy. For maintenance therapy, MMF can be used in patients unable to tolerate azathioprine or who flare while on treatment. Although data with MMF are encouraging, in the opinion of the committee the drug cannot replace at present the combination of i.v. CY with i.v. MP as the treatment of choice for severe lupus nephritis [123]. Small, non-controlled trials with short follow-up suggest that up to 50% of refractory patients to CY may have a clinically significant response to rituximab, a monoclonal antibody directed against B cells [132, 133].

Modern immunosuppressive therapies are effective but none of them cures lupus with approximately one third of them flaring after remission. Initial management of moderate to severe flare requires induction therapy with immunosuppressive agents, which usually prevent the loss of renal function [134, 135].

End-stage renal disease

Despite recent advances in therapy of lupus nephritis, a number of patients may eventually progress to ESRD and will require dialysis treatment or even kidney transplantation. Both dialysis and transplantation in SLE have comparable rates for long-term patient or graft survival as those in non-diabetic/non-SLE patients[136 137, 138 139-142]. Anti-phospholipid antibodies are associated with increased risk for thrombotic events, graft loss, and poor transplantation outcome [106, 141, 143, 144]. There is no evidence from SLE-specific studies to support the superiority of either treatment option. Nonetheless, two retrospective studies including large numbers of patients with ESRD, have demonstrated superiority of renal transplantation over dialysis in terms of long-term patient survival (relative risk 0.19−0.32 at 12−18 months post-transplant) [145, 146].

DISCUSSION

An initial set of statements and recommendations regarding important aspects of the management of SLE has been developed based on systematic review of the literature and expert opinion with an excellent level of agreement among the experts (average 8.8 out of 10). These recommendations should facilitate the medical care of lupus patients without restricting the autonomy of the provider physicians who have the ultimate responsibility for the management.

Only a few RCTs have been performed to establish optimal management of SLE and several important issues have not been adequately addressed. Furthermore, there are no RCTs to evaluate the effectiveness of lifestyle modifications and/or primary prevention interventions focused on SLE patients. These findings underscore the need to establish international networks to facilitate clinical trials addressing management issues and testing new therapies. To this end, the committee proposes a Research Agenda for the years to come (**Table 3**).

Establishing a diagnosis and managing patients with SLE requires an integration of patient's symptoms, physical examination findings, and the results of diagnostic testing. In the case of lupus, there are management issues with safety and financial implications that they have not been addressed. There is a need to determine which laboratory tests should be performed at initial presentation and during follow-up of SLE patients, and how often. In the mean time, recommendations have to be based solely on expert opinion. The committee recommends examination and laboratory monitoring every 3 months, in patients who are doing well and more frequently for those with uncontrolled disease.

Clinical practice recommendations require a framework to assess their quality, assure that potential biases have been adequately addressed and that are valid and feasible for practice. To this end, we used as a framework the Appraisal of Guidelines Research and Evaluation (AGREE) instrument [147], which rates six individual domains and 23 key items. Throughout the process, we made a consientius effort to comply with as many of these as possible. Due to paucity of strong data for several management issues, the development of review criteria for monitoring and/or audit purposes to measure the adherence to the recommendations is not feasible at this point. Moreover, we were not able to seek systematically patient views and preferences. Following this first round of recommendations, we intend to update them every three years with the inclusion of patients and individuals from other relevant professions and the development of tools that will facilitate the dissemination and application of the recommendations.

Aknowledgements
This work is dedicated to the memory of Dr. Jose Font, a member of the committee. Support for this work was provided via a grant from the EULAR Excecutive Committee. We thank Dr. Maxime Dougados for his encouragement, guidance and support. We also thank: a) the staff of the EULAR House in Zurich (Fred and Elly Wyss, Robert Buff, and Ernst Isler and their associates) for their warm hospitality and outstanding organization, b) Mrs. Natassa Mpizaki for expert secretarial assistance and, c) Drs Gabor Illei and Michael Ward for critical review of the manuscript. Dr. George Bertsias is a graduate student of the Graduate Program in Molecular Basis of Human Disease (University of Crete School of Medicine).

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TABLES

Table 1. Summary of the statements and recommendations on the management of systemic lupus erythematosus based on evidence and expert opinion

GENERAL MANAGEMENT
Prognosis
In patients with SLE, new clinical signs (rashes, arthritis, serositis, neurological manifestations -seizures/psychosis), routine laboratory (CBC, serum creatinine, proteinuria and urinary sediment), and immunological tests (serum C3, anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-phospholipid, anti-RNP), may provide prognostic information for the outcome in general and involvement of major organs, and thus should be considered in the evaluation of these patients. Confirmation by imaging (brain MRI), and pathology (renal biopsy) may add prognostic information and should be considered in selected patients.
Monitoring
New clinical manifestations such as number and type of skin lesions, or arthritis, serositis, and neurological manifestations (seizures/psychosis), laboratory tests (CBC), immunological tests (serum C3/C4, anti-C1q, anti-dsDNA), and validated global activity indices have diagnostic ability for monitoring for lupus activity and flares, and may be used in the monitoring of lupus patients.
Co-morbidities
SLE patients are at increased risk for certain co-morbidities, either due to the disease and/or its treatment. These co-morbidities include infections (urinary track infections, other infections), atherosclerosis, hypertension, dyslipidaemias, diabetes, osteoporosis, avascular necrosis, malignancies (especially non-Hodgkin lymphoma). Minimization of risk factors together with a high-index of suspicion, prompt evaluation, and diligent follow-up of these patients is recommended.
Treatment
In the treatment of SLE without major organ manifestations antimalarials and/or glucocorticoids are of benefit and may be used. NSAIDs may be used judiciously for limited periods of time at patients at low risk for their complications. In non-responsive patients or patients not being able to reduce steroids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine, mycophenolate mofetil, and methotrexate should also be considered.
Adjunct therapy
Photo-protection may be beneficial in patients with skin manifestations and should be considered. Lifestyle modifications (smoking cessation, weight control, exercise) are likely to be beneficial for patient outcomes and should be encouraged. Depending on the individual medication and the clinical situation, other agents (low-dose aspirin, calcium/vitamin D, biphosphonates, statins, anti-hypertensives (including angiotensin converting enzyme inhibitors)) should be considered. Estrogens (oral contraceptives, hormonal replacement therapy) may be used but accompanying risks should be assessed.
NEUROPSYCHIATRIC LUPUS
Diagnosis
In SLE patients the diagnostic work-up (clinical, laboratory, neuropsychological, and imaging tests) of neuropsychiatric manifestations should be similar to that in the general population presenting with the same neuropsychiatric manifestations.
Treatment
SLE patients with major neuropsychiatric manifestations considered to be of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressive therapy.
PREGNANCY IN LUPUS
Pregnancy affects mothers with SLE and their off-springs in several ways. a) Mother. There is no significant difference in fertility in lupus patients. Pregnancy may increase lupus disease activity but these flares are usually mild. Patients with lupus nephritis and anti-phospholipid antibodies are more at risk of developing pre-eclampsia and should be monitored more closely. b) Fetus. SLE may affect the fetus in several ways, especially if the mother has a history of lupus nephritis, anti-phospholipid, anti-Ro and/or anti-La antibodies. These conditions are associated with an increase of the risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction and fetal heart block. Prednisolone, azathioprine, hydroxychloroquine, and low dose aspirin may be used in lupus pregnancies. At present evidence suggests that mycophenolate mofetil, cyclophosphamide and methotrexate must be avoided.
ANTI-PHOSPHOLIPID SYNDROME
In patients with SLE and anti-phospholipid antibodies low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss. Other risk factors for thrombosis should also be assessed. Estrogen-containing drugs increase the risk for thrombosis. In non-pregnant patients with SLE and APS–associated thrombosis, long-term anticoagulation with oral anticoagulants is effective for secondary prevention of thrombosis. In pregnant patients with SLE and anti-phospholipid syndrome combined unfractionated or LMW heparin and aspirin reduce pregnancy loss and thrombosis and should be considered.

LUPUS NEPHRITIS

Monitoring

Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have only limited ability to predict the response to treatment and may be used only as supplemental information.

Treatment

In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however, associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared to pulse cyclophosphamide and a more favorable toxicity profile: failure to respond by 6 months should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

End-stage renal disease

Dialysis and transplantation in SLE have comparable rates for long-term patient and graft-survival as those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

Table 2. Category of evidence and strength of statements

Recommendation / item	No. of studies evaluated	Category of evidence	Strength of statement	Mean level of agreement [1]
Prognosis. Prognostic value of:				
Clinical features				
Rashes	4	4	B	8.6
Arthritis	4	4	B	8.7
Serositis	6	4	B	8.6
Seizures/Psychosis	9	4	B	9.0
Laboratory findings				
Severe anemia	10	4	B	8.0
Leukopenia/lymphopenia	4	5	C	8.0
Thrombocytopenia	15	4	B	8.0
Serum creatinine	20	4	B	9.2
Proteinuria/urinary sediment	24	4	B	9.3
C3/C4	13	4	B	8.4
Anti-dsDNA	17	4	B	8.7
Anti-Ro/SSA	6	4	B	7.7
Anti-La/SSB	1	5	C	7.7
Anti-phospholipid	19	4	B	8.5
Anti-RNP	3	4	B	7.6
Imaging				
Brain MRI	7	4	B	8.7
Pathology				
Renal biopsy	33	4	B	9.5
Monitoring. Diagnostic ability of:				
Rashes	1	5	C	8.8
Anemia	1	4	B	
Lymphopenia	1	4	B	8.3
Thrombocytopenia	1	5	C	
C3/C4	13	4	B	8.8
Anti-C1q	8	4	B	7.7
Anti-dsDNA	15	4	B	8.7
Comorbidities. Increased risk for:				
Infections	13	5	C	8.6
Urinary tract infections	1	4	B	8.9
Atherosclerosis	14	4	B	8.8
Hypertension	7	4	B	9.4
Dyslipidaemia	7	4	B	9.2
Diabetes	3	5	C	8.9
Osteoporosis	6	5	C	9.1
Avascular necrosis	8	5	C	8.6
Neoplasms				8.7
Non-Hodgkin lymphomas	6	4	B	
Other	10	4	B	
Therapy of uncomplicated SLE				
Antimalarials	4	2	A	9.4
NSAIDs	1	--	D	8.8
Glucocorticoids	3	2	A	9.1
Azathioprine	1	4	B	9.3
Mycophenolate mofetil	4	6	D	6.9
Methotrexate	3	2	A	8.0
Adjunct therapy in SLE				
Photoprotection	1	4	B	9.2
Smoking cessation	--	--	D	
Weight control	--	--	D	9.3
Exercise	--	--	D	
Low dose aspirin	1	4	D [2]	9.0
Calcium / vitamin D	5	2	A	9.2
Biphosphonates	2	2	A	8.5
Statins	--	--	D	8.9

Antihypertensives	--	--	D	8.9
Oral contraceptives (safe use)	2	2	A	9.1
Hormone replacement therapy	3	2	A	9.1
Diagnosis of neuropsychiatric lupus				**8.1** [3]
Clinical features				
Headache (not related)	1	3	A	
Anxiety	1	5	C	
Depression	1	5	C	
Cognitive impairment	3	4	B	
Laboratory tests				
EEG	3	4	B	
Anti-P	6	4	B	
Anti-phopholipid	4	4	B	
Neuropsychological tests	3	5	C	
Imaging tests				
CT	3	4	B	
MRI	9	4	B	
PET	2	4	B	
SPECT	5	5	C	
MTI	5	5	C	
DWI	1	5	C	
MRS	3	5	C	
T2 relaxation time	2	5	C	
Treatment of neuropsychiatric lupus				
Immunosuppressants (CY) in combination with glucocorticoids	10	2	A	9.2
Pregnancy				
Fertility not impaired	4	5	C	8.8
Increased lupus activity / flares	11	3	B	8.8
Increased risk for pre-eclampsia	6	4	B	9.8
Increased risk for miscarriage/ stillbirth/premature delivery	30	4	B	
Increased risk for intrauterine growth restriction	6	5	C	9.4
Increased risk for fetal heart block	7	4	B	
Therapy during pregnancy				
Prednisolone	6	6	D	9.6
Azathioprine	5	6	D	9.2
HCQ	9	2	A	9.5
Low dose aspirin	1	6	D	9.3
Antiphospholipid syndrome				
Primary prevention of thrombosis / pregnancy loss				
Low dose aspirin	--	--	D	8.7
Secondary prevention of thrombosis / pregnancy loss				
Oral anticoagulants (non-pregnant patients)	8	2	A	9.0
Unfractionated/LMW heparin and aspirin (pregnant patients)	14	1	A	9.1
Nephritis: monitoring				
Repeat renal biopsy	6	4	B	
Urinary sediment	2	4	B	9.5
Proteinuria	10	4	B	
Serum creatinine	8	4	B	
Anti-dsDNA	3	4	B	8.7
C3	2	4	B	
Nephritis: treatment				
Combined glucocorticoids and immunosuppressants are effective against ESRD	21	1	A	9.3

MMF has similar efficancy to pulse CY in short-/medium-term trials	8	2	A	9.2
CY efficacy in long-term trials	13	1	A	9.5
End-stage renal disease in SLE				
Dialysis is safe in SLE	7	3	B	8.8
Transplantation is safe in SLE	9	3	B	
Transplantation is superior to dialysis	2	5	C [4]	9.4

[1] Mean level of agreement of the Task Force members on each sub-item/statement.
[2] In elderly SLE patients, low dose aspirin is associated with improved cognitive function (4 / B).
[3] This refers to the statement that "*in SLE patients, the diagnostic work-up (clinical, laboratory, neuropsychological, and imaging tests) of neuropsychiatric manifestations should be similar to that in the general population presenting with the same neuropsychiatric manifestations*".
[4] Non-SLE studies.

Table 3. Research agenda

Epidemiology
- Relative importance of environmental factors (exposure to sun, smoking, diet) in the pathogenesis of SLE
- Incidence, prevalence, and severity of SLE in various European populations? Is there a North-to-South gradient?

Pathogenesis
- Genetic factors for disease susceptibility and severity
- Effector mechanisms and repair of tissue injury

Early diagnosis – Primary prevention
- Identification of patients at higher risk for SLE
- Feasibility of primary prevention
- Primary prevention of cardiovascular disease in high-risk patients (e.g. aspirin, statins, others)

Initial diagnostic work-up and monitoring
- Minimum diagnostic work-up for suspected SLE
- Work-up for disease limited to a single organ (e.g skin, blood, others)

Diagnosis – prognosis
- Diagnostic criteria with improved sensitivity and specificity
- Classification criteria to identify subpopulations of SLE with distinct pathogenetic, clinical, and laboratory features and response to therapy
- Diagnostic algorithms for neuropsychiatric lupus

Treatment
- Indications and optimal targets for autologous stem cell therapy in SLE
- Major indications for biologic therapies in SLE (B cell depletion, inhibition of B cell differentiation, costimulation blockade, toleragens)
- Optimum management of membranous nephropathy
- Options for resistant disease involving major and non-major organs
- Indications, efficacy, toxicity of combined immunosuppressive and anticoagulant therapy for patients with anti-phospholipid syndrome and SLE

Flares
- Mechanisms of flare: residual vs sub-clinical disease vs *de novo* flare
- Biomarkers for residual disease and for early relapse
- Optimal management of flares

Comorbidities
- Primary prevention of cardiovascular disease
- Primary prevention and screening for osteoporosis
- Strategies to increase compliance with therapy and preventive medicine
- Strategies to decrease morbidity and mortality from infection
- Validation of the Charlson Comorbidity score in SLE trials for optimal patient stratification

Neonatal lupus
- Epidemiology, risk factors, and management

Pregnancy
- Impact of assisted fertilization on disease activity
- Effect of maternal immunosuppressive treatment on offspring long term outcome

Anti-phospholipid antibodies
- Determine whether individuals with persistently positive anti-phospholipid antibodies should receive prophylaxis (and type of) for thrombosis or pregnancy-related type morbidity
- Recommended treatment for pregnant patients with APS who had pregnancy loss on low dose aspirin and heparin

Pediatric and adolescent SLE
- Epidemiology, optimal management, and long-term outcome

Geriatric lupus
- Epidemiology, optimal management, and long-term outcome

The management of Lupus

This is the lay version of the EULAR recommendations for the management of people with Lupus. The original publication can be downloaded from the EULAR website: www.eular.org.

Bertsias G, et al. EULAR recommendations for the management of systemic lupus erythematosus (SLE): Report of a Task Force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2008;67(2):195–205. doi:10.1136/ard.2007.070367

Introduction

Recommendations give advice to doctors and patients about the best way to treat and manage diseases. EULAR has written recommendations on the management of people with systemic lupus erythematosus (also called SLE or Lupus for short). Lupus is an autoimmune disease where the immune system attacks the body's own tissues and causes inflammation. Lupus is a complicated disease. It has many different symptoms, including joint pain, fatigue (tiredness) and skin rash. Lupus can also affect internal organs such as the kidneys and cause neurological problems.

The recommendations were written by doctors. They looked at the evidence on the management of people with Lupus. They also discussed their expert opinion to achieve a level of agreement.

More recently EULAR has created additional recommendations for specific aspects in the care of people with Lupus, namely Neuropsychiatric Lupus, Lupus Nephritis, and fertility and pregnancy in Lupus (see 'other recommendations' at the end of this document). The recommendations summarised here look at Lupus in general.

What do we already know?

Lupus is a complicated disease, and can be hard to manage. Often the disease comes and goes, sometimes called 'waxing and waning' or flares and remission. Because of the variety of different symptoms and parts of the body that can be affected, many different doctors are involved in the care of people with Lupus. Lupus is most common in women in their child-bearing years.

What do the recommendations say?

The recommendations fall into five categories: general management, pregnancy in Lupus, blood clotting and miscarriage (antiphospholipid syndrome), Lupus affecting the brain (Neuropsychiatric Lupus), and Lupus affecting the kidneys (Lupus Nephritis).

Overall, there are 12 statements or recommendations. Each recommendation is based on available scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is and the more important it is that you and your doctor follow it.

One star (*) means it is a weak recommendation with limited evidence.

Two stars (**) means it is a weak recommendation with some evidence.

Three stars (***) means it is a strong recommendation with some evidence.

Four stars (****) means it is a strong recommendation with a lot of evidence.

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1. General management

- **Symptoms and tests should be considered when evaluating a person with Lupus and deciding on their prognosis, or how well they are likely to do in the future.****
  Symptoms and the results of laboratory tests may predict a person's disease outcome, and can tell us which major organs are affected by the Lupus. Lupus patients should receive the same tests as anyone else going to their doctor with neuropsychiatric symptoms. These might include a physical examination, laboratory tests and imaging such as MRI (magnetic resonance imaging).

- **New symptoms and changes may be used to diagnose flares and monitor disease activity.****
  The appearance of new symptoms or changes in laboratory test results can be used to monitor disease. They can also help your doctor to diagnose and recognise flares or changes in the disease.

- **People with Lupus are more likely to have other diseases and need to be carefully managed and treated.****
  People with Lupus have a higher than normal risk of having infections and other diseases such as diabetes, high blood pressure, osteoporosis (brittle bones), cancer and heart disease. If you have Lupus you should try to minimise your risks. Doctors need to diagnose and quickly treat any other diseases that their Lupus patients have.

- **Drug choice will depend on the symptoms of the disease and how severe it is.**/*****
  For people with no major organs affected, antimalarial drugs or steroids may be used. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used for short periods to reduce pain and swelling. Immunosuppressive drugs may be used if you cannot take steroids.

- **Add-on (adjunct) treatments may be used in some people.**/******
  If you have Lupus and suffer from skin rashes, take steps to protect yourself from the sun. General lifestyle modifications will help to keep you healthy, such as stopping smoking, controlling your weight, and taking exercise. Some people may need to take drugs to control their blood pressure or dietary supplements that contain calcium and vitamin D. Oral contraceptives should be used carefully if you have Lupus.

2. Neuropsychiatric Lupus (that affecting the brain and cognition)

- **Diagnosis should be similar to that for anyone else with neuropsychiatric symptoms.******
  Lupus patients should receive the same tests as anyone else going to their doctor with neuropsychiatric symptoms. These may include a physical examination, laboratory tests and imaging such as MRI (magnetic resonance imaging).

- **Immunosuppressive drugs may be used in people with neuropsychiatric lupus.***
  If neuropsychiatric symptoms are thought to be due to inflammation in the eyes, brain or nervous system, immunosuppressive drugs can be used.

  For additional information on Neuropsychiatric Lupus, you could look at reference 1 in the list below.

3. Pregnancy

- **Women with Lupus are more at risk of developing complications during pregnancy.******
  Women with Lupus are just as fertile as those without the disease. However, pregnancy may cause your Lupus to worsen. Women with Lupus are more likely to develop a complication called pre-eclampsia during pregnancy, and should be carefully monitored until they give birth.

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- **The babies of women with Lupus may be more at risk of birth complications, and some drugs should be avoided during pregnancy.******
  Women with Lupus have a higher risk of miscarriage, stillbirth and premature birth. The babies of mothers with Lupus may also have complications with their growth and heart development.

  Some drugs for Lupus can be used during pregnancy – for example:
  - Prelone, Orapred, Predicort or Milliepred (a steroid, also called prednisolone)
  - Imuran (also called azathioprine)
  - Plaquenil (also called hydroxychloroquine).
  - Low-dose aspirin.

  Other drugs for Lupus must be avoided during pregnancy – including:
  - CellCept (also called mycophenolate mofetil)
  - Cytoxan, Endoxan, Noesar, Procytox, Revimmune or Cycloblastin (also called cyclophosphamide)
  - Trexall or Rheumatrex (also called methotrexate).

  For additional information on fertility and pregnancy in people with Lupus, you could look at reference 3 in the list below.

4. Antiphospholipid syndrome

- **Low-dose aspirin may be used to prevent antiphospholipid syndrome, which may cause blood clotting and miscarriage.*/****
  In people with Lupus and antiphospholipid syndrome, anticoagulant drugs can be used to prevent thrombosis. In pregnant women with Lupus and antiphospholipid syndrome, heparin and aspirin can be used to reduce the chances of miscarriage.

5. Lupus nephritis (affecting the kidneys)

- **Kidney tests may help to predict how well drugs will work in people with lupus nephritis.****
  Tests such as renal biopsy, urine sediment analysis, proteinuria, and kidney function may predict outcomes of therapy of lupus nephritis, but the results need to be interpreted carefully. Changes in immunological tests have a lower ability to predict the response to treatment and should be used only for additional information.

- **Drug therapy can slow the progression to end-stage kidney disease.******
  In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive drugs or CellCept (also called mycophenolate mofetil) can slow the progression to end-stage disease. Cytoxan, Endoxan, Noesar, Procytox, Revimmune or Cycloblastin (also called cyclophosphamide) also work, but can cause side effects. Some people have flares of their disease again after remission, so your doctor should monitor you carefully.

- **Dialysis or kidney transplant may be needed in some people with lupus nephritis.*****
  Dialysis and kidney transplant both work well in people with Lupus who have end-stage kidney disease, although transplantation is preferred.

  For additional information on Lupus Nephritis, you could look at references 2 and 3 in the list below.

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Summary

Overall, the recommendations say that it is important for you and your doctor to work together to monitor and manage your disease and particular symptoms, and to get the best possible results from treatment. If you have Lupus these recommendations will give you tips about what to expect from your doctor.

If you have any questions or concerns about your disease or your medication, speak to your doctor.

Other recommendations and further reading

1. Bertsias G, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010; 69(12): 2074–82. doi: 10.1136/ard.2010.130476
2. Bertsias G, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71(11): 1771–82. doi: 10.1136/annrheumdis-2012-201940
3. Andreoli L, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2016 Jul 25. doi: 10.1136/annrheumdis-2016-209770 [Epub ahead of print]

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