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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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ABSTRACT

Objective: SLE is a complex disease with variable presentations, course and prognosis. Because of the systemic nature of the disease, multiple medical specialties are involved in its care, dictating an integrated approach based on widely-accepted principles. 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.

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 approximately 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]. In the course of their disease, most patients present with arthritis, different types of rashes (sometimes scarring), serositis, cytopenias of various types, neurological symptoms, and nephritis. 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]. Evidence suggests that recommendations/guidelines may curb unwarranted variations in clinical practice and health-related costs, and could potentially improve clinical practice. The extent of the improvement depends not only upon the quality of their content, but also upon their dissemination and implementation [5].

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 [6]. In this paper, we present 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 expert committee and selection of questions

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 [6]. To this end, an expert committee was formed as a platform for these discussions, which comprised 19 specialists, 1 clinical epidemiologist (JPAI) and 1 research fellow (GB), representing 12 European countries.

Following extensive discussions, the committee voted to define the focus of the process (management – including diagnosis, treatment, monitoring – of common problems in the average adult lupus patients of any ethnic background) and the target population (all practicing physicians, not restricted to specialists). Each participant was asked to contribute independently propositions relevant to the management of SLE, to create a comprehensive list of potential topics of interest. A Delphi technique was then used to reduce these to a predefined final 12 propositions over two rounds. The selected topics included general management of SLE (5 questions), neuropsychiatric lupus (2 questions), pregnancy in lupus (1 question), anti-phospholipid syndrome (1 questions), and lupus nephritis (3 questions) (**Table 1**). The research questions were adjusted for further literature search and key index terms were derived by three of us (GB, JPAI, and DB).

Systematic literature search

A systematic search of PubMed the Cochrane library was performed, and all publications in the English language up to January 2006 were considered. For questions of etiological, diagnostic, prognostic, and therapeutic focus, the Clinical Queries' strategy (PubMed) was used as implemented by the McMaster Hedges Team with narrow, specific thresholds. For therapy, the searches were complemented with an updated comprehensive database that includes all randomized controlled trials on SLE patients (for details on search strategy, see reference 6)[7], and the Cochrane Central Trials Registry. For prognostic factors, the searches were limited further using terms that describe the outcomes and organ manifestations of interest. For co-morbidities, the etiology searches were limited further using terms that describe specific co-morbidities. For pregnancy questions, the search did not use any clinical query filters; rather, an array of pregnancy-relevant terms was used. For antiphospholipid syndrome (APS) in particular, a highly sensitive search was used in conjunction with an array of APS-relevant terms. When the searches above failed to identify any pertinent relevant study for a specific sub-question, more sensitive searches were performed using the specific terms/names of the factor / treatment / disease / co-morbidity for which no relevant studies were identified.

Literature screening and categories of evidence

Retrieved items from electronic searches were screened for eligibility based on their title, abstract and/or full content. Animal studies, narrative review articles, commentaries, conference abstracts or statements, expert opinion statements, and guidelines were excluded. For questions of prognosis, diagnosis, etiology or co-morbidities in general, studies were considered as eligible if they had studied at least 50 SLE patients. For questions of therapy, randomized studies were eligible if they had studied at least 5 SLE patients. For non-therapy questions of specific organ manifestations (e.g. nephritis, neuropsychiatric lupus) or specific problems (pregnancy, APS), studies were eligible if they had studied at least 20 SLE patients with the relevant manifestation or problem. Since the topics varied widely and the retrieved items were heterogeneous in many methodological aspects, no systematic scoring system was used. 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 (**Table 2**).

Expert opinion approach and strength of statements

The results of the literature search were summarized, aggregated and distributed to the expert committee. A set of 12 draft recommendations was prepared by two of us (GB, DB), which formed the basis for discussion during a second meeting. Following discussion, voting and adjusting the formulation, the expert committee arrived at 12 final recommendations for the management of SLE (**Table 3**). Further, the expert committee proposed topics for a Research Agenda (**Table 4**). The strength of the statements/recommendations was graded A–D by three of us (GB, JPAI, DB), and ratified by the expert committee. Each member of the committee was then asked to rate their strength of agreement for each statement on a 0–10 rating scale (10 being full agreement), based on both the research evidence presented and their own clinical expertise (**Table 5**).

RESULTS

Prognosis (Tables 3, 5)

Results of the systematic literature research

SLE can run a highly variable clinical course, ranging from a relatively benign illness to a rapidly progressive disease with fulminant organ failure and death. Determination of prognosis, both short- and long-term, together with the development of reliable indicators of active disease, disease severity and damage accrual is important. Several clinical manifestations have been associated with adverse outcome in terms of development of major organ involvement (nephritis, neuropsychiatric lupus), end-stage renal disease, and damage accrual or decreased survival.

Discoid lesions have been related to lower incidence of damage (8% vs. 21%) in one prospective study of 182 patients (mean follow-up 45 months) [8], whereas retrospective studies have also shown association of new discoid lesions with favourable outcome [9, 10] and decreased prevalence of discoid rash in neuropsychiatric vs. non-neuropsychiatric SLE (3% vs. 29%) [11]. In a prospective study of 130 patients, arthritis predicted severe neuropsychiatric lupus [12]; in contrast, retrospective studies have indicated favourable associations between arthritis and disease outcome or neuropsychiatric involvement [11, 13, 14]. In one lupus nephritis trial, serositis was more common in patients who developed doubling of serum creatinine but only in the multivariate model [15]. Other non-prospective studies enrolling >1,000 patients in total have also identified serositis as a correlate of severe disease or worse outcome in SLE [9, 13, 14, 16, 17]. In a cohort of 600 SLE patients, serositis was more common in patients with renal involvement (37% vs. 23%), and serositis was associated with renal involvement in full multivariate analysis [16].

Several prospective [17-24] and retrospective [9, 13, 14, 25-29] studies have shown that renal involvement (proteinuria, urinary casts, history of nephritis) is a predictor of adverse outcome in SLE. In a prospective study of 1,000 SLE patients, 10-year survival was lower in patients who presented with nephropathy at the beginning of the study (88% vs. 94%, p=0.045) [22]. Proteinuria also correlates with outcome and development of end-stage renal disease [30-36]. Central nervous system (CNS) disease – including psychosis or seizures – predicts future neuropsychiatric involvement [12, 20] and correlates with general outcome in SLE patients [8, 13, 14, 17, 21, 27, 28, 37]. In a cohort of 408 patients followed-up for a median of 11 years, seizures was associated with poorer overall survival (odds ratio [OR] = 1.8, $p<0.05$) [14]. In another prospective study, CNS disease was related to development of damage (OR = 8.4, 95% confidence interval [95% CI]: 2.5–26) [8].

Severe anemia (Hg <10g/dL or Ht <30%) has been associated with renal involvement (31% vs. 13%) [16], progression to end-stage renal disease [38, 39], and survival [10, 14, 19, 26, 31, 37, 40] in SLE. In the LUMINA cohort, 34 of 288 patients died within the first 5 years of follow-up, and prevalence of Ht <30% at enrollment was 12.6% in surviving compared to 41.2% in deceased patients [19].

Thrombocytopenia (defined as platelets $<100\times10^3/\mu L$ or $<150\times10^3/\mu L$ in other studies) has been associated with renal disease in the Hopkins Lupus Cohort (n=574 patients) [41], and with progression to end-stage renal disease in two retrospective cohorts (RR = 4.1 [32] and 14 [42]). Three other retrospective studies [16, 43, 44] have identified thrombocytopenia as correlate of CNS involvement although associations are lost in multivariate models. Thrombocytopenia is also mentioned as an indicator of unfavourable general outcome in SLE patients [8-10, 14, 18, 23, 28, 35, 45]. In a retrospective analysis of 532 SLE patients who were followed for 25 years, thrombocytopenia was associated with decreased survival (RR = 1.9) [10]. There is less evidence on the prognostic value of leucopenia or lymphopenia. In three retrospective studies leucopenia was related to neuropsychiatric involvement or general outcome [9, 10, 44] but favourable associations with outcome have also been reported [14].

Several immunological tests have been examined for their prognostic value in SLE patients. Serum anti-dsDNA titers – measured by the Farr assay but not by ELISA – have been correlated with nephritis in large cohorts (OR ranging 1.8–6.0) [16, 22, 46-52], progression to end-stage renal disease [27, 32, 53] (OR = 4.1; 95% CI: 1.4–12 [32]), and increased damage or poor survival [12, 35, 41, 54-56] in both prospective and retrospective studies with large number of patients. In the LUMINA cohort (n=150 patients with no damage at baseline), anti-dsDNA antibodies were borderline associated with shorter time to damage (SDI >0) (hazard ratio = 1.8; 95% CI: 1.0–3.2) in the univariate model [54].

In retrospective studies of <200 patients, high anti-C1q titers have been associated with presence of nephritis [50, 57-59], with a relative risk [RR] = 2.0 (1.4–2.9) [58]. Anti-phospholipid antibodies have also been strong predictors for damage accrual (OR ranging 1.9–2.8) [10, 49, 54, 60-62], CNS involvement (including severe neuropsychiatric manifestations) [11, 12, 16, 20, 21, 44, 63-68] (OR ranging 3.1–4.5 for any neuropsychiatric involvement/damage, 16–22 for cerebrovascular incidents), nephritis (OR ranging 2.0–2.6) [48, 69, 70], and progression to end-stage renal disease [71] (RR = 2.2; 95% CI: 1.1–4.5 in the multivariate model) in SLE cohorts.

A few studies have related anti-RNP titers with nephritis in SLE (RR ranging 2.1–4.2) [47, 48, 72, 73], although two other studies [27, 74] have demonstrated favourable associations with nephritis or outcome. Anti-Ro/SSA antibodies have been associated with photosensitivity and other skin manifestations [75-81] but there is less evidence correlating them with major organ involvement or outcome in SLE. In prospective studies of lupus nephritis patients, anti-Ro/SSA titers correlate with progression to end-stage renal disease (RR ranging 2.2–3.0 in multivariate models) [82, 83]. A single prospective study has also documented association between anti-Ro/SSA and severe neuropsychiatric involvement (OR = 2.2; 95% CI: 1.0–7.9) [12]. In one retrospective study [84], anti-Ro/SSA antibodies correlated with nephritis although two other similar studies [10, 27] have reported favourable associations between anti-Ro/SSA and outcome in SLE. There is only one retrospective study correlating anti-La/SSB antibodies with neuropsychiatric involvement in SLE (22% vs. 8%, p=0.01) [11].

Serum creatinine concentrations may be used in assessment of renal function but have also important prognostic implications for overall outcome in SLE patients. Data from several longitudinal

and retrospective studies have demonstrated associations between serum creatinine and poor outcome in SLE patients [19, 26, 31, 33-35, 37, 40, 85]. In the LUMINA cohort, prevalence of serum creatinine >2.0 mg/dL at baseline was 4% in surviving vs. 17.6% in deceased patients [19]. Serum creatinine concentrations have also been related to development of end-stage renal disease in lupus nephritis patients (OR = 2.0–3.0 per 1mg/dL increase in severe lupus nephritis) [30, 32, 36, 38, 42, 71, 82, 83, 86-89]. Low serum complement concentrations (C3 and/or C4) have been associated with renal disease (40% vs. 23%) [41, 90], end-stage renal disease (OR for low C3 = 3.0) [27, 32, 38], neuropsychiatric disease (OR = 3.5 for low C4, 3.8 for low C3) [11], and poor outcome [16, 17, 33, 35, 41, 91].

Several case-series have demonstrated correlation between brain MRI findings and neuropsychiatric damage and severity of neuropsychiatric manifestations in SLE [92-97]. The prognostic value of brain MRI has been assessed in a single prospective study where SLE patients with abnormal MRI at baseline (including focal lesions in white matter, white matter hyperintensity, increased intensity in grey matter, fluid-attenuated inversion recovery lesions, areas of infarction, intracerebral bleed, demyelination and cortical atrophy) were more prone to develop severe neuropsychiatric lupus during follow-up of a mean 7 years [12]. However, in the full multivariate model, baseline MRI was not a significant predictor of future damage, and four other studies [98-101] indicate that brain MRI has only little predictive value in SLE patients without overt neuropsychiatric manifestations.

Renal biopsy is often indicated in SLE patients with renal involvement to document the presence of nephritis and accurately classify its time and prognosis. In numerous prospective [15, 30, 54, 71, 83, 86, 102-104] and retrospective [29, 31-33, 35, 38, 42, 85, 87, 88, 105-120] studies, the findings of renal biopsy, classified according to the WHO definition or assigned with activity or chronicity scores, have been established as strong predictors of renal outcome (doubling of serum creatinine, development of end-stage renal disease, or death).

In summary, several prognostic factors of various prognostic values have emerged in SLE. However, 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 from these studies that could accurately predict the outcome. Most of these candidate predictors have strong correlation patterns and the extent of independent information provided by each one of them is typically not well known. Thus the various prognostic factors in a single patient need to be evaluated in conjunction. In general, involvement of major organs – especially if multiple – denotes a worse prognosis.

Recommendation

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 (Tables 3, 5)

Results of the systematic literature research

SLE has a chronic course that is often complicated by exacerbations and flares of varying severity. Several global and organ-specific activity indices are widely used in the evaluation of SLE patients in routine clinical practice and in the context of clinical trials [121-125]. These include British Isles Lupus Assessement Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and less commonly, Lupus Activity Index (LAI), National Institutes of Health SLE Index Score (SIS), and Systemic Lupus Activity Measure (SLAM). BILAG, ECLAM, and SLEDAI have been developed in the context of long-term observational studies and have been shown to be strong predictors of damage and mortality, and reflect change in disease activity. Moreover, they have been validated against each other [126-128]. The committee encourages the use of at least one of these indices for the monitoring of disease activity.

In one retrospective study, the number and type of skin lesions was associated with increased disease activity, as determined by measurement of SLEDAI [129]. Anemia and lymphopenia could predict future lupus flares (defined as an increase in SLEDAI by 3 points) ($p<0.01$ for both) and disease activity (SLEDAI) after a year ($p<0.001$ for anemia, $p<0.01$ for lymphopenia) in a single prospective study [130]. In a retrospective case-control study, thrombocytopenia was associated with disease severity (defined as ECLAM $\geq$4) (OR = 2.6; 95% CI: 1.1–6.0) [131].

Low serum C3 and/or C4 concentrations have been associated with increased disease severity in both prospective [89, 90, 132-138] and retrospective cohorts [50, 139, 140]. In a prospective study of 53 SLE patients, decreases in C3 and C4 were associated with a concurrent increase in renal disease activity (OR 2.2, 95%: CI 1.4–3.5, and OR 1.9, 95% CI 1.1–3.4, respectively) [133]. Decreases in C3 were also associated with concurrent decreases in the hematocrit (OR 4.6, 95% CI 1.7–12.3), platelet (OR 2.5, 95% CI 1.5–4.1), and white blood cell (OR 2.2, 95% CI 1.3–3.6) counts.

Anti-dsDNA titers also correlate with disease activity [50-52, 55, 134, 137, 141-148] and have been shown to predict future flares in a longitudinal cohorts [130, 149, 150]. In the prospective study of Ho *et al.* [149], a previous increase in anti-dsDNA levels occurred before SLE flares, as measured by the modified versions of SLEDAI ($p=0.002$) and Lupus Activity Index (LAI) ($p<0.001$) which did not include the anti-dsDNA descriptor. However, during lupus flares, including the subset of renal flares, anti-dsDNA

levels frequently decreased. Anti-C1q measurement may also be useful in monitoring SLE activity as determined by two prospective [151, 152] and a few retrospective studies [50, 51, 57-59, 153].
While these activity 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. Moreover, it is entirely unknown whether outcomes would be improved with use of one battery of indices and tests versus using another monitoring strategy. Given that several indices require familiarity and proper training in their use, physicians may wish to use the indices they are most familiar with. 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 [137, 145, 149] runs into the risk of over-treating patients although shown to prevent relapses in a RCT [154]. In these cases most experts advice closer follow-up for clinical disease activity.

Recommendation

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 (Tables 3, 5)

Results of the systematic literature research

SLE patients may be at increased risk for several co-morbidities including infections, cardiovascular disease, osteonecrosis/osteoporosis and malignancies; 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. The incidence of hospital admissions for patients with SLE followed at tertiary referall centers is 0.69 admissions per patient-year; infections (35%) and coronary artery disease (6%) are prominent reasons for hospitalization [155]. Morbidity and mortality in SLE patients remain high, with mortality rates of 5–10% at 5 yr and 15–30% at 10 yr [18, 22, 25, 37, 49, 156-158]. Patients with SLE have a nearly 5-fold increased risk of death compared with the general population [18, 156].

Several observational cohorts have identified infections in general [22, 24, 27, 49, 91, 156, 159-162] (most commonly bacterial – including M. *tuberculosis* infections [163, 164] – but also viral, fungal and protozoan) as a common cause of morbidity and mortality in SLE patients accounting for almost one third of deaths. The percentage of deaths from infections has does not seem to have decreased over recent years [22]. In retrospective studies, high anti-dsDNA titers and hypocomplementaemia have been

associated with an increased risk for death due to infection [91], and arthritis and renal disease with an increased risk for tuberculosis [165].

In a prospective study with 12-month follow-up, SLE patients had significantly more frequent urinary tract infections (especially of the lower tract) than healthy controls (OR = 7.0, 95% CI: 1.2–17) [166]. Careful titration of corticosteroids and other immunosuppressive agents to disease activity, prompt evaluation with aggressive search for infections, prophylactic use of antibiotics for patients at high risk for certain infections (such as subacute bacterial endocarditis in patients with valvular abnormalities and *Pneumocystis carinii* in patients on intense immunosuppressive treatment), immunizations similar to the general populations, and simple hygiene measures and education have been suggested. However, there are no randomized studies supporting their effectiveness in SLE patients [167]. Data may be exptrapolated cautiously from other immunosuppressed populations.

Cardiovascular disease (CVD) and atherosclerosis are a common cause of morbidity and mortality in various SLE cohorts. Analysis of the Swedish Hospital Discharge Register followed by linkage to the Cause of Death Register during the period 1964–1995 showed that SLE patients were at increased risk for death due to coronary heart disease or stroke (standardized mortality ratio [SMR] 3.0, 95% CI 2.8–3.2] [168]. The risk was substantially higher in the younger group of patients (20-39 years, SMR = 16, 95% CI 10–24). Other studies have also demonstrated that SLE patients carry an increased risk for myocardial infarction or stroke compared to the healthy population [169-171]; this risk cannot be fully explained by the traditional CVD risk factors [172, 173]. Atherosclerosis – defined as coronary-artery calcification or carotid plaque size – is also more common in SLE patients than healthy controls (e.g. 31% vs. 9%, in subjects with an average age of 40, RR = 4.7, 95% CI: 1.7–12.6) [174]), even after adjustment for possible confounding factors, and it correlates with disease activity and damage scores [174, 175].

In the general population, among cardiovascular risk factors hypertension seems to be stronger for cerebrovascular disease, while dyslpidaemia for CVD. Major CVD risk factors are more common in SLE patients. In a case-control study of 250 SLE patients and 250 healthy controls, SLE patients were at increased risk for hypertension (OR = 2.6, 95% CI 1.8–3.8) [176] and similar results have been reported elsewhere [175]. In another study SLE patients with a mean age of 36 years, hypertension was found in 24/55 (44%) patients with nephritis, compared to only 4/45 (9%) patients without nephritis [177]. Dyslipidaemia is also more common in patients with SLE [174-176, 178] and lupus nephritis [177]. There is less available data on diabetes mellitus, with a single case-control study showing increased prevalence in SLE patients, although the prevalence in the control population was spuriously low in that study (5% vs. 1%) [176].

The presence of inflammatory disorder and long-term use of corticosteroids are well-established risk factors for increased bone mass loss, osteoporosis, and osteoporosis-related fractures [179]. In two studies, bone mass density was inversely related to disease activity or damage scores [180, 181]. One study compared SLE patients, rheumatoid arthritis (RA) patients and healthy controls, and found

decreased bone mass density (lumpar spine, femoral neck, total hip) in SLE patients compared to healthy controls but similar to RA patients [182]. Rates of osteopenia (T score < –1 SD) in femoral neck was 41% in SLE patients, 22% in healthy controls, and 44% in RA patients. In another study, the frequency of self-reported fractures was increased in SLE patients compared to the general population [183]. Avascular necrosis of the hip has also been reported to be a common cause of morbidity in SLE cohorts affecting up to 13% of patients [22, 184-190], especially those who receive glucocorticoids or cytotoxic treatment and those with arthritis [191]. In a retrospective analysis of the U.S. Renal Data System, the strongest risk factor for total hip arthroplasty in dialysis patients was end-stage renal disease due to SLE, in whom avascular necrosis of the hip was the most common indication (68%) [192]. However, in a prospective study of 19 SLE patients who had not previously received glucocorticoids, none developed asymptomatic avascular necrosis of the femolar head (as detected by MRI) during the six-month follow-up [193].

Several prospective and retrospective cohort studies have indicated increased prevalence and mortality from certain neoplasms in SLE patients compared to the general adult population. The evidence is stronger for non-Hodgkin lymphomas with 3 prospective [194-196] and 3 retrospective studies [197-200] showing heterogeneous relative risks ranging between 1.5 and 44. Other malignancies that have been reported to be more common in SLE patients include lung [195, 197, 199-201], Hodgkin's lymphoma [202], soft tissue sarcomas [196], liver [197, 200], vagina/vulvar [200], cervical [194], breast [201, 203, 204], prostate [195], and skin cancer [199, 205], but evidence is more fragmented. A multisite international cohort of 9,547 SLE patients with an average follow-up of 8 years confirmed an increased risk for cancer (all types) (standardized incidence ratio [SIR] = 1.2; 95% CI: 1.1–1.3), for non-Hodgkin's lymphoma (SIR = 3.6; 95% CI: 2.6–4.9), for lung cancer (SIR = 1.4; 95% CI: 1.1–1.8), and for hepatobiliary cancer (SIR = 2.6; 95% CI: 1.3–4.8) [197]. In three studies [194, 196, 202] the relationship between cytotoxic therapy and risk for malignancy was assessed and there was no clear association.

In summary, several comorbidities have been associated with SLE, but no randomized trials exist suggesting that intensified screening for these 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.

Recommendation

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 tract 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 of non-major organ involvement (Tables 3, 5)

Results of the systematic literature research

Glucocorticoids, antimalarials, non-steroid anti-inflammatory drugs (NSAIDs), and in severe, refractory cases immunosuppressive agents (azathioprine, mycophenolate, methotrexate) are used in the treatment of SLE patients without major organ involvement. Despite their widespread use, there are few RCTs demonstrating their efficacy in uncomplicated SLE. The effectiveness of glucocorticoids has been shown in two small-sized RCTs of 46 and 10 patients [154, 206] and one [54] controlled study. In the open-label study of Bootsma *et al.* [154], patients with a rise in anti-dsDNA titers were randomized to either conventional treatment or early treatment with increased prednisone dose (30mg above the baseline dose to a maximum of 60mg/day). During a mean follow-up of 18.5 months, 20 of 24 patients in the conventional group (7 major relapses, 13 minor) and 2 (both major) of 22 patients in the early treatment group relapsed. The results from this trial should be interpreted cautiously since even increases in anti-dsDNA titers within the normal range were treated, a strategy which may have resulted in overtreatment of a significant number of patients. Thus, the committee does not endorse it but recommends closer follow-up especially for patients with a combination of decreased C3 levels and increased anti-dsDNA titers.

Antimalarials (HCQ, hydroxyl-chloroquine) have been examined for their efficacy in one 24-week randomized controlled withdrawal trial of 47 patients [207]. In this double-blind trial, patients who discontinued the drug were 2.5 times more likely to have a clinical flare (usually skin rashes, oral ulcers, arthritis, and constitutional signs and symptoms). With longer-follow-up (an additional 3 years), a non-significant trend towards reduction of major flares (defined as a need to increase prednisone by at least 10 mg/day of prednisone or institution of therapy with immunosuppressive agents) was observed supporting the clinical belief that the drug has a long-term effect in preventing major flares in SLE [208]. The rate of major flares was 50% vs. 28% in the two arms (p= 0.08). Two additional non-randomized studies have demonstrated favourable effects of HCQ on disease activity, damage accrual, and serum total cholesterol [209, 210].

In a double-blind RCT of 37 SLE patients, the patients randomized to receive methotrexate for 6 months had statistically significant reduced articular complaints, pain, cutaneous lesions, hypocomplementemia, steroid dose requirements, and disease activity (measured by SLEDAI) than the placebo group [211]. In a retrospective analysis of patients with persistently active arthritis despite previous antimalarial therapy, treatment with methotrexate significantly improved arthritis and overall disease activity [212]. The results of these two studies along with those from case-series [213, 214] indicate

beneficial effects of methotrexate on disease activity, articular and cutaneous manifestastions in SLE [215].

In SLE patients without CNS or renal involvement, azathioprine therapy has been associated with fewer hospitalizations (0.02/patient-year vs. 0.17/patient-year, $p<0.05$) but no decrease in prednisone maintenance requirement [216, 217]. Mycophenolate mofetil has also been used in the treatment of lupus without major organ involvement in few uncontrolled studies [218-222]. Non-steroid anti-inflammatory drugs (NSAIDs) are believed to be effective in treatment of musculoskeletal disorders and complaints in SLE patients, based mostly on experience for treating musculoskeletal complaints in other conditions [223]. In view of their gastrointenstinal toxicity together with concerns about the cardiovascular safety of NSAIDs [224, 225], the committee suggests that judicious use of NSAIDs may be acceptable for patients at low risk for gastrointenstinal, renal and cardiovascular toxicity. Dehydroepiandrosterone (DHEA), an adrenal hormone with androgenic properties, has been shown to modestly reduce disease activity (SLEDAI) in mild lupus in double-blind, randomized controlled trials [226-231]. However, the committee noted that its use is limited in SLE. There are no adequate data to support an increased toxicity of lupus patients compared to the general population from the regular use of acetaminophen (paracetamol).

In summary, several agents have been shown to be effective in the management of SLE patients although different outcome criteria have been used. 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.

Recommendation

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 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 (Tables 3, 5)

Results of the systematic literature research

In a double blind, intra-individual comparative study, 11 patients with SLE were photo-provoked according to a standard protocol [232]. All patients developed SLE-specific skin lesions upon photoprovocation with a combination of UVA plus UVB radiation. Each of the three sunscreens

tested prevented the development of skin lesions to various extents with one of them protecting all 11 patients.

Current evidence suggests that low-dose aspirin should be considered for all apparently healthy men and women whose 10-year risk of CVD event is 10% or greater [233]. Although no data are available in SLE specifically, the committee felt that low-dose aspirin may be considered in adult lupus patients receiving corticosteroids (as an indirect measure of a significant inflammatory burden from the disease), in those with anti-cardiolipin antibodies in moderate-to high-titers, in those with lupus anticoagulant or anti-β2 glycoprotein I antibodies, and in those with at least one traditional risk factor for atherosclerotic disease [234]. However, the use of aspirin has to be balanced with the potential risk for bleeding. In the Antithrombotic Trialists' Collaboration, which analyzed data from three trials involving 3,570 patients, the risk for a major extracranial bleeding in chronic aspirin users compared to control was 1.7 (95% CI: 0.8–3.3) for <75 mg/day, 1.5 (95% CI: 1.0–2.3) for 75–150 mg/day, and 1.4 (95% CI: 1.0–2.0) for 160–325 mg/day [235]. A meta-analysis of eight placebo-controlled trials showed significantly increased risk for gastrointestinal bleeding at 28 months in aspirin users (50–162.5 mg/day) (2.3% vs. 1.5% in placebo group) [236]. The Antithrombotic Trialists' Collaboration found an absolute excess risk for hemorrhagic stroke of 1–2 per 1,000 patients [235, 237]. The estimated excess risk for upper gastrointestinal complications in real clinical practice has been found to be around 5 extra cases per 1,000 aspirin users per year. However the excess risk varies in parallel to the underlying gastrointestinal risk and might be above 10 extra cases per 1,000 person-years in over 10% of aspirin users [237]. In a non-randomized prospective study of 41 SLE patients aged 42–69 years , regular use of low-dose aspirin has been associated with improved congnitive function as determined by higher Automated Neuropsychological Assessment Metrics (ANAM) scores [238].

In type 2 diabetes, a major risk factor for cardiovascular disease, data from the CARDS study assessing the efficacy of primary prevention, suggest that the use of statins (atorvastatin 10 mg daily in CARDS) reduces the risk of first cardiovascular events, including stroke in patients without high LDL-cholesterol [239, 240]. It is unknown whether this strategy may also be beneficial for the primary prevention of cardiovascular disease in high risk patients with lupus but without high LDL.

Considerable attention has recently been given to the metabolic syndrome, a constellation of cardiovascular risk factors that includes central obesity, dyslipidaemias, hypertension, and insulin resistance, which is an independent predictor for increased cardiovascular and diabetes risk. Preliminary data suggest that lupus patients have an increased prevalence of metabolic syndrome as compared to normal controls (32% vs 11%), associated with higher concentrations of CRP and higher ESR [241]. Data from the Diabetes Prevention Program suggest that both metformin (850 mg twice daily) or intensive lifestyle intervention designed to achieve or maintain a 7% weight reduction and 150 minutes of exercise per week, reduce the 3-year cumulative incidence of metabolic syndrome (per 100 person-years) from 61% in the placebo group to 50% in the metformin group and 38% in the lifestyle group, emphasizing the importance of lifestyle modifications [242].

With regard to protection from bone mass loss in patients receiving long-term glucocorticoid therapy, evidence on the efficacy of calcium and vitamin D comes from a single RCT of 103 patients (including 20 SLE patients) who were randomized to calcium (1000mg/day) and either calcitriol (0.5-1μg/d) plus salmon calcitonin (400 IU/day intranasally), calcitriol plus a placebo nasal spray, or double placebo for one year [243]. Calcitriol (with or without calcitonin) prevented more bone loss from the lumpar spine (mean change -0.2% and -1.3% per year, respectively) than calcium alone (-4.3% per year, p = 0.004). However, in Chinese SLE women (premenopausal) on chronic steroids, a randomized, double-blind trial of calcium and vitamin D for 2 years (n = 81 patients) did not give different results than calcium-alone or placebo [244]. In three other studies [245-247] treatment with calcium and vitamin D was not sufficient to prevent bone mass loss in SLE patients. Two studies (one RCT of 21 SLE patients [247] and one non-randomized controlled study [245]) have demonstrated beneficial effects of biphosphonates in mixed population of patients with SLE and other inflammatory diseases. Because of insufficient data on its safety, expert opinion suggests that pregnancy should be postponed for 6 months after withdrawal of biphosphonates [248].

Although estrogen use has been associated with increased risk for developing SLE (OR = 1.9; 95% CI: 1.1–3.3) [249, 250], two RCTs (n=183 and n=162 patients) have concluded that oral estrogen contraceptives do not increase the risk for flare in stable disease [251, 252]. In the former study, patients with antiphospholipid antibodies were not included. Two other double-blind RCTs (n=32 and n=351) in osteopenic post-menopausal women with SLE have shown that hormone replacement therapy (HRT) results in significantly better change in BMD compared to placebo or calcitriol, without increasing the risk for flares [253, 254]. Another RCT in 28 young hypogonadal women (i.e. amenorrhoeic for >2 years due to proven ovarian failure) with SLE on chronic steroid treatment, has also demonstrated beneficial effects of estrogen replacement therapy on BMD without significant changes in disease activity [246]. Nonetheless, 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. The overall risk-benefit ratio for HRT in post-menopausal women is currently not favorable on average, and decisions need to be individualized.

Despite the lack of SLE-specific literature on the benefits of smoking cessation, patients should be advised against smoking considering the high risks of malignant and vascular disease conferred by smoking. Moreover, there are reported associations between tobacco use and risk for discoid lupus erythematosus [255, 256], SLE [257-259], thrombotic incidents [260], high anti-dsDNA titers [261] or increased disease activity [262]. Similarly, weight control and physical exercise are recommended, especially for SLE patients with increased CVD risk. Statins and anti-hypertensives (ACE-inhibitors) have not been tested for their efficacy in SLE studies but should be considered in selected patients based on non-SLE-specific recommendations.

Recommendation

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.

Diagnosis of neuropsychiatric lupus (Tables 3, 5)

Results of the systematic literature research

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 available for SLE patients presenting with neuropsychiatric manifestations. However, their diagnostic ability to differentiate SLE- from non-SLE-related neuropsychiatric involvement has not been adequately established. Moreover, only a few studies have actually focused on their ability in differentiating primary from secondary neuropsychiatric lupus. Current imaging techniques do not adequately discriminate between immune mediated demyelination as a result of immune-mediated injury to myelin, and demyelination as a result of ischemic injury within the CNS.

A recent meta-analysis of epidemiological studies found no association between headache (any type) and neuropsychiatric SLE [263]. NPSLE patients were found to have higher anxiety and depression scores compared to SLE patients without overt neuropsychiatric manifestations [264]. One prospective [265] and two retrospective [264, 266] cohort studies have also demonstrated increased frequency of cognitive impairment in NPSLE patients compared to non-NPSLE. NPSLE patients also tend to have poorer performance in memory and other neuropsychological tests [264, 267, 268].

Cererbrospinal fluid (CSF) analysis is a time-honoured examination in the evaluation of patients presenting with neurophychiatric manifestations and its primary use is to exclude non-SLE-related conditions especially infections and cerebral bleeding. In a prospective cohort of SLE patients presenting with neuropsychiatric disease, >90% of patients with diffuse or complex manifestations had abnormal results in the CSF analysis compared to approximately 10% in patients with focal presentation or non-NPSLE patients with similar neuropsychiatric symptoms [269]. Approximately 60% of patients with diffuse or complex manifestations had abnormal oligoclonal bands compared to 10% in patients with focal manifestations. CSF tests showed pleocytosis in 9/50 (18%) NPSLE patients vs. 2/13 (15%) non-NPSLE patients; an elevated CSF protein was found in 16/50 (32%) NPSLE vs. 4/13

(31%) non-NPSLE patients. Other studies have measured the intrathecal levels of additional biomarkers such as cytokines, autoantibodies with reactivity against neurons or their receptors, matrix metalloproteinases, and markers of neuronal and astrocytic damage [270-272] but their utility in routine clinical practice remains to be shown.

In a retrospective cohort of 60 SLE patients with epileptic seizures, all seven patients who presented recurrent epileptic seizures had interictal epileptic abnormalities on electroencephalograph (EEG) [20]. However, EEG could not differentiate primary from secondary neuropsychiatric lupus in a prospective study of patients presenting with neuropsychiatric manifestations [269]. The discriminating ability of quantitative EEG (qEEG) was evaluated in a prospective study of 52 SLE patients, including patients with objective evidence of NPSLE, patients with neuropsychiatric symptoms, patients with no evidence of NPSLE, and patients with a prior history of NPSLE [273]. qEEG results were abnormal in 74% of the SLE patients with neuropsychiatric symptoms and in 28% of the patients with no evidence of active NPSLE.

Although anti-P antibodies are commonly encountered in SLE patients with active/severe CNS involvement [147, 269, 274-277], an international meta-analysis of 1,537 patients has demonstrated very limited diagnostic utility for NPSLE [278]. Anti-phospholipid antibodies have been associated with focal NPSLE in a small (n=52 patients) prospective study [269]. In retrospective studies, associations between anti-phospholipid titers and seizures in SLE patients have been reported [66, 67, 279]. Yet, two other studies found no association between antiphospholipid antibodies and neuropsychiatric manifestations [280, 281].

Brain CT indentifies abnormal changes in 30−60% of NPSLE patients but may be useful in the acute setting for detection of large infarcts, intracerebral haemorrhage, massive edema, and exclusion of brain abscess, meningitis, and mass lesions [269, 273, 282-288]. Conventional cranial magnetic resonance imaging (MRI) has been shown to be neither sensitive nor specific in the diagnosis of NPSLE, with estimates of sensitivity being 30−40%, and chronic lesions being present in 25−50% of patients without active NPSLE [20, 93-95, 98-100, 269, 282, 288-291]. Nevertheless, its sensitivity increases for detection of large infarcts and brain hemorrhage, and is more likely to show abnormalities in patients with focal – rather than diffuse – deficits, seizures, and antiphospholipid syndrome. Moreover, neither CT nor MRI can easily distinguish small vessel vasculitis from multiple small vessel thrombosis. Position emission tomography (PET) scan appears to be sensitive in detecting metabolism and perfusion abnormalities in virtually all patients with overt or subclinical CNS involvement, and has been claimed to correlate with disease course, but evidence comes from small studies of 41 patients [291, 292]. Moreover, it lacks specificity and generalized neuronal cell loss, decreased neuronal density, and focal lesions may also result in hypometabolism and reduced perfusion, and therefore, abnormal PET scan results. Importantly, in interpretation of the results a parallel anatomic imaging (MRI or CT) is necessary to exclude any obvious focal lesion. In view of these considerations and due to limited availability and excessive cost, PET is still of limited value in routine practice.

Other imaging techniques such as SPECT (single photon emission computed tomography), MTI (magnetization transfer imaging), DWI (diffusion-weighted imaging), and MRS (magnetic resonance spectroscopy) have also been used in evaluation of SLE patients with neuropsychiatric manifestations. SPECT can identify brain abnormalities in up to 88% of patients with overt CNS involvement especially when used in conjunction with MRI [293-296]. In a prospective study of 20 SLE patients (10 with NPSLE, 10 without clinical neuropsychiatric involvement) and 9 healthy controls, SPECT perfusion defects were present in 8/10 NPSLE patients, 1/10 non-NPSLE patients, and 0/10 healthy controls [297]. SPECT also correlates with disease activity and cumulative damage (SLICC) in SLE [298], and clinical improvement in treatment of NPSLE with methylprednisolone pulse therapy [299]. Several studies, however, have argued that SPECT lacks specificity adding only little diagnostic information in the evaluation of neuropsychiatric lupus [97, 280, 287, 300]. MTI measures normalized for intracranial volume, reflecting abnormalities of the brain parenchyma as well as atrophy have been found to be lower in NPSLE patients than in non-NPSLE patients and healthy controls [301-304]. Quantitative volumetric estimates of global brain damage based on MTI and a measure of global brain atrophy have also been correlated with neurological, psychiatric, and congnitive functioning in NPSLE patients [305]. DWI [303, 306, 307], MRS [303, 308-314], and T2 relaxation time measurements [303, 315] have also been studied and seem to add diagnostic information in SLE patients with neuropsychiatric involvement but their clinical utility has not been established yet.

In summary, 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. Based on current evidence, the diagnostic evaluation should be similar to what the evaluation would be in patients without SLE who exhibit the same neuropsychiatric manifestations.

Recommendation

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 of severe, inflammatory neuropsychiatric lupus (Tables 3, 5)

Results of the systematic literature research

In general, 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]. Distinction of the pathogenic processes involved, while of outmost importance for therapeutic purposes, may not be always feasible; in these cases patients are treated with a combination of immunosuppressive therapy and anticoagulation if there is no contraindication.

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 [316]. 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 (defined as at least 20% improvement from basal conditions on clinical, laboratory, or specific neurological testing variables). Beneficial effects of CY in treatment of severe NPSLE have also been suggested in non-randomized controlled studies [317, 318] and case-series [319-325]. Collectively, these data indicate that patients presenting with severe inflammatory neuropsychiatric lupus (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from therapy with CY.

Recommendation

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 (Tables 3, 5)

Results of the systematic literature research

Occurrence of pregnancy in SLE patients is not uncommon since the disease affects women of childbearing age and advances in therapy have resulted in decreased morbidity and increased time of well being. 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 [326-328].

A cross-sectional survey conducted by the Endometriosis Association (USA) in 3680 women with surgically diagnosed endometriosis, which may impact on fertility, showed increased prevalence of SLE compared to the general population (0.8% vs. 0.04%, p<0.001) [329]. The efficacy and safety of ovarian induction and fertilization (OI/IVF) has been studied in a retrospective cohort of 19 SLE patients who underwent 68 cycles OI/IVF [330]. Five of 16 cycles (31%) in 7 SLE patients, and 5 of 48

cycles (10%) in 10 primary APS patients resulted in liveborn children. Four OI/IVF cycles (25%) resulted in increased lupus activity and 2 (13%) in ovarian hyperstimulation syndrome. Seven of 14 living children (50%) were premature, 3 had neonatal lupus, 1 had pulmonic stenosis, and 5 surviving infants (38%) had complications unrelated to prematurity.

A meta-analysis of epidemiological studies that were published during 1980-1992 [331] and subsequent controlled [332-339] and uncontrolled studies [340-344] have indicated that pregnancy may increase lupus disease activity and cause flares (reported frequency of flares ranging 13-74%) but these flares are usually (33-88%) mild-to-moderate, involving mostly skin, joints, and blood.

Lupus may affect the outcome of pregnancy. Lupus nephritis has been identified as a risk factor for hypertensive complications and pre-eclampsia [333, 337, 345-347]. In a prospective study of SLE pregnancies, patients with pre-existing lupus nephritis developed more frequently hypertension (50% vs. 12%) than those without nephritis [337]. Presence of anti-phospholipid antibodies is also associated with increased risk for pre-eclampsia during pregnancy [160, 348-352], and the relative risk was estimated to be 17 (95% CI, 1.3-258) in a study of 121 Chinese patients [353].

SLE patients are also at risk for various adverse pregnancy outcomes, including miscarriage, stillbirth, and premature delivery (RR ranging 2.2-5.8) [344, 352, 354-356]. This risk may be even higher for patients with anti-phospholipid antibodies as suggested by several prospective and retrospective studies [65, 70, 338, 340, 342, 353, 355, 357-371], with relative risks ranging 1.4−12.3 depending on the adverse outcome studied.

Patients with active nephritis carry also increased risk for adverse pregnancy outcomes although evidence comes from fewer studies [332, 372-374]. In a retrospective analysis of 70 pregnancies in 48 women with lupus nephritis, prevalence of fetal loss was 52% in active nephritis compared to 11% in cases of complete remission [373, 375]. A single retrospective study in black women with SLE has demonstrated that anti-Ro positivity is associated with fetal wastage syndrome (71% vs. 18% in anti-RNP positive women) [376].

SLE pregnancies are accompanied by increased rates (12-35%) of intra-uterine growth restriction [333, 337, 338, 341, 344, 352], with a relative risk of 8.6 (95% CI, 3.0-24) determined in a retrospective case-control study [355]. Anti-phospholipid antibodies [365, 377, 378] and nephritis are also associated with low birth weight and intra-uterine growth restriction. Fetal heart block (formerly known as congenital heart block) is another complication of SLE pregnancies (2–4.5%) [341, 379-381], and it is linked to the presence of anti-Ro/SSA [380-386] or anti-La/SSB [380, 382, 384, 387] autoantibodies. A prospective study of 100 anti-Ro/SSA positive women (53 SLE patients) identified two cases of fetal heart block in the first 100 pregnancies (2%, 95% CI: 0.2-7%) [379].

There is only little evidence regarding therapy of SLE during pregnancy. Prednisolone and other non-fluorinated glucocorticoids, and azathioprine have been used in lupus pregnancy [332, 342, 346, 374, 388, 389] but their efficacy and safety has not been demonstrated in randomized trials. Low-dose aspirin has been used in SLE pregnancy [374]. Evidence is stronger for hydroxychloroquine and its

efficacy and safety has been evaluated in one RCT [390], three non-randomized studies (one prospective [391], two retrospective [353, 392]), and several case series [332, 346, 374, 388, 393, 394]. It should be noted that 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; this is because often the risk assessment is based on animal data and are not updated as data in humans accumulate [248]. There is no evidence to support the use of mycophenolate mofetil or CY, and methotrexate and these agents must be avoided during pregnancy [395, 396]. Also, although cyclosporine A has been used in pregnancy [397-401], its safety has not been established.

Recommendation

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.

Antiphospholipid syndrome in lupus (Tables 3, 5)

Results of the systematic literature research

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 secondary prevention of thrombosis in (non-pregnant) SLE patients with history of anti-phospholipid antibodies and thrombosis has been established in several retrospective controlled studies [402-407]. The intensity of

anticoagulation, however, has been a matter of debate. Two RCTs of 114 and 109 patients with APS (both primary and SLE-related)[408, 409] have demonstrated no superiority of high-intensity warfarin (target INR 3.1−4.0) over moderate-intensity warfarin (target INR 2.0−3.0) for secondary prevention, and increased risk for minor bleeding incidents in the high-intensity arm (27.8% vs. 10.9%, hazard ratio [HR] 2.9, 95% CI: 1.1−7.5 [409]). 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, and it carries a risk for major bleeding episode that is similar to that of lower intensity anticoagulation [402-406]. There are no RCTs to assess the prevention of recurrence of arterial thrombosis in SLE patients with anti-phospholipid antibodies. Based on these findings, 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 [410] concluded that combined unfractionated heparin and aspirin may reduce the risk for pregnancy loss (RR 0.46, 95% CI: 0.29−0.71). The combination of low molecular weight heparin and aspirin also seems to be effective, although the results did not reach statistical significance (RR 0.78, 95% CI: 0.39−1.57). These results are based on findings from four RCTs [411-413], three prospective [388, 414, 415], and four retrospective controlled studies [351, 403, 416, 417] in lupus pregnancies complicated with antiphospholipid antibodies or APS and previous history of pregnancy loss or thrombosis. 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 anticoagulation for the prevention of APS-related thrombosis during pregancy.

Recommendation

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: diagnosis and monitoring (Tables 3, 5)

Results of the systematic literature research

Nephritis is a common manifestation of SLE and a major cause of morbidity. In patients with suspected lupus nephritis, renal biopsy may be used to confirm the diagnosis, evaluate disease activity (and thus reversibility) and chronicity/damage (and thus irreversibility), and determine prognosis and appropriate therapy. It is not uncommon (10–20%) to find pathologic evidence of substantial nephritis in patients with low-grade laboratory abnormalities. The predictive value of second renal biopsy (i.e. after treatment initiation) has been assessed in one prospective [102] and a few retrospective studies [106, 111, 112, 418, 419]. It was found that some pathology findings (chronicity index, mesangial/endothelial deposits, cresents, karyorhexis/fibrinoid necrosis, immune deposits, interstitial inflammation, glomerulosclerosis, and interstitial volume density) were associated with clinical response and outcome in lupus nephritis. In a retrospective analysis of renal biopsies and clinical data from 71 SLE patients who had an initial renal biopsy and a systematic second biopsy at 6 months after induction treatment, a composite index of second biopsy inflammation predicted in Cox proportional hazard models renal relapse (HR = 1.38), doubling of serum creatinine (HR = 1.84), and end-stage renal disease (HR = 1.65) [112]. Nevertheless, repeat renal biopsies pose a risk to the patient and may not be feasible for all patients. There is some evidence [420] to support the predictive ability of urine sediment analysis in monitoring lupus nephritis therapy. In a prospective study of 17 SLE patients with diffuse proliferative glomerulonephritis who were followed-up for 1,129 patient-months, red blood cell and or white blood cell casts had a sensitivity of 81% to predict future renal relapse (35 of the 43 relapses), with a median interval between appearance of casts and onset of relapse of 8 weeks [421]. However, central or community-based laboratories may not be reliable in identifying cellular casts [422].

Results from several prospective and retrospective studies and trials indicate that improvement in proteinuria [83, 89, 136, 141, 423-427] correlates with favourable outcome in therapy of lupus nephritis. In the context of a lupus nephritis trial (n=85 patients), reduction of 24-hour urinary protein to <1g at 6 months had a positive predictive value of 87% for good long-term (>5 years) outcome (defined as normal serum creatinine at last follow-up) [426].

Reduction in serum creatinine also correlates with better outcome in treatment of lupus nephritis [82, 83, 88, 89, 106, 426-428]. Analysis of data from the Lupus Nephritis Collaborative Study (n = 86 patients) showed that of 27 patients with persistently elevated serum creatinine at 6 months, 8 (30%) had subsequent renal failure, compared with none of the 14 patients with resolution of serum creatinine elevations [427]. Also, data from the long-term follow-up (median 73 months) of 85 patients participating in the Euro-Lupus Nephritis Trial indicated that decreased serum creatinine at 6 months after treatment initiation compared to baseline levels, is associated with increased risk for good long-term outcome (likelihood ratio 11, 95% CI: 2.7−42) [426].

In univariate analyses, changes in anti-dsDNA titers [89, 141, 425] and serum C3 concentrations [141, 425] have been shown to correlate with renal flares and outcome. Also, low serum C4 concentrations (<11 mg/dL) at the time of response are associated with increased risk for renal flares (likelihood ratio

14, 95% CI: 4.7−43) but not for development of end-stage renal disease [89, 429]. In one of the earliest lupus nephritis trials, patients (n=6) who relapsed after 6 months of treatment demonstrated increase in proteinuria, reduction in creatinine clearance, re-appearance of hematuria and fluctuations in serum DNA binding [430]. It should be emphasized, however, that the previously cited 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.

Recommendation

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.

Lupus nephritis: treatment (Tables 3, 5)

Results of the systematic literature research

To date, most experts agree - although the data to support this concept are lacking at present - that the treatment of lupus nephritis (LN) consists of a period of intensive immunosuppressive therapy (*induction therapy*) followed by a longer period of less intensive *maintenance therapy*. Despite numerous therapeutic trials in lupus nephritis, opinions regarding optimal therapy vary widely. Unfortunately, most studies – even those that are prospective and controlled – are plagued by "generic" problems, which include small number of patients, diverse racial and socio-economic backgrounds, heterogeneous inclusion criteria, and most importantly, short follow-up. Studies from the National Institutes of Health have shown the importance of duration of follow-up in accurately assessing the efficacy of a given treatment regimen with important differences in hard-renal outcomes such as end-stage renal disease requiring at least 5 years of follow-up before they become apparent [431]. The committee decided to use working definitions for the length of follow-up for the various studies examined as follows: short-term (up to 2 years); medium-term (up to 5 years); long-term (over 5 years). Short-term studies are best to depict the effectiveness of various regimens as induction therapies while medium-term can access both induction and maintenance regimens. Risk stratification of the severity of nephritis according to clinical, demographic, laboratory and histologic features is essential for the choice of optimal therapy [432].

Several RCTs [425, 426, 428, 430, 431, 433-438] have been conducted in proliferative nephritis patients and their results are summarized in a recent Cochrane Review [439, 440]. Cyclophosphamide plus steroids reduced the risk for doubling of serum creatinine level (4 RCTs, 228 patients, RR = 0.6; 95% CI: 0.4–

0.9) compared with steroids alone, but had no impact on overall mortality (5 RCTs, 226 patients, RR = 1.0; 95% CI: 0.5–1.8). Azathioprine plus steroids reduced the risk for all-cause mortality compared with steroids alone (3 RCTs, 78 patients, RR = 0.6; 95% CI: 0.4–1.0), but had no effect on renal outcomes. In these studies CY was found to be superior to azathioprine and/or corticosteroids with high-dose, intermittent administration of CY (pulse therapy) demonstrating a more favourable efficacy to toxicity ratio than long-term oral CY [431]. In a recent trial, 87 patients with proliferative lupus nephritis were randomized to either CY (750 mg/m^2, 13 pulses in 2 years) combined with oral prednisone or to azathioprine (2 mg/kg/day in 2 years) combined with intravenous pulses of methylprednisolone (3 x 3 pulses of 1000 mg) and oral prednisone. After a median follow-up of 5.7 years, doubling of serum creatinine was more frequent in the azathioprine group compared to the CY group (RR 4.1; 95% CI: 0.8–20) [441]. Relapses occurred more often in the azathioprine group (RR = 8.8; 95% CI: 1.5–32). Overall, studies employing i.v. CY demonstrate high rates of efficacy with over 70% of the patients responding to therapy and/or achieving remission. The committee felt that daily oral CY may be used for short-periods of time (usually 3–6 months) to induce remission, in the rare cases that administration of pulse CY is not feasible. Administration of daily, oral CY for longer periods of time should be discouraged.

In a long-term follow-up (median 11 years) of a RCT in 82 SLE patients with proliferative nephritis, combination therapy with glucocorticoids and CY demonstrated efficacy (83% preserved renal function), without substantially increasing the risk for adverse effects [437]. Among those who completed the protocol (n=65), the proportion of patients who had doubling of serum creatinine concentration was significantly lower in the combination group than in the CY group (RR = 0.1; 95% CI: 0.0–0.8) [437]. Similarly, an extended follow-up (mean 10 years) of 86 patients who participated in a controlled trial of high-dose prednisone plus oral CY alone or with plasmapheresis for treatment of severe lupus nephritis, showed that in the remission group renal survival rate was 94% at 10 years [82]. Recent studies continue to provide evidence of efficacy of several dosing regimens, including daily oral, intermittent low and high-dose pulses of i.v. CY alone or in combination with pulse i.v. MP [436, 442]. Although high-dose, intermittent administration of CY (pulse therapy) has significantly reduced the toxicity of cyclophospamide, premature ovarian failure and infections remain a considerable problem. Ovarian failure after CY therapy is both dose- and age-dependent [433]. To reduce morbidity from CY treatment gonadal protection and less intensive regimens of CY have been advocated. Preliminary data suggest that gonadal protection from CY may be feasible, a finding requiring further confirmation. In a non-randomized trial [443], the use of depot leuprolide acetate, a synthetic GnRH-analogue, significantly decreased rates of gonadal failure (30% vs 5%) in young women with severe SLE treated with CY (N= 20 in both groups). Moreover, for Caucasian patients with proliferative disease, sequential therapy with a short course of i.v. CY followed by azathioprine to decrease the cumulative dose of CY, has been found to be effective [436].

Mycophenolate mofetil (MMF) is an immunosuppressive agent used in solid organ transplantation that has been evaluated in five short- to medium-term RCTs [423, 444-447] and has demonstrated at least similar efficacy and more favorable toxicity profile compared to pulse CY for both induction and maintenance. The efficacy of MMF as induction therapy in lupus nephritis has been assessed in 4 RCTs including a total of 268 patients (42% Asian, 30% African American) and concluded that MMF was associated with reduced risk for treatment failure (RR = 0.7; 95% CI: 0.5–0.9) and reduced risk for the composite end point of death or end-stage renal disease (RR = 0.4; 95% CI: 0.2–0.9) compared to CY [423, 445-447]. Amenorrhea occurred more frequently in CY-treated patients. The usefulness of MMF as a maintenance agent in proliferative lupus nephritis has been assessed in a 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 [444]. The patient survival was higher among patients in the AZA group than those in the CY group (p=0.02), and the cumulative rate of renal survival was similar among the three groups (74% in the CY, 80% in the AZA, 95% in the MMF group). The event-freee survival rate for the composite end point of death or chronic renal failure was higher in the AZA and MMF groups that in the CY group (p = 0.009 and p = 0.05, respectively). As for the adverse effects of therapy, the cumulative probability that hospitalization would not be required was lower in the CY group than the AZA group (p = 0.03) or the MMF group (p = 0.007). There was a significantly higher incidence of sustained amenorrhea in the CY group (32%) than in the MMF (6%) or the AZA (8%) group (p = 0.03 for both).

Additional, long-term trials involving more representative patient populations and harder outcomes such as rates of doubling of serum creatinine are needed to further substantiate superiority over CY, especially for patients with the more severe forms of the disease. While waiting for these studies, 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 [448]) should evoke discussions for intensification of therapy. For maintenance therapy the committee recomends the use of MMF for patients unable to tolerate azathioprine or who flare while on treatment with this drug. Moreover, 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 [437]. 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 [449-457]. In the absence of RCTs, the committee recommends this therapy for selected patients with disease refractory to standard therapy with CY and/or MMF.

Modern immunosuppressive therapies are effective but none of them cures lupus with approximately one third of them flaring after remission. Although not all flares are severe, they pose a significant problem because of the risk of deterioration of renal function due to cumulative damage as well as the additional immunosuppressive therapy that may result in additional toxicity [458]. In general,

initial management of moderate to severe flare requires induction therapy with immunosuppressive agents, which usually prevent the loss of renal function [458, 459].

Membranous lupus nephritis represents about 20% of clinically significant renal disease in lupus. Natural history studies suggest a relatively low rate (<10%) of progression to end-stage renal disease but a high rate of significant co-morbidities. Patients with membranous lupus nephropathy are usually treated early with angiotensin antagonists to minimize proteinuria, together with lifestyle changes and appropriate drugs to reduce attendant cardiovascular risk factors. The paucity of data derived from randomized controlled trials makes it difficult to establish solid recommendations [460]. In patients with protracted nephrotic syndrome, consideration should be given to immunosuppressive therapies, including corticosteroids, cyclosporine, azathioprine, mycophenolate and CY [460, 461].

Recommendation

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 (Tables 3, 5)

Results of the systematic literature research

Despite recent advances in therapy of lupus nephritis, a number of patients may eventually progress to end-stage renal disease and will require dialysis treatment or even kidney transplantation. One meta-analysis of epidemiological studies conducted up to 1995 [462] and several retrospective controlled studies have indicated that both dialysis [463, 464] and transplantation [465-472] in SLE have comparable rates for long-term patient or graft survival as those in non-diabetic/non-SLE patients. However, in a retrospective cohort of 26 Chinese SLE patients with end-stage renal disease who started dialysis, survival rates were poorer than those in non-SLE patients (73 and 38% vs. 95 and 88%, at 5 and 10 years, respectively) [473]. Also, in a cohort of 97 SLE patients who underwent renal transplantation, renal allograft loss rates were twice as much as those in matched controls [474]. The presence of anti-phospholipid antibodies is associated with increased risk for thrombotic events, graft loss, and poor transplantation outcome [407, 471, 475-477]. In a retrospective study of 33 adults with lupus nephritis who received 35 kidney allografts and were followed-up for a mean 91 months, 6/7 (86%) anti-phospholipid-positive patients vs. 3/17 (18%) anti-phospholipid-negative patients experienced

thrombotic events (p = 0.015). 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 end-stage renal disease, 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) [478, 479]. There is also a single retrospective study in SLE patients with end-stage renal disease which showed a statistically significant greater incidence of lupus activity after dialysis but not after renal transplantation [480].

Recommendation

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.

DISCUSSION

We have scrutinized over 8,000 articles to create the evidence-base for these recommendations. 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, Table 5). 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. It is important to emphasize that these statements and recommendations are not “rules” or “recipes”, but they merely represent a “checklist” to serve as reminders to the physicians at different stages during the management of their patients.

This is the first attempt to develop comprehensive management guidelines in SLE. Given the remarkable heterogeneity of the disease, it is probably unrealistic to expect that management recommendations could cover all aspects of disease for each individual patient. The selection of the items by the experts reflects the major challenges in the care of SLE today. The committee elected not to dwell on other important issues such as SLE diagnostic criteria (e.g. the potential usefulness of the ACR classification criteria for diagnosing SLE especially at early stages, and the overrepresentation of the mucocutaneus manifestations in the ACR classification criteria) or the detailed management of cutaneous lupus (a significant issue for most patients especially those with mild to moderate lupus). These issues will be addressed in future sessions with the inclusion of experts from other fields.

The methods used to develop the recommendations were based on the standardized operating procedures published by EULAR, developed to assist comparability among studies on the management of musculoskeletal diseases according modified to best fit the needs of our project. We used a standardized hierarchical approach to grade the evidence. We did not consider very small studies, especially for questions where much larger-scale evidence of good quality was available. We should caution however that reported study design is not a perfect surrogate of the quality of any study. The same applies to sample size: larger studies are not necessarily better than smaller ones. We therefore tried also to appraise specific issues about the strengths and weaknesses of particular studies.

It is of interest that-in spite of the large volume of publications, only a few randomized controlled trials have been performed to establish optimal management of SLE. Lupus nephritis is a notable exception to this, but even for nephritis, trials have been generally of small sample size. Important issues in the management of SLE such as the role of low-dose aspirin in primary prevention of thrombotic events or pregnancy loss in SLE patients with anti-phospholipid antibodies have not been adequately addressed. Furthermore, there are no randomized controlled trials to evaluate the effectiveness (or lack of) of lifestyle modifications and/or primary prevention interventions (aspirin, protection from bone-loss, statins, and antihypertensives) 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 4).

Establishing a diagnosis and managing patients with SLE requires an integration of a patient's symptoms, physical examination findings, and the results of diagnostic testing on which occasionally some clinicians tend to rely heavily upon. Laboratory testing is important in the care of the patients but uncritical use of any test may result in misleading information and unnecessary costs. In the case of lupus, there are additional management issues with important safety and financial implications that they have not been addressed. To cite a few, the validity of renal biopsy, urinary sediment analysis, proteinuria, and immunological tests as surrogate markers in treatment of lupus nephritis have not been established. Establishing truly surrogate markers should facilitate monitoring of the patients and testing of new agents in a timely fashion. Moreover, none of them has been tested in randomized trials to document that their measurement alters patient management and outcome. Obviously there is a need to determine which laboratory or immunological 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. To this end, the committee recommends examination and laboratory monitoring every 3 months, in patients who are doing well and more frequently for those with uncontrolled disease.

Because of the low prevalence of the disease, most general adult physicians do not have sufficient experience in its management. Nevertheless, the role of general primary care physicians and general internists is of paramount importance in early diagnosis, appropriate referral monitoring patients with mild, stable disease, and in collaborating with the specialist in the management of severe disease. Expert-based guidelines for the initial evaluation, reasons for referral and management of mild and severe SLE have already been published [482]. Our recommendations should further facilitate interactions between generalists and specialists.

Approximately 15-20% of all cases of SLE are diagnosed in childhood [483]. Pediatric SLE may differ from adult SLE, in disease expression, physiologic, developmental and psychosocial issues. Because of paucity of data in pediatric SLE, little is known about its epidemiology, long-term outcome, and optimal management [484]. These recommendations could serve as a framework for the management of pediatric and adolescence SLE until the development of specific guidelines based on evidence for this age group that take into account the special needs of this population. Similarly, management decisions in geriatric patients with SLE will have to take into consideration changes in the physiology associated with ageing, the usually lower disease activity and the increased frequency in co-morbid conditions [485].

SLE is a challenging disease both for the patients and their families. Newly diagnosed patients have anxieties for a potentially fatal chronic illness with unpredictable flares, and the potential disability. At the same time, the majority of patients have a more benign course. The committee recognized the potential unnecessary anxiety that the historic name “lupus” may evoke to

patients and their families who tend to associate it with the worst forms of the disease. To this end, the committee reiterated the importance of education and psychological support to the patient and the family, and discussed the pros and cons to a potential change of the name to one that more accurately depicts the nature of the disease.

Clinical practice recommendations like this require a framework to assess their quality, assure that potential biases have been adequately addressed and that are both internally and externally valid, and that are feasible for practice. To this end we used as a framework the Appraisal of Guidelines Research and Evaluation (AGREE) instrument [481], 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. In view of the lack of paucity of strong data for several management issues in lupus, 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. Moreover we plan for the future to a) include more individuals from other relevant professional groups including patients; b) further expand the external review process; and c) discuss the development of tools that will facilitate the dissemination and application of the recommendations.

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TABLES

Table 1. Selected research questions for literature search

GENERAL MANAGEMENT
Prognosis
What are the prognostic implications of clinical, laboratory, imaging, and pathology tests, for the outcome of SLE in general and specific major organ manifestations (nephritis, CNS lupus)?
Monitoring
What is the diagnostic ability of clinical signs and symptoms and laboratory tests for monitoring lupus activity and flares?
Co-morbidities
Are SLE patients at higher risk for certain comorbidities (malignancies, infections, atherosclerosis, hypertension, dyslipidaemia, diabetes, osteroporosis, avascular necrosis)?
Treatment
What are the relative benefits and harms of treatment of SLE patients (antimalarials, glucocorticoids, immunosuppressants) with and without major organ involvement?
Adjunct therapy
What other treatment (vitamin D, calcium, biphosphonates, antihypertensives, statins, NSAIDs, aspirin), lifestyle modifications (photoprotection, smoking cessation, estrogen), and preventive measures (screening for comorbidities) are particularly indicated in lupus patients, including lupus nehpritis?
NEUROPSYCHIATRIC LUPUS
Diagnosis
What is the diagnostic discriminating ability of clinical, laboratory, neuropsychological testing and imaging tests, in SLE patients with neuropsychiatric manifestations?
Treatment
Which of the neuropsychiatric features need to be treated with cytotoxic therapy, including high-dose glucocorticoids?
PREGNANCY IN LUPUS
Does SLE affect pregnancy and vice versa? Are SLE patients normally fertile? Is pregnancy harmful to lupus? Is SLE harmful to the baby? Which medications can be used in lupus pregnancy?
ANTI-PHOSPHOLIPID SYNDROME
In SLE patients with anti-phospholipid antibodies what are the relative benefits and harms of primary and secondary prevention regimens (for asymptomatic patients, pregnancy loss, arterial thrombosis, venous thrombosis)?
LUPUS NEPHRITIS
Monitoring
How good are renal biopsy, proteinuria, kidney function, and immunological tests as surrogate markers in therapy of lupus nephritis?
Treatment
What are the relative benefits and harms of different regimens for induction, maintenance, and treatment resistance in lupus nephritis (proliferative, membranous)?
End-stage renal disease
What is the optimal management for end-stage renal disease in lupus (dialysis, immunosuppressants, transplantation/timing, anti-coagulation)?

Table 2. Category of evidence and strength of statements rating scales

Category of evidence		Strength of statements	
1	Meta-analysis of randomized controlled trials	A	Based on category 1 or 2 evidence without concerns for the validity of the evidence
2	Randomized controlled trials	B	Based on category 1 or 2 evidence but with concerns about the validity of the evidence; or category 3 or 4 evidence without major concerns about the validity of the evidence
3	Meta-analysis of epidemiological studies		
4	Prospective controlled or quasi-experimental cohort (non-randomized) studies	C	Based on category 5 or 6 evidence without major concerns about the validity of the evidence
5	Non-prospective controlled trials: case-control, cross-sectional or retrospective cohort studies	D	Based on category 3-6 evidence with major concerns about the validity of the evidence; or no data (expert opinion)
6	Uncontrolled studies		

Table 3. 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 4. 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

Table 5. 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	21	1	A	9.3

immunosuppressants are effective against ESRD				
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.