

REVIEW

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Systemic lupus erythematosus and thrombosis

Mario Bazzan*, Antonella Vaccarino and Fabio Marletto

Abstract

Systemic Lupus Erythematosus (SLE) is an acquired, multiorgan, autoimmune disease. Clinical presentation is extremely variable and heterogeneous. It has been shown that SLE itself is an independent risk factor for developing both arterial and venous thrombotic events since SLE patients have an Odds Ratio (OR) for thrombosis that varies depending on the clinical and laboratory characteristics of each study cohort. The risk of developing a thrombotic event is higher in this setting than in the general population and may further increase when associated with other risk factors, or in the presence of inherited or acquired pro-thrombotic abnormalities, or trigger events. In particular, a striking increase in the number of thrombotic events was observed when SLE was associated with antiphospholipid antibodies (aPL). The presence of aPLs has been described in about 50% of SLE patients, while about 20% of antiphospholipid syndrome (APS) patients have SLE. While APS patients (with or without an autoimmune disease) have been widely studied in the last years, fewer studies are available for SLE patients and thrombosis in the absence of APS. Although the available literature undoubtedly shows that SLE patients have a greater prevalence of thrombotic events as compared to healthy subjects, it is difficult to obtain a definite result from these studies because in some cases the study cohort was too small, in others it is due to the varied characteristics of the study population, or because of the different (and very copious) laboratory assays and methods that were used. When an SLE patient develops a thrombotic event, it is of great clinical relevance since it is potentially life-threatening. Moreover, it worsens the quality of life and is a clinical challenge for the clinician.

Keywords: Systemic lupus erythematosus, Thrombosis, Risk factors

Introduction

Systemic Lupus Erythematosus (SLE) is an acquired, multiorgan, autoimmune disease. The clinical presentation is extremely variable and heterogeneous with regard to the possible involvement of various organs and systems, to the varying severity of the clinical picture, and to the abnormalities (when present) of laboratory tests. Diagnosis is often complex, and both clinical and laboratory criteria are usually used. Criteria for the diagnosis of SLE were first published in 1971, while the SLICC (Systemic Lupus International Collaborating Clinics) 2012 criteria are currently used to diagnose SLE (see Table 1) [1-5]. SLE mainly affects women in their childbearing years and may potentially affect any organ or system apparatus. The calculated prevalence is about 20-150/100,000 [6,7], mainly affecting people between 15 and 44 years of age, with a two-fold prevalence for black women [8,9]. On average, Hispanics and African-Americans are diagnosed with SLE

at a younger age and with more severe forms of the disease than Caucasians. Cervera [10] showed that 10-year survival in a cohort of 1,000 SLE patients was 90%, and that 25% of the deaths were secondary to active disease, to thrombotic events, or to intercurrent infections. Recently, other authors [11] calculated a 10-year survival rate of 70%. According to some authors, thrombotic events and cardiovascular accidents are the first complications of SLE after reactivation ("flares") of the disease and infections [12]. It has been widely described that SLE itself is an independent risk factor for developing arterial and venous thrombotic events since SLE patients have an Odds Ratio (OR) for thrombosis that varies depending on the clinical and laboratory characteristics of each study cohort. The risk of developing a thrombotic event, which is higher in this setting than in the general population, could further increase when associated with other general, demographic risk factors, or in the presence of inherited or acquired pro-thrombotic abnormalities or of triggering events (such as infections) [13,14]. Thrombotic events are not included in the diagnostic criteria for SLE (see Table 1),

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Table 1 SLE diagnostic criteria (modified from [1])

Systemic lupus erythematosus: diagnostic criteria (2012 – SLICC)	
Cutaneous manifestation – 4 Items	Acute Cutaneous Lupus Erythematosus/Subacute Cutaneous Lupus Erythematosus Chronic Cutaneous Lupus Erythematosus Oral ulcers Non-scarring alopecia
Joints – 1 Item	Synovitis > 2 peripheral joints (pain, tenderness, swelling or morning stiffness > 30 min)
Serositis – 1 item	Pleuritis, typical pleurisy ≥ 1 day, history, rub, evidence of pleural effusion, pericarditis, typical pericardial pain ≥ 1 day, EKG evidence of pericardial fusion)
Renal disorder – 1 Item	Urine protein/creatinine ratio or urinary protein concentration of 0.5 g of protein/24 h, Red blood cell casts
Haematological disorder – 3 Items	Haemolytic anaemia Leukopenia (<4000/mm ³) or lymphopenia (<1000/mm ³) separately at least once Thrombocytopenia (<100,000/mm ³) at least once
Immunologic abnormal – 6 Items	Positive ANA Positive anti-dsDNA (except ELISA) on ≥ 2 occasions Anti-Sm Antiphospholipid antibody (including lupus anticoagulant, false-positive RPR, anti-cardiolipin, anti-beta2glycoprotein I) Low complement (C3, C4 or CH50) Direct Coombs test in the absence of haemolytic anaemia
Diagnosis	Fulfil 4 items (at least one clinical and one immunologic item)

but considering that they are a relatively frequent and serious complication of the natural history of the disease, they have been studied in SLE patients both from a physiopathological and from a clinical point of view in an effort to define the therapeutic strategies of prevention and treatment (secondary prevention). In particular, in 1983, a striking increase in thrombotic events was described when the associated presence of anti-phospholipid antibodies (aPL) was observed in SLE patients [15]. The antiphospholipid syndrome (APS) [16] is characterized by the presence of arterial or venous thrombotic events and/or by serious obstetrical complications associated with the persistent presence of aPLs in the serum. “Lupus anticoagulant” (LA) testing identifies the presence of aPLs in the serum that is evaluable by coagulation tests (historically

aPTT-based). This name was given since it was initially found in patients with “lupus” and that it prolonged the aPTT, thus simulating the presence of a circulating anticoagulant. The current classification criteria were defined in 2005 at the Consensus Conference of Sydney (see Classification criteria for the APS) [17]. APS can be diagnosed in patients with or without a previously diagnosed autoimmune disease, such as SLE. aPLs have been widely shown to be a significant and independent risk factor for thrombotic events and obstetric complications. It is extremely important to identify the characteristics of aPL positivity according to the Sydney criteria. Three laboratory tests must be performed i.e., LA by functional tests, and anticardiolipin antibodies (ACL) and anti-beta2-GP1 antibodies (anti-β2-GP1) by immunoassay, evaluating both IgG and IgM isotopes. If at least one of the tests is positive [18], it must be confirmed at least 12 weeks after the first assay. A “high titre” of antibodies in the serum, which needs to be confirmed over time, must be present (see classification criteria) to define the positivity of the result. Recently, the term “aPL profile” has been used to define the number and type of positive tests: the higher the number of positive tests, the higher the thrombotic risk. “Triple positivity” (LA plus ACL plus anti-β2-GP1) has the strongest prognostic value in terms of thrombotic events and recurrences [19-21]. Current consensus on classification criteria recommends stratifying the risks faced by APS patients according to their laboratory profile. The overall risk of thrombotic recurrences in APS patients should be stratified considering both clinical and laboratory features. Furthermore, the presence of associated SLE has been considered a factor of “higher risk” for these patients. The presence of aPLs has been described in about 50% of SLE patients, while about 20% of APS patients have SLE [22,23]. Ultimately, when an SLE patient develops a thrombotic event, it is of great clinical relevance since it is potentially life-threatening. Moreover, it worsens the quality of life and is a challenge for the clinician. Herein, we will describe some aspects of the association of SLE and thrombosis.

Classification criteria for the APS (modified from [17])

Clinical criteria

- 1) **Vascular thrombosis:** one or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ confirmed by imaging or Doppler studies or histopathology (except superficial venous thrombosis, except histopathological evidence of vasculitis)
- 2) **Pregnancy morbidity:**
 - a) one or more unexplained deaths of a morphologically normal foetus > 10th week of gestation, or

- b) one or more premature births of a morphologically normal neonate < 34th week of gestation because of eclampsia, preeclampsia or placental insufficiency, or
- c) three or more unexplained consecutive spontaneous abortions < 10th week of gestation with the exclusion of anatomical, hormonal, chromosomal parental abnormalities.

Laboratory criteria

- 1) anticardiolipin antibody IgG and/or IgM isotype in serum or plasma present in medium or high titre (i.e., >40 GPL or MPL or >99th percentile) on 2 or more occasions at least 12 weeks apart
- 2) lupus anticoagulant present in plasma on 2 or more occasions at least 12 weeks apart
- 3) anti-beta2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma, present on 2 or more occasions at least 12 weeks apart

Definite APS: one clinical criteria and one laboratory criteria^c present with first measurement of the laboratory test performed at least 12 weeks from clinical manifestation^d.

^acoexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. Two subgroups of APS patients should be acknowledged according to 1) presence or 2) absence of additional risk factors for thrombosis.

^binclude 1) abnormal or non-reassuring foetal surveillance tests 2) abnormal Doppler flow velocimetry waveform analysis suggestive of foetal hypoxaemia 3) oligohydramnios 4) post natal birth weight less than 10th percentile for gestational age investigators should classify APS patients in I) more than one laboratory criteria present or IIa) ACA present alone or IIb) LA present alone or IIc) anti-beta2GP-I ab present alone^d if less than 12 weeks or more than 5 years have gone by since clinical manifestation and confirmation of aPL positivity, then APS should not be defined.

Search strategy

To identify all available studies, a detailed search pertaining to Systemic Lupus Erythematosus and thrombosis was conducted. A systematic search was performed in the electronic database (PubMed –NCBI) using the following search terms in all possible combinations: systemic lupus erythematosus, arterial thrombosis, vein thrombosis, risk factor, antiphospholipid antibodies, inherited thrombophilia, acquired thrombophilia, cardiovascular disease, atherosclerosis, ethnicity, treatment, antithrombotic treatment, antithrombotic prophylaxis, pregnancy, contraception,

catastrophic APS. The last search was performed the 16th January, 2014.

Physiopathology of atherosclerosis and arterial thrombosis in SLE

Atherosclerosis is a pathological process characterized by the formation of fibro-fatty deposits in the intima layer of large and medium calibre arteries. It is recognized as the most frequent cause of death in Western countries [24]. Studies conducted in the 70's on patients with SLE showed that a bimodal mortality pattern (at 1 year and 8 years after diagnosis) may be observed in patients with SLE. The first peak is due to the disease and to the infectious complications, while the second peak, in the phase of quiescent disease, is due to the long-term glucocorticoid therapy and to cardiovascular morbidity [25]. Over the years there has been a decrease in the number of deaths occurring in the first year after diagnosis, mainly due to the increased effectiveness of the therapies and especially to the prevention of end-stage renal disease, while the mortality for cardiovascular disease (CVD) has not decreased [26] (relative risk compared to the general population for non lethal myocardial infarction RR 10.1, for fatal cardio-coronary heart disease RR 17, for stroke RR 7.9) [27]. A study by the Karolinska Institute [28] on a cohort of SLE patients showed that 50% of SLE patients died of some form of CVD. The main consequences of atherosclerosis in SLE patients include myocardial infarction, stroke and peripheral vascular disease [29]. The presence of atherosclerosis for the stratification of CVD risk was evaluated by Doppler ultrasound which was used to search for and measure carotid plaques and to measure carotid intima media thickness (IMT), while Electron-Beam Computed tomography (EBTC) was used to evaluate the calcium score in the coronary vessels [29]. Results showed early and accelerated onset of atherosclerosis in SLE patients (40% vs. 6-10% of a homogeneous sample among controls) [30,31]. This is associated with the early onset of cardiovascular disease (first event 47–64 years of age) [32], even in pre-menopausal women, thus resulting in a 2- to 10-fold greater risk of developing cardiovascular disease [29] as compared to the general population. There are currently no studies quantifying the burden of early onset atherosclerosis as compared to the development of future cardiovascular events [33]. Atherosclerosis in SLE patients is favoured both by general risk factors and by SLE-related risk factors. General risk factors include age, sex, arterial hypertension, dyslipidemia, obesity, genetic or acquired thrombophilia and ethnicity [34]. The presence of diabetes in SLE patients is surprisingly little-studied: data from a study carried out at Johns Hopkins [35] suggest a two-fold risk of cardiovascular disease. Lastly, the lack of vitamin D [36] in SLE patients has been linked to an increase in atherosclerotic plaques, to high disease

activity, to a high body mass index and to the presence of dyslipidemia and insulin resistance. A high homocysteine level is an independent risk factor [37]. The risk factors that are directly related to the pathology (see Table 2) are linked to extensive immune dysregulation, to systemic inflammation, and to endothelial dysfunction (partly mediated by autoantibodies) [29]. SLE patients are known to undergo changes in their lipid profiles, which are mediated by the pro-inflammatory activation of TNF-alpha [29], MCP-1 and IL-6 [38]. Total cholesterol and triglycerides increase, while HDL decreases and loses its anti-inflammatory and scavenger characteristics due to an immune-mediated mechanism. It then becomes pro-inflammatory (piHDL) [39] and correlates to an increased risk of coronary heart disease. It has recently been shown that serum cholesterol efflux capacity (CEC) is impaired in SLE patients thus increasing the atherosclerotic risk of these subjects in a non dependent way with respect to serum HDL levels [40]. Increased lipid oxidation has been reported in these patients [41]. Concomitant nephropathy may contribute to further worsening dyslipidemia. The mechanisms underlying endothelial dysfunction are present from the early stages of the disease with increased expression of cell adhesion molecules (ICAM, VEGF, Von Willebrand

factor, VCAM) which are associated with the development of CVD in SLE [32]. The increased expression of Von Willebrand factor (mediated by the production of inflammatory-cytokines) also has a pro-aggregating effect [42]. It has been demonstrated that SLE patients are unable to degrade the NETs (neutrophil extra-cellular traps) complex which regulates apoptotic processes [43]; NETs emerge as a possible mediator of vascular damage and an activator of the thrombotic process. The increase in inflammatory interleukins (IL-17, IL-12 and IL-18) [44], the altered response of B lymphocytes and the production of IgG class autoantibodies with pro-inflammatory meaning [45], and the selective deficiency of T reg lymphocytes are all mechanisms that are present in SLE patients and are associated with an increased risk of CVD [24]. High disease activity is linked to earlier onset of cardiovascular damage, to a worse prognosis (because of the increased risk of CVD), to the increase in IMT thickness (early atherosclerosis) and to the presence of arthritis-serositis (a sign of greater systemic inflammation with increased risk of CVD) [29]. The presence of antibodies to SS-A and SS-B is usually associated with less active disease, but these patients have a pattern of CVD damage and related mortality that is significantly worse [29]. The nephrotic syndrome is correlated with an increased thrombotic risk. In a wide, recently performed meta-analysis on case-control studies of APS patients, APS itself was shown to be related to markers of subclinical atherosclerosis and endothelial damage [46]. In a systematic review on the main predictors of cardiovascular events in SLE patients, [47], the presence of autoantibodies and of neurological disorders were found as “non traditional” risk factors, with an OR of about 5 in both cases. A polymorphism in the toll-like receptor 2 (TLR2) has recently been linked to the pathogenesis of thrombosis in SLE patients. In particular, African Americans and European Americans show an association between TLR2 mutation and thrombosis [48]. Treatment may have an effect on thrombotic risk. Steroids have been reported to increase the atherogenic risk in two ways: the first (direct) via plasma lipoproteins, the second (indirect) by favouring hypertension, diabetes and hyperlipidemia. Moreover, the cumulative dose of steroids, more than the daily dosage alone, seems to be related to the development of atherosclerosis. [49-51]. Antimalarials have an anti-thrombotic, anti-inflammatory effect and control dyslipidemia [52]. Moreover, by blocking toll like receptors 7 and 9, hydroxychloroquine inhibits interferon alpha production which plays a pathogenetic role in SLE pathogenesis [53]. Mycophenolate mofetil reduces the activation of T lymphocytes and increases the presence of regulatory T lymphocytes in carotid plaques [52]. An animal model of SLE showed that Atorvastatin reduces the level of autoantibodies and improves proteinuria and renal histology, however, there is still no general consensus for its extensive use

Table 2 Factors influencing atherosclerosis and cardiovascular diseases (CVD) in SLE patients

SLE-related factors	Effects
TNF-alpha, MCP-1, IL-6, kidney disease	Dyslipidemia worsening, dysfunctional piHDL production
ICAM, VEGF, vWF, VCAM overexpression	Pro-aggregation/pro-thrombotic behaviour
Acute phase reactants elevation	Tissue damage
INF-alpha elevation	Endothelial damage, pro-thrombotic behaviour
Neutrophil extra-cellular traps	Vascular damage/pro-thrombotic behaviour
IL-17, IL-12, IL-18 elevation, IgG overexpression	Pro-inflammatory
Cystatin C	Early kidney damage marker, pro-inflammatory
SS-A/SS-B positivity profile, photosensibility	Higher risk of CVD
Medications	Effects
Corticosteroids	Higher risk of CVD
Antimalarial (OH-chloroquine)	Anti-thrombotic, anti-inflammatory, anti-dyslipidemic
Mycophenolate mofetil	Lower immune activity in carotid plaque, protective
HMG-CoA reductase inhibitors (atorvastatin)	Fewer autoantibodies and improvement of kidney function in animal models, to be confirmed in humans
NSAIDs	Higher risk of CVD (less with naproxene)

in SLE patients [52]. Treatment with non steroidal anti-inflammatory drugs (NSAIDs) may increase cardiovascular risk (rofecoxib is associated with a greater risk of myocardial infarction, ibuprofen is associated with a higher risk of stroke, diclofenac with higher cardiovascular toxicity, naproxen seems to be the least harmful [54] though it can worsen kidney function. The therapeutic strategy for lowering the risk of CVD should be aimed at an even more aggressive treatment of the disease during the active phase [24]. Other emerging indications include: the immediate cessation of smoking, the use of hydroxychloroquine in all SLE patients who do not have contraindications to such treatment, the use of statins for dyslipidemia, the treatment of arterial hypertension (SBP <120 mmHg), and therapy with acetylsalicylic acid (ASA) which may be useful in SLE patients with general or lupus-related CVD risk factors. The role of immunosuppressive agents in the prevention of atherosclerosis is tentative and must be further investigated [24].

Clinical risk factors for thrombosis in SLE: prevention and treatment

The clinical risk factors for thrombosis

In SLE have been widely studied. A recent Swedish study [32] showed that in a cohort of 182 SLE patients (with an average follow-up of 8.3 years) who have not had a thrombotic event, 13% developed a cardiovascular event (CVE). CVE events included: ischaemic heart disease (IHD), ischaemic cerebrovascular disease (ICVD), ischaemic peripheral vascular disease (IPVD), or death related to a thrombotic event. The authors concluded that the presence of aPLs increased the Von Willebrand factor, and that the absence of thrombocytopenia significantly correlated to a higher risk of developing an ischaemic event. Retinal vein occlusion is reportedly more frequent in patients with SLE compared to an age-matched control group, with a Hazard Ratio (HR) = 3.883 [55]. Age above 50 years was an independent risk factor, with an HR = 4.8. [55]. A higher incidence of thrombotic events has been reported in SLE patients with lupus nephropathy (LN) [56]. Twenty-five thrombotic events were observed in a cohort of 200 SLE patients who had LN. Sixty-eight % of the events were venous, with an overall incidence of thrombotic events of 29.1 per 1,000 patients/year. The concomitant presence of aPLs (odds ratio 126!), or of serositis (OR 5), and a history of arterial thrombosis (OR 24) was associated with thrombotic events, while treatment with ACE inhibitors showed a protective effect. Chung et al. evaluated the incidence of venous thromboembolic events in a large Chinese SLE cohort (13,084 patients) and compared it to that of a healthy control group without SLE [57]. After adjusting for age, sex and comorbidities, the risk of developing a deep vein thrombosis (DVT) or a pulmonary embolism (PE) in the

SLE patient group was found to be 12.8 and 19.7, respectively, as compared to the control group. The risk of developing IHD, coronary artery disease (CAD) and stroke was calculated in another large cohort of 2,000 patients enrolled in Sweden that included 277 subjects who had American College of Rheumatology (ACR) criteria > 4 [58]. They found an 8- to 9-fold greater risk in middle-aged women with respect to the control population. The presence of IgG ACL was predictive of thrombotic events. A meta-analysis concerning different clinical variables that predict a cardiovascular event in SLE patients was carried out [47]. After a median follow up of 8 years, a prevalence of 25.4% of new thrombotic events was calculated, of which 4% were IHD and 7% were strokes. In this study, the most significant risk factors that were found were male gender, dyslipidemia, family history for CAD, and arterial hypertension, while the presence of autoantibodies and neurological disorders were among the "specific" risk factors. Low correlation was found with respect to organ damage and disease activity. Infectious episodes *per se* could represent an additional risk factor for thrombosis [59,60] in SLE patients. In the last few years, "scores" to calculate the risk of thrombosis in SLE patients have been devised and proposed. Available literature clearly shows that SLE patients have a greater prevalence of thrombotic events with respect to healthy subjects. However, it is difficult to obtain definitive results from these studies because in some cases the study cohort was too small, in other cases it was due to the different characteristics of the study population, or even because of the different (and very copious) laboratory assays and methods that were used.

Primary prevention of venous thromboembolism (VTE)

Although SLE *per se* seems to be a risk factor for thrombosis, mainly in the active phases, it is not generally mentioned as a risk factor in the more common risk assessment models (RAM) for medical thromboprophylaxis [61], such as the Caprini RAM [62] or Rogers scores [63]. The presence of LA and of ACL are instead mentioned in these RAM as risk factors. Moreover, the Padua Prediction score risk assessment model [64] also mentions the presence of APS among thrombotic risk factors (regardless of whether it is primary or secondary), thus increasing the score itself. In the absence of available guidelines in this clinical setting, we believe that SLE patients must be considered at higher thrombotic risk, even in the absence of APS and aPLs, mainly during the active phases.

VTE and arterial thrombosis treatment

Based on current guidelines, treatment of the acute phase of VTE is no different in these patients from the standard treatment [65]. A higher intensity of anticoagulation therapy (INR 3–4 or low dose ASA associated to avK with an INR range 2–3) (see Table 3) has been

Table 3 Treatment recommendations for patients with SLE, associated or not with aPLs or APS, and thrombosis (modified from [14])

Clinical scenario	Recommendations
Patients with definite APS (+/- SLE) and first venous event	aVK, INR range of 2.0-3.0
Patients with definite APS (+/- SLE) and venous recurrent thromboembolism during aVK or arterial thrombosis*	aVK, target INR > 3.0 ^a or combination of aspirin (100 mg daily) and aVK, INR range 2.0-3.0 ^a
APS patients (without SLE) with a first non cardioembolic cerebral arterial event, low-risk aPL profile, and reversible predisposing factors	Antiplatelet agents
SLE patients with venous or arterial thrombosis who do not fulfil APS laboratory classification criteria	Same as patients from the general population who develop venous or arterial thrombosis

^aThere was a lack of consensus on these recommendations.

APS, antiphospholipid syndrome; INR international normalized ratio; SLE, systemic lupus erythematosus; aPL, antiphospholipid antibodies.

recommended in APS patients (with or without SLE) with venous thrombotic recurrence or with arterial events. If indicated, direct oral anticoagulants (dabigatran, rivaroxaban or apixaban) could be used for VTE. Results from studies focusing on this clinical setting are not yet available, though they are in progress. Clinicians must take into consideration that SLE patients often have renal disease and chronic kidney failure, thus there is a need to avoid these drugs or to reduce the doses, according to the manufacturer's recommendations. The possible association with NSAIDs must also be considered because of the increased bleeding risk. Concerning the optimal duration of anticoagulant treatment, no definite evidence or guidelines are currently available. Considering that a persistent risk of thrombosis is present in these patients, mostly in subjects with SLE and APS, long term anticoagulation is recommended. Shorter anticoagulant treatment should be considered for patients with SLE alone after the first venous thrombotic event, or if SLE is associated with a low risk aPL profile provided that SLE is not in an active phase and that the thrombosis had a well-defined, transitory trigger event. Thrombotic and bleeding risk assessment must be carried out periodically in all of these patients, both at the start of treatment and then at least every year after that. Further evaluation must be performed in case of intercurrent pathologies, or if new drugs to treat SLE are introduced.

Primary prevention of acute arterial diseases

Good quality evidence is also missing in this setting. Some consensus exists [66-69] concerning the use of low dose ASA (i.e., 100 mg daily) in patients with SLE and aPLs who have never had a thrombotic event. Even in the absence

of aPLs, associated risk factors such as age, smoking, hypertension, obesity, dyslipidemia, etc. must be taken into consideration when starting primary arterial prevention.

Pregnancy, contraception and thrombosis

Pregnancy in SLE patients carries a burden of increased risk of morbidity and mortality, both for the mother and for the foetus/newborn [70]. The most frequently reported drawbacks include: pre-eclampsia, pre-term delivery, venous and arterial thrombosis, infections, haematological complications (cytopenias, mainly thrombocytopenia). Increased mortality has been described in this clinical setting [71]. As already reported, a high percentage of SLE patients have aPLs. [70] Furthermore, if these subjects are still asymptomatic (no previous thrombotic event or obstetrical complication), they are at high risk of miscarriage and pregnancy morbidity. In particular, LA positivity [72] proved to have strong positive predictive value for an adverse event during pregnancy. It was recently demonstrated that by using appropriate pharmacological strategies, it is possible to significantly increase the probability of good pregnancy outcome up to 80% of live born babies [70,22]. In SLE patients with asymptomatic aPL positivity, low dose ASA (100 mg/die) is recommended [73]. Low dose ASA associated with LMWH at prophylactic doses (i.e., 4000 U/die) is recommended for SLE with obstetrical APS (miscarriages or foetal loss), but no previous thrombotic event [74,75]. For SLE patients with vascular APS (i.e., a previous thrombotic event), therapeutic LMWH doses (i.e., 100 U/Kg twice a day) are recommended throughout pregnancy and puerperium. Warfarin must be avoided during pregnancy, particularly during the first trimester; data concerning treatment with fondaparinux are scant but encouraging for LMWH-intolerant patients [76]. In the presence of a venous thrombotic event during pregnancy, therapy with full doses of LMWH are recommended, and if possible, factor Xa should be evaluated in order to adjust LMWH dosage. LMWH treatment must be discontinued at least 24 hours before delivery (induction or caesarean section) [77]. LMWH treatment must be extended at least until the 6th week after delivery. Possible further extension of the anticoagulant treatment must be evaluated for each individual patient taking into consideration the presence of aPLs, the aPL profile, the degree of SLE activity, and the degree and quality of the resolution of the thrombotic event. In the clinical context of SLE patients, it is extremely important to provide these patients with information concerning the best contraceptive approach in order to schedule a pregnancy during a stable phase of the disease, and while on drugs that are not contraindicated in pregnancy. Contraceptives containing progesterone alone (progesterone intrauterine devices or drugs) should be considered preferable and safer in SLE patients. Oestro-progestin preparations must be used

with great caution and only in SLE patients with stable disease, but are contraindicated in patients with a previous thrombotic event or in the presence of aPLs [78].

Catastrophic APS

Since a high percentage of patients with SLE are also affected by secondary APS, in this paragraph we will describe a severe and acute thrombotic syndrome that may complicate the outcome of patients affected by APS. Catastrophic APS (CAPS) is a rare and life-threatening form of APS and is characterized by the involvement, over a very short time (less than a week), of several organs/tissues as the target of intravascular thrombosis of microcirculation. The diagnostic criteria for CAPS include: 1) involvement of three or more organs/tissues 2) occurrence of events in less than a week 3) histological evidence of intravascular thrombosis 4) the presence in the patient's serum/plasma of antiphospholipid antibodies (see Criteria for the classification of catastrophic APS [79]). A previous diagnosis of APS and/or the persistence of clinically significant aPL positivity is useful in the diagnosis of CAPS, however, nearly half of the patients who develop CAPS do not have a history of aPL positivity [80]. CAPS is predominantly characterised by widespread thrombosis of the microcirculation, even though arteries, veins or both may also be involved in the thrombotic process. Histological specimen investigation shows acute thrombotic microangiopathy with inflammatory infiltrate in the interstitial space in one third of cases, immunofluorescence shows strong immunoreactivity and anti-fibrin antibodies, while immune complex deposition is uncommon [81]. An analysis of a large cohort showed that these patients are mainly female (72%) with a mean age of 37 years. Triggering events, such as infections, surgery, discontinuing anticoagulant therapy, medications, obstetric complications or malignancy are usually identifiable [22]. A pre-existing condition of autoimmune disease is quite common (SLE in 40% of patients). CAPS is often accompanied by a systemic inflammatory response syndrome likely due to the extremely extensive tissue damage [82]. Laboratory examinations show positivity in the majority of patients for LA and ACL.

Antinuclear antibodies (ANA) are present in approximately two thirds of patients even though titres are not as high (<1: 320). There may be non-severe thrombocytopenia and haemolytic anaemia (about one third of patients), while the presence of a significant number of schistocytes in the peripheral blood smear is observed in only about one-tenth of patients, probably due to the high speed with which they establish the thrombotic process involving the microcirculation [83]. Differential diagnosis primarily includes haemolytic-uraemic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation and heparin-induced thrombocytopenia (HIT). Bleedings and infections often complicate the course of the disease

resulting in a worse prognosis. Recent data show a decrease in mortality from 53% to 33% due to a combination of therapeutic strategies in association; these associations include anticoagulants (mainly heparin, which also inhibits complement activation), antiplatelet agents, corticosteroids, plasma-exchange (useful for removing pathological aPLs, cytokines and complement and also incorporating natural anticoagulants like antithrombin and protein C), cyclophosphamide (which could be useful in patients with active autoimmune disease or systemic vasculitis), rituximab (quite promising, especially in patients with severe thrombocytopenia) and high-dose i.v. immunoglobulin (this treatment is based on its ability to block pathological antibodies, to increase clearance, to act on the complement system and to suppress cytokines). Recently, long-lasting remission was obtained in a patient with recurrent CAPS by inhibiting the terminal complement with eculizumab, a recombinant humanized monoclonal IgG2/4 antibody that selectively targets and inhibits the terminal portion of the complement cascade [84]. CAPS patients require adequate management in the intensive care unit which should include haemodialysis, mechanical ventilation or cardiovascular support for shock.

Criteria for the classification of catastrophic APS (modified from [79])

Definite catastrophic APS: All 4 criteria

- Evidence of involvement of three or more organs, systems and/or tissues.^a
- Development of manifestations simultaneously or in less than a week.
- Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.^b
- Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anti-cardiolipin antibodies).

Probable catastrophic APS:

- All 4 criteria except for the involvement of only two organs, systems and/or tissues
- All 4 criteria except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPLs before catastrophic APS
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

^aVessel occlusion confirmed by imaging techniques, renal involvement defined as a 50% rise in serum creatinine,

severe systemic hypertension (>180/100 mmHg) and/or proteinuria (>500 mg/24 h).

^bSignificant evidence of thrombosis must be present for histopathological confirmation, and vasculitis may coexist.

^cIf not present, previous diagnosis of APS lab confirmation requires the presence of antiphospholipid antibodies which must have been detected on two or more occasions at least 6 weeks ^capart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Conclusions

A great deal of physiopathological data concerning SLE and thrombosis is available. Unfortunately, as far as the clinical approach in this setting is concerned, few guidelines are available and however, are not based on strong evidence. These patients are generally very complicated, and consequently are often treated with an association of multiple drugs. Moreover, SLE patients often have cytopenias, mainly thrombocytopenia, and this complicates the anticoagulant strategies and their standardization. Starting from these premises, the presence of well performed clinical studies in this setting is an unmet clinical need.

Abbreviations

SLE: Systemic Lupus Erythematosus; OR: Odds Ratio; aPL: Antiphospholipid antibodies; APS: Antiphospholipid syndrome; SLICC: Systemic Lupus International Collaborating Clinics; LA: Lupus anticoagulant; ACL: Anticardiolipin antibodies; anti-β2-GP1: Antibeta 2 GP1 antibodies; CVD: Cardiovascular disease; IMT: Carotid intima media thickness; EBTC: Electron-Beam Computed tomography; NETs: Neutrophil extra-cellular traps; NSAIDs: Non steroidal anti-inflammatory drugs; CVE: Cardiovascular event; IHD: Ischaemic heart disease; ICVD: Ischaemic cerebrovascular disease; IPVD: Ischaemic peripheral vascular disease; HR: Hazard Ratio; LN: Lupus nephropathy; DVT: Deep vein thrombosis; PE: Pulmonary embolism; CAD: Coronary artery disease; VTE: Venous thromboembolism; RAM: Risk assessment models; LMWH: Low molecular weight heparin; CAPS: Catastrophic APS; ANA: Antinuclear antibodies; HIT: Heparin-induced thrombocytopenia.

Competing interests

The authors have no competing interest to declare.

Authors' contribution

All the authors contributed to the writing of the article, and read and approved the final manuscript.

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