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Review

The clinical significance of antiphospholipid antibodies in systemic lupus erythematosus

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Abstract

Antiphospholipid syndrome (APS) is the association of thrombosis and/or pregnancy morbidity with antiphospholipid antibodies (aPL). Thirty to forty percent of systemic lupus erythematosus (SLE) patients are tested positive for aPL, which may have an impact on the SLE presentation, management, and prognosis. Compared with SLE patients without aPL, those with aPL have a higher prevalence of thrombosis, pregnancy morbidity, valve disease, pulmonary hypertension, livedo reticularis, thrombocytopenia, hemolytic anemia, acute/chronic renal vascular lesions, and moderate/severe cognitive impairment; worse quality of life; and higher risk of organ damage. The use of low-dose aspirin (LDA) is controversial for primary thrombosis and pregnancy morbidity prevention because of the lack of strong prospective controlled data. Similarly, the use of anticoagulation is controversial for patients with an aPL-related nephropathy. Until further studies are available, physicians should discuss the risk/benefits of LDA or anticoagulation as well as the available literature with patients.

Keywords: Lupus, antiphospholipid antibodies, thrombocytopenia, hemolytic anemia, livedo, nephropathy

Introduction

Antiphospholipid syndrome (APS) is the association of thrombosis and/or pregnancy morbidity with antiphospholipid antibodies (aPL) (lupus anticoagulant [LA], anticardiolipin antibodies [aCL], and/or anti-β_2-glycoprotein-I antibodies [aβ_2GPI]) (1). Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, and/or central nervous system manifestations (2).

Antiphospholipid syndrome can occur in otherwise healthy persons without an underlying systemic autoimmune disease (primary APS) or with other systemic autoimmune diseases, particularly SLE. In addition, valvular heart disease, pulmonary hypertension (PH), livedo reticularis (LR)/racemosa, thrombocytopenia, hemolytic anemia, renal thrombotic microangiopathy (TMA), and cognitive dysfunction are some clinical problems that SLE- and/or aPL-positive patients can develop (3).

Irreversible organ damage can occur in SLE- and/or aPL-positive patients. One-third of SLE patients develop organ damage within five years of diagnosis (4); similarly, one-third of primary APS patients with more than 10 years of disease have organ damage (5).

Given the relatively high prevalence of aPL in SLE patients (6) (discussed below), one assumes that aPL-positive SLE patients, would have a more severe clinical phenotype and worse prognosis than those without aPL. Thus, this paper reviews the clinical significance of aPL in SLE patients, i.e., how positive aPL may change the presentation, management, and prognosis of SLE. The etiopathogenesis of aPL-related clinical manifestations and the general management of SLE and/or aPL-positive patients can be found elsewhere (7).

What is the prevalence of antiphospholipid antibodies in SLE?

In SLE, 30%-40% of patients are positive for aPL (6); when each aPL is investigated individually, the prevalence of a positive LA test and aCL varies between 11%-30% and 17%-40%, respectively (8-10).The prevalence of a "clinically significant" (defined below) aPL profile in lupus patients is approximately 20% (11).

What is a "clinically significant" antiphospholipid antibody profile?

Every positive aPL test in lupus patients is not clinically significant, and every aPL-positive lupus patient does not have the same risk of aPL-related clinical manifestations.

Transient aPL is common during infections. The documentation of aPL positivity tested on two occasions at least 12 weeks apart (1) is important. Based on prospective follow-up of healthy blood donors who were

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tested twice for aPL, 10% and 1% positivity was detected for aCL and LA tests, respectively, at baseline. One year later, less than 1% of healthy blood donors tested positive for aCL or LA (12).

Lupus anticoagulant test positivity (compared with aPL ELISA tests) (13), moderate to high titer (≥40 U or ≥99th percentile) aCL or aβ_2GPI IgG/IgM (compared with lower titers) (1), IgG or IgM isotype (compared with IgA isotype) (1), and triple aPL (LA, aCL, and aβ_2GPI) positivity (compared with single or dual aPL test positivity) (14) correlate better with aPL-related clinical events.

Patients on any type of anticoagulant, including new direct oral anticoagulants, may have false-positive results on the LA test should be performed before administering anticoagulants. The lupus anticoagulant test requires a four-step process: 1) demonstration of a prolonged phospholipid-dependent coagulation screening test; 2) failure to correct the prolonged screening test by mixing study; 3) correction of the prolonged screening test by excess phospholipid; 4) exclusion of other inhibitors (16, 17).

Antiphospholipid antibody tests that are not part of the updated Sapporo Classification Criteria, e.g., antiphosphatidylserine prothrombin or antibodies directed against domain I of the aβ_2GPI, may be more specific for APS diagnosis and predict incident thrombotic events more accurately (18) than criteria aPL tests (19). However, their use in clinical practice is limited because of the lack of standardization and the fact that they have been mostly utilized for research purposes. In the future, these tests may play a major role for predicting thrombosis risk (20); however further studies are required.

Lastly, in 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group developed new SLE classification criteria to improve clinical relevance, meet stringent methodology requirements, and incorporate new knowledge regarding the immunology of SLE (21). These new classification criteria now include the IgA isotype of aCL and aβ_2GPI, which has not been part of the revised American College of Rheumatology SLE Classification Criteria (22). However, the association between the IgA isotype and aPL-related clinical events remains controversial (23); the Laboratory Trends and Diagnostics Task Force of the 14th International Congress on aPL recently concluded that low-quality evidence exists to include the IgA isotype as part of the APS Classification Criteria (particularly, given the fact that these isotypes are usually associated with other aPL, making it difficult to understand the role of IgA alone) (19).

Table 1. Selected meta-analysis studies demonstrating the increased risk of clinical manifestations in antiphospholipid antibody (aPL) -positive systemic lupus erythematosus (SLE) patients compared with that in aPL-negative SLE patients

Manifestations	Increased risk [OR (95% CI)]			
	LA	aCL	aβ_2GPI	aPL
Venous thromboembolism (51)	5.6 (3.8-8.2)	2.1 (1.5-3.1)	N/A	N/A
Pregnancy morbidity (56)	N/A	N/A	N/A	Increased[a]
Valvular disease (71)	5.8 (2.9-11.8)	5.6 (3.5-8.9)	N/A	3.1 (2.3-4.2)
Pulmonary hypertension (77)	2.4 (1.5-3.9)	3.1 (2.0-4.8)	NS	2.5 (1.8-3.3)
Livedo reticularis (83)	4.7 (2.4-9.2)	3.3 (2.2-4.9)	3.4 (1.5-7.5)	3.4 (2.5-4.6)
Thrombocytopenia (85)	3.4 (2.6-4.5)	2.0 (1.6-2.4)	2.7 (1.4-5.0)	2.7 (2.4-3.2)
Hemolytic anemia (91)	4.6 (2.6-8.0)	2.9 (2.2-3.9)	4.0 (1.5-10.7)	3.2 (2.4-4.3)
Renal impairment (96)	2.8 (1.1-7.6)	3.1 (1.1-9.0)	NS	2.9 (1.9-4.3)

aCL: anticardiolipin antibodies, aβ_2GPI: anti-β_2-glycoprotein-I antibodies, CI: confidence interval, LA: lupus anticoagulant, NS: not significant, OR: odds ratio; aPL: antiphospholipid antibodies
[a]Odds Ratio is not available for this study, which is based on lupus nephritis patients

Our recommendation for "clinically significant aPL profile" is a positive LA test based on the guidelines of International Society of Thrombosis and Haemostasis (16), aCL IgG/IgM greater than or equal to 40 U, and/or aβ_2GPI IgG/IgM greater than or equal to 40 U, tested twice at least 12 weeks apart. Clinical judgment are required when interpreting aPL tests in the following cases: 1) the LA test is performed on anticoagulated patients; 2) aCL or aβ_2GPI IgG/IgM titers are in the medium range of 20 to 39 U; 3) only one aPL determination is available; and/or 4) aCL or aβ_2GPI IgA is the only positive aCL ELISA test.

How do antiphospholipid antibodies alter the presentation of lupus?

Thrombosis

Independent of aPL, because of the increased incidence of traditional cardiovascular disease (CVD) and non-traditional lupus-related risk factors, e.g., inflammation, renal disease, or corticosteroids, SLE patients are at significantly increased risk of premature atherosclerosis and/or thrombosis (24, 25). In general, the prevalence of vascular events in SLE patients is 10%-30% (26), symptomatic coronary artery disease (CAD) 6%-20% (27-29), stroke 2%-15% (28-30), and subclinical CAD 30%-40% (27, 31). A Patient Discharge Database analysis has estimated that women with SLE, aged 18-44 years, are hospitalized with myocardial infarction or stroke almost twice more often than the general population (28).

Although aPL increases the risk of vascular events and death in SLE (32-36), the role of aPL in the development of atherosclerosis in humans remains controversial (37, 38). Antiphospholipid antibodies crossreact with antibodies against oxidized low-density lipoprotein (LDL) (39, 40) and may enhance its uptake by macrophages (41), which represents the initial step of atherosclerotic plaque formation (42). Antiphospholipid antibodies can also crossreact with high-density lipoprotein complex (HDL-C) and apolipoprotein A-I (Apo A-I) (a major constituent of the HDL-C), possibly reducing the antiatherogenic effects of HDL (43). In primary APS patients, particularly those older than 40 years, the carotid intima-media thickness (cIMT) is increased compared with that in controls (44). However, an independent association between aPL and carotid atherosclerosis, coronary artery calcification (CAC), and CVD in SLE patients has not been confirmed by all the studies (33, 36, 44-49).

Among all SLE patients, approximately 40% of the aPL-positive patients develop arterial and/or venous thrombosis, in comparison with 10%-20% of aPL-negative patients ($p<0.001$) (50). According to a meta-analysis by Wahl et al. (51), patients with SLE and LA are at approximately six times greater risk of venous thromboembolism (VT) (odds ratio [OR]:5.6; 95% confidence interval [CI]:3.8-8.2) ($p<0.0015$) (deep venous thrombosis [DVT] and pulmonary embolism [PE] [OR: 6.3; CI: 3.7-10.8] [$p<0.03$]) and 11 times greater risk of recurrent VT than those without LA (OR:11.6; 95% CI: 3.6-36.9) ($p>0.05$). Patients with SLE and aCL are at approximately two times greater risk of DVT/PE (OR: 2.2; 95% CI:1.5-3.1) ($p<0.05$) and four times greater risk of recurrent DVT after the first event than those without aCL (OR: 3.9; 95% CI: 1.1-13.4) ($p>0.05$) (Table 1).

Table 2. Selected studies analyzing the effect of aPL on pregnancy morbidity in SLE patients

Study (Year)	Study Design	n	aPL	PM in aPL + SLE	PM in aPL - SLE	Odds Ratio	95% CI
Park et al. (2015) (57)	Retrospective	50	aCL	53.8%	34.7%	2.2	0.6-7.6
			$a\beta_2GPI$	16.7%	9.1%	2	0.1-39.1
			LA	25%	40.7%	0.5	0.1-2.6
Jakobsen et al. (2014) (58)	Retrospective	39	aCL, $a\beta_2GPI$, or LA	43.5%	13.1%	N/A	N/A
Buyon et al. (2015) (60)	Prospective	385	LA	55.9%	15.3%	8.3	3.6-19.3
			aCL, $a\beta_2GPI$, or LA	43.8%	15.4%	4.3	2.2-8.1
Cortes Hernandes et al. (2002) (61)	Prospective	60	aCL	72.5%	41.8%	3.7	1.5-8.8
			$a\beta_2GPI$	84.8%	38.7%	8.9	3-26.1
			LA	70%	43.6%	3	1.3-7.1

aCL: anticardiolipin antibodies; $a\beta_2GPI$: anti-β_2-glycoprotein-I antibodies; CI: confidence interval; LA: lupus anticoagulant; N: number of patients; N/A: not applicable; PM: pregnancy morbidity; aPL: antiphospholipid antibodies; SLE: systemic lupus erythematosus

Pregnancy morbidity

Pregnancy in lupus patients is associated with a higher risk of morbidity than that in the general population. A large national database study of 16.7 million deliveries reported an increased risk of maternal death, preeclampsia, preterm labor, thrombosis, infection, and hematologic complications in SLE pregnancies (52).The major concern was the three- to five-fold increased risk of pre-eclampsia, complicating 16%-30% of SLE pregnancies (53).

The frequency of obstetric morbidity in SLE patients without and with aPL ranges between 0%-38% and 25%-47%, respectively (54, 55). A meta-analysis by Smyth et al. (56), including 1842 SLE patients and 2751 pregnancies, demonstrated that in patients with lupus nephritis, aPL increases (magnitude not reported) the risk of maternal hypertension (p=0.03) and premature births (p=0.004) (56); aPL also correlates with an increased rate of induced abortion (p=0.02).

No meta-analysis exists analyzing the effect of aPL on pregnancy morbidity in SLE patients without nephritis, and the available studies are controversial (Table 2). In one retrospective study, 62 pregnancies were observed in 50 SLE patients; adverse fetal outcome was not affected by aPL (LA test, aCL, or $a\beta_2GPI$) or APS diagnosis (57). In another retrospective study of 84 pregnancies observed in 39 SLE patients, there was approximately three times higher risk of spontaneous abortion in patients with aPL (58). Based on prospective studies, a) in 96 SLE patients (132 pregnancies), aPL (LA, aCL, or $a\beta_2GPI$) and/or APS diagnosis did not increase the risk of fetal loss; however, preeclampsia and preterm delivery were predicted by the positive LA test and APS diagnosis (59); b) in 385 SLE patients, a positive LA test was the only predictor of adverse pregnancy outcomes (APO) (fetal or neonatal death; birth before 36 weeks due to hypertension, placental insufficiency, or preeclampsia; and small-for-gestational-age neonate); although the rate of aPL positivity was significantly different between patients with or without APO, aPL was not found to be a predictor of APO in multivariate analysis (60); and c) in 60 SLE patients (103 pregnancies), spontaneous abortion was associated with aPL (61).

Valvular heart disease

Valvular involvement (global thickening of leaflets, vegetation also known as Libman-Sacks endocarditis, and valvular dysfunction, e.g., regurgitation and/or stenosis) is relatively common in SLE. The prevalence of valvular involvement in SLE patients depends on the imaging technique; transesophageal echocardiogram (TEE) is more sensitive than transthoracic echocardiogram (TTE). Valvular involvement is detected in approximately 40% of lupus patients by TEE and in 0%-12% by TTE (62). In contrast, valvular abnormalities are detected in 0%-4% of healthy control subjects (63-66). Immunoglobulin, aPL, immune-complex and complement depositions (67), inflammation, or fibrin-platelet thrombi may lead to valvular lesions (67, 68); valve disease for most patients is mild and asymptomatic (69, 70).

Based on a meta-analysis of 23 studies by Zuily et al. (71), while 40%-50% of aPL-positive SLE patients have valvular lesions, the prevalence is approximately 20% in aPL-negative SLE patients in whom systematic TTE or TEE was performed (71); these findings were consistent with a previous review of 13 studies (72). The meta-analysis by Zuily et al. (71) demonstrated that SLE patients with LA or IgG aCL have approximately six times higher risk of valve disease than those without aPL (OR: 5.88 [95% CI: 2.92-11.84] and OR: 5.63 [95% CI: 3.53-8.9]; respectively), whereas SLE patients with IgM aCL do not have a significantly increased risk of valve disease in comparison with those without IgM aCL. Furthermore, the risk of valve vegetations was significantly increased in patients with aPL in comparison with those without aPL (OR: 3.51 [95% CI, 1.93-6.38]).

Pulmonary hypertension

According to the new classification of PH defined by Simmoneau et al. (73) in 2013, PH can be grouped as follows: 1) pulmonary arterial hypertension (PAH); 1') pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis; 1'') persistent PH of the newborn; 2) PH due to left heart disease; 3) PH due to lung diseases and/or hypoxia; 4) chronic thromboembolic PH (CTEPH); and 5) PH with unclear multifactorial mechanisms. All forms of PH, except group 1" to a lesser extent, could be seen in SLE- and/or aPL-positive patients. However, none of the publications studying PH in SLE stratified their findings according to different types of PH; therefore, with current literature, it is difficult to know which group of PH is associated with aPL in SLE patients (74).

The frequency of PH in SLE varies between 1%-18% (75). Typically, PH occurs after prolonged SLE disease duration, often after five years, and in women under the age of 40 years (75, 76).

The frequency of aPL in SLE patients with and without PH is 15%-100% and 11%-55%, respectively (74). All studies showed either a significant or a non-significant increase in the risk of PH in SLE patients with aPL in comparison with those without aPL (74). In a recent meta-anal-

ysis by Zuily et al. (77), of 36 studies included, corresponding to 4,190 SLE patients and 478 PH cases, the prevalence of PH in aPL-positive patients was found to be 16% (n=231/1,443) and that aPL-negative SLE patients was found to be 9% (n=247/2,747). The overall pooled OR for PH in aPL-positive SLE patients compared with aPL-negative SLE patients was 2.5 (95% CI, 1.8-3.3). The risk of PAH associated with aPL in SLE patients without a history of PE was also significantly increased (OR: 3.1 [95% CI, 1.7-5.6]). The risk of PH was the highest for LA (OR: 2.4 [95% CI, 1.5-3.9]) and IgG aCL (OR: 3.1 [95% CI, 2.0-4.8]), while IgM aCL and aβ_2GPI were not significantly associated with PH (OR: 1.8 [95% CI, 0.9-3.7] and OR: 1.9 [95% CI, 0.6-6.3], respectively).

Livedo reticularis and racemosa

LR is a "persistent, not reversible with rewarming, violaceous, red or blue, reticular or mottled pattern of the skin of trunk, arms, or legs, consisting of regular unbroken circles" (1). Livedo racemosa is a striking violaceous netlike pattern, and compared with LR, it is more generalized and widespread, non-infiltrated, and has irregular, broken, circular segments (78-81). Data on livedo racemosa, which is more closely associated with aPL-related clinical problems, are limited; the distinction between LR and livedo racemosa has not been addressed well in the literature, and the term "LR" is generally used for both.

In one report, LR was observed in 17% of 66 lupus patients; 80% of patients with LR had aCL (82). A recent meta-analysis by DeFilippis et al. (83) showed that of 28 studies included, corresponding to 3,413 SLE patients and 564 LR cases, the prevalence of LR in aPL-positive and aPL-negative SLE patients was 27% (n=320/1,207) and 11% (n=244/2,206), respectively. Compared with SLE patients without LR, the overall pooled OR for LR in aPL-positive SLE patients was 3.4 (95% CI, 2.5-4.6). The risk of LR was the highest for LA (five studies, OR: 4.7 [95% CI, 2.4-9.2]) and IgG aCL (seven studies, OR: 3.3 [95% CI, 2.2-4.9]), while IgM aCL, aβ_2GPI IgG, and IgM did not reach statistical significance.

Thrombocytopenia

The cumulative percentage incidence of the platelet count less than 100,000/mL is 7%-30% in SLE patients (62). In a 1990 systematic review by Love et al. (84), SLE patients with either LA or aCL were, on average, three times more likely to have moderate to severe thrombocytopenia than aPL-negative patients. In this study, 38% SLE patients with LA had thrombocytopenia in comparison with 10% without LA. In a recent meta-analysis by Chock et al. (85) including 11,877 SLE patients, the prevalence of thrombocytopenia in aPL-positive and aPL-negative SLE patients was 31% (n=1,261/4,128) and 15% (n=1,138/7,749), respectively. Antiphosphoipid antibody positivity was associated with a two- to four-fold increased risk of thrombocytopenia in SLE patients and the risk was the highest for the LA test (OR: 3.4 [95% CI, 2.6-4.5]) (85). The risk of thrombocytopenia was also significantly increased in SLE patients with IgG (27 studies, OR: 2.0 [95% CI, 1.6-2.4]) or IgM aCL (17 studies, OR: 1.7 [95% CI, 1.3-2.1]) and IgG (five studies, OR: 2.0 [95% CI, 1.2-3.4]) or IgM aβ_2GPI (three studies, OR: 2.7 [95% CI, 1.4-5.00]). Finally, while high titer aCL was associated with an increased risk of thrombocytopenia (three studies, OR: 3.9 [95% CI, 1.1-14.2]), low titer aCL did not reach statistical significance (54).

Hemolytic anemia

Anemia is seen in half of SLE patients (86) and can occur because of non-immune and immune reasons. The most common type of immune anemia in SLE is autoimmune hemolytic anemia (AIHA), which is seen in approximately 15% of SLE patients (87).

The prevalence of AIHA in aPL-positive SLE patients can vary between 20%-28%; however the prevalence is 1%-9% in aPL-negative SLE patients (88-90). In a recent meta-analysis by our group that included 7,967 SLE patients, we demonstrated that the prevalence of AIHA in aPL-positive and aPL-negative SLE patients is 22% (n=488/2,177) and 8% (n=486/5,790), respectively (91). Antiphospholipid antibody positivity was associated with a significant two- to four-fold increased risk of AIHA in SLE patients. The risk of AIHA was the highest for LA (OR: 4.6 [95% CI, 2.6-8.0]) and IgG aβ_2GPI (OR: 4.0 [95% CI, 1.5-10.7]). The risk of AIHA was also significantly increased in SLE patients with IgG (10 studies, OR: 2.3 [95% CI, 1.7-3.0]) or IgM aCL (12 studies, OR: 2.9 [95% CI, 2.2-3.9]) and IgM aβ_2GPI (three studies, OR: 3.0 [95% CI, 1.5-6.1]). Furthermore, in studies explicitly reporting a positive Coombs test, the risk of AIHA was significantly increased (OR: 3.17 [95% CI, 1.93-5.20]) (91).

Renal impairment

Kidney lesions other than nephritis are described in SLE patients with or without aPL. These lesions are located in intrarenal microvessels and are defined as either a thrombotic occlusion or a narrowing of the lumen due to intimal hyperplasia, leading to a cortical ischemic atrophy. Thus, the diagnosis of "aPL-nephropathy" in aPL-positive patients is based on the following: a) acute lesions of TMA with thrombi with fibrin-consistent staining properties by light microscopy in glomeruli and/or arterioles or chronic lesions; b) fibrous intimal hyperplasia (FIH), i.e., intimal "mucoid" thickening (in early phases and myofibroblastic-fibrotic intimal thickening); and c) focal cortical atrophy (FCA), i.e., cortical renal scarring that results from severe ischemic damage usually occurring in the subcapsular zone (92). Lupus patients with TMA have a higher likelihood of treatment failure than those without TMA (93).

The prevalence of "aPL-nephropathy" in SLE patients without aPL varies between 4%-16 %, whereas 25%-39% of the aPL-positive SLE patients have "aPL-nephropathy" (92, 94). Erre et al. (92) demonstrated that double aPL positivity (aCL and LA) is associated with aPL-nephropathy in the course of lupus nephritis; Gerhardsson et al. (95) recently showed that aPL-nephropathy is associated with triple aPL positivity in SLE patients. However, the association between different aPL was inconsistent among studies, and while TMA is recognized as a classification criterion for definite APS (small vessel thrombosis), it was unknown whether the frequency of chronic lesions (FIH and FCA) was significantly increased in aPL-positive vs. aPL-negative SLE patients.

A recent meta-analysis on 1820 patients by Domingues et al. (96) showed that the prevalence of renal lesions in aPL-positive vs. aPL-negative SLE patients was 31.9% (n=243/761) vs. 17.5% (n=239/1,367). Furthermore, compared with aPL-negative SLE patients without acute (TMA including "glomerular thrombosis" and "intra-renal thrombosis) and chronic (e.g., FIH, FCA) renal lesions, the overall pooled OR for renal lesions in aPL-positive SLE patients was 2.9 (95% CI, 1.88-4.32). The risk of renal lesions was the highest for LA (nine studies, OR: 4.7 [95% CI, 2.4-9.4]) and IgG aCL (four studies, OR: 3.1 [95% CI, 1.1-9.0]), while IgM aCL (two studies, OR: 1.5 [95% CI, 0.03-88.6]) and aβ_2GPI (four studies, OR: 1.7 [95% CI, 0.5-5.1] did not reach statistical significance. Furthermore, among all aPL assays, LA was the only test to be significantly associated with both acute (four studies, OR: 2.8 [95% CI, 1.1-7.6]) and chronic renal lesions (two studies, OR for LA: 3.5 [95% CI, 1.1-12.1]).

Cognitive dysfunction

Cognitive dysfunction is common in SLE, with a prevalence ranging from 20% to 80% (97, 98). There is no meta-analysis comparing cognitive impairment of SLE patients with or without aPL.

Murray et al. (99) demonstrated that the prevalence of cognitive impairment in aPL-negative SLE patients, measured by verbal memory and verbal fluency metrics, is 11.9% (50/420) in comparison with 21% (57/274) in aPL-positive SLE patients with a 2.1-fold increased risk (95%

CI 1.3-3.4). Coin et al. (100) demonstrated that the prevalence of mild and moderate-to severe cognitive impairment in aPL-positive SLE patients is 41.7% and 33.3%, respectively (compared with 25.9% and 22.2%, respectively in aPL-negative SLE patients. Tomietto et al. (101) also reported that aPL positivity was associated with an increased risk of moderate/severe cognitive impairment in comparison with aPL negativity in a total of 52 SLE patients (51.4% vs. 14.7%; OR 4.9, 95% CI 1.2-20.3, p=0.03).

Catastrophic antiphospholipid syndrome

Encountered in less than 1% of APS patients, catastrophic APS is characterized by accelerated widespread small/medium vessel thromboses with unusual organ involvement and has a mortality of 30%-50% despite aggressive multimodal intensive treatment (102-104).

A cohort study conducted by our group investigating the clinical spectrum of catastrophic APS with and without SLE demonstrated that at the time of CAPS, patients with SLE, were more likely to be female and younger, have cerebral and pancreatic involvement, receive corticosteroids and cyclophosphamide, and have a higher risk of mortality after adjusting for age, sex, organ involvement, and treatment than those without SLE (105).

How do antiphospholipid antibodies alter the management of lupus?

For the majority of the clinical scenarios, there is no difference in the management of persistently aPL-positive patients with or without lupus. However, some clinical scenarios in which the management strategy may differ are discussed below.

First thrombosis prevention

The most important step in patients with clinically significant aPL profiles is the assessment and elimination of non-aPL thrombosis risk factors. In addition to the standard cardiovascular risk modification, aggressive management of systemic autoimmune disease activity is also crucial.

Prospective cohort studies investigating aPL-positive lupus patients (106, 107) as well as retrospective cohort (108) and cross-sectional (109) studies investigating aPL-positive patients with or without systemic autoimmune diseases demonstrated that low-dose aspirin (LDA) may be protective against first thrombosis in aPL-positive SLE patients. Wahl et al. (110) suggested that primary prophylaxis with LDA is beneficial in SLE patients, particularly those with aPL. However, not all studies found a protective effect of LDA against first thrombosis (111-113), and it is important to note that the only randomized, double-blind, placebo-controlled trial investigating the role of LDA in persistently aPL-positive patients (~60% SLE) with no history of thrombosis demonstrated that LDA is not superior to placebo (111).

More recently, two meta-analyses have concluded that the rate of a first thrombotic event in aPL-positive subjects was significantly lower in those receiving LDA than in non-treated patients (7.8% and 15.2%, respectively p<0.0001). However, in the first meta-analysis (11 studies), subgroup analysis demonstrated that LDA was effective only in retrospective (not in prospective) studies (110), while in the second one (five studies), six studies were excluded and no subgroup analysis regarding the study design was performed (114, 115).

LDA is suggested or recommended by several groups for first thrombosis prevention in aPL-positive SLE patients (116-118); however, the low level of evidence and grade of recommendation are highlighted in all publications. Treat-to-target in SLE recommendations from an international task force also states that "the prevention and management of APS-related morbidity in SLE patients should be similar to that in primary APS patients" (119, 120).

In summary, some studies suggest that LDA is protective against first thrombosis in aPL-positive patients; however, the effectiveness of aspirin has not been demonstrated in randomized clinical trials. In addition, the protective role of aspirin against cardiovascular events in the general population remains controversial (121), and LDA increases the bleeding risk. Thus, we suggest that because no lupus-specific CVD risk prediction tool exists, general population prevention guidelines, e.g., those of the American Heart Association (122), should play a role in the decision of LDA in lupus patients with clinically significant aPL profiles. In the absence of other CVD risk factors, physicians should discuss the risk/benefits of LDA as well as the available literature with the patients.

First pregnancy morbidity prevention

Based on a meta-analysis of 34 clinical trials, LDA started at 16 weeks or earlier is associated with a significant reduction in preeclampsia (relative risk [RR]: 0.5, 95% CI 0.3-0.7) and intrauterine growth restriction (RR: 0.4, 95% CI 0.3-0.7) in women who are at a moderate-to-high risk of preeclampsia, e.g., chronic hypertension, history of preeclampsia (123). A later follow-up meta-analysis demonstrated that LDA initiated at or before 16 weeks reduces the risk of severe, but not mild, preeclampsia (124). Although lupus and/or aPL-positive patients are not included in these studies, these patients are at increased the risk of preeclampsia (125). Thus, independent of aPL, several groups recommend LDA for all lupus patients, even without a history of pregnancy morbidity (117, 118, 126-128); however, there are no clinical trials supporting this recommendation.

Although Schramm and Clowse estimated that aspirin may offer a 20% risk reduction for pre-eclampsia development in lupus patients, decreasing the incidence from 15% to 12% (125), the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study suggested that LDA is not protective against APO after adjusted for other predictors (it is important to note that the treatment decisions were made by patients' own physicians in this study; thus, it was not a blinded or randomized clinical trial) (60, 129). Furthermore, a recent systematic review did not find evidence that LDA prevents unfavorable obstetric outcomes (including preeclampsia and fetal death) in otherwise healthy women with aPL during the first pregnancy (130).

In summary, in theory, LDA use during the first pregnancy of a persistently aPL-positive SLE woman can be justified as follows: a) both pregnancy and aPL may be additive risk factors for vascular thrombosis and b) LDA may decrease the risk of preeclampsia in high-risk patients. However, given the lack of strong clinical data, in the absence of other preeclampsia risk factors or other pregnancy morbidity, physicians should discuss the risk/benefits of LDA as well as the available literature with the patients.

Valvular heart disease management

The role of anticoagulation or antiplatelet agents in the prevention or treatment of valve disease in SLE patients with or without aPL remains controversial. Some case reports reported improvement or disappearance of valve vegetations after treatment with oral anticoagulants (131, 132-134); however, the majority of case reports or series did not demonstrate that corticosteroids, anticoagulants, or antiplatelet agents prevent the progression of valvular disease (131, 132, 135, 136). A 2003 committee consensus report, based on limited data, stated that "prophylactic antiplatelet therapy may be appropriate for asymptomatic (no history of thrombosis) aPL-positive patients with valvular heart disease" (137).

In summary, how to treat asymptomatic aPL-positive patients with valvular heart dis-

ease remains controversial; however, the additional diagnosis of SLE does not necessarily change the management, except the fact that controlling the lupus disease activity may prevent the progression of valve disease.

Pulmonary hypertension management

Based on the rationale that a) there is a high prevalence of thrombosis at post-mortem examination in patients with PH (particularly, idiopathic PAH) (138) and b) coagulation abnormalities and VT risk factors are often present in PH patients (139, 140), current guidelines suggest anticoagulation in idiopathic (class of recommendation IIa, C) and connective tissue disease-associated PAH (class of recommendation IIb, C) (141, 142). The recent Comparative, Prospective Registry of Newly Initiated Therapies for PH (COMPERA) study confirmed the survival benefit of anticoagulation in idiopathic PAH (143) but not in other forms of PAH, e.g., in systemic sclerosis-related PAH. The number of patients with SLE was too small to draw any conclusion regarding the beneficial effect of anticoagulation in this group. The recommended target international normalization ratio (INR) in patients with idiopathic PAH ranges from 1.5-2.5 to 2.0-3.0 (142).

In summary, in lupus patients with PAH but no history of thrombosis, the risk of thrombosis is increased but the effect of anticoagulation is unknown (143). In theory, aPL would further increase the risk of thrombosis and anticoagulation can be justified; however, no clinical data exist.

Primary thrombosis prevention in patients with livedo reticularis/racemosa, thrombocytopenia, and/or hemolytic anemia

Based on a limited number of studies, it remains controversial whether livedo racemosa, thrombocytopenia, and/or hemolytic anemia increase the risk of first thrombosis in aPL-positive patients (121). In theory, in lupus patients with active thrombocytopenia and/or hemolytic anemia, aPL may further increase the risk of thrombosis. However, no controlled data have demonstrated the protective effect of any medication against first thrombosis in these patients.

Renal impairment

There are case reports demonstrating that adding warfarin, heparin, or aspirin to the standard treatment offers advantages in aPL-nephropathy patients by improving their renal function (144-146) and enhancing blood flow in interlobar, segmental, and arcuate arteries (147). However, there are no controlled studies and, despite adequate anticoagulation, renal lesions develop in some APS patients (148, 149) and recur after kidney transplantation, often leading to graft loss (150). In the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations on the management of lupus nephritis (118), it was stated that "hydroxychloroquine and/or antiplatelet/anticoagulant treatment should be considered for lupus patients with aPL nephropathy based on a low level evidence." Thus, there are no strong data to recommend the routine use of anticoagulation in lupus nephritis patients with aPL nephropathy; however, it should be considered in refractory cases.

A recent study investigating the role of the mechanistic target of rapamycins (mTOR) pathway in aPL-nephropathy demonstrated that intrarenal cells of aPL-nepthropathy patients showed mTOR pathway activation. Lupus patients with APS had significantly higher activation of the mTOR pathway than those without APS (151). In patients with aPL-nephropathy who required kidney transplantation, those who were treated with rapamycin (10 patients) had decreased vascular proliferation and no recurrence of vascular lesions proliferation. At 144 months after transplantation, seven of 10 (70%) aPL-nephropathy patients treated with rapamycin had a functioning allograft in comparison with only three of 27 (11%) patients who were not treated with rapamycin (151). Future controlled prospective studies should be conducted on mTOR pathway inhibition as a potential approach in patients with aPL-nephropathy.

Renal biopsy is the gold standard method for both diagnostic and prognostic purposes in the clinical management of lupus nephritis (152). One of the significant complications of renal biopsy is bleeding (153); a recent study demonstrated that major bleeding is more common in patients with aPL and LA is a significant independent risk factor for increased bleeding risk (154). Therefore, particular caution should be warranted in patients with aPL undergoing renal biopsy, and increased bleeding risks should be considered while starting an antiplatelet/anticoagulant treatment.

Cognitive dysfunction

No strong evidence exists that pharmaceutical agents or behavioral treatments are effective in treating cognitive dysfunction in lupus patients with or without aPL. Controlling the disease activity, treatment of depression and/or anxiety if present, exercise, and cognitive behavioral techniques to improve sleep, reduce pain and reduce fatigue are some of the important points that need to be considered in these patients.

How Do Antiphospholipid Antibodies Alter the Prognosis of Lupus?

Organ damage

A recent study of 262 lupus patients by Taraborelli et al. (155), based on the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), demonstrated that 21%, 42%, and 57% of SLE patients have new organ damage in 5, 10, and 15 years, respectively; a clinically significant aPL-profile (defined above), older age at diagnosis, and male sex were associated with an increased risk of organ damage accrual during a 15-year follow-up. Another study suggested that persistently high aPL profiles, particularly those with higher thresholds for persistence, are associated with higher (≥2 or ≥3 points) SDI score accrual in lupus patients (156).

Quality of life (QoL)

Health-related QoL (HRQoL) is an important outcome measure in patients with chronic diseases (157, 158); HRQoL is impaired in SLE (159), particularly when associated with APS (160-162). Recently, Zuily et al. (160) demonstrated that SLE patients without aPL have better HRQoL than SLE patients with APS. The Mental Component Summary score, representing mental impairment, was lower in SLE patients with aPL than in SLE patients without aPL (mean MCS: 39 vs 46). Furthermore, SLE-APS patients had a dramatic impairment of QoL (both physical component summary score and MCS), mainly due to a history of stroke (160).

Conclusion

Compared with SLE patients without aPL, SLE patients with aPL have a higher prevalence of thrombosis, pregnancy morbidity, valve disease, PH, LR, thrombocytopenia, hemolytic anemia, acute/chronic renal lesions, and moderate/severe cognitive impairment; worse QoL; and higher risk of organ damage. Quality analyses of completed meta-analyses will better determine the relevance of the association between aPL and aPL-related clinical manifestations in SLE patients.

The use of LDA is controversial for the primary thrombosis and pregnancy morbidity prevention due to lack of strong prospective controlled data. Similarly, the use of anticoagulation is controversial for lupus nephritis patients with aPL-nephropathy. Until further studies are available, physicians should discuss the risk/benefits of LDA or anticoagulation as well as the available literature with the patients.

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