Secondary antiphospholipid syndrome in systemic lupus erythematosus – screening, diagnosis and treatment methods

Andrei-Bogdan Mihaiescu1, Ioana Cristina Saulescu1,2, Daniela Opris-Belinski1,2, Andra Balanescu1,2, Violeta Bojinca1,2, Florian Berghea1,2, Laura Groseanu1,2, Cosmin Constantinescu1,2, Andreea Borangiu1,2, Sanziana Daia-Iliescu1,2, Diana Mazilu1,2, Magda Negru1,2, Claudia Cobilinschi1,2, Denisa Predeteanu1,2, Ruxandra Ionescu1,2

1“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2“Sf. Maria” Hospital, Internal Medicine and Rheumatology Department, Bucharest, Romania
3“George Emil Palade” University of Medicine, Pharmacy, Science, and Technology, Targu Mures, Romania

ABSTRACT

Systemic Lupus Erythematosus is the hallmark of autoimmune diseases, being characterized by multiple organ involvements and immune abnormalities, amongst which the presence of antiphospholipid antibodies with or without specific clinical manifestations (vascular thromboses and pregnancy morbidities) has a significant impact on the disease course, both short and long term, causing the accumulation of irreversible damage. This study evaluates the aforementioned impact, highlighting the importance of very early screening for these antibodies.

Keywords: antiphospholipid syndrome, systemic lupus erythematosus, thrombosis, autoimmunity

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease defined by the association of certain clinical manifestations, such as vascular thromboses and pregnancy-specific pathology, with the presence of certain antiphospholipid antibodies (APA), relevant for the diagnosis, such as lupus anticoagulant (LA), anti-cardiolipin antibodies (ACA) and anti-beta-2-glycoprotein-1 antibodies (AB2GP1A) [1–3].

Systemic lupus erythematosus (SLE) represents the prototype of systemic autoimmune diseases, being characterized by the production of specific and nonspecific autoantibodies, by the formation of immune complexes prone to tissue deposition and by the phenomena linked to chronic inflammation. The clinical picture of SLE can be extremely polymorph, as many internal organs may be affected, and the evolution of the disease can be sinuous and quite unpredictable, with bouts of exacerbation and periods of remission [4–6].

APS can be classified as primary, a disease in its own right, or secondary, associated with various other autoimmune and non-autoimmune pathologies, amongst which SLE is the most frequent one [7,8].

Just to clarify, SLE represents the principal diagnosis, while APS is always a secondary one and a comorbidity [4,6,9]. However, it’s worth mentioning that SLE is also considered a triggering factor for catastrophic APS and thus patients diagnosed with both pathologies require careful monitoring [7,10,11].

The main focus of this article is to study the general impact of APA and APS on the prognosis of patients diagnosed with SLE. We would also like to underline the importance of early testing, through screening, of diagnostic APA and the significance of primary and secondary thromboprophylaxis for the above-mentioned patients.
MATERIALS AND METHODS

Studied population

In this observational, analytical and retrospective cohort study we included patients diagnosed with SLE that have been evaluated at least once throughout the course of 2019 in the internal medicine and rheumatology department of St. Mary Clinical Hospital, Bucharest, Romania.

The cohort will be split twice into two groups, firstly depending on the presence of APA and secondly depending on the presence of APS. Subsequently, we will compare various parameters between our study groups using statistical tests.

Studied parameters

Demography: sex, age (current and when diagnosed with SLE).

Clinical: venous thrombosis (VT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke (IS), pregnancy-specific pathology (PSP), ischemic heart disease (IHD), valvulopathies (VV), cardiomyopathy (CMP), myocarditis (MCD), pulmonary hypertension (PHT), lupus pneumonitis (LP), interstitial lung disease (ILD), alveolar hemorrhages (AH), acute respiratory distress syndrome (ARDS), lupus nephritis (LN), migraine (MGR), seizures (SZR), chorea (CHR), cognitive impairment or psychosis (CIP), autoimmune hemolytic anemia (AHA), thrombocytopenia (TCP), leucopenia (LeP), lymphopenia (LyP), livedo reticularis (LR), cutaneous vasculitis (CV), aseptic osteonecrosis (AO), digestive impairment (DI), ocular impairment (OI), arterial hypertension (AHT), dyslipidemia (DYS).

Paraclinical: LA, ACA, AB2GP1A.

Therapy: hydroxychloroquine (HCQ), glucocorticoids (GC), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYP), tacrolimus (TAC), cyclosporine (CYS), leflunomide (LEF), belimumab (BEL).

Scores: Systemic Lupus International Collaborating Clinics & American College of Rheumatology Damage Index (SLICC & ACR D.I.), Global Anti-Phospholipid Syndrome Score (GAPSS).

All clinical manifestations were linked to SLE only after excluding other etiologies, except for AHT and DYS, which were considered comorbidities.

Paraclinical: LA, ACA, AB2GP1A.

Therapy: hydroxychloroquine (HCQ), glucocorticoids (GC), methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CYP), tacrolimus (TAC), cyclosporine (CYS), leflunomide (LEF), belimumab (BEL).

Scores: Systemic Lupus International Collaborating Clinics & American College of Rheumatology Damage Index (SLICC & ACR D.I.), Global Anti-Phospholipid Syndrome Score (GAPSS).

All data was acquired from the available medical documents, except for the scores, which were manually calculated for each patient using the internationally-approved formulas.

Data processing and statistical analysis

Collected data will be processed and statistically analyzed using two programs: Microsoft Office Excel 2016 and IBM SPSS Statistics 26. Graphical representations of certain results will be generated in the same way.

We will use 3 statistical tests to calculate the p value and therefore assess the statistical significance: Student's t-test, Pearson's chi-squared test and Fisher's exact test. The first one will be used when comparing means of quantitative (numeric) variables. The last two will be used when comparing frequencies of qualitative (nominal) variables, picking one depending on the size of the tested groups.

The relative risk (RR) will also be calculated for differences that are statistically significant (p < 0.05) in order to further evaluate the potency of these results.

RESULTS

Demographics

In this study we included a total of 134 patients diagnosed with SLE. Sex distribution of the cohort shows an uneven distribution, strongly gravitating towards the female component (121 patients i.e. 90.29%). Mean current age (46.63 ± 2.42 years, range from 20 to 82 years), mean age when diagnosed with SLE (35.32 ± 2.38 years, range from 11 to 74 years) and mean SLE “age” (11.31 ± 1.47 years, range from 1 to 41 years) were also calculated (Table 1).

The most important division of our cohort is presented below (Figure 1). The first study group or the control group contains APA negative patients (96 patients i.e. 71.64%), while the second and third (sub) groups or the experimental (sub)groups contain APA positive patients (38 patients i.e. 28.36%), being differentiated in between them by the presence (APS positive – 22 patients i.e. 16.42% of the cohort or 57.89% of the experimental groups) or absence (APS negative – 16 patients i.e. 11.94% of the cohort or 42.11% of the experimental groups) of APS-specific clinical manifestations. It's worth mentioning that in the control group we included patients who didn’t have their APA tested at all.

In regards to the mean age when diagnosed with SLE and conversely the mean SLE “age” (Figures 2 - 3), there is a statistically relevant difference (p = 0.04) between patients affected only by SLE (36.55 ± 2.97 years; 10.54 ± 1.66 years) and those who also have positive APA (32.24 ± 3.83 years & 32.55 ± 5.54 years; 13.24 ± 3.10 years & 14.55 ± 4.48 years).
FIGURE 1. Cohort division, depending on the presence of APA and APS

FIGURE 2. Age when diagnosed with SLE in our 3 study groups

FIGURE 3. SLE “age” in our 3 study groups.
In the following section we successively compared the frequencies of various clinical manifestations between the control group and the two experimental (sub)groups, partitioning them depending on the calculated statistical significance (p value).

Table 2 shows statistically relevant differences when comparing the control group with the first experimental group for: valvulopathies, pulmonary hypertension, interstitial lung disease, lupus nephritis, migraine, seizures, autoimmune hemolytic anemia, thrombocytopenia, digestive impairment, ocular impairment and dyslipidemia.

Table 3 shows statistically irrelevant differences when comparing the control group with the first experimental group for: ischemic heart disease, cardiomyopathy, myocarditis, lupus pneumonitis, alveolar hemorrhages, acute respiratory distress syndrome, chorea, cognitive impairment or psychosis, leucopenia, lymphopenia, livedo reticularis, cutaneous vasculitis, aseptic osteonecrosis, arterial hypertension.

Table 4 shows statistically relevant differences when comparing the control group with the second experimental group for: venous thrombosis, pulmonary embolism, ischemic stroke, pregnancy-specific pathology, valvulopathies, pulmonary hypertension, interstitial lung disease, lupus nephritis, migraine, thrombocytopenia, ocular impairment and dyslipidemia.

Table 5 shows statistically irrelevant differences when comparing the control group with the second experimental group for: myocardial infarction, ischemic heart disease, cardiomyopathy, myocarditis, lupus pneumonitis, alveolar hemorrhages, acute respiratory distress syndrome, seizures, chorea, cognitive impairment or psychosis, autoimmune hemolytic anemia, leucopenia, lymphopenia, livedo reticularis, cutaneous vasculitis, aseptic osteonecrosis, digestive impairment, arterial hypertension.

**Clinical**

Next up, we decided to focus on the two experimental (sub)groups in order to establish how many diagnostic APA (1, 2 or 3) were positive for each patient (Figures 4-5).
TABLE 5. Statistically irrelevant (p ≥0.05) clinical manifestations when comparing the control group i.e. (-) APA patients with the second experimental group i.e. (+) APS patients

|                | (-) APA | (+) APS | p value |
|----------------|---------|---------|---------|
| MI             | 0 (0%)  | 0 (0%)  | –       |
| IHD            | 15 (15.62%) | 4 (18.18%) | 0.5     |
| CMP            | 11 (11.45%) | 1 (4.54%)  | 0.3     |
| MCD            | 1 (1.04%)  | 0 (0%)   | 0.8     |
| LP             | 1 (1.04%)  | 1 (4.54%) | 0.3     |
| AH             | 0 (0%)    | 0 (0%)   | –       |
| ARDS           | 1 (1.04%)  | 1 (4.54%) | 0.3     |
| SZR            | 3 (3.12%)  | 3 (13.63%)| 0.07    |
| CHR            | 0 (0%)    | 0 (0%)   | –       |
| CIP            | 7 (7.29%)  | 3 (13.63%)| 0.2     |
| AHA            | 29 (30.20%)| 9 (40.90%)| 0.3     |
| LeP            | 28 (29.16%)| 9 (40.90%)| 0.2     |
| LyP            | 47 (48.95%)| 14 (63.63%)| 0.2    |
| LR             | 6 (6.25%)  | 2 (9.09%) | 0.4     |
| CV             | 13 (13.54%)| 3 (13.63%)| 0.6     |
| AO             | 8 (8.33%)  | 2 (9.09%) | 0.6     |
| DI             | 12 (12.50%)| 3 (13.63%)| 0.5     |
| AHT            | 36 (37.50%)| 11 (50%)  | 0.2     |

As for comparing the presence of certain diagnostic antibodies in between the same two experimental (sub)groups, ACA stood out for getting very close to the statistical significance threshold, although not actually reaching it (Table 6).

TABLE 6. APA comparison between the (+) and (-) APS (sub)groups.

|                | (+) APS | (-) APS | p value | RR (95% C.I.) |
|----------------|---------|---------|---------|---------------|
| LA             | 10 (45.45%) | 8 (50%) | 0.7     | –             |
| ACA            | 20 (90.90%) | 11 (68.75%) | 0.09   | –             |
| AB2GP1A        | 12 (54.54%) | 8 (50%)  | 0.7     | –             |

Another important aspect we studied is the APA testing tendency in the control group, with two thirds of those patients (64 of them i.e. 66.67%) never having been tested for the 3 diagnostic APA (Figure 6).

For the patients where APA presence was actually assessed it is also important to establish the testing moment, early APA testing meaning before or right after the SLE diagnosis is confirmed (32 patients i.e. 23.88% of the whole cohort) and late APA testing meaning at a subsequent medical evaluation or after vascular thromboses and or pregnancy-specific pathology occurred (38 patients i.e. 28.36% of the whole cohort) (Figure 7).
Therapy

In Table 7 we successively compared the approach to SLE therapy in the control group to the ones employed for the experimental groups, again using the calculated statistical significance (p value). As it turns out, from all the available medication cyclophosphamide was the only one required far more frequently for the APA positive patients, but we should also emphasize that mycophenolate mofetil obtained a close to statistically significant result in both comparisons.

Scores

When comparing the mean SLICC & ACR D.I. of the negative APA group (1.63 ± 0.35 points) with the means of the same score for the positive APA (sub)groups (3.53 ± 0.85 points for the negative APS subgroup and 4.27 ± 1.26 points for the positive APS subgroup) there is a statistically significant difference in both cases (p = 0.0001).

As for GAPSS, which can be calculated only for patients of the positive APA (sub)groups, the difference between the mean of the positive APS subgroup (10.95 ± 1.87 points) and the mean of the negative APS subgroup (9.31 ± 2.05 points) isn’t statistically significant (p = 0.1).

DISCUSSIONS

The study cohort contains 134 patients diagnosed with SLE, out of which 38 (28.36%) have tested positive to one or more APA and 22 (16.42%) also have developed APS-specific clinical manifestations. While the scientific literature mentions higher percentages of SLE patients with positive APA (30-40%), our data can overlap with previous analyses considering that 64 (47.76%) cohort subjects didn’t have their antibodies tested at all [4]. No cases of catastrophic APS were registered in our research.
SLE was diagnosed between the age of 16 and 55 for more than 65% of our patients, a result in accordance with previous data [12]. The mean age of disease debut was significantly lower (4 - 4.3 years) for subjects with positive APA.

Another important finding of our study was that APA presence can be directly linked to the amplified expression of certain clinical manifestations in SLE: valvopathies, pulmonary hypertension, interstitial lung disease, lupus nephritis, migraine, thrombocytopenia, ocular impairment and dyslipidemia. Strangely enough, the two comparisons yielded different results for seizures, autoimmune hemolytic anemia and digestive impairment in terms of statistical significance, thus the pathophysiological link between APA presence and these clinical manifestations cannot be certified in our research. It was also confirmed that APS is a triggering factor for venous thrombosis, pulmonary embolism, ischemic stroke and pregnancy-specific pathology. All those results can be aligned to the exiguous available data [13–22]. It's also worth mentioning that myocardial infarction, alveolar hemorrhages and seizures couldn't be comparatively evaluated due to the lack of such manifestations in our cohort.

Out of all the patients included in our study, only 70 (52.24%) have had at least one diagnostic APA tested, 32 (23.88%) benefitting from an early assessment and 38 (28.36%) being evaluated at a later stage. When comparing APA presence in the APS positive (sub)group versus in the APS negative (sub)group, ACA stood out for getting very close to the statistical significance threshold, although not actually reaching it. As such, we cannot state for certain that ACA presence in SLE patients predisposes to APS-specific clinical manifestations [23,24].

In terms of SLE treatment, CYP was used far more often for APA positive patients than for APA negative ones. We should also emphasize that MMF obtained a close to statistically significant result in the same comparison, while the scientific literature also mentions a higher use of AZA in the first study group [25–32].

Considering that SLICC & ACR D.I. evaluates the entire evolution of the SLE, from beginning until present time, we can therefore infer that APA presence and/or APS determine clinical manifestations that meaningfully alter the disease's prognosis and the patient's quality of life and this data are in accordance with the literature [33–35].

GAPSS evaluates the risk of occurrence and recurrence of APS-specific clinical manifestations and as such we can argue that all patients from the positive APA group present an important risk which justifies thromboprophylaxis, both primary and secondary [36,37].

The main limitation of this research is its retrospective nature, meaning the heavy reliance on available documents for data gathering. This shortcoming is best reflected in the antibodies testing, which was much harder to track than other parameters. There is no mention whatsoever of any non-diagnostic APA,
therefore it’s impossible to ascertain a seronegative APS or to calculate a complete GAPSS, which requires the testing for anti-phosphatidylserine-prothrombin-complex antibodies [38].

CONCLUSIONS

APS testing or searching at least for LA, ACA and AB2GP1A positivity must be done invariably before or soon after SLE is diagnosed. In the end, these three antibodies are part of the 2019 classification criteria for the disease.

APS positivity constitutes a genuine aggravating factor for SLE patients, determining life threatening clinical manifestations, such as cardiovascular, pulmonary, renal and neurological involvement. Periodic monitoring for SLE with APS positivity should be more frequent and minute than for SLE without APA presence. For example, echocardiography may prove extremely useful in the screening and surveillance of valvopathies and pulmonary hypertension.

SLE therapy must be flexible and frequently checked for patients with APS positivity in order to maintain a favorable long-term prognosis and a high quality of life.

Thromboprophylaxis, both primary and secondary, represents a necessity for APA positivity in SLE and for APS associated with SLE, because it minimizes the risk of occurrence and recurrence of vascular thromboses and pregnancy-specific pathology.

Traditional cardiovascular risk factors should also be managed thoroughly for APA positive SLE patients, considering the common association with dyslipidemia.

Long term survival rate for APA positive SLE patients can be as high as that of APA negative subjects, if the protocol for screening, diagnosis and treatment is rigorously respected and applied by both the physician and the patient.

Conflict of interest: none declared  
Financial support: none declared

REFERENCES

1. Bertolaccini ML, Khamashta MA, Hughes GR V. Diagnosis of antiphospholipid syndrome. *Nat Clin Pract Rheumatol.* 2005 Nov;1(1):40–6.
2. Meroni PL, Raschi E, Grossi C, Pregnohallo F, Trespidi L, Acaia B et al. Obstetric and vascular APS: Same autoantibodies but different diseases? *Lupus.* 2012 Jun;21(7):708–10.
3. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295–306.
4. Wallace DJ, Hahn BH. Dubois’ Lupus Erythematosus and Related Syndromes: Eighth Edition. Saunders; 2012. 712 p.
5. Ardoni SP, Pisetsky DS. Developments in the scientific understanding of lupus. *Arthritis Res Ther.* 2008;10:218.
6. Gill JM, Quisel AM, Rocca PV, Walters DT. Diagnosis of Systemic Lupus Erythematosus. *Am Fam Physician.* 2003;68(11):2179–86.
7. Ionescu R. Reumatologie - curs universitar. București: Editura Universitară “Carol Davila”; 2017. 464 p.
8. Mackworth-Young CG. Antiphospholipid syndrome: Multiple mechanisms. *Clin Exp Immunol.* 2004;136(3):393–401.
9. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R et al. 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(9):1151–9.
10. Cervera R, Buc carielli S, Plasin MA, Gómez-Puerta JA, Plaza J, Pons Estel G et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of a series of 280 patients from the “CAPS Registry.” *J Autoimmun.* 2009;32:240–5.
11. Cervera R, Rodríguez-Pinto I, Colafrancesco S, Conti F, Valesini G, Rosário C et al. 14th International Congress on antiphospholipid antibodies Task Force report on catastrophic antiphospholipid syndrome. *Autoimmun Rev.* 2014;13:699–707.
12. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. *Expert Rev Clin Immunol.* 2017;13(8):799–814.
13. Silbiger JJ. The Cardiac Manifestations of Antiphospholipid Syndrome and Their Echocardiographic Recognition. *J Am Soc Echocardiogr.* 2009;22(10):1100–8.
14. Koniaris I, Siminelakis SN, Baikoussis NG, Papadopoulos G, Goudevenos J, Apostolakis E. Antiphospholipid syndrome - Its implication in cardiovascular diseases: A review. *J Cardiothorac Surg.* 2010;5:101.
15. Hughson MD, McCarty GA, Brumback RA. Spectrum of vascular pathology affecting patients with the antiphospholipid syndrome. *Hum Pathol.* 1995;26:716–24.
16. Tektonidou MG. Renal involvement in the antiphospholipid syndrome (APS) - APS nephropathy. *Clin Rev Allergy Immunol.* 2009;36(2–3):131–40.
17. Roldán JF, Brey RL. Neurologic manifestations of the antiphospholipid syndrome. *Curr Rheumatol Rep.* 2007;9(2):109–15.
18. Hughes GRV. Migraine, memory loss, and “multiple sclerosis” - Neurological features of the antiphospholipid (Hughes’) syndrome. *Postgrad Med J.* 2003;79:81–3.
19. Francés C, Niang S, Laffitte E, Le Pelletier F, Costo doat N, Piette JC. Dermatologic manifestations of the antiphospholipid syndrome: Two hundred consecutive cases. *Arthritis Rheumatol.* 2005;52(6):1785–93.
20. Uthman I, Khamashta M. The abdominal manifestations of the antiphospholipid syndrome. *Rheumatology.* 2007;46:1641–7.
21. Uthman I, Godeau B, Taher A, Khamashta M. The hematologic manifestations of the antiphospholipid syndrome. *Blood Rev.* 2008;22(4):187–94.
22. Deák M, Bocskai M, Burcsár S, Dányi O, Fekete Z, Kovács L. Non-thromboembolic risk in systemic lupus erythematosus associated with antiphospholipid syndrome. *Lupus.* 2014;23(9):913–8.
23. Moore GW. Recent guidelines and recommendations for laboratory detection of lupus anticoagulants. *Semin Thromb Hemost.* 2014;40(2):163–71.
24. Lakos G, Favaloro EJ, Harris EN, Meroni PL, Tincani A, Wong RC et al. International consensus guidelines on anticardiolipin and anti-b2-glycoprotein1 testing: Report from the 13th International Congress on Antiphospholipid Antibodies. *Arthritis Rheumatol.* 2012;64(1):1–10.
25. Cervera R, Espinosa G. Antiphospholipid syndrome: Long-time research on pathogenic mechanisms has finally led to new therapeutic strategies. *Expert Opin Ther Targets.* 2010;14(12):1279–82.
26. Kelling D, Mackie I, Moore GW, Greer IA, Greaves M. Guidelines on the investigation and management of antiphospholipid syndrome. *Br J Haematol.* 2012;157:47–58.
27. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. *N Engl J Med.* 2018;378(21):2010–21.
28. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis.* 2019;78:1296–304.
29. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women’s health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis.* 2017;76:476–85.
30. Chighizola CB, Andreoli L, Gerosa M, Tincani A, Ruffatti A, Meroni PL. The treatment of antiphospholipid syndrome: A comprehensive clinical approach. *J Autoimmun.* 2018;90:1–27.
31. Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis.* 2019;78(6):736–45.
32. Franco JS, Molano-González N, Rodríguez-Jiménez M, Acosta-Ampudia Y, Mantilla RD, Amaya-Amaya J, et al. The coexistence of antiphospholipid syndrome and systemic lupus erythematosus in Colombians. *PLoS One.* 2014;9(10).
33. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, De Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: A multicentre prospective study of 1000 patients. *Ann Rheum Dis.* 2015;74(6):1011–8.
34. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis.* 2010;69:1269–74.
35. Fors Nieves CE, Izmirly PM. Mortality in Systemic Lupus Erythematosus: An Updated Review. *Curr Rheumatol Rep.* 2016;18(4):21.
36. Arnaud L, Mathian A, Ruffatti A, Erkan D, Tektonidou M, Cervera R et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: An international and collaborative meta-analysis. *Autoimmun Rev.* 2014;13:281–91.
37. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. *Lupus.* 2011;20:206–18.
38. Cervera R, Conti F, Doria A, Iaccarino L, Valesini G. Does seronegative antiphospholipid syndrome really exist? *Autoimmun Rev.* 2012;11(8):581–4.