Immune Thrombocytopenia in Antiphospholipid Syndrome

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Antiphospholipid syndrome (APS) is frequently associated with thrombocytopenia, in most cases mild and in the absence of major bleedings. In some patients with a confirmed APS diagnosis, secondary immune thrombocytopenia (ITP) may lead to severe thrombocytopenia with consequent major bleeding. At the same time, the presence of antiphospholipid antibodies (aPL) in patients with a diagnosis of primary ITP has been reported in several studies, although with some specific characteristics especially related to the variety of antigenic targets.

Keywords: antiphospholipid antibodies ; antiphospholipid syndrome ; thrombocytopenia ; lupus anticoagulant ; immune thrombocytopenia

1. Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune acquired thrombophilia characterized by recurrent thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL), anti-β2 glycoprotein I (Anti-β2GPI) antibodies, and lupus anticoagulant (LA) [1][2][3]. The aPL are a heterogenous group of antibodies that react with phospholipids (PLs), PL-protein complexes, and PL-binding proteins. The main antigenic targets of these antibodies are β2GPI and prothrombin, which together account for more than 90% of the antibody-binding activity in APS; antigenic targets also include tissue plasminogen activator (tPA), phosphatidylserine (PS), plasmin, annexin 2, activated protein C (APC), thrombin, antithrombin III (AT-III), and annexin V [4][5][6][7][8][9][10]. Antiphospholipid antibodies represent the strongest acquired risk factors for arterial and venous thrombosis and also the most common acquired thrombophilia. Clinical symptoms of APS include thrombosis in any blood vessel of any organ, with no substantial differences between veins and arteries.

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia due to both immune-mediated platelet destruction by antiplatelet antibodies that generally recognize platelet membrane glycoproteins (GPs) and impaired platelet production without other causes or disorders that may be associated with low platelets count. Primary ITP leads to an increased risk of bleeding, although some patients may be asymptomatic [11].

2. APS and Thrombocytopenia

Thrombocytopenia occurs in APS with a frequency ranging from 20% to 50%, and the estimated bleeding risk associated with it is much lower than the thrombotic risk associated with aPL. That said, it is important to explore the mechanism behind thrombocytopenia in order to establish the most appropriate treatment strategy in these patients, especially when anticoagulant or antiplatelet agents are needed [12].

The pathogenesis of thrombocytopenia in antiphospholipid antibody-positive patients is not fully understood. However, based on currently available data [13][14][15][16][17][18][19], we here summarize four different mechanisms, reported in Table 1.

Table 1. Pathogenetic mechanisms involved in thrombocytopenia within the context of APS.

Pathogenesis Hypothesis	Pathway
Secondary Immune Thrombocytopenia	• Expression of platelet membrane glycoproteins, especially GPIIb/IIIa, increases after aPL stimulation, and the binding of anti-β2GPI-β2GPI complex to receptors on the platelet membrane induces the activation and aggregation of platelets. • Antibodies directed against GP on the cell wall of platelets (GPIIb/IIIa, GPIb/IX, GPIa/IIa, and GPIV) have been identified in 40%–70% of thrombocytopenic patients with APS.
Decreased platelet production	• APS can associate with Hemophagocytic Syndrome, although it is extremely rare, and bone marrow necrosis. Both conditions may cause a decrease in platelet production.
Increased platelet pooling	• This condition can be suspected in patients with splenomegaly secondary to portal vein or splenic vein thrombosis due to APS.
Increased platelet consumption	• aPL can mediate upregulation of Von Willebrand Factor (vWF) production by endothelial cells and by direct platelet activation, resulting in an increased vWF-platelet binding.

Clinical Significance of APL-Positivity in ITP

An international consensus introduced the definition of “aPL-associated thrombocytopenia” when the laboratory findings of aPL are associated with thrombocytopenia in the absence of APS-defining criteria [3].

According to ITP guidelines, when aPL are detected in an ITP patient without a history of thrombosis or obstetric complications, this finding will not change the diagnosis of primary ITP nor the recommended treatment (with an important caveat on thrombopoietin receptor agonists, discussed in a dedicated section). The latest ASH “ITP Practice and Guideline Panel” on the contrary, stated that evaluating ITP patients for aPL is unnecessary [20] due to the lack of good evidence of clinical association [21]. Several studies, on the other hand, go in a different direction:

- A study by Diz-Kücükkaya et al. found that 45.1% of a cohort of ITP patients who were persistently positive for aPL developed later APS [22];
- A study by Machin et al. showed that the statistically most relevant risk factor for thrombosis in patients with thrombocytopenia is the co-diagnosis of APS, over an average 5-years follow-up [23];
- A study by Hisada et al. found that the combination of aPL and thrombocytopenia doubled the risk of future thrombosis over an average 10-years follow-up [20]
- A study by Funauchi et al. demonstrated that women with ITP and aPL-positivity had increased thrombosis and obstetric complications risks when compared to the aPL-negative group [24];
- An interesting cross-sectional study reported that the platelet counts of patients with a diagnosis of high-risk APS (triple positive: LAC, anti-beta2-GPI, and aCL) decreased earlier before the appearance of a full clinical picture of CAPS [25]. Therefore, the screening for aPL may identify a subgroup of ITP patients at higher risk of thrombosis.
- The already mentioned International Consensus Panel stated that thrombocytopenia occurring in patients with persistent aPL-positivity is associated with increased thrombotic risk and therefore should be considered different from simple ITP [3];
- Data from the Italian Registry of Antiphospholipid Antibodies reported that 40% of the APS patients with moderate thrombocytopenia and 9% of the APS patients with severe thrombocytopenia developed thrombosis [17];
- A review by Frison et al. on the records of 233 outpatients with primary or secondary thrombocytopenia (platelet count < 100 × 109/L) concluded that triple-positive patients had a significantly lower median platelet count compared to other patients with aPL-positivity [26].

Even though it does not enter the APS defining criteria, thrombocytopenia should be regarded as a warning sign, at least in the assessment of high-risk APS and thoroughly evaluated. At the same time, the presence of aPL during ITP should be assessed to stratify the risk of thrombosis.

3. The Treatment of Antiphospholipid Antibodies Syndrome

Standard care for thrombotic APS is long-term (LT) anticoagulation with a vitamin K antagonist (VKA) [27]. There is currently insufficient evidence to recommend the use of direct oral anticoagulants (DOACs) over VKA in thrombotic APS. The largest studies conducted on this topic showed that DOACs were associated with an increase in hemorrhagic adverse events and an increased thrombosis incidence when compared to VKA [28].

While the recommendation on VKA in APS with a history of venous thromboembolism (VTE) is strong, it is not yet clear if patients with APS and arterial thromboses can really benefit from long-term anticoagulation with VKA rather than prophylaxis with antiplatelet agents, such as LDA. Many experts, in fact, recommend VKA treatment for patients with APS and a history of arterial thromboses because they have a general tendency to recur, thus suggesting that a therapeutic approach based on long-term anticoagulation may be safer than LDA alone. Some authors indicate maintaining a INR target of 3–4 for APS patients with recurrent arterial thrombosis (versus 2–3 of APS patients with a history of recurrent VTE) [29]; however, patients with a history of stroke and a low-titer of aCL may be treated with LDA alone [27].

Pregnant women with thrombotic APS should be treated with LDA in association with therapeutic-dose heparin, regardless of the pregnancy history. LDA or prophylactic-dose low molecular weight heparin (LMWH) can be used in pregnant women with APS but no prior history of thrombosis (including 6 weeks postpartum) [27].

A combined therapy of anticoagulant treatment, glucocorticoids, plasma exchange (PEX), and intravenous high dose immunoglobulin (HD-IVIG) can be used in catastrophic APS (CAPS). Cyclophosphamide can also be used in CAPS when associated with a secondary autoimmune disease, such as SLE. Rituximab can be used in refractory cases, after failure or inability to take the above-mentioned combined therapies or in the presence of micro-angiopathic hemolytic anemia [27], Table 2.

Table 2. Potential treatments of APS with or without thrombosis.

Patient Group	Clinical History	I Line Therapy
non-triple-positive aPL carrier	No thrombotic events	No prophylaxis required
triple-positive aPL carrier	No thrombotic events	Primary prophylaxis with LDA may be considered
thrombotic APS	VTE	Secondary prophylaxis with LT-VKA (target INR 2.5, range 2–3)
thrombotic APS	Arterial thrombosis	Secondary prophylaxis with LT-VKA (target INR 3.5, range 3–4) or LDA
obstetric APS	VTE/arterial thrombosis	LDA + LMWH
CAPS	Without secondary CTD *	Anticoagulation + glucocorticoids + HD-IVIG + PEX
CAPS	Secondary CTD	Anticoagulation + glucocorticoids + HD-IVIG + PEX + cyclophosphamide
Thrombotic APS/CAPS	Refractory disease; Microangiopathic hemolytic anemia	Anticoagulation + glucocorticoids + HD-IVIG + PEX + rituximab

*: connettive tissue disease, including SLE.

4. Management of aPL-Associated Thrombocytopenia

4.1. The Role of anti-CD20 MoAb in Treating aPL-Associated Thrombocytopenia

The chimeric anti-CD20 monoclonal antibody rituximab is commonly adopted as a second-line treatment for immune thrombocytopenia or other immune cytopenias; available studies have reported the efficacy of this treatment with response rates at 1 year ranging from 50% to 60% for immune thrombocytopenia [30] to 75% for warm autoimmune hemolytic anemias [31]. Rituximab has also been evaluated for its efficacy on renal and extra-renal symptoms of SLE.

However, primary study endpoints were not reached in two trials [32][33]. An observational cohort study reported in patients with SLE treated with ituximab [34] a clinical response in up to 70% of cases. A pilot phase 2 study confirmed the safety of rituximab in aPL-positive patients and suggested, even in the absence of any change in aPL levels, the efficacy of rituximab in controlling some non criteria manifestations of APS [35]. There are no controlled clinical trials exploring if rituximab is effective in the antiphospholipid syndrome. However, it could balance the effect of bleeding and thrombosis in APS patients with severe thrombocytopenia. By reducing the production of autoantibodies, rituximab could simultaneously raise the platelets count and reduce the risk of thrombosis [36].

4.2. Thrombopoietin Receptor Agonists in the II Line Treatment of Connettive Tissue Disease-Associated Thrombocytopenia

Thrombopoietin receptor agonists are a novel class of molecules that interact with the thrombopoietin receptor exposed by hematopoietic stem cells promoting proliferation and differentiation of megakaryocytes in the bone marrow, thus increasing peripheral blood functioning platelet count through a dose-dependent mechanism [37].

The TPO-RA Eltrombopag was approved by FDA in 2008 for the treatment of chronic ITP with a solid efficacy and safety profile that has been well defined in the course of the last ten years. There are currently no clinical trials evaluating the efficacy or safety of Eltrombopag in second or further lines treatment of secondary ITP or Connettive Tissue Disease (CTD)-associated thrombocytopenia, with the unique exception of SLE. A few case reports showed that both Eltrombopag and Romiplostim can be successfully used in cases of SLE-associated thrombocytopenia, refractory to first-line immunosuppression therapy [38].

Some studies found an association between TPO-RA and incidence of VTE and arterial thrombosis in patients with chronic liver disease or acquired thrombophilia, such as aPL-positivity or APS. This may be due to the potential role of TPO-RA in enhancing the autoimmune response [39].

4.3. Hydroxychloroquine as a Possible Second Line Agent in APS-Associated Thrombocytopenia

HCQ is commonly adopted for the treatment of SLE. So far, only a few studies have explored the role of HCQ in the treatment of thrombocytopenia associated with SLE; in detail, combined treatment with prednisone and HCQ resulted effective in 7/11 (64%) patients among a cohort of 59 subjects affected by thrombocytopenia and SLE [40]. More recently, HCQ has been administered to treat thrombocytopenia after the failure of first-line oral prednisone treatment (N = 40), either in patients with SLE (N = 12) or with positive antinuclear antibodies (ANA), without overt SLE (N = 28) with a good response rate (60%), [41]. Interestingly, among the enrolled patients, LA, aPL, aCL, and antib2GP1 were also detected in the group without overt SLE. Based on these data, the administration of HCQ for the management of aPL-associated thrombocytopenia should be taken into account as a potential second-line option. Eular recommendations [42] have recently included in the “research agenda “, the evaluation of HCQ administration as a prophylactic treatment option in patients with high-risk aPL profile, including those with non criteria APS manifestations (i.e., thrombocytopenia). A study by Nuri et al. demonstrated that chronic therapy with HCQ can decrease aCL and anti-β2GPI IgG and IgM titers with seemingly no impact on thrombosis risk [43].

HCQ may also be able to prevent paradoxical clots by decreasing endothelial dysfunction induced by aPL [44].

References

1. Harris, E.N. Syndrome of the Black Swan. Rheumatology 1987, 26, 324–326.
2. Wilson, W.A.; Gharavi, A.E.; Koike, T.; Lockshin, M.D.; Branch, D.W.; Piette, J.C.; Brey, R.; Derksen, R.; Harris, E.N.; Hughes, G.R. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an International workshop. Arthritis Rheum. 1999, 42, 1309–1311.
3. Miyakis, S.; Lockshin, M.D.; Atsumi, T.; Branch, D.W.; Brey, R.L.; Cervera, R.H.; Derksen, R.H.; De Groot, P.G.; Koike, T.; Meroni, P.L.; 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. McNeil, H.P.; Simpson, R.J.; Chesterman, C.N.; Krilis, S.A. Antiphospholipid antibodies are directed against a complex antigen that in-cludes lipid binding inhibitor of coagulation: β2 glycoprotein I (apolipoprotein H). Proc. Natl. Acad. Sci. USA 1990, 87, 4120–4124.
5. Galli, M.; Barbui, T.; Comfurius, P.; Maassen, C.; de Baets, M.H.; van Breda-Vriesman, P.J.; Barbui, T.; Zwaal, R.F.; Bevers, E.M. Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990,

335, 1544–1547.

6. Amengual, O.; Atsumi, T.; Koike, T. Antiprothombin antibodies and the diagnosis of antiphospholipid syndrome. Clin. Immunol. 2004, 112, 144–149.
7. Permpikul, P.; Rao, L.; Rapaport, S. Functional and binding studies of the roles of prothrombin and beta 2- glycoprotein I in the expression of lupus anticoagulant activity. Blood 1994, 83, 2878–2892.
8. Chen, P.P.; Giles, I. Antibodies to Serine Proteases in the Antiphospholipid Syndrome. Curr. Rheumatol. Rep. 2010, 12, 45–52.
9. Cesarman-Maus, G.; Ríos-Luna, N.P.; Deora, A.B.; Huang, B.; Villa, R.; Cravioto Mdel, C.; Alarcón-Segovia, D.; Sánchez-Guerrero, J.; Hajjar, K.A. Autoantibodies against the fibrinolytic receptor, annexin 2, in antiphospholipid syndrome. Blood 2006, 107, 4375–4382.
10. Rand, J.H.; Wu, X.X.; Quinn, A.S.; Taatjes, D.J. Resistance to annexin A5 anticoagulant activity: A thrombogenic mechanism for the antiphospholipid syndrome. Lupus 2008, 17, 922–930.
11. Rodeghiero, F.; Stasi, R.; Gernsheimer, T.; Provan, D.; Arnold, D.M.; Bussel, J.B.; Cines, D.B.; Chong, B.H.; Cooper, N.; Godeau, B.; et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: Report from an international working group. Blood 2009, 113, 2386–2393.
12. Bobba, R.S.; Johnson, S.R.; Davis, A.M. A review of the sapporo and revised Sapporo criteria for the classification of antiphos-pholipid syndrome. Where do the revised sapporo criteria add value? J. Rheumatol. 2007, 34, 1522–1527.
13. Campbell, A.L.; Pierangeli, S.S.; Wellhausen, S.; Harris, E.N. Comparison of the effects of anticardiolipin antibodies from patients with the antiphospholipid syndrome and with syphilis on platelet activation and aggregation. Thromb. Haemost. 1995, 73, 529–534.
14. Martinuzzo, M.E.; Maclouf, J.; Carreras, L.O.; Lévy-Toledano, S. Antiphospholipid antibodies enhance thrombin-induced platelet activation and thromboxane formation. Thromb. Haemost. 1993, 70, 667–671.
15. Macchi, L.; Rispal, P.; Clofent-Sanchez, G.; Pellegrin, J.L.; Nurden, P.; Leng, B.; Nurden, A.T. Anti-platelet antibodies in patients with systemic lupus erythematosus and the primary antiphospholipid antibody syndrome: Their relationship with the observed thrombocytopenia. Br. J. Haematol. 1997, 98, 336–341.
16. Panzer, S.; Gschwandtner, M.E.; Hütter, D.; Spitzauer, S.; Pabinger, I. Specificities of platelet autoantibodies in patients with lupus anticoagulants in primary antiphospholipid syndrome. Ann. Hematol. 1997, 74, 239–242.
17. Italian Registry of Antiphospholipid Antibodies. Thrombosis and thrombocytopenia in antiphospholipid syndrome (idio-pathic and sec- ondary to SLE): First report from Italian Registry. Haematologica 1993, 78, 313–318.
18. Cikrikcioglu, M.A.; Hursitoglu, M.; Erkal, H.; Inan, B.; Ozturk, T.; Cakirca, M.; Canpolat, F.; Erkal, S.; Bahtiyar, I.; Cordan, I.; et al. Splenomegaly in Primary Antiphospholipid Syndrome without Accompanying Portal Hypertension or Comorbidity. Pathophysiol. Haemost. Thromb. 2009, 37, 104–109.
19. Ng, C.J.; McCrae, K.R.; Ashworth, K.; Sosa, L.J.; Betapudi, V.; Manco-Johnson, M.J.; Liu, A.; Dong, J.-F.; Chung, D.; White Adams, T.C.; et al. Effects of anti-β2GPI antibodies on VWF release from human umbilical vein endothelial cells and ADAMTS13 activity. Res. Pract. Thromb. Haemost. 2018, 2, 380–389.
20. Hisada, R.; Kato, M.; Sugawara, E.; Fujieda, Y.; Oku, K.; Bohgaki, T.; Amengual, O.; Yasuda, S.; Atsumi, T. Thrombotic risk stratification by platelet count in patients with antiphospholipid anti-bodies: A longitudinal study. J. Thromb. Haemost. 2017, 15, 1782–1787.
21. George, J.N.; Woolf, S.H.; Raskob, G.E.; Wasser, J.S.; Aledort, L.M.; Ballem, P.J.; Blanchette, V.S.; Bussel, J.B.; Cines, D.B.; Kelton, J.G.; et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996, 88, 3–40.
22. Diz-Küçükkaya, R.; Hacihanefioğlu, A.; Yenerel, M.; Turgut, M.; Keskin, H.; Nalçaci, M.; Inanç, M. Antiphospholipid antibodies and antiphospholipid syndrome in pa-tients presenting with immune thrombocytopenic purpura: A prospective cohort study. Blood 2001, 98, 1760–1764.
23. Machin, N.; Ragni, M.V.; Comer, D.M.; Yabes, J.G. Prevalence and correlates of thrombosis in adults with immune thrombocyto-penia: An NIS study. Thromb. Res. 2018, 172, 80–85.
24. Funauchi, M.; Hamada, K.; Enomoto, H.; Ikoma, S.; Ohno, M.; Kinoshita, K.; Horiuchi, A. Characteristics of the clinical findings in patients with idiopathic thrombocyto-penic purpura who are positive for antiphospholipid antibodies. Intern. Med. 1997, 36, 882–885.
25. Pontara, E.; Banzato, A.; Bison, E.; Cattini, M.G.; Baroni, G.; Denas, G.; Calligaro, A.; Marson, P.; Tison, T.; Ruffatti, A.; et al. Thrombocytopenia in high-risk patients with antiphospholipid syndrome. J. Thromb. Haemost. 2018, 16, 529–532.

26. Frison, L.; Lombardi, A.; Caputo, I.; Semenzato, G.; Fabris, F. Vianello FRelevance of antiphospholipid antibody profile in the clinical outcome of ITP: A sin-gle-centre study. Hematology 2019, 24, 134–138.
27. Garcia, D.; Erkan, D. Diagnosis and Management of the Antiphospholipid Syndrome. N. Engl. J. Med. 2018, 378, 2010–2021.
28. DOACs not recommended for people with antiphospholipid syndrome. Drug Ther. Bull. 2019, 57, 182.
29. Park, J.-M.; Eah, K. Recurrent stroke due to antiphospholipid syndrome remitted by immunotherapy, not by anticoagulation therapy: A case report and literature review. Ann. Indian Acad. Neurol. 2019, 22, 250–252.
30. Deshayes, S.; Khellaf, M.; Zarour, A.; Layese, R.; Fain, O.; Terriou, L.; Viallard, J.F.; Cheze, S.; Graveleau, J.; Slama, B.A.; et al. Long-term safety and efficacy of rituximab in 248 adults with immune thrombocytopenia: Results at 5 years from the French prospective registry ITP-ritux. Am. J. Hematol. 2019, 94, 1314–1324.
31. Chao, S.-H.; Chang, Y.-L.; Yen, J.-C.; Liao, H.-T.; Wu, T.-H.; Yu, C.-L.; Tsai, C.-Y.; Chou, Y.-C. Efficacy and safety of rituximab in autoimmune and microangiopathic hemolytic anemia: A systematic review and meta-analysis. Exp. Hematol. Oncol. 2020, 9, 1–14.
32. Rovin, B.H.; Furie, R.; Latinis, K.; Looney, R.J.; Fervenza, F.C.; Sanchez-Guerrero, J.; Maciuca, R.; Zhang, D.; Garg, J.P.; Brunetta, P.; et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab study. Arthritis Rheum. 2012, 64, 1215–1226.
33. Merrill, J.T.; Neuwelt, C.M.; Wallace, D.J.; Shanahan, J.C.; Latinis, K.M.; Oates, J.C.; Utset, T.O.; Gordon, C.; Isenberg, D.; Hsieh, H.-J.; et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: The randomized, double-blind, phase ii/iii systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2009, 62, 222–233.
34. Terrier, B.; Amoura, Z.; Ravaud, P.; Hachulla, E.; Jouenne, R.; Combe, B.; Bonnet, C.; Cacoub, P.; Cantagrel, A.; de Bandt, M.; et al. Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the French autoimmunity and rituximab registry. Arthritis Rheum. 2010, 62, 2458–2466.
35. Erkan, D.; Vega, J.; Ramón, G.; Kozora, E.; Lockshin, M.D. A pilot open-label phase II trial of rituximab for non-criteria manifestations of antiphospholipid syndrome. Arthritis Rheum. 2013, 65, 464–471.
36. Gadó, K.; Domján, G. Antiphospholipid Syndrome and Thrombocytopenia. Thrombocytopenia 2018, 53.
37. Wang, J.; Dai, M.; Fu, Q. Eltrombopag for the treatment of refractory thrombocytopenia associated with connective tissue disease. Sci. Rep. 2021, 11, 1–8.
38. Martinez, M.J.M.; Gallego, P.; Ramos, M.J.M. Agonista del receptor de trombopoyetina como tratamiento de trombocitopenia asociada a lupus eritematoso sistémico. Reumatol. Clín. 2015, 12, 57.
39. Khemichian, S.; Terrault, N.A. Thrombopoietin Receptor Agonists in Patients with Chronic Liver Disease. Semin. Thromb. Hemost. 2020, 46, 682–692.
40. Arnal, C.; Piette, J.C.; Léone, J.; Taillan, B.; Hachulla, E.; Roudot-Thoraval, F.; Papo, T.; Schaeffer, A.; Bierling, P.; Godeau, B. Treatment of severe immune thrombocytopenia associated with systemic lupus erythema-tosus: 59 cases. J. Rheumatol. 2002, 29, 75–83.
41. Khellaf, M.; Chabrol, A.; Mahevas, M.; Roudot-Thoraval, F.; Limal, N.; Languille, L.; Bierling, P.; Michel, M.; Godeau, B. Hydroxychloroquine is a good second-line treatment for adults with immune thrombocytopenia and positive antinuclear antibodies. Am. J. Hematol. 2013, 89, 194–198.
42. Tektonidou, M.G.; Andreoli, L.; Limper, M.; Amoura, Z.; Cervera, R.; Costedoat-Chalumeau, N.; Cuadrado, M.J.; Dörner, T.; Ferrer-Oliveras, R.; Hambly, K.; et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann. Rheum. Dis. 2019, 78, 1296–1304.
43. Nuri, E.; Taraborelli, M.; Andreoli, L.; Tonello, M.; Gerosa, M.; Calligaro, A.; Argolini, L.M.; Kumar, R.; Pengo, V.; Meroni, P.L.; et al. Long-term use of hydroxychloroquine reduces antiphospholipid antibodies levels in patients with primary antiphospholipid syndrome. Immunol. Res. 2016, 65, 17–24.
44. Miranda, S.; Billoir, P.; Damian, L.; Thiebaut, P.A.; Schapman, D.; Le Besnerais, M.; Jouen, F.; Galas, L.; Levesque, H.; Le Cam-Duchez, V.; et al. Hydroxychloroquine reverses the prothrombotic state in a mouse model of antiphospholipid syndrome: Role of reduced inflammation and endothelial dysfunction. PLoS ONE 2019, 14, e0212614.