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ANTIPHOSPHOLIPID SYNDROME (RAS ROUBEY, SECTION EDITOR)

Potential Use of Statins in the Treatment of Antiphospholipid Syndrome

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Abstract Antiphospholipid syndrome (APS) is a disorder characterized by the association of arterial or venous thrombosis and/or pregnancy morbidity with the presence of antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant antibodies, and/or anti–β2-glycoprotein I antibodies). Several studies have contributed to uncovering the basis of antiphospholipid antibody pathogenicity, including the targeted cellular components, affected systems, involved receptors, intracellular pathways used, and the effector molecules that are altered in the process. Therapy for thrombosis traditionally has been based on long-term oral anticoagulation; however, bleeding complications and recurrence despite high-intensity anticoagulation can occur. Based on all the data obtained, new potential therapeutic agents have been proposed. Statins have a variety of direct effects on gene expression and the function of cells of both the innate and adaptive immune systems, many of which are related to blockade of GTPase isoprenylation. In APS, statins have multiple profound effects on monocyte, lymphocyte, and endothelial cell activities, all of which may contribute to thrombosis prevention in APS patients. Nevertheless, larger randomized trials are needed to validate the role of statins in the treatment of this autoimmune disease.

Keywords Antiphospholipid syndrome · Statins · Thrombosis · Treatment · Proteomic approaches

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Introduction

Antiphospholipid syndrome (APS) is a disorder characterized by thrombosis and pregnancy morbidity associated with the persistent presence of antiphospholipid antibodies (aPLs), including anti–β2-glycoprotein I (anti-β2GPI) and/or lupus anticoagulant antibodies [1]. Thrombosis is the major manifestation in patients with aPLs, but the spectrum of symptoms and signs associated with aPLs has broadened considerably, and other manifestations, such as thrombocytopenia, nonthrombotic neurological syndromes, psychiatric manifestations, livedo reticularis, skin ulcers, hemolytic anemia, pulmonary hypertension, cardiac valve abnormality, and atherosclerosis, have also been related to the presence of those antibodies [2].

Many mechanisms have been proposed to explain the thrombotic tendency of patients with APS, but the pathogenesis seems to be multifactorial. Procoagulant cell activation, accompanied by tissue factor (TF) expression and TF pathway upregulation, is one of the key events in the pathophysiology of thrombosis in patients with APS. Previous studies showed elevated plasma levels of soluble TF in APS patients, and thereafter we reported that monocytes isolated from APS patients had high TF expression [3–5]. At the molecular level, the signal transduction mechanisms induced by aPLs have been explored. In a recent study, we showed that aPLs induced TF in monocytes from APS patients by activating—simultaneously and independently—the phosphorylation of mitogen-activated protein kinase (MAPK)/extracellular regulated kinase protein, and the p38 MAPK-dependent nuclear translocation and activation of nuclear factor-κB (NF-kB)/Rel proteins [6]. Similar results have been reported in platelets, monocyte cell lines, and in vivo models of aPL-induced thrombogenicity [7–9]. Parallel studies performed in endothelial cells (ECs) further concluded that 1) NF-κB plays an

essential role in TF activation by aPLs [10]; and 2) p38 MAPK phosphorylation and NF-κB activation are involved in the aPL-induced increase in TF transcription, function, and expression; interleukin (IL)-6 and IL-8 upregulation; and inducible nitric oxide synthase expression [11]. Previous reports indicate a close relationship between TF and vascular endothelial growth factor (VEGF), a family of proteins involved in normal vascular development and in relevant pathophysiologic settings, including cancer, wound healing, and inflammation [12]. Precedent studies had reported increased plasma levels of VEGF in APS patients [13]. In a recent study, we analyzed the VEGF and fms-related tyrosine kinase 1 (*FLT1*) expression levels in monocytes of APS patients, the molecular mechanisms involved in their aPL-induced expression, and their association with the elevated TF expression found in these patients [14]. Our data primarily showed that monocytes from APS patients expressed increased levels of both VEGF and *FLT1* in comparison with monocytes from healthy donors. Furthermore, in vitro results indicated that this cytokine was produced by monocytes when treated with aPLs, and that the p38 MAPK signaling pathway played an important role. Thus, VEGF might act as a regulatory factor in aPL-mediated monocyte activation and TF expression, thereby contributing to the proinflammatory–prothrombotic phenotype of APS patients.

Experimental studies and human observations suggest that APS is associated with atherosclerosis. In fact, innate and adaptive immune responses participate in the pathogenesis of both diseases. Anti-oxLDL, anti-aPL, anti-β2GPI, and anti-HSP antibodies, among others, have been found in patients with APS and atherosclerosis [15]. Endothelial dysfunction, oxidative stress, an increase in cell adhesion molecules, and active platelets are common findings in both diseases. In addition, macrophages, dendritic cells, T-cell activation, and CD40–CD40 ligand interaction are considered pathogenic mechanisms of atherosclerosis and APS [16–18].

Obstetric complications are the second major feature associated with APS. Results from studies in mice show a pivotal role for complement activation in fetal loss induced by aPLs [19, 20]. Moreover, C4d and C3b fractions are deposited in the placentas of patients with aPLs. Interference with annexin V, a natural anticoagulant, might also favor placental thrombosis and fetal loss [21]. Furthermore, abnormalities in placentation have been described in pregnancy loss related to aPLs [22]. The trophoblasts of the placenta express anionic phospholipids on their cell membrane, enabling them to bind exogenous β2GPI [23]. Moreover, it was also noted that these trophoblasts are capable of synthesizing their own β2GPI [24]. β2GPI directly binds to cultured cytotrophoblast cells and is subsequently recognized by antibodies to β2GPI [25]. The aPL binding reduces the secretion of human chorionic gonadotropin. Moreover, aPLs might trigger an inflammatory response mediated by the Toll-like receptor 4/MyD88 pathway, resulting in trophoblast damage [26].

Therapeutic Management of Antiphospholipid Syndrome

Control of conventional risk factors for thrombosis and prophylaxis during high-risk periods is crucial for primary and secondary thrombosis prevention in persistently aPL-positive individuals. Traditional treatment of thrombosis has been based on long-term oral anticoagulation. As more insight is gained about the pathophysiology of the disease and the involved receptors and intracellular pathways, targeted treatment modalities have been proposed as possible alternatives to the current treatment options. Thus, in the past few years, several potential new therapeutic approaches to APS are emerging, including combination of antiaggregant therapy, oral antifactor Xa drugs, direct thrombin inhibitors, hydroxychloroquine, and B-cell depletion [27•].

Anti-inflammatory and immunomodulatory approaches also have been increasingly investigated by different research groups. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, generically referred to as statins, have emerged as the leading therapeutic regimen for treating hypercholesterolemia and reducing cardiovascular morbidity and mortality. In addition, statins have comprehensive immune-modulating properties that affect many aspects of the inflammatory response.

Pleiotropic Effects of Statins on Inflammation and Vascular Function

In the general population, clinical trials have demonstrated beneficial effects of statins in primary and secondary prevention of coronary heart disease as well as ischemic stroke [28–30]. The statin family of drugs comprises naturally occurring members (eg, lovastatin, mevastatin, pravastatin, and simvastatin) and synthetic members (fluvastatin, atorvastatin, and rosuvastatin), which differ in their lipophilicity, half-life, and potency. Statins inhibit the conversion of HMG-CoA to L-mevalonate through competitive inhibition of the rate-limiting enzyme HMG-CoA reductase. This inhibition results in a decrease in the downstream biosynthesis of cholesterol and other intermediate metabolites, including the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These isoprenoid pyrophosphates serve as essential adjuncts in the post-translational modification of many key proteins that function as molecular switches, including the small GTPases Ras, Rac, and Rho. The post-translational modifications enable these signaling proteins to associate with membranes, a prerequisite for most of their biological functions [31]. By altering isoprenylation, which in turn induces the inhibition of the small GTP-binding proteins

Rho, Ras, and Rac, statins are able to improve the endothelial function, enhance the stability of atherosclerotic plaques, decrease oxidative stress and inflammation, inhibit the thrombogenic response, and exert beneficial effects on the immune system [32].

Several recent publications have demonstrated the pleiotropic effects of statins on T-cell and antigen-presenting cell function, leukocyte adhesion and migration, endothelial and monocyte/macrophage function, as well as on in vivo models and human studies of several autoimmune and cardiovascular diseases [33]. In the following paragraphs, we briefly summarize the cellular and molecular mechanisms involved.

Effects of Statins on T-Cell and Antigen-Presenting Cell Functions

Statins inhibit cytokine-inducible expression of major histocompatibility complex class II molecules and co-stimulatory molecules by antigen-presenting cells and prevent antigen presentation to $CD4^+$ T cells. T-cell proliferation is abrogated through modulation of GTPase-linked regulation of cell cycle progression and proliferation. In addition, the effects of statins on cytoskeletal organization interfere with formation of the immunologic synapse. Statins also alter the T-cell profile by inhibiting the secretion of proinflammatory cytokines (eg, interferon [IFN]-γ) through inhibition of signal transducer and activator of transcription 4 (STAT4) and the transcription factor T-bet, which are required for T-helper type 1 (Th1)-cell differentiation. Conversely, statins might also increase the secretion of anti-inflammatory Th2-type cytokines (eg, IL-4) through the activation of both STAT6 and GATA-binding protein 3 (GATA3), which are involved in Th2-cell differentiation [34–36].

Effects of Statins on Leukocyte Adhesion and Migration and Endothelial Cell Immune Function

Cell adhesion molecule expression by leukocytes and ECs is attenuated by statins, resulting in reduced adhesion and transvascular migration. In addition, statins inhibit chemokine and matrix metalloproteinase (MMP) secretion, which further interferes with leukocyte migration. In the endothelium, adhesion molecule signaling that is required for leukocyte migration is blocked through the modulation of Rho and other small GTPases. This might also result in stabilization of the endothelial cell–cell junction. The effect of statins on the cytoskeleton alters leukocyte motility and directional migration in response to chemotactic gradients [37–40].

Effects of Statins on Monocyte Function

Statins induce a shift from the production of monocyte proinflammatory (Th1) cytokines (IL-2, IL-12, IFN-γ, and tumor necrosis factor [TNF]-α) to the production of Th2 cytokines (IL-4, IL-5, and IL-10) [41]. Moreover, statins have been shown to mediate increases in suppressor of cytokine secretion 3 and suppressor of cytokine secretion, which negatively regulate the STAT/Janus kinase (JAK) signal transduction pathway and *IL-6* and *IL-23* gene expression in monocytes. Statins also have been demonstrated to induce IFN-γ, IL-4, and IL-27 production in monocytes, which together inhibited IL-17 transcription and secretion in $CD4^+$ T cells [42]. Furthermore, statins decrease the expression of adhesion molecules, prevent low-density lipoprotein oxidation, and decrease secretion of MMPs and TF expression in monocytes.

Pharmacogenomic and Pharmacoproteomic Profiles of Statin Treatment

Various studies have used genomics and proteomics to analyze modifications in the protein map of plasma and blood cells after statin treatment of hypercholesterolemic patients, patients with autoimmune diseases associated with cardiovascular disease, and patients with atherosclerosis. Data obtained suggest that multiple polymorphisms are responsible for the different responses to these drugs observed in humans. In addition to cholesteryl ester transfer protein (*CETP*) and *APOE*, other genes were recently reported to exhibit polymorphisms that influence the response to this class of drugs. Recently, two common and tightly linked single nucleotide polymorphisms in the 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) gene (a A>T substitution at position 74726928 and a T>G substitution at position 74739571) were found to be related to the response to pravastatin treatment [43]. Individuals with a single copy of the minor allele of these single nucleotide polymorphisms had their overall efficacy for modifying total cholesterol concentration reduced to 22%. On the other hand, pleiotropic genes whose variations have been studied with statins are the genes coding for the angiotensin-converting enzyme (*ACE*), β-fibrinogen (*FGB*), glycoprotein IIIa (*GPIIIa*), stromelysin-1 (*MMP3*), *CD36*, and estrogen receptor-α (*ESR1*) [44].

Pharmacoproteomic approaches are clearly very useful during the development of new drugs to control some toxicity, including drug interactions and in different pathological status. The modulation of the levels of proteins secreted by cultured atherosclerotic plaques and in the blood of patients with atherosclerosis after atorvastatin treatment was evaluated recently [45]. This study showed 24 proteins that were increased and 20 that were decreased after statin treatment. Some of the increased proteins, such as cathepsin D (which could play a significant role in plaque stability), reverted to control values after atorvastatin administration, becoming a potential therapeutic target

for statin treatment. Furthermore, recent studies by Grobbee and Bots [46] have examined the evidence for imaging studies showing the efficacy of statins in slowing atherosclerosis progression and promoting disease regression.

Finally, Anderson and Anderson [47] have described—via proteomic studies—key modifications after statin treatment in carbohydrate metabolism, stress proteins, calcium homeostasis, and protease activity. It also has been suggested that changes in other enzymes from the mevalonate pathway could provide important information regarding the problems with the use of different statin derivatives or some of their side effects.

Statins in Primary Antiphospholipid Syndrome

The contribution of TF and proinflammatory mediators (eg, IL-6 or VEGF) to a prothrombotic state in the APS, as well as the proven interference of statins with aPL-mediated thrombosis have provided a renewed focus on antithrombotic therapies in current use. Several publications have reported the pleiotropic effects of different statins on cultured ECs, platelets, monocytes/macrophages, and in vivo models and human studies of several cardiovascular diseases [33, 48, 49].

First, Meroni et al. [50] showed that statins interfere with aPL-induced EC activation via inhibition of the expression of adhesion molecules and IL-6, which is mediated by NF-κB. Then, Ferrara et al. [51, 52] demonstrated in vivo that fluvastatin inhibited the thrombogenic and inflammatory properties of aPLs and inhibited TF upregulation in aPL-treated ECs. Martinez et al. [53] demonstrated that rosuvastatin decreased expression of vascular cell adhesion molecule 1 by human umbilical venous endothelial cells exposed to APS serum in an in vitro model.

More recently, our group delineated the global effects of fluvastatin on the prothrombotic tendency of monocytes from APS patients (Fig. 1) [54•]. Forty-two APS patients with thrombosis received fluvastatin, 20 mg/d, for 1 month. Blood samples were obtained before the start of treatment, at the end of treatment, and 2 months after the end of treatment. After 1 month of treatment, monocytes showed significant inhibition of TF, protease-activated receptor (PAR)-1 and PAR-2, VEGF, and *FLT1* expression that was related to the inhibition of p38 MAPK and NF-κB/Rel DNA-binding activity. Proteomic analysis further showed proteins involved in thrombotic development (annexin II, RhoA, and protein disulphide isomerase) with altered expression after fluvastatin administration. In vitro studies indicated that the inhibition of HMG-CoA by fluvastatin might inhibit protein prenylation and MAPK activation.

Our data agree with those from the study by Redecha et al. [55], which by using a murine model demonstrated the beneficial effects of statins in the setting of APS, showing that statins prevented neutrophil activation by downregulating TF and PAR-2 and protected mouse fetuses from aPL–IgG-induced injury. Moreover, that research group later demonstrated (by using a murine model of recurrent spontaneous miscarriages that shares features with human recurrent miscarriage and fetal growth restriction) that by inhibiting TF with pravastatin, release of antiangiogenic factor sFlt-1 is inhibited, trophoblast proliferation and placental flow are restored, placental oxidative damage is prevented, and pregnancies are rescued [56].

A recent study by Jajoria et al. [57•] showed a significant decrease in the titers of VEGF in the plasma of APS patients after 30 days of treatment with fluvastatin. Moreover, that study further addressed the beneficial effects of fluvastatin in other prothrombotic/proinflammatory markers induced by aPLs in APS patients, including TF and TNF-α.

From these studies, it seems clear that the inhibition of HMG-CoA reductase by fluvastatin, which is a rate-limiting enzyme of the mevalonate pathway, might reduce the expression and activity of specific subfamilies of small GTPases, therefore inhibiting protein prenylation and MAPK activation. This inhibition is likely to have profound effects on key cellular processes, including the suppression of TF and PAR expression, and anti-inflammatory activities on macrophages through the inhibition of proinflammatory cytokines such as VEGF/*FLT1*. Furthermore, these studies provide significant evidence that fluvastatin has profound and multiple effects in monocyte activity, which might lead to the prevention of thrombosis in APS patients. Elucidating the mechanisms of action of statins will help rationalize the design of such alternative and/or complementary therapy in APS patients.

In summary, wide experimental evidence found in APS models and the recent randomized clinical trial demonstrating a protective effect for rosuvastatin against first major cardiovascular event in the general population without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels [58] justify clinical studies of statins in aPL-positive patients. Nevertheless, many studies have allowed the qualification of statins as category X by the US Food and Drug Administration and are therefore contraindicated in pregnancy. That qualification has been based on their proved teratogenicity, placental disruption, and theoretical long-term fetal neurological damage [59–61]. Statins also have been involved in the disruption of gonadal stem cell development in fetuses, potentially leading to infertility or other problems [62]. Nevertheless, some studies, mainly developed by Redecha and colleagues [55], have demonstrated—by using a murine model—the beneficial effects of statins in preventing pregnancy losses in the setting of APS. That group supports the development of clinical trials to confirm its application to humans, yet many other authors argue that the

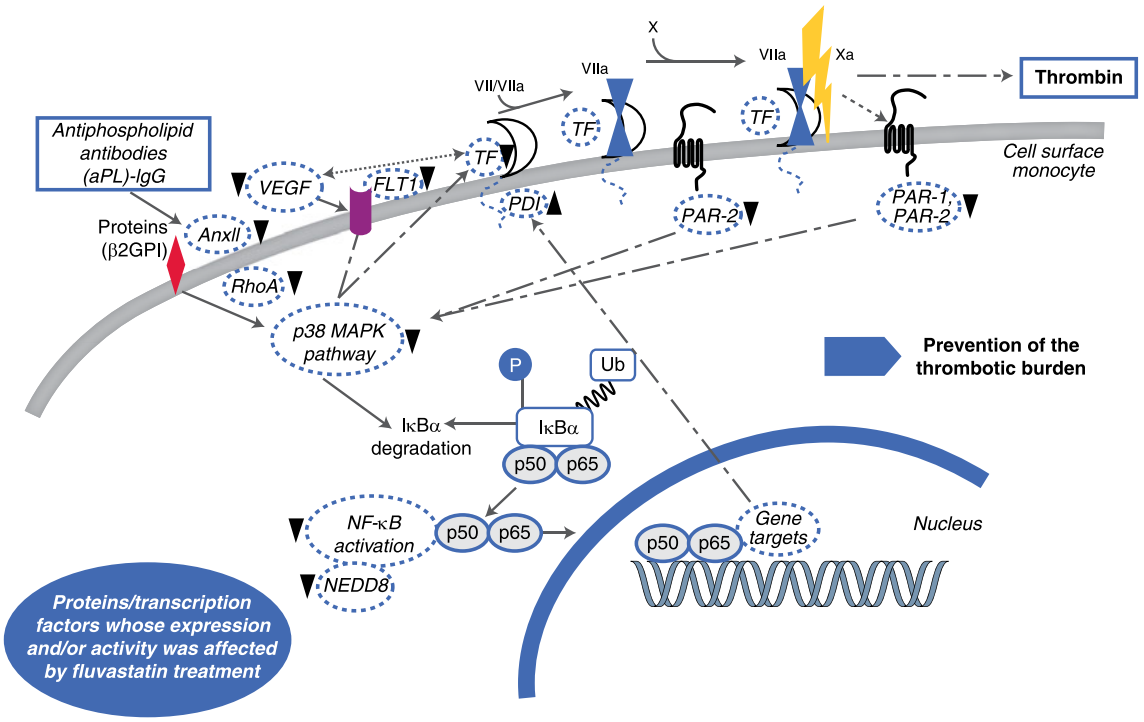

Fig. 1 Antithrombotic/anti-inflammatory mechanisms underlying the effects of fluvastatin on monocytes from antiphospholipid syndrome (APS) patients. The diagram shows cell surface receptors, proteins, and intracellular pathways affected by IgG-APS antibodies in monocytes and the effects promoted on their expression or activity by fluvastatin treatment in APS patients. AnxII, annexin II; β2GPI, β2-glycoprotein I; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PAR, protease-activated receptor; PDI, protein disulphide isomerase; TF, tissue factor; VEGF, vascular endothelial growth factor

experience in mice is insufficient to suggest a clinical trial in pregnant women. Because many studies have shown that it is possible to prevent repeated miscarriages in women with APS by using safer therapeutic approaches, most probably believe that this kind of "dangerous" trial would hardly ever be developed in the future.

Statins in Systemic Lupus Erythematosus

Statins also may play an important role in the treatment of systemic lupus erythematosus (SLE) patients with regard to the prevention of cardiovascular disease as well as the immunomodulation over the chronic inflammatory activity of the disease. A study by Ferreira et al. [63] demonstrated a surprising reduction on the SLE Disease Activity Index (SLEDAI) after atorvastatin therapy, in addition to the improvement of the endothelial-dependent vasodilatation in SLE patients after an 8-week controlled trial. In support of this observation, Kotyla et al. [64] observed a similar reduction on the SLEDAI in a group of female patients treated with another statin, simvastatin. Reduction on the SLEDAI was accompanied by a prominent suppression of TNF-α concentration in the sera of treated patients. That phenomenon was observed after just 4 weeks of treatment with simvastatin at a dose of 20 mg. They also reported improvement in endothelial function, leading to the thesis that restoration of endothelial function was not restricted to the single compound (atorvastatin), but may be recognized as a class of drug effect. As TNF-α is believed to mediate endothelial damage, the authors speculated that suppression of TNF-α levels after statin therapy might be one mechanism via which restoration of endothelial function occurs.

In lupus-prone NZB/W mice receiving atorvastatin orally or intraperitoneally, contradictory results were obtained [65]. No significant effects of fluvastatin on cardiac events in renal transplant recipients with SLE were observed in a recent study [66]. Therefore, the preliminary positive findings must be confirmed in multicenter and long-term studies to determine whether statin treatment in SLE patients is associated with a relevant reduction in cardiovascular morbidity and mortality, as well as with an amelioration of the inflammatory status, and whether this drug category should be broadly indicated for SLE patients.

Conclusions

Most experimental data lead us to believe that statins, alone or probably in combination with other therapeutic

approaches, will improve clinical outcomes in APS patients. The greatest therapeutic attribute of statins is their ability to modulate a broad range of proinflammatory immune mechanisms through inhibition of small GTPases and other prenylated proteins. Their ability to induce downregulation without provoking complete inhibition of these crucial signaling proteins is fundamental to their efficacy (a complete blockade of these molecular switches would be lethal in most cases). The relative safety of these agents and their ease of delivery also provide a compelling case for their evaluation in the clinical setting. Although caution must be applied, the high degree of patient tolerance to statins and their simplicity of delivery make them a highly attractive addition to currently available immunosuppressive drugs. It is likely that the cell type, the statin used, the dose, and the duration will all determine which outcome predominates.

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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Espinosa G, Cervera R, Font J, Shoenfeld Y. Antiphospholipid syndrome: pathogenic mechanisms. Autoimmun Rev. 2003;2:86–93.
2. Koike T, Bohgaki M, Amengual O, Atsumi T. Antiphospholipid antibodies, Lessons from the bench. J Autoimmun. 2007;28:129–33.
3. Cuadrado MJ, Lopez-Pedrera C, Khamashta MA, et al. Thrombosis in primary antiphospholipid syndrome: a pivotal role for monocyte tissue factor expression. Arthritis Rheum. 1997;40:834–41.
4. Dobado-Berrios PM, Lopez-Pedrera Ch, Velasco F, et al. Increased levels of tissue factor mRNA in mononuclear blood cells of patients with primary antiphospholipid syndrome. Thromb Haemost. 1999;82:1578–82.
5. Dobado-Berrios PM, Lopez-Pedrera Ch, Velasco F, Cuadrado MJ. The role of TF in the antiphospholipid syndrome. Arthritis Rheum. 2001;44:2467–76.
6. López-Pedrera Ch, Buendía P, Cuadrado MJ, et al. Antiphospholipid antibodies from antiphospholipid syndrome patients induce monocyte expression through the simultaneous activation of both NFkB/Rel proteins via p38 MAPK pathway, and the MEK1/ERK pathway. Arthritis Rheum. 2006;54:301–11.
7. Vega-Ostertag M, Harris EN, Pierangeli SS. Intracellular events in platelet activation induced by antiphospholipid antibodies in the presence of low doses of thrombin. Arthritis Rheum. 2004;50:2911–9.
8. Bohgaki M, Atsumi T, Yamashita Y, et al. The p38 mitogen-activated protein kinase (MAPK) pathway mediates induction of the tissue factor gene in monocytes stimulated with human monoclonal anti-beta2glycoprotein I antibodies. Int Immunol. 2004;16:1633–41.
9. Montiel-Manzano G, Romay-Penabad Z. Papalardo de Martinez E, et al.: In vivo effects of an inhibitor of nuclear factor-kappa B on thrombogenic properties of antiphospholipid antibodies. Ann N Y Acad Sci. 2007;1108:540–53.
10. Dunoyer-Geindre S, de Moerloose P. Galve-de Rochemonteix B, et al.: NFkappa B is an essential intermediate in the activation of endothelial cells by anti-beta(2)- glycoprotein 1 antibodies. Thromb Haemost. 2002;88:851–7.
11. Vega-Ostertag M, Casper K, Swerlick R, et al. Involvement of p38 MAPK in the upregulation of tissue factor on endothelial cells by antiphospholipid antibodies. Arthritis Rheum. 2005;52:1545–54.
12. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol. 2002;20:4368–80.
13. Williams FMK, Parmar K, Hughes GRV, Hunt BJ. Systemic endothelial cell markers in primary antiphospholipid syndrome. Thromb Haemost. 2000;84:742–6.
14. Cuadrado MJ, Buendía P, Velasco F, et al. Vascular endothelial growth factor expression in monocytes from patients with primary antiphospholipid syndrome. J Thromb Haemost. 2006;4:2461–9.
15. George J, Harats D, Gilburd B, et al. Immunolocalization of beta2-glycoprotein I (apolipoprotein H) to human atherosclerotic plaques: potential implications for lesion progression. Circulation. 1999;99:2227–30.
16. Shoenfeld Y, Sherer Y, George J, Harats D. Autoantibodies associated with atherosclerosis. Ann Med. 2000;32:37–40.
17. Veres K, Lakos G, Kerenyi A, et al. Antiphospholipid antibodies in acute coronary syndrome. Lupus. 2004;13:423–7.
18. Jara LJ, Medina G, Vera-Lastra O. Systemic antiphospholipid síndrome and atherosclerosis. Clin Rev Allergy Immunol. 2007;32:172–7.
19. Pierangeli SS, Girardi G, Vega-Ostertag M, et al. Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia. Arthritis Rheum. 2005;52:2120–4.
20. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10:1222–6.
21. Pierangeli SS, Chen PP, Raschi E, et al. Antiphospholipid antibodies and the antiphospholipid syndrome: pathogenic mechanisms. Semin Thromb Hemost. 2008;34:236–50.
22. Stone S, Khamashta MA, Poston L. Placentation, antiphospholipid syndrome and pregnancy outcome. Lupus. 2001;10:67–74.
23. Di Simone N, Luigi MP, Marco D, et al. Pregnancies complicated with antiphospholipid syndrome: the pathogenic mechanism of antiphospholipid antibodies: a review of the literature. Ann N Y Acad Sci. 2007;1108:505–14.
24. Chamley LW, Allen JL, Johnson PM. Synthesis of beta2 glycoprotein 1 by the human placenta. Placenta. 1997;18:403–10.
25. Di Simone N, Raschi E, Testoni C, et al. Pathogenic role of anti-beta 2-glycoprotein I antibodies in antiphospholipid associated fetal loss: characterisation of beta 2-glycoprotein I binding to trophoblast cells and functional effects of anti-beta 2-glycoprotein I antibodies in vitro. Ann Rheum Dis. 2005;64:462–7.
26. Mulla MJ, Brosens JJ, Chamley LW, et al. Antiphospholipid antibodies induce a pro-inflammatory response in first trimester trophoblast via the TLR4/MyD88 pathway. Am J Reprod Immunol. 2009;62:96–111.
27. • Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA: Antiphospholipid syndrome. Lancet 2010;376:1498-1509. *This is an elegant revision centered on the recent suggestions for therapy*

of thrombosis as well as obstetric care in APS patients, including a perspective on the future use of therapies such as hydroxychloroquine, statins, rituximab, and new anticoagulant drugs.

28. Cortellaro M, Cofrancesco E, Arbustini E, et al. Atorvastatin and thrombogenicity of the carotid atherosclerotic plaque: the ATROCAP study. Thromb Haemost. 2002;88:41–7.
29. Ridker PM, Danielson E, Fonseca FA, et al. JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009;373:1175–82.
30. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360:1851–61.
31. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol. 2006;6:358–70.
32. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005;45:89–118.
33. Undas A, Brummel-Ziedins E, Mann KG. Statins and blood coagulation. Arterioscler Thromb Vasc Biol. 2005;25:1–8.
34. Kuipers HF, Biesta PJ, Groothuis TA, et al. Statins affect T cell-surface expression of major histocompatibility complex class II molecules by disrupting cholesterol-containing microdomains. Hum Immunol. 2005;66:653–65.
35. Ghittoni R, Patrussi L, Pirozzi K, et al. Simvastatin inhibits T-cell activation by selectively impairing the function of Ras superfamily GTPases. FASEB J. 2005;19:605–7.
36. Dunn SE, Youssef S, Goldstein MJ, et al. Isoprenoids determine Th1/Th2 fate in pathogenic T cells providing a mechanism of modulation of autoimmunity by atorvastatin. J Exp Med. 2006;203:401–12.
37. Greenwood J, Walters CE, Pryce G, et al. Lovastatin inhibits brain endothelial Rho-dependent lymphocyte migration and attenuates experimental autoimmune encephalomyelitis. FASEB J. 2003;17:905–7.
38. Yoshida M, Sawada T, Ishii H, et al. HMG-CoA reductase inhibitor modulates monocyte-endothelial cell interaction under physiological flow conditions in vitro: involvement of Rho GTPase-dependent mechanism. Arterioscler Thromb Vasc Biol. 2001;21:1165–71.
39. Rezaie-Majd A, Prager GW, Bucek RA, et al. Simvastatin reduces the expression of adhesion molecules in circulating monocytes from hypercholesterolemic patients. Arterioscler Thromb Vasc Biol. 2003;23:397–403.
40. Turner NA, O'Regan DJ, Ball SG, Porter KE. Simvastatin inhibits MMP-9 secretion from human saphenous vein smooth muscle cells by inhibiting the RhoA/ROCK pathway and reducing MMP-9 mRNA levels. FASEB J. 2005;19:804–6.
41. Youssef SO, Stuve JC, Patarroyo PJ, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature. 2002;420:78–84.
42. Zhang X, Jin J, Peng X, Ramgolam VS, Markovic-Plese S. Simvastatin inhibits IL-17 secretion by targeting multiple IL-17-regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in CD4+ lymphocytes. J Immunol. 2008;180:6988–96.
43. Chasman DI, Posada D, Subrahmanyan L, et al. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA. 2004;291:2821–7.
44. Siest G, Marteau JB, Maumus S, et al. Pharmacogenomics and cardiovascular drugs: need for integrated biological system with phenotypes and proteomic markers. Eur J Pharmacol. 2005;527:1–22.
45. Duran MC, Martin-Ventura JL, Mohammed S, et al. Atorvastatin modulates the profile of proteins released by human atherosclerotic plaques. Eur J Pharmacol. 2007;562:119–29.
46. Grobbee DE, Bots ML. Atherosclerotic disease regression with statins: studies using vascular markers. Int J Cardiol. 2004;96:447–59.
47. Anderson NG, Anderson NL. Twenty years of two-dimensional electrophoresis: past, present and future. Electrophoresis. 1996;17:443–53.
48. Undas A, Celiska-Lowenhoff M, Kaczor M, Musial J. New nonlipid effects of statins and their clinical relevance in cardiovascular disease. Thromb Haemost. 2004;91:1065–77.
49. Krysiak R, Okopien B, Herman ZS. Effects of HMG-CoA reductase inhibitors on coagulation and fibrinolysis processes. Drugs. 2003;63:1821–54.
50. Meroni PL, Raschi E, Testoni C, et al. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis Rheum. 2001;44:2870–8.
51. Ferrara DE, Liu X, Espinola RG, et al. Inhibition of the thrombogenic and inflammatory properties of antiphospholipid antibodies by fluvastatin in an in vivo animal model. Arthritis Rheum. 2003;48:3272–9.
52. Ferrara DE, Swerlick R, Casper K, et al. Fluvastatin inhibits up-regulation of tissue factor expression by antiphospholipid antibodies on endothelial cells. J Thromb Haemost. 2004;2:1558–63.
53. Martínez LA, Amigo MC, Orozco A, et al. Effect of rosuvastatin on VCAM-1 expression by HUVEC exposed to APS serum in an in vitro model. Clin Exp Rheumatol. 2007;25:18–9.
54. • López-Pedrera C, Ruiz-Limón P, Aguirre MA, et al.: Global effects of fluvastatin on the prothrombotic status of patients with antiphospholipid syndrome. Ann Rheum Dis 2011;70:675-682. *This study delineates the cellular and molecular mechanisms of action of fluvastatin on monocytes from APS patients through both an in vivo study and a confirmatory in vitro study.*
55. Redecha P, Franzke CW, Ruf W, et al. Neutrophil activation by the tissue factor/factor VIIa/PAR2 axis mediates foetal death in a mouse model of antiphospholipid syndrome. J Clin Invest. 2008;118:3453–61.
56. Redecha P, van Rooijen N, Torry D, Girardi G. Pravastatin prevents miscarriages in mice: role of tissue factor in placental and foetal injury. Blood. 2009;113:4101–9.
57. • Jajoria P, Murthy V, Papalardo E, et al.: Statins for the treatment of antiphospholipid syndrome? Ann NY Acad Sci 2009;1173:736–745. *This study examined whether fluvastatin affects the plasma levels of various proinflammatory/prothrombotic markers in APS patients. The authors found that fluvastatin significantly reduced those markers in the majority of treated patients. The data from this study show that statins may be beneficial in aPL-positive patients.*
58. Ridker PM, Danielson E, Fonseca FA. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;20:2195–207.
59. Kenis I, Tartakover-Matalon S, Cherepnin N, et al. Simvastatin has deleterious effects on human first trimester placental explants. Hum Reprod. 2005;20:2866–72.
60. Forbes K, Hurst LM, Aplin JD, Westwood M, Gibson JM. Statins are detrimental to human placental development and function; use of statins during early pregnancy is inadvisable. J Cell Mol Med. 2008;12:2295–6.
61. Ponce J, de La Ossa NP, Hurtado O, et al. Simvastatin reduces the association of NMDA receptors to lipid rafts: a cholesterol mediated effect in neuroprotection. Stroke. 2008;39:1269–75.

62. Ding J, Jiang D, Kurczy M, et al. Inhibition of HMG CoA reductase reveals an unexpected role for cholesterol during PGC migration in the mouse. BMC Dev Biol. 2008;8:120.
63. Ferreira GA, Navarro TP, Telles RW, et al. Atorvastatin therapy improves endothelial-dependent vasodilation in patients with systemic lupus erythematosus: an 8 weeks controlled trial. Rheumatology. 2007;46:1560–5.
64. Kotyla PJ, Sliwinska-Kotyla B, Kucharz EJ. TNF-alpha as a potential target in the treatment of systemic lupus erythematosus: a role for the HMG-CoA reductase inhibitor simvastatin. J Rheumatol. 2006;33:2361–3.
65. Graham KL, Lee LY, Higgins JP, Steinman L, Utz PJ, Ho PP. Failure of oral atorvastatin to modulate a murine model of systemic lupus erythematosus. Arthritis and Rheumatism. 2008;58:2098–104.
66. Norby GE, Holme I, Fellström B, et al. Effect of fluvastatin on cardiac outcomes in kidney transplant patients with systemic lupus erythematosus a randomized placebo controlled study. Arthritis Rheumatism. 2009;60:1060–4.